Oral cancer and early detection

Oral cancer is a broad term that includes various malignant diagnoses that present in the oral tissues.

- Even though the management and prognosis may be different between types and stages of oral cancer, it always has a dramatic impact on the patient's life.

- The cancer and cancer therapy are associated with morbidities that may negatively affect the quality of life—from the time of diagnosis, during cancer therapy, in the immediate period after the cancer treatment, and continue throughout the life of the patient.

- Cultural habits, including betel quid chewing, alcohol consumption, and reverse smoking, as well as low socioeconomic status and low consumption of fruits and vegetables contribute to this high prevalence.

- The trend differs between countries in this region (increases in Pakistan and decreases in Philippines and Sri Lanka) and even between provinces of the same country (Thailand).
- The majority of oral cancers are squamous cell cancers.

Other malignant diseases that can occur in the oral cavity include tumors of the salivary glands, lymph nodes, bone, and soft tissue.

- Approximately 95% of oral cancer occur in people older than 40 years, with an average age at diagnosis of approximately 60 years.

- However, OSCC at a young age and even in pediatric may be seen.
- The majority of oral cancers involve the lateral borders and base of the tongue.
- The lips, gingiva, dorsal tongue, palate, and salivary glands are less common sites.

- Primary squamous cell carcinoma (SCC) of bone is rare; however, a tumor may develop from epithelial rests and from epithelium of odontogenic lesions, including cysts and benign lesions.

- Individuals who have had a previous cancer are at high risk of developing a second primary oral cancer.

Oral cancer nomenclature

➢ Oral cancer nomenclature represents basically the histopathological characteristics of the lesion.

To facilitate communication between health-care providers, a classification system was established by the World Health Organization (WHO); which is updated from time to time based on advances in technology and outcome data.

According to the WHO classification of tumors,
The morphology of the cells
The tissue architecture

As seen in light microscopy is used to define the neoplasm, which may correlate with the biology and behavior of the cancer

WHO Classification of Oral Cancer

Epithelial cancer

Squamous cell carcinoma
Verrucous carcinoma
Basaloid squamous cell carcinoma
Papillary squamous cell carcinoma
Spindle cell carcinoma (sarcomatoid SCC)
Acantholytic squamous cell carcinoma
Adenosquamous carcinoma
Carcinoma cuniculatum
Lymphoepithelial carcinoma

Salivary gland cancer

Salivary gland carcinoma
Acinic cell carcinoma

Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Polymorphous low-grade

adenocarcinoma

Basal cell adenocarcinoma
Epithelial-myoepithelial carcinoma
Clear cell carcinoma, NOS
Cystadenocarcinoma

Hematolymphoid cancer

Diffuse large B-cell lymphoma
Mantle cell lymphoma
Follicular lymphoma
Extranodal marginal zone B-cell lymphoma of MALT type
Burkitt lymphoma
T-cell lymphoma
Extramedullary plasmacytoma
Langerhans cell hystiocytosis
Extramedullary myeloid sarcoma Follicular
dendritic cell sarcoma

Soft tissue cancer

Kaposi sarcoma

Secondary tumors

Mucinous adenocarcinoma
Oncocytic carcinoma
Salivary duct carcinoma
Myoepithelial carcinoma
Carcinoma ex pleomorphic adenoma
Salivary gland adenomasa

Squamous Cell Carcinoma

Etiology and Risk Factors

- The incidence of oral cancer is **age related**, which may reflect time for the accumulation of genetic changes and duration of exposure to initiators and promoters.
- These include
  - chemical and physical irritants, viruses, and hormonal effects.
  - In addition, decreased immunologic surveillance over time may be another explanation to the age relation, such as seen in individuals following solid organ and hematopoietic stem cell transplantations, individuals treated with chemotherapy, and HIV-infected individuals.

Tobacco and Alcohol

- Tobacco products and alcohol are acknowledged risk factors for oral cancer.

- Tobacco contains potent carcinogens, including nitrosamines, polycyclic aromatic hydrocarbons, nitrosodiethanolamine, nitrosoproline, and polonium.
- Tobacco smoke contains carbon monoxide, thiocyanate, hydrogen cyanide, nicotine, and metabolites of these constituents.
- Nicotine is a powerful and addicting drug.

- Epidemiologic studies have reported that up to 80% of oral cancer patients were smokers. In addition to the risk of developing primary cancers, the risk of recurrent and second primary oral cancers is related to continuing smoking after cancer treatment.

- The effect of smoking on cancer risk diminishes 5 to 10 years after quitting.
  - Other forms of tobacco use ;smokeless tobacco have been associated with oral cancers.

- Benign hyperkeratosis and epithelial dysplasia have been documented after short-term use of smokeless tobacco products, and it is likely that chronic use is associated with an increasing incidence of malignant lesions.

- The potential risk of oral cancer with cannabis is unclear as data are inconsistent

All forms of **alcohol**, including —hardǁ liquor, wine, and beer, have been implicated in the etiology of oral cancer.

- In some studies, beer and wine are associated with greater risk than hard liquor.
- The combined effects of tobacco and alcohol result in a synergistic effect on the development of oral cancer.

- The mechanisms by which alcohol and tobacco act synergistically may include
  - ✓ **dehydrating effects of alcohol on the mucosa**,
  - ✓ increasing mucosal permeability,
  - ✓ and the effects of potential carcinogens in alcohol or tobacco.

- Various **enzymatic pathways** have been suggested as playing a role in the mechanism of the synergistic effect of smoking and alcohol on the oral mucosa.

- Likewise, it was speculated that smoking and alcohol interaction may **influence central nervous system activity**.

Betel quid (Areca Nut)

- People with a betel quid chewing habit, with or without added tobacco, are at a higher risk to develop oral cancer.

- In parts of Asia where the use of betel nut mixed with lime to form a quid is widespread (e.g., India, Taiwan), the incidence of oral cancer is high and more commonly involves the buccal mucosa.

- It was suggested that similar pattern may exist among immigrants originating from Asia.

- Furthermore, substitutes for betel quid, such as gutkha and pan masala, are potential carcinogenic as well.

Human Papilloma Virus

- HPVs are DNA viruses that infect various epithelial surfaces.
- There are more than 120 types of HPVs. HPV-16 and -18 are considered high-risk subtypes due to their association with malignant tumors.
- HPV-16 alone is associated with about 85 to 95% of HPV-positive **oropharyngeal (**OPCs).
- The virus penetrates the host cell and integrates into the host cell genome where it can replicate.

- Malignant transformation occurs through the expression of two HPV viral oncogenes, E6 and E7.
- There are many unanswered questions of the biology of HPV infection that include clearance versus persistence of virus, latency and carcinogenesis, site localization, recurrence, and second primary cancers.
- HPV is transmitted by direct contact, primarily by means of vaginal, anal, and oral sex

Risk of developing HPV-positive oropharyngeal carcinoma (OPC) increases with:

- Increasing number of self-reported lifetime sexual partners (oral and vaginal),
- Younger age at first sexual activity,
- And history of having a same-sex partner; in addition, the level of risk can vary according to tumor site.

It is important to note that these findings are related to oropharyngeal carcinoma, whereas HPV is not well defined as risk factor for oral cancer.

Nutritional Factors

- Consumption of fruits and vegetables is associated with a reduced risk for oral cancer.

- This may be due to the antioxidant vitamins C and E and flavonoids. Elevated but inconsistent oral cancer risks have been observed for diets high in eggs and butter and for certain types of meats.
  - Vitamin A may play a protective role in oral cancer

This hypothesis is based on population studies of vitamin A deficiency where an association with the risk of SCC was observed and on studies of reduction in carcinogenesis in cultured head and neck SCC cell lines.

This hypothesis was supported by the fact that vitamin A may cause regression of premalignant leukoplakia.

A decreased risk of head and neck cancer was observed with long-term intake of vitamin C and with term intake of calcium supplement.

In recent years, vitamin D deficiency has also been associated with a plethora of pathologies. However, the association with oral cancer was only based on preliminary studies.

Other Risk Factors

- There is no evidence that denture use, denture irritation, irregular teeth or restorations, and chronic cheek-biting habits are related to oral cancer risk.

However, the role of **local trauma** in the development of oral cancer remains controversial.

It is possible that chronic trauma, in the presence of other risk factors and carcinogens, may promote the transformation of epithelial cells, as has been demonstrated in animal studies.

- High alcohol content in mouthwashes has been implicated in oral cancer in the past.

More recent studies suggest no significant trend in risk with increasing daily use; Furthermore, the alcohol content of mouthwashes has been reduced, and increased use of non alcohol-based mouthwash has been an ongoing trend.

- **In lip cancer**, sun exposure, fair skin and a tendency to burn, pipe smoking, and alcohol are identified risk factors
- Recurrent Herpes simplex virus of the lip **has not been** associated with increased cancer risk.

- Patients undergoing allogeneic hematologic stem cell transplantation are at an increased risk of developing secondary neoplasms, particularly **leukemias and lymphomas**, which may manifest in the oral tissues.

- Likewise OSCC has been reported up to a 20-fold increase in risk in these patient populations.
- OSCC is documented after an extended period of immunosuppression post transplantation and with similar molecular changes, as seen in nonmedically induced immunosuppression.

Oral cancer may behave more aggressively in patients post hematopoietic stem cell transplantation with chronic graft versus host disease and associated immunosuppression.
Other immunosuppressed patients show increased risk for oral cancer as well, such as patients after liver transplantation

These cancers may be associated with HPV.

- Certain **inherited cancer syndromes** show increased risk for oral cancer. For example, oral cancer is one of the cancers that are typical **for Fanconi anemia patients**.

Fanconi anemia is usually diagnosed in an early age.

Cowden syndrome, xeroderma pigmentosum, and dyskeratosis congenita have also been reported in association with oral cancer.

The WHO has listed several oral conditions as having the potential to transform into oral cancer, including lichen planus, leukoplakia, erythroplakia, actinic cheilitis, and submucous fibrosis.
It is clear that even within the umbrella of potentially malignant disorders, there is a spectrum of risks for the development of oral cancer.
For example, the risk for oral cancer **in erythroleukoplakia** is higher than the risk for oral cancer in **lichen planus**.
Even within a certain oral condition, there may be variable risk for transformation.
For example, under the term —**leukoplakia**,‖ **proliferative verrucous leukoplakia** is more aggressive and has a high risk of progression to SCC.
Carcinogenesis is a genetic process that leads to a change in molecular function, cell morphology, and ultimately in cellular behavior.
This process is not limited to the epithelium but involves a complex epithelial, connective tissue, and immune function interaction.

Function interaction.

Major genes involved in OSCC include oncogenes and tumor suppressor genes (TSGs).
Regulatory genetic molecules may be involved as well.
The genetic changes may be reflected in allelic loss or addition at chromosome regions corresponding to proto-oncogenes and TSGs, or epigenetic changes such as DNA methylation or histone deacetylation.

Extracellular enzymes, cell surface molecules, and immune function play a role in the development and spread of oral cancer; viruses and carcinogens are involved as well.

Oncogenes

- Oncogenes may encode for growth factors, growth factor receptors, protein kinases, signal transducers, nuclear phosphoproteins, and transcription factors.

- Although proto-oncogenes increase cell growth and effect differentiation and are likely involved in carcinogenesis, few have been consistently reported in head and neck squamous cell carcinoma.

- Proto-oncogenes associated with head and neck squamous cell carcinoma include ras (rat sarcoma), cyclins, myc (myelocytomatosis),

erb-b (erythroblastosis), bcl (B-cell lymphoma), int-2, CK8, CK19, and epidermal growth factor receptor (EGFR)

Tumor Suppressor Genes

- TSGs negatively regulate cell growth and differentiation.
- Functional loss of TSGs is common in carcinogenesis and in OSCC.
- Both copies of a TSG must be inactivated or lost for loss of function (the —two-hitll hypothesis).
- Chromosomes are numbered (1–23), and the arms of each chromosome are divided by the centromere into a short arm (designated P) and a long arm (designated Q).
- These TSGs have been associated with sites of chromosome abnormalities where loss of genetic nucleic segments has been reported to commonly involve chromosome arms 3p, 4q, 8p, 9p, 11q, 13q, and 17p.
- TSGs involved in head and neck squamous cell carcinoma are P53, Rb (retinoblastoma), and p16INK4A.
- Other candidates include FHIT (fragile histidine triad),

APC (adenomatous polyposis coli), DOC1 VHL (gene for von Hippel–Lindau syndrome), and TGF-R-II (gene for transforming growth factor type II receptor).

Gene-Regulating Proteins

Part of the oncogenic gene regulation is performed by transcription factors. These transcription factors are proteins binding to DNA sequences to permit or inhibit co-binding to RNA polymerase, which in turn regulates the activation of the DNA segment respective gene.

Loss of Heterozygosity

Loss of heterozygosity (LOH) or allelic loss has been studied in oral premalignant lesions and predicts the malignant risk of low-grade dysplastic oral epithelial lesions.

The importance of allelic loss has been shown in retrospective and crosssectional study and confirmed in a prospective study of patents with dysplasia, where lesions with allelic loss at 3p, 9p, and 17p predict risk of progression to SCC, even in histologically benign or tissue with mild dysplasia.

Hypermethylation

The role of promoter hypermethylation of CpG islands is being investigated in OSCC as methylation of epigenetic DNA has been shown to result in a loss of function in some genes involved in cell cycle regulation and DNA repair that may lead to loss or change in TSGs involved in carcinogenesis

MicroRNA

- MicroRNAs are small segments of non encoding single-stranded RNAs that mediate gene expression at the posttranscriptional level by mRNA degradation or translational repression.
- Aberrant microRNA may disrupt the normal regulation and lead to malignancy. MicroRNAs function either as oncogenes or as tumor suppressors and were suggested to play a role in oral cancer.

Extracellular Enzymes

- ✓ Matrix metalloproteinase (MMP) 2 and tissue inhibitor of metalloproteinase play a role in cancer initiation and development.
- ✓ Others have also supported the prognostic significance of tissue inhibitors of MMP.
- ✓ The development of malignant epithelial neoplasms is associated with disruption of cell-to-cell and cell-to-matrix adhesion.
- ✓ Syndecans are a family of heparin sulfate proteoglycan receptors that are thought to participate in both cell-to-cell and cell-to-matrix adhesion.
- ✓ A reduction of syndecan 1 correlated with histologic grade, tumor size, and mode of invasion.

The initiation or progression of oral cancer may be associated with polymorphism of the vascular endothelial growth factor (VEGF) gene Cell Surface Changes

Changes in cell surface receptors and major histocompatibility class I and class II antigens have been reported and may indicate that immune surveillance and immune function may be affected in patients with oral cancer.

Other cell surface changes include a loss of cytoplasmic membrane binding of lectins, which has been shown to correlate to the degree of cellular atypia

Immunosuppression

- The development of malignant disease at a higher rate in immunosuppressed patients indicates the importance of an intact immune response.
- Mononuclear cell infiltration correlates with prognosis, and more aggressive disease is associated with limited inflammatory response.
- Total numbers of T cells may be decreased in patients with head and neck cancer, and the mixed lymphocyte reaction is reduced in some patients, and a diminished migration of macrophages has been demonstrated.
- Cluster of differentiation 8 lymphocytes (T suppressor cells) predominate in the infiltrate, suggesting that immunosuppression is associated with progression of disease.

- Langerhans' cells may be altered in neoplastic epithelium

Viruses

- The potential role of viruses in oral cancer is under continuing study.
- The interaction of viruses with other carcinogens and oncogenes may be an important mechanism of disease.
- HPV is a documented risk factor for oropharyngeal cancer OPC.
- It was also identified in oral cancer.
- Current epidemiology show HPV much more commonly associated with OPC. However, as the change in risk factors with HPV continues to evolve, HPV-related lesions are increasingly reported at other head and neck sites including the oral cavity.

Up to 75% of OPC and 26% of oral SCC have been associated with high-risk HPV, showing a continuing trend to increasing HPV in SCC.

The most common HPV subtypes detected in OPC are HPV 16 and 18 (68% and 34%, respectively).

Other types of HPV detected in OSCC are HPV-6,11,31,33,35, and 56.

- **Herpes simplex virus** has been reported to produce a number of mutations in cells.
- A co-carcinogenic effect between Herpes simplex virus and chewing tobacco has been demonstrated in animal studies, but not in human studies.

- Smokers demonstrate higher antibody titers to Herpes simplex virus, suggesting reactivation.
- Neutralizing antibodies to Herpes simplex virus are present in the serum of patients with oral cancer at higher titers in those who have advanced cancer, and antibody response to Herpes simplex virus antigen is greater in patients than in controls.

However, Herpes simplex virus has not been detected in human OSCC

Presenting Signs and Symptoms

- Unfortunately, patients are most often identified after the development of symptoms associated with advanced stages of disease.

- **Discomfort** is the most common symptom that leads a patient to seek care and may be present at the time of diagnosis in up to 85% of patients.
- Individuals may also present with a mass in the mouth or neck.
- Dysphagia, odynophagia, otalgia , limited movement, oral bleeding, neck masses, and weight loss may occur with advanced disease.
- Loss of sensory function, especially when it is **unilateral**, is a red flag that may indicate neural involvement and requires that cancer be ruled out.
- Loss of function involving the tongue can affect speech, swallowing, and diet.

- **Lymphatic spread of oral carcinoma** most commonly involves the submandibular and digastric nodes, and the upper cervical nodes, but can also involve the remaining nodes of the cervical chain.

- The nodes most commonly involved are those that are on the same side as the primary tumor, although the closer the tumor is to the midline and the more posterior in the oral cavity or oropharynx, the more common are the involvement of the bilateral and contralateral nodes.

- Lymph node involvement may not occur in an orderly fashion.
- Lymph nodes associated with cancer become enlarged and firm to hard in texture, and with progression may become fixed and not mobile.

- The nodes are not tender unless they are associated with secondary infection or an inflammatory response is present, which may occur after a biopsy.

❑ The fixation of nodes to adjacent tissue due to invasion of cells through the capsule is a late occurrence and is evidence of aggressive disease.

❑ The fixation of the primary tumor to adjacent tissue overlying bone suggests the involvement of the periosteum and possible spread to bone.

- Spread of tumor is critical for prognosis and for selection of treatment. The **understaging** of nodes by superficial assessment or the **overstaging** of nodes following a biopsy, when an inflammatory component may be present, impacts the selection of treatment.

- Therefore, accurate node examination is needed before biopsy.

Diagnosis and Histopathology

- The diagnosis is primarily based on histopathology.
- Within the epithelial tumors, SCC is the most prevalent oral malignancy.
- It has several subtypes based on histopathology
- Some of the variants may have unique clinical presentation.

- For the diagnosis of OSCC, dysplasia involves the full thickness of the epithelium and the basement membrane is violated.
- Dysplasia describes a range of cellular abnormalities that includes changes in cell size and morphology, increased mitotic figures, hyperchromatism, nuclear size and

nuclear-cytoplasmic ratio, and alteration in normal cellular orientation and maturation.

Well-differentiated carcinoma **retains** some anatomic features of epithelial cells including the ability to produce keratin, whereas **poorly differentiated carcinoma** **loses** the anatomic pattern and function of epithelium.

Staging of Oral Cancer—TNM System

- The American Joint Committee on Cancer (AJCC) has developed Tumor-Nodes-Metastasis (TNM) staging system of cancer, which reflects the prognosis, and is therefore determinants for the treatment strategy.

T is the **size** of the primary **tumor,**

N indicates the presence of regional **lymph nodes**, and **M** indicates distant **metastasis.**

- The staging system for OSCC combines the T, N, and M to classify lesions as **stages 1** through **4**.

- The AJCC classification is principally a clinical description of the disease. Many clinicians combine an imaging-based assessment of the size, lymph nodes, and metastasis with the AJCC clinical staging.

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Table (8-4) Staging of oral cancer and oropharyngeal cancer

Diagnostic Aids

Diagnostic Aids for Early detection

- Early detection of potentially malignant and malignant lesions is a continuing goal.

- Patient history, thorough head and neck and intraoral examinations, is a prerequisite.

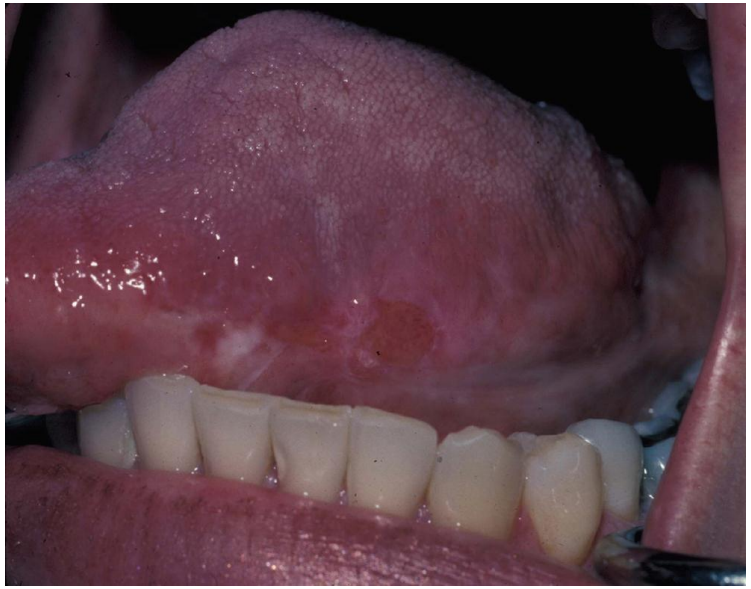
- The definitive test for diagnosis remains tissue biopsy.

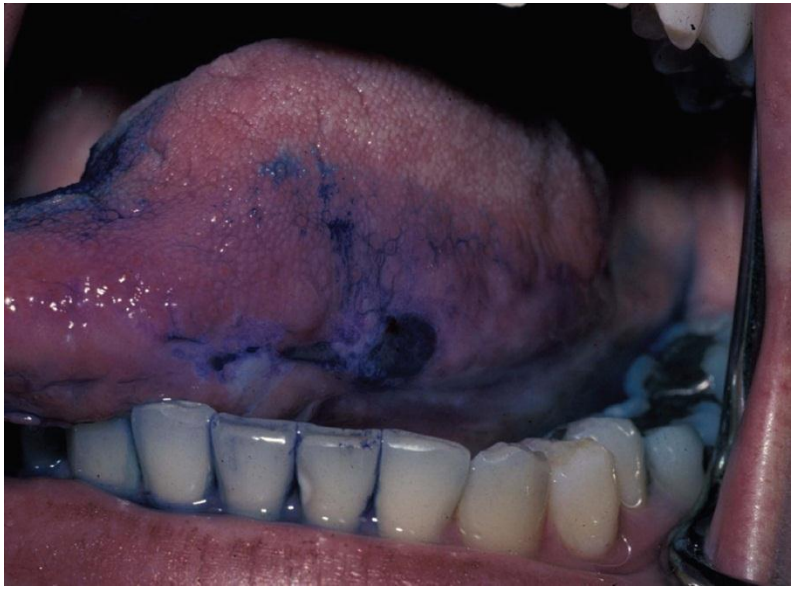
- Several aids to the oral examination have been suggested in the past, including:
  light technologies,
- vital tissue staining using toluidine blue (TB),
- and computer-assisted cytology of oral brush biopsy specimens.
- Additional markers based on blood or saliva samples are also under investigation.

Toluidine Blue

- Vital staining with TB may be used as an adjunctive aid in assessing potentially malignant oral mucosal lesions.

- TB is a metachromatic dye, which has an affinity to bind with DNA.
- TB staining has been correlated with LOH profiles in tissue biopsies.
- TB can be applied directly to suspicious lesions or used as an oral rinse.
- The assessment of dye uptake depends on clinical judgment and experience
- Positive retention of TB (particularly in areas of leukoplakia, erythroplakia, and uptake in a peripheral pattern of an ulcer) may indicate the need for biopsy or assist in identifying the site of biopsy.





- **False-positive** dye retention may occur in inflammatory and ulcerative lesions, but **false-negative** retention is uncommon.
- A return appointment in 14 days, providing time for inflammatory lesions to improve, may lead to a decrease in false-positive results.

- TB has been suggested as a **diagnostic tool** in potentially malignant oral lesions at risk of progressing to squamous cell cancer, where it may provide guidance for the selection for the biopsy site and accelerates the decision to biopsy.

- In postradiotherapy follow-up, the retention of TB may assist in distinguishing Non-healing ulcers and persistent or recurrent disease.

Visualization Adjunctive Tools

- **Chemiluminescent devices** generate **light based on chemical reactions**. The suspected area of mucosa appears **brighter**.

- Other products **generate fluorescent light using a LED source**, sometimes combined with **optical filtration of a viewfinder**, to enhance natural tissue fluorescence.
- When using the **fluorescence light**, the suspected area shows **loss of fluorescence, which appears dark.**

- **Oral cavity fluorescence**, using **blue light excitation**, is thought to represent the tissue structure, metabolic activity, presence of hemoglobin, vessel dilatation, and possibly inflammation.

- Localized modification in these factors may change the reflective features of the tissue.

- These products are promoted to assist the practitioner in discovering mucosal abnormalities, specifically oral potentially malignant disorders and evaluate margins of resection site.

- There is no consensus regarding the sensitivity and specificity of these devices, and their ability to detect early disease. Nonetheless, fluorescence has been shown to provide evidence on lesion margins in patients with known malignant lesions.
- There is an increasing interest in the use of confocal microscopy and optical coherent tomography systems to provide tissue diagnosis in real time, noninvasively, and in situ.

- Such diagnostic approach is available in dermatology and anticipated to be developed for oral mucosal application in the future.

- Other imaging modalities are being studied due to the need for improved detection and to assist in diagnosis and treatment.

Cytology

- Cytology of the oral mucosa is used to assess cellular morphology. The introduction of a brush designed to sample the entire thickness of the oral epithelium renewed interest in cytology for oral disease.

Originally, the cytobrush was combined with a computer- assisted analysis of the cytologic sample, assessing the cell morphology and keratinization.

- The final diagnosis was made by a pathologist based on the standard histomorphologic criteria.

- Further developments in cytology include molecular evaluation of exfoliated cells for molecular markers of dysplasia or carcinoma to improve the diagnostic and prognostic value.

Molecular Analysis

- Molecular markers obtained from tissue specimens have been suggested to assist with detection and evaluation of cancerous lesions including c-erbB2, Ki67/Mcm2, Cyclin D1, p53, COX-1 and 2, telomerase, loss of 3p or 9p, 8p, 4q, 11q, 13q, 17p.
- Studies have also shown that biomarkers of OSCC are present in saliva

Imaging

- Routine radiology, computed tomography (CT), nuclear scintiscanning, magnetic resonance imaging, and ultrasonography can provide evidence of bone involvement or can indicate the extent of some soft tissue lesions.

- The selection of the appropriate imaging modality is dependent on the type and location of the suspected tumor.

- Positron emission therapy using the radiolabeled glucose analog 18fluorodeoxyglucose offers a functional imaging approach for the entire body.
- Positron emission tomography (PET) is a type of nuclear medicine procedure that measures metabolic activity of the cells of body tissues.

- PET is actually a combination of nuclear medicine and biochemical analysis.

- Used mostly in patients with brain or heart conditions and cancer,
- PET helps to visualize the biochemical changes taking place in the body, such as the metabolism.

- PET differs from other nuclear medicine examinations in that PET detects **metabolism** within body tissues, whereas other types of nuclear medicine examinations detect the amount of a **radioactive substance** collected in body tissue in a certain location to examine the tissue's function.
- PET is most often used by oncologists, neurologists, neurosurgeons, cardiologists
- PET may also be used in conjunction with other diagnostic tests, such as computed tomography (CT) or magnetic resonance imaging (MRI) to provide more definitive information about malignant (cancerous) tumors and other lesions.

Acquisition of a Tissue Specimen

- In addition to standard surgical biopsy techniques, tissue can be acquired for histopathology by using fine-needle aspiration (FNA) or core needle biopsy (CNB).

- Open biopsy of enlarged lymph nodes is not recommended; in such cases, FNA biopsy should be considered.

- FNA/CNB also may aid in the evaluation of suspicious masses in other areas of the head and neck, including masses that involve salivary

glands, tongue, and palate, or when there is contraindication for conventional biopsy (e.g., thrombocytopenia).

- Ultrasound may assist in guiding FNA/CNB.

Treatment

- The principal objective of treatment is to cure the patient of cancer.
- The choice of treatment depends on cell type and degree of differentiation, the site and size of the primary lesion, lymph node status, the presence of local bone involvement, the ability to achieve adequate surgical margins, and the presence or absence of metastases.
- Treatment decisions are also impacted by appraisal of the ability to preserve oropharyngeal function, including speech, swallowing, and esthetics, as well as the medical and mental status of the patient.

❑Surgery

Surgery is indicated for
(1) early or localized oral cancer,
(2)tumors involving bone, and when the side effects of surgery are expected to be less significant than those associated with radiation,
(3) tumors that lack sensitivity to radiation, and
(4) recurrent tumor in areas that have previously received radiotherapy.

Surgery also may be used in palliative cases to reduce the bulk of the tumor and to promote drainage from a blocked cavity (e.g., antrum).

- Surgical excision of dysplastic and malignant lesions can be accomplished with laser therapy.
- Such therapy for these lesions is generally well tolerated and usually decreases the period of hospitalization and may have similar outcomes as traditional surgical interventions.

- However, laser therapy has the disadvantage of limiting the assessment of the margins for histopathologic confirmation.

- New surgical approaches and new approaches to reconstruction, such as vascularized flaps, microvascular reconstruction, and neurologic anastomoses of free grafts.
- Reconstruction with the use of osseointegrated implants offers the ability to provide stable prostheses and enhanced esthetic and functional results.
- The ability to place implants in irradiated bone has increased options for rehabilitation

Radiation Therapy

- Radiation therapy may be administered with intent to cure, as a single modality, as part of a combined radiation surgery and/or chemotherapy management, or for palliation.
- Radiotherapy with intent to cure causes early and late toxicities.
- In palliative care, radiation may provide symptomatic relief from pain, bleeding, ulceration, and oropharyngeal obstruction.
- Hyperfractionation of radiation (usually twice daily dosing) is one of the strategies to increase intensity of treatment to increase tumoricidal effects, which results in more severe acute effects.

- High-dose re-irradiation is offered in some centers as save treatment and may be considered in case of recurrent or second primary head and neck cancer, particularly when salvage surgery is not feasible.

- Radiation kills cells by interaction with water molecules in the cells, producing charged molecules that interact with biochemical processes in the cells and by causing direct damage to DNA
- The affected cells may die or remain incapable of division.
- Due to a greater potential for cell repair in normal tissue than in malignant cells and a greater susceptibility to radiation due to the higher growth fraction of cancer cells, a differential effect is achieved.

- To achieve therapeutic effects, radiation therapy is delivered in daily fractions for a planned number of days.

The biologic effect of radiation depends on the dose per fraction, the number of fractions per day, the total treatment time, the total dose of radiation, and the radiation used (electron, neutron, proton).

Methods for representing the factors of dose, fraction size, and time of radiation with a single calculation using the time-dose fraction (TDF) and the nominal standard dose (NSD) calculations have been described.

- Radiation therapy has the advantage of treating the disease in situ and avoiding the need for the removal of tissue and may be the treatment of choice for many T1 and T2 tumors, particularly in the base of the tongue and oropharynx.

- Radiation may be administered to a localized lesion by using implant techniques (brachytherapy) or to a region of the head and neck by using external beam radiation.

Cancer Treatment Planning

The radiation treatment plan is determined by the tumor site and size, relation to vital structures, the volume to be radiated, radiation technology available, the number of treatment fractions, the total number of days of treatment, and the tolerance of the patient.

Chemotherapy Cytotoxic Chemotherapy

- Chemotherapy may be used as induction therapy prior to local therapies, concurrent chemoradiotherapy (CCRT), and adjuvant chemotherapy after local treatment.
- The common chemotherapy protocols are listed in Table (8-6).
- The objective of induction chemotherapy is to promote initial tumor reduction and to provide early treatment of micrometastases due to the recognition that local control.

The principal agents that have been studied alone or in combination in head and neck cancer are taxol and derivatives, platinum derivatives (cisplatin and carboplatin), 5-fluorouracil, and hydroxyurea, although hydroxyurea is rarely used in current protocols.

Photodynamic Therapy

- Photodynamic therapy applies light over a tissue that initially absorbed exogenous sensitizer.

- The sensitizing agent may be delivered systemically or topically and then after it selectively accumulates in target tissue.

- The subsequent light delivery to the target tissue results in cellular destruction.

- Due to the focused cellular destruction, the complications and disfigurement associated with this treatment are relatively small.

- Although photodynamic therapy in oral cancer has some encouraging preliminary results, it is not accepted routine treatment.

Gene Therapy

- Gene therapy is being studied with the objective of reversing dysplasia in oral epithelial lesions.

- The modalities evaluated include suicide gene therapy, immunotherapy, oncolytic virus therapy, inhibition of tumor angiogenesis, gene deletion therapy, and antisense RNA.

- Considering the high rate of mutation in p53 in oral cancer, gene therapy focused on p53 gene, mostly with adenoviral vectors, shows promise.

- Additional target genes and vectors are currently being studied.
- None of these approaches have reached conventional clinic care settings

Immunotherapy

- Immunotherapy offers the potential for additional approaches to management, alone or in combination with other therapies.
- Clinical practice guidelines for management of malignant melanoma and other cancers are forthcoming.
- **Keytruda** May be used with the chemotherapy medicines fluorouracil and a platinum as first treatment when head and neck cancer has spread or returned and cannot be removed by surgery.
- Based on an analysis of a gene expression profile in matched tumor and normal fibroblast cell lines, a number of proteins have been detected that might be potential targets for immunotherapy in individuals with head and neck cancer.

- Cell lines studies and animal models support the introduction of immunotherapy for treatment of head and neck cancer.

Introduction of the Oral Medicine.

Oral medicine is defined as "the dental speciality placed at the interface between medicine and dentistry and is concerned with the diagnosis and management of (non-dental) pathology affecting the oral and maxillofacial region.

"Oral medicine specialists provide clinical care to

1. Patients with a wide variety of orofacial conditions, including oral mucosal diseases,

2. Orofacial pain syndromes,

3. Salivary gland disorders, and oral manifestations of systemic diseases.

4. managing the dental and oral condition of medically compromised patients such as cancer patients suffering from related oral mucositis, osteonecrosis of the jaws or oral pathology related to radiation therapy.

5. Additionally, it is involved in the diagnosis and management of dry mouth conditions (such as Sjögren's syndrome).

6.non-dental chronic orofacial pain, such as burning mouth syndrome, trigeminal neuralgia and temporomandibular joint disorder .

,So in order to get an accurate diagnosis of the patient we have to take adequate history from the patient by the followings sequins Introduce yourself, identify your patient and gain consent to speak with them. At first we start with the age of the patient.

1. **The age** of the patient is important in the following major problem:

- Degeneration bone and joint disease that affected the TMJ
- Chronic brain syndrome
- Malnutration, mental disorder,
- Drugs. This because the old patients have a related changes in the pharmadynamic and pharmakinetic of the drugs also the drug to drug reaction,

drug –food reaction all of these will alter the absorption,distribution, metabolism,exertion.Other changes include.

- Bone and cortical trabecular bone decreased as a result it will be more potential for osteoporotic fractures
- Muscle. The number of the muscle fiber decreased, atrophy as a result the flexion of the joint decreased which lead to slowly muscle regression.
- Increased auto immune diseases.

Changes in the Joints include

1. Cartilage erosion
2. Calcium deposit increased
3. Water in cartilage decreased
4. Osteoarthritis increased

Other changes

- dentin decreased, gingival retraction , bone density lost , the papilla of the tongue decreased which lead to taste change, taste threshold for salt and sugar increased , salivary secretion decrease, potential loss of the teeth.

While other changes on the mucosal surface

- increase in the potential infection on the mucosal surface
- malignancy incidence
- response to acute infection reduced
- potential recurrence of latent herpes zoster

also **the immune system changes**

- secretary immunoglobulin IgA decline
- thymus gland involved
- thymopoietin decreased
- lymphoid tissue decreased
- antibody production impaired
- T. lymphocyte decreased

- autoantibody increased

2. SEX.

- Malignant melanoma the incidence is increasing in male
- Mucous membrane pemphigoid ,cicatrical pemphigoid more in female
- Epulis and pregnancy epulies occur in female because of the circulating estrogen are highest
- S.C.C more in males
- mucocele more in female

3. Presenting complaint (PC)

4. History of presenting complaint (HPC)

The dentist should gain as much information about the specific complaint.**S**ite:

Where exactly is the pain?

- **O**nset: When did it start, was it constant/intermittent, gradual/ sudden?
- **C**haracter:What is the pain like e.g. sharp, burning, tight?
- **R**adiation: Does it radiate/move anywhere?
- **A**ssociations: Is there anything else associated with the pain e.g. sweating, vomiting
- **T**ime course: Does it follow any time pattern, how long did it last?
- **E**xacerbating/relieving factors: Does anything make it better or worse?
- **S**everity: How severe is the pain, consider using the 1-10 scale?

5. past medical history (PMH)

Gather information about a patients with other medical problems

6. Drug history (DH)

Find out what medications the patient is taking, including dosage and how often they are taking them e.g. once-a-day, twice-a-day,… etc.At this point it is important idea to find out if the patient has any allergies.

7 .Family history (FH)

A family health history is a compilation of relevant information about medical conditions affecting a patient and his/her close family members. It represents an essential component of a patient's medical history, e.g diabetes or cardiac history. Find out if there are any genetic conditions within the family e.g. Polycystic kidney disease, hematological diseases LIKE HAEMOPHILIA .

8 .Social history (SH)

Remember to ask about smoking and alcohol.

Smoking. There are lesions related to the smoking like leukoplakia nictonic stomatities

Alcohol history the elevated of MCV mean corpuscular volume in the absence of vitamin B 12 or folate deficiency or unexplained abnormal liver function test

9. Review of systems (ROS)

These are the main systems you should cover:

- CVS, Respiratory, GIT, Neurology, Genitourinary/renal system, Musculoskeletal, Psychiatry.

THE ART OF HISTORY TAKING

Consultation skills The skills required to obtain the patient's true story can be learned and go beyond knowing what questions to ask. Indeed 'questions' may need to be avoided, as they limit the patient to 'answers'..

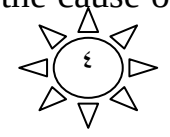
What types of questions the dentist should ask the patient

1. Open questions , 2.Questions with options, 3.Leading questions.

Extra oral. Head and neck examination

1. Asymmetries

Asymmetries of the head and neck are assessed by standing directly in front of the patient. Most people are not completely symmetrical, but significant asymmetries should be noted and the cause obtained from the patient if known.



Examples of asymmetries are: previous surgeries, nerve paralysis from CVA/stroke, tumors, and infections.

The General Examination: briefly assesses the patient's general appearance

The Extraoral Head and neck Soft Tissue examination;

The Intraoral soft tissue examination: determines if the soft tissue is within normal limits (WNL).

A. General examination:

As the patient enters the room, and during history taking, observe the patient's general appearance, symmetry, gait, and mobility. During the history taking, note any facial asymmetries, lesions or scars.

The patient's exposed skin should also be examined. If petechiae, ecchymosis, or hematoma are seen, then further information should be obtained from the patient about bleeding problems, or medications such as blood thinners. Clubbing of the fingers may be a sign of heart or respiratory problems.

The lymph node examination

Consistency

Soft (insignificant), rubbery (classically lymphoma), hard (classically malignancy & granulomatous infection).

- Tender (classically infection) vs. non-tender (classically malignancy) for example

- Patient 2-12 years old commonly present with insignificant lymph nodes in neck secondary to frequent viral infection

Lymph Node Exam Technique

Left supraclavicular node (Virchow's node) classical sign of abdominal process. **Right superclavicular node** classic sign of intrathoracic process. **Infraclavicular fossa** nodes: classically breast cancer or malignant lymphoma. Epitrochlear lymph nodes: best felt when moving fingers up and down.

+Anterior Cervical (both superficial and deep): Nodes that lie both on top of and beneath the sternocleidomastoid muscles (SCM) on either side of the neck, from the angle of the jaw to the top of the clavicle.

Drainage: The internal structures of the throat as well as part of the posterior pharynx, tonsils, and thyroid gland. Tongue (except apex), Ear Pinna, Parotid Gland .

Tonsillar: Located just below the angle of the mandible. Drainage: The tonsilar and posterior pharyngeal regions.

Sub-Mandibular: Along the underside of the jaw on either side. Drainage: The structures in the floor of the mouth,Tongue, Submaxillary gland.

Sub-Mental: Just below the chin. **Drainage:** The teeth and intra-oral cavity, Pattern Lower lip, Floor of Mouth ,Tip of Tongue, Skin of Chee.

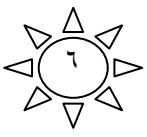
Supra-clavicular: In the hollow above the clavicle, just lateral to where it joins the sternum. Drainage: Part of the throacic cavity, abdomen.

Infections can either originate from the organs that they drain or primarily within the lymph node itself, referred to as lymphadenitis.

Infected lymph nodes tend to be: Firm, tender, enlarged and warm. Inflammation can spread to the overlying skin, causing it to appear reddened. If an infection remains untreated, the center of the node may become necrotic, resulting in the accumulation of fluid and debris within the structure.

This is known as an abscess and feels a bit like a tensely filled balloon or grape (Fluctuance). Knowledge of which nodes drain specific areas will help the dentist to search efficiently.

Malignancies may also involve the lymph nodes, either primarily (e.g. lymphoma) or as a site of metastasis. In either case, these nodes are generally: Firm, non-tender, matted (i.e. stuck to each other), fixed (i.e. not freely mobile but rather stuck down to underlying tissue), and increase in size over time.



Enlargement of nodes located only on the right side of the neck in the anterior cervical chain, for example, would be consistent with a squamous cell carcinoma, frequently associated with an intra-oral primary cancer.

So in order to make clinical examination of the L.n we need inspection and palpation technique: use the pads of the index and middle finger (The "flat" of the fingers not the tip) to move the skin in circular motions over the underlying tissues in each area; palpate both sides of the neck simultaneously small nodes are normal unless in unusual location (preauricular).

In abnormal nodes, describe in terms of

Location, Size, delimination (discrete or matted together), mobile or fixed, consistency (soft, hard, firm), tenderness.

Differentiation from lymphomas requires the use of clinical features, histology, immunophenotyping, and gene rearrangement studies for monoclonal population detection. Common differential diagnoses to be considered are listed below.

Neoplasms These include the following: Squamous cell carcinoma, Nasopharyngeal carcinoma, Thyroid carcinoma.

Generalized lymphadenopathy is defined as enlargement of more than 2 noncontiguous lymph node groups. A thorough history and physical examination are critical in establishing a diagnosis. Causes of generalized lymphadenopathy include infections, autoimmune diseases, malignancies, histiocytoses, storage diseases, benign hyperplasia, and drug reactions.

Infections:

Generalized lymphadenopathy is most often associated with systemic viral infections. Infectious **mononucleosis** results in widespread adenopathy.

Roseola infantum (caused by human herpes virus 6), **cytomegalovirus (CMV), varicella**, and **adenovirus** all cause generalized lymphadenopathy.

Human immunodeficiency virus (HIV) Children with HIV are at increased risk for tuberculosis, as well.

Although usually associated with localized node enlargement, some **bacterial infections** present with generalized adenopathy. Examples include typhoid

fever caused by Salmonella typhi, syphilis, plague, and tuberculosis. Less common bacteremias, including those caused by endocarditis, result in generalized lymphadenopathies.

Malignant etiologies

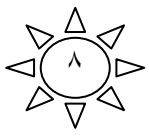
Malignancy is often associated with constitutional signs, such as fever, anorexia, nonspecific aches and pains, weight loss, and night sweats. The acute leukemias and lymphomas often present with these nonspecific findings.

Generalized lymphadenopathy is present at diagnosis in two thirds of children with acute lymphoblastic leukemia (ALL) and in one third of children with acute myeloblastic leukemia (AML). Abnormalities of peripheral blood counts usually lead to the correct diagnosis.

Constitutional signs and symptoms observed in the leukemias are less reliable findings in the lymphomas. Only one third of children with Hodgkin disease and 10% with non-Hodgkin lymphoma display them. Malignancies usually present with nodes that tend to be firmer and less mobile or matted; however, this finding can be misleading. Benign reactive lymph nodes may be associated with fibrotic reactions that make them firm.

Storage diseases: Generalized lymphadenopathy is an important manifestation of the lipid storage diseases. In Niemann-Pick disease, sphingomyelin and other lipids accumulate in the spleen, liver, lymph nodes, and CNS. In Gaucher disease, the accumulation of the glucosylceramide leads to the engorgement of the spleen, lymph nodes, and the bone marrow

Drug reactions: Adverse drug reactions can cause generalized lymphadenopathy. Within a couple of weeks of initiating phenytoin, some patients experience a syndrome of regional or generalized lymph node enlargement, followed by a severe maculopapular rash, fever, hepatosplenomegaly, jaundice, and anemia. These symptoms abate 2-3 months after discontinuation of the drug. Several other drugs are implicated in similar symptomatology, including mephenytoin, pyrimethamine, phenylbutazone, allopurinol, and isoniazid.



Autoimmune etiologies

Include juvenile rheumatoid arthritis, which often presents with adenopathy, especially during the acute phases of the disease. Sarcoidosis and graft versus host disease also merit consideration.

Cervical lymphadenopathy: Cervical lymphadenopathy is a common problem in children cervical nodes drain the tongue, external ear, parotid gland, and deeper structures of the neck, including the larynx, thyroid, and trachea.

Infectious etiologies

Cervical adenopathy is a common feature of many viral infections. Infectious mononucleosis often manifests with posterior and anterior cervical adenopathy. Firm tender nodes that are not warm or erythematous characterize this lymph node enlargement. Other viral causes of cervical lymphadenopathy include adenovirus, herpesvirus, coxsackievirus, and CMV. In herpes gingivostomatitis, impressive submandibular and submental adenopathy reflects the amount of oral involvement.

Bacterial infection often results in enlarged lymph nodes that are warm, erythematous, and tender. Localized cervical lymphadenitis typically begins as enlarged, tender, and then fluctuant nodes.

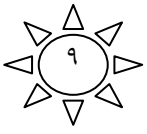
The classic manifestation of group A streptococcal pharyngitis is sore throat, fever, and anterior cervical lymphadenopathy. Other streptococcal infections causing cervical adenopathy include otitis media, impetigo, and cellulitis.

Mycobacterium tuberculosis may manifest with a suppurative lymph node. A biopsy may be necessary to establish the diagnosis.

Cat scratch disease, presents with subacute lymphadenopathy often in the cervical region. The disease develops after the infected pet (usually a kitten) inoculates the host, usually through a scratch. Approximately 30 days later, fever, headache, and malaise develop, along with adenopathy that is often tender

Noninfectious etiologies

Kawasaki disease is an important cause of cervical adenopathy. These children have fever for at least 5 days, and cervical lymphadenopathy is one of the 5 diagnostic criteria (of which 4 are necessary to establish the diagnosis).



Generalized Acute Cervical Lymphadenopathy Causes Common Causes Tinea Capitis ,Infectious Mononucleosis (Epstein Barr Virus), cytomegalovirus, Adenovirus

Less common causes Secondary Syphilis, Lice infestation, Serum Sickness ,Severe drug allergy (e.g. Penicillin), Cat Scratch Disease, Rubella Generalized Furunculosis .

- **Sub maxillary and submental lymphadenopathy**: These nodes drain the teeth, tongue, gums, and buccal mucosa. Their enlargement is usually the result of localized infection, such as pharyngitis, herpetic gingivostomatitis, and dental.
- **Posterior Cervical Nodes (behind sternocleidomastoid)** ,
- Drainage Pattern ,Scalp, Neck, Arm and pectoral skin, Thorax, drainage Lymphadenopathy Causes Tuberculosis Lymphoma (especially Hodgkin's Lymphoma) **Head and neck cancer.**

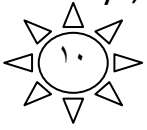
- ●**Preauricular nodes (anterior to ear tragus)** Drainage Pattern Lateral Eyelids ,Palpebral Conjunctiva, Temporal skin, Anterior Ear Pinna, External auditory canal, Lymphadenopathy . Lymphadenopathy Causes: Non-ocular Squamous Cell Carcinoma or Basal Cell Carcinoma ,Epithelioma ,Chancre on face ,,Herpes Zoster ,Rubella, Trachoma ,Atypical Mycobacterial Infection, Cat Scratch Disease, Type I Branchial Cleft Cyst , Parotid Gland tumor, Parotid Gland inflammation (Parotitis).

●**Occipital or Suboccipital nodes (base of skull, below occiput)** Suboccipital Lymphadenopathy may causes Headache, Drainage Pattern, Back of Scalp and Head ,Lymphadenopathy Causes, Local infection ,TineaCapitis Lice, Seborrheic Dermatitis ,Secondary Syphilis ,Neoplasm including metastases, lymphoma.

3. TMJ examination we will discuss that in details like pain, limitation, deviation, clicking.

4. Facial features :

A.Symptoms and Causes of Moon may cause the face to gradually become round, full, or puffy. Fat deposits in the sides of the skull can also make the face look rounder. A high release of hormones, especially cortisol, is a cause of moon face. This is called hypercortisolism.(The adrenal glands, triangular-shaped glands that sit on top of the kidneys, release the cortisol).



Conditions Related to Moon Facies The conditions that most commonly lead to hypercorticolism and the **symptom of moon facies include**: Increased release of a hormone (ACTH) from the pituitary gland; ACTH prompts the adrenal gland to produce cortisol.

Non pituitary tumors -- such as tumors of the lung, pancreas, or thymus -- which may also cause big releases of ACTH Benign tumors or cancers in the adrenal gland Long-term use of steroid medications like prednisone for conditions such as rheumatoid arthritis or other autoimmune conditions .blood and urine tests Should be done to confirm the cause of high cortisol levels, other tests, such as an MRI or CT scan.

With steroid use, an increase in appetite and food intake may contribute to weight gain. Symptoms usually occur as the result of long-term use of oral steroids. But less commonly, injected or inhaled steroids .

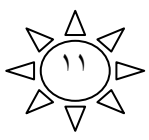
B. Rash or "butterfly rash," is characteristically red or purplish and mildly scaly . In medicine, malar rash also called butterfly rash, is a medical sign consisting of a characteristic form of facial rash. It is often seen in lupus erythematosus but is not pathognomonic - it is also seen in other diseases such as pellagra, dermatomyositis, and Bloom syndrome.

A malar rash is present in approximately 46–65% of lupus sufferers and varies between different populations.

C. The Hippocratic face The change produced in the face by impending death or long illness, excessive evacuations, excessive hunger, appearance may be described thus: the nose sharp, the eyes sunken, the temples fallen in, the ears cold and drawn in and their lobes distorted, the skin of the face hard, stretched and dry, and the colour of the face pale or dusky. A related term is cachexia.

D .Down syndrome ,For facial features, they may have:

Eyes shaped like almonds (may be shaped in a way that's not typical for their ethnic group). Flatter faces, especially the nose Small ears, which may fold over a bit at the top, tiny white spots in the colored part of their eyes, A tongue that sticks out of the mouth. They may have small hands and feet.



E .People with a GIT carcinoid tumor may experience the following symptoms or signs: Facial flushing, which is redness and a warm feeling over the face, Abdominal pain caused by blockage of the intestines ,Asthma Rash, Heart disease ,Intestinal bleeding, Pellagra & diarrhea.

F.SPIDER NAVUS very important for the dentist.

G.MYSASTHENIA GRAVES

4. Abnormal facial movements, however, are more serious and can be associated with neurologic disorders such as multiple sclerosis, brainstem tumor, peripheral neuropathy, and Guillain-Barré syndrome. Occasionally, an abnormal movement of the face is the first sign of such an underlying disorder.

Extra oral head and neck examination:

4 : Eye examination

Double vision/orbital problems Red or painful eye , Reduced vision, Foreign body **,** Headache/problems suggesting neurological cause.

There are some systemic diseases have manifestation on eye

a. **Hypertension -**

High blood pressure can cause damage to the retina's blood vessels

,Limit the retina's function, and put pressure on the optic nerve

Causing vision problems. This condition is called **hypertensive Retinopathy (HR):** eye swelling, bursting of a blood vessel

reduced vision, double vision accompanied by headaches. Hypertensive **-** retinopathy ranges from grade 1 to grade 4, grade 4 being severe form called malignant hypertensive retinopathy. The retinal changes and swelling of the optic nerve resulting in vision loss is associated with a systolic pressure of > 220 mm Hg and a diastolic pressure of >110mm Hg.

b. Diabetes mellitus; the underlying cause of diabetic retinopathy is microvascular leakage leading to exudation which occurs in the layers of retina affecting vision. Excess glucose interferes with normal metabolism of the lens and result in premature cataracts.

c. Thyrotoxicosis Excessive thyroid levels may cause protruding eyes, limitation of eye movements, double vision and corneal disease due to exposure and dryness. In severe form, the optic nerve may get damaged resulting in permanent loss of vision. exophthalmus it could be bilateral as in Graves disease or unilateral often seen in orbital tumor .

d. Cancer

Cancer can start in the eye or spread from anywhere in the body. It especially holds true in children who can have cancer called retinoblastoma. The cancer may be evident as a white reflex, squint, recurrent redness, vision loss and in advanced cases may threaten life.

.Naffzigers methods. Stand behind the seated patient. Tilt the head backwards and observe the eye ball our plane of vision should be on the superciliary ridges by the examination the globes in this manner it will be possible to confirm or eliminate the presence the protruism.

5. Examination of facial color

Pallor: The presence of pallor depends on the thickness and quality of the skin. Amount of blood in the capillaries and quality of the blood in the capillaries

#. Generalized pallor is present in anemia. Pallor can also be found in hypopituitarism, thick or opaque skin, and diminished capillary blood flow as in shock, syncope, left heart failure.

Jaundice

A yellowish discoloration of the skin and mucous membrane due to deposition of bilirubin is known as jaundice (icterus).

Sclerae have a high affinity for bilirubin due to their rich elastin content. The normal total serum bilirubin level is 0.3-1.0 mg/dL. Jaundice is clinically apparent in sclera when the bilirubin level is raised above 3 mg/dL.

The clinical detection of jaundice is difficult in artificial light. Hence, it should be examined preferably in day light. Besides sclera, other sites to be looked for the evidence of jaundice are mucosa of oral cavity underneath the tongue and skin. Yellow discoloration of the skin can also occur in carotenemia.

sclera is typically not involved in carotenemia .

Other points to be noticed in the skin

- **Sweating usually in hyperthyroidism,psychonearoces cold clammy skin**
- **dry skin mostly in fever ,hypothyroidism,dehydration.**
- **Pigmentation of the skin in the Addison disease .adrenal insufficiency**

Also may occur in the followings:

- **Arsenic poising , Chronic liver disease , Therapeutic irradiation, Intestinal malabsorption, Malignant cachexia,**
  - **Gangrene may lead to blackness,**

- **Flashings of the skin may be occur due to emotional causes hormone imbalance ,fever hyperthyroidism.**

- **Physical Examination of The Thyroid Gland**
    - The thyroid scan, the serum T4 and T3 determination, and the ultrasound rarely improve the accuracy of the clinical diagnosis that is derived mainly from physical examination. the patient is asked to swallow saliva or small quantities of fluid repeatedly during the examination. A normal thyroid gland is rarely palpable.

Examine the major salivary glands:

The parotid glands:

- Swellings of the parotid are apparent as a loss of the angle of the jaw. The accessory lobe may also cause a lump anterior to the ear. The deep lobe needs to be inspected and palpated through the mouth. Swelling can displace the ipsilateral tonsil.
- Ask the patient to clench their teeth to allow palpation of the masseter. The anterior part of the parotid duct can be felt as it crosses the anterior border of the masseter muscle and occasionally a stone can be palpated in this part of the duct. Inspect the orifice of the duct in the mouth opposite the second upper molar by retracting the cheek with a spatula.
- **The submandibular gland**
- Submandibular gland pathology usually involves swelling beneath and anterior to the angle of the jaw.
- Inspect the orifices of the duct by asking the patient to lift their tongue to the roof of the mouth, noting the presence of inflammation or pus or indeed a visible impacted stone.
- Examine bimanually with the index finger of one hand inside the mouth and fingers of the other hand over the outer surface of the lump in the neck. Under normal circumstances, the gland is not palpable but, if enlarged, can be

felt 2-3 cm anterior to sternomastoid, below the horizontal ramus of the mandible. The gland has a rubbery consistency. The gland should not be fixed to the floor of the mouth or tongue. Check the course of the duct for a stone.

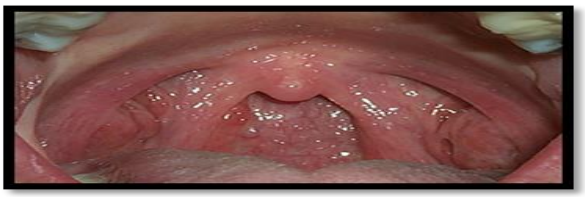
- Sublingual gland pathology may cause swelling on the floor of the mouth.

During the examination of the salivary gland the followings important notices should be taking into consideration by the dentist

- Is this swelling a salivary gland? Differentiating a swollen parotid gland and cervical lymphadenopathy may be very difficult clinically. Usually it is possible to feel in front of lymph nodes but it is impossible to get in front of the parotid. Similarly, attempt to differentiate between a submandibular swelling and superior cervical lymph nodes which are deep to sternomastoid.

• Intraoral examination

Normal anatomy of the oropharyngeal area.



Posterior Pharyngeal Wall The tissue in this area should appear very vascular but otherwise homogenous in color tending towards reddish pink. The surface may be smooth or appear to have small coral pink to translucent, gelatin-like, homogenous surface prominences which are consistent with normal areas of scattered lymph tissues (lymphoid aggregates). Pathologic findings include:

- Homogenous and non-tender erythema associated with post nasal drip and/or smoking
- Erythema and purulent exudate associated with pharyngitis (infection of the pharynx) may cover portions of the pharyngeal wall
- Ulcers, erosions or noticeable enlargements or growths.

Anterior and Posterior Pharyngeal Pillars The anterior and posterior pillars should appear vascular, smooth and symmetrical Atypical findings one may encounter include lymphoid aggregates (as found on the posterior pharyngeal wall), areas of pale scarring in a radial or stellate pattern from tonsillectomy, or torn or absent pillars also a result of this surgery. Erythema associated with tenderness or exudates

Tonsillar Crypt

dentist will observe rough, lobular, and coral to light pink tissue of varying amounts between the anterior and posterior pharyngeal pillars.
Occasionally, individuals have large crypts in the tonsils that collect food debris, bacteria and hardened material. Patients with this type of cryptic tonsil often complain of halitosis, After a tonsillectomy one may observe residual tonsil tissue or a regrowth of lymph tissue in the area. Pathologic findings include: •
Dysphagia (painful or difficult swallowing)

• Swelling, asymmetry, erythema and/or surface exudates

• Erythema and/or dysphagia may also be associated with mouth breathing and may indicate a nasal obstruction.

Soft Palate and Uvula

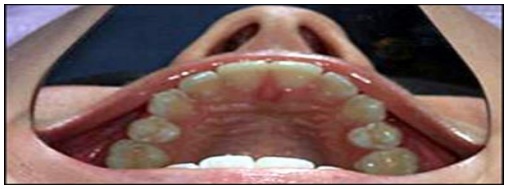
This area is examined using direct vision and is normally not palpated unless necessary. If palpation is necessary a topical anesthetic should be used by the dentist and the tissues should be palpated from the mid line out towards the lateral surfaces. Normally, this area is slightly less vascular than the oropharynx and is usually reddish pink in color .Observe the area as the patient says “ah.” The tissue should appear loose, mobile and symmetrical during function. The tissue will have a homogenous, spongy consistency on palpation. Atypical observations include yellowish coloring due to increased adipose tissue (especially in older patients), excessively long or short uvulas and uvulas that appear slightly asymmetrical at rest. Occasionally one will discover a bifid (cleft) uvula. Pathologic findings include:

Hard palate

• In general, the tissue is a homogenous pale pink color, firm to palpation towards the anterior and lateral to the midline while more compressible

towards the posterior and medial to the apices of the teeth. The normal structures of the hard palate should be identified:

- Incisive papilla – protuberance of soft tissue lingual to the maxillary central incisors which covers the incisive foramen and normally appears redder than the surrounding tissues .
- Raphe – slightly elevated line extending from the incisive papilla to the soft palate)
- Rugae – corrugated ridges radiating laterally from the raphe

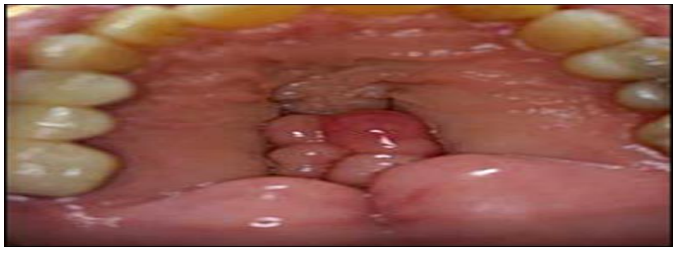


- Vault – relates to the depth and width of the palate

Normal structures of the posterior hard palate.

Maxillary tuberosities – area distal to the last molars the tissue should be a homogenous pink color and firm to palpation:

The torus palatinus is the most common atypical finding in the hard palate. These tori may range have a smooth surface texture. Often the larger tori will have traumatic ulcers or other traumatic lesions on their surfaces.



Extreme example of a multilobulated torus palatinus.

Tori are not usually considered a problem unless prosthetic appliances are being considered. Tori also make it difficult to expose intraoral radiographic films. While Pathologic findings include:

Pigmented macules –The palate is also a common area for unintentional tattoos resulting from pencil leads being jabbed into the tissues while playing with a pencil or holding it in the mouth.

Thermal burns – the anterior palate is the most common area for this type of traumatic injury

Nicotine stomatitis – whitening and fissuring of the attached gingiva of the hard palate and inflammation of the minor salivary gland ducts

Papillary hyperplasia – development of finger-like projections usually under a poorly fitting full or partial denture

Systemic related lesions – lesions related to lupus are commonly found in the palate and the palate is a prime location for the blue nevus

Buccal Mucosa The buccal mucosa is examined using direct and indirect vision followed by bidigital palpation of the entire area. Be sure to pull the tissues away from the retromolar area and stretch the mucosa away from the mucogingival junction.

Palpating the buccal mucosa. Normal tissues of the buccal mucosa appear moist and pink/dark pink. Stensen's duct should be identified with or without the presence of a parotid papilla. Linea alba, Fordyce's granules and leukoedema are common atypical findings on the buccal mucosa. feeling small papules within the tissues usually indicative of sclerotic or fibrotic minor salivary glands. Varicosities may often present on the buccal mucosa of older patients. The buccal mucosa is also a prime area for stress related habits such as cheek chewing (morsicatio buccarum).

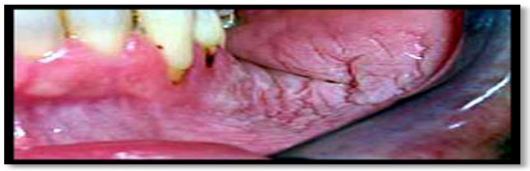
Pathologic findings associated with the buccal mucosa include:

- Traumatic injuries – thermal burns, cheek bites, ulcers, traumatic fibroma .
- Leukoplakia associated with spit tobacco

• Neoplastic changes – erythroplakia, speckled leukoplakia and pigmented lesions

• Systemic disease – oral lichen planus, lupus, lipomas, aphthous ulcers, erythema multiforme, and Crohn's disease.

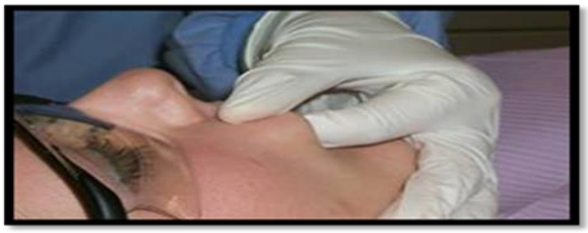
Leukoplakia associated with spit tobacco.

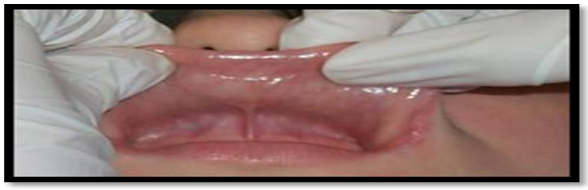


Labial Mucosa

The labial mucosa is examined using direct vision by averting the tissues over the fingers or thumbs followed by bidigital palpation of the tissues of the lips.

Visual examination of the upper labial mucosa.





Visual examination of the lower labial mucosa.

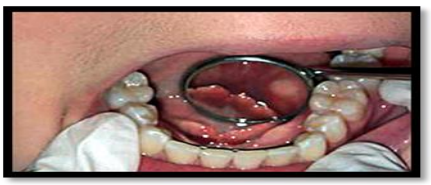
Move the tissues from side to side and visualize the frena. Normal lip tissues are a homogenous deep pink color which changes gradually to a deep red color with more prominent vascularity near the mucolabial vestibule. The tissues should be moist and have uniform consistency and thickness when palpated.

Bidigital palpation of the upper labial mucosa.

Sclerotic minor salivary glands are common atypical findings as are Fordyce's granules. Pathologic findings include the following:

• Traumatic injuries – abrasions, lacerations

- Dry, cracked lips
- Angular cheilitis – human herpes virus, Candida Albicans
- Neoplastic changes

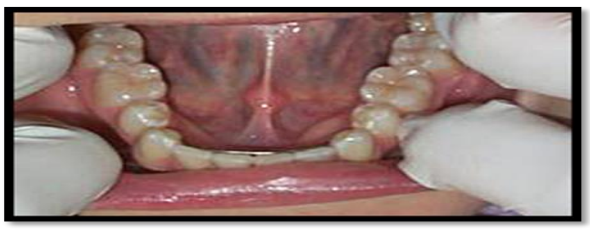
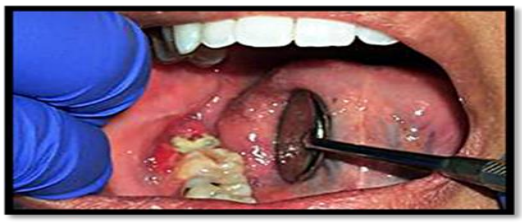
Mandible The body of the mandible will be examined using direct and indirect vision followed by digital palpation of the entire structure. The tissues of the floor of the mouth should be stretched away from the inferior border of the mandible with a mouth mirror. 

Use the mirror to stretch the tissue away from the inferior border of the mandible. • Leukoplakia associated with spit tobacco

Use digital palpation pressing the tissues against the body of the mandible for both the lingual and the facial aspects.

Painful pericoronitis surrounding partially erupted tooth

The mirror is used to visualize the anterior lingual portion of the Normal tissues will be a homogenous coral pink and have a firm consistency with no visible or palpable lesions. Mandibular tori and exostoses are the most common atypical findings in this area. The retromolar area may present with partially erupted third molars or scarring from third molar extraction. This area is also prone to hyperkeratosis from constant friction from masticatory function. **Pathologic findings include:** Traumatic lesions – ulcers, abrasions, Infections – pericoronitis , Neoplastic growths .

Floor of the Mouth

The floor of the mouth is examined using direct and indirect vision followed by bimanual palpation of the entire area. The patient should be asked to raise the tongue making direct visual examination of the tissues

toward the midline of the floor of the mouth possible.

Visual examination of the floor of the mouth. Note the normal structures of the area

The mirror should be used to examine the areas near the inferior border of the mandible. The tissues should appear moist and very vascular. The normal anatomy of the area should be identified including:

- Sublingual caruncle – small rounded projection at the base of the lingual frenum which houses Wharton's duct from the submandibular salivary gland.
- Sublingual folds – two oblique elevations found radiating laterally away from the lingual frenum on either side of the caruncle which house the ducts from the sublingual salivary gland
- Lingual frenum – muscle attachment from the ventral surface of the tongue to the floor of the mouth. This attachment varies in length from person to person.

Varicosities are the most common atypical observation in this area. Other atypical findings are enlarged lingual folds and caruncle and a short lingual frenum (ankyloglossia). Ankyloglossia is only considered a problem if it begins to affect the speech development of the individual. Pathologic findings include:

- Traumatic injuries – ulcers mucoceles
- Salivary gland pathology – ranula, sialoliths, enlargement
- Neoplastic changes
- Ankyloglossia – this is considered pathologic only if it interferes with the normal development of proper speech

Tongue

The tongue is examined using both direct and indirect vision.

Proper use of the mirror to aid in the visual examination of the tongue.

The tissues should appear pink in color with a rough surface texture on the dorsal surface and a smoother surface texture on the ventral surface.

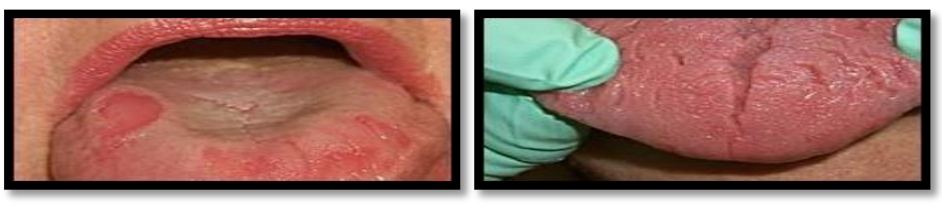
.normally:

- Dorsal surface – papillae (filiform, fungiform, circumvallate), median sulcus, sulcus terminalis
- Lateral borders – foliate papillae
- Ventral surface – lingual veins, lingual frenum

Atypical findings on the dorsal surface of the tongue are common. They include: **fissuring scalloping, benign migratory glossitis** ,and enlarged papillae, among others. A lingual thyroid may rarely be found on the posterior dorsal surface at the foramen cecum. Lingual varicosities are a common finding on the ventral surface of the tongue, especially in older patients. The Glands of Blandin-Nuhn (minor salivary glands found on the ventral surface of the tongue) may become enlarged prompting the need for a referral or diagnostic procedure to confirm the origin.

neurological examination of the tongue • Note any atrophy or fasciculations (spontaneous quivering movements caused by firing of muscle motor units) of the tongue while it is resting on the floor of the mouth. Ask the patient to stick their tongue straight out and note whether it curves to one side or the other. Ask the patient to move their tongue from side to side and push it forcefully against the inside of each cheek.

• Fasciculations and atrophy are signs of lower motor neuron lesions. Unilateral tongue weakness causes the tongue to deviate toward the weak side. Tongue weakness can result from lesions of the tongue muscles, the neuromuscular junction, the lower motor neurons of the hypoglossal nerve (CN XII), or the upper motor neurons originating in the motor cortex. Lesions of the motor cortex cause contralateral tongue weakness.



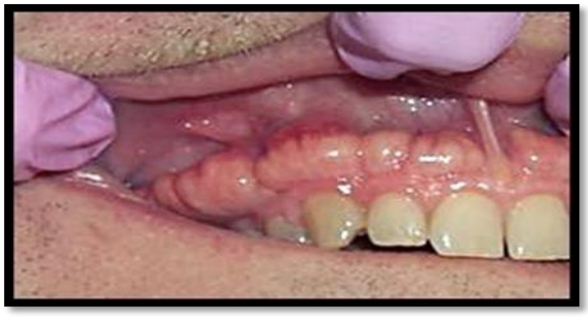
Some of the pathological findings that are found on the tongue include:

- Hairy tongue – filiform papilla become elongated due to a variety of reasons from overuse of mouth rinses to not cleaning the tongue adequately.
- Candidiasis – fungal infection of the tongue often associated with deeply fissured tongues.
- Glossitis – inflammation of the tongue due to anemia, nutritional deficiencies and others.

Bacteria located on the tongue have been associated with halitosis, increased pH of the saliva, and periodontal disease.

Attached Gingiva

The tissues should appear pale pink and homogenous in color. The tissue should feel firm to touch and tightly attached to the bone. The most common atypical finding in the area of the attached gingiva is exostoses **Extensive exostoses on the maxillary facial surfaces.**



Pathologic findings include:

• Inadequate zones of attached gingiva – the clinician should determine the presence of adequate amounts of attached gingiva in all areas. Less than 1 mm of attached gingiva is considered to be inadequate in most cases and the patient should be referred to a periodontist for evaluation of the affected area.

- Mucogingival involvement – areas with no attached gingiva or areas of extreme recession

- Frena problems – tight frenum attachments or pulls

- Traumatic lesions – ulcers, abrasions, burns

- Mucosal disease such as lichen planus, pemphigus vulgaris, mucous membrane pemphigoid, lupus, and allergic type responses

Normal structures that may be mistaken for lesions

- Stensen's duct is the duct of the parotid gland. It opens into the mouth on the posterior buccal mucosa opposite the maxillary molars. The duct opening may be flat or slightly raised.

- The circumvallate papillae form a V-shaped row of rounded papillae at the junction of the anterior 2/3s and the posterior 1/3 of the tongue.

- The lingual tonsils are found on the posterior-lateral aspect of the oral tongue. They may become enlarged with viral infections.

- Plicafimbriata are folds of mucosa on the ventral surface of the tongue on either side of the lingual frenum. The folds may looked fringed due to mucosal tags.

Morsicatio buccarum or cheek biting appears as a ragged slightly translucent area on the buccal mucosa. Most patients, when asked, will admit that they bite their cheek repeatedly.

Lecture 5.

Laboratory Tests

Test for the diabetes

Diagnostic Tests

● usually diagnose type 1 diabetes in children and young adults. Because type 1 diabetes can run in families,.

●Type 2 diabetic Experts recommend routine testing for type 2 diabetes if the patients are age 45 or older usually over weight or obese ,have one or more other diabetes risk factor

Though type 2 diabetes most often develops in adults, children also can develop type 2 diabetes. Experts recommend testing children between the ages of 10 and 18 who are overweight or obese and have at least two other risk factors for developing diabetes.1

●Gestational diabetes

All pregnant women who do not have a prior diabetes diagnosis should be tested for gestational diabetes. pregnant will take a glucose challenge test between 24 and 28 weeks of pregnancy.

What tests are used to diagnose diabetes and prediabetes?

Health care professionals most often use the fasting plasma glucose (FPG) test or the A1C test to diagnose diabetes. In some cases, they may use a random plasma glucose (RPG) test.

1.Fasting plasma glucose (FPG) test

The FPG blood test measures blood glucose level at a single point in time. For the most reliable results, it is best to have this test in the morning, after you fast for at least 8 hours. Fasting means having nothing to eat or drink except sips of water.

2.A1C test

The A1C test is a blood test that provides average levels of blood glucose over the past 3 months. Other names for the A1C test are hemoglobin A1C, HbA1C, glycated hemoglobin, and glycosylated hemoglobin test. the patient can eat and drink before this test. When it comes to using the A1C to diagnose diabetes, age and ,anemia or another problem with blood. The A1C test is not accurate in people with anemia.

The A1C test result as a percentage, such as an A1C of 7 percent. The higher the percentage, reflect the higher average blood glucose levels.

People with diabetes also use information from the A1C test to help manage their diabetes

NOTE

The results can be affected by problems due to interactions with the investigative procedure used in the measurement such as in renal failure and disorders of hemoglobin, and conditions that affect lifespan of red blood cells such as iron deficiency anemia. Hence, in these conditions, alternative methods of monitoring glucose control such as capillary glucose monitoring is needed.

3.Random plasma glucose (RPG) test

The RPG test to diagnose diabetes when diabetes symptoms are present and we don't want to wait until you have fasted. do not need to fast overnight for the RPG test. this blood test can do at any time.

4.What tests are used to diagnose gestational diabetes?

Pregnant women may have the glucose challenge test, the oral glucose tolerance test, or both. These tests show how well the body handles glucose.

5.Glucose challenge test

Pregnantis checking for gestational diabetes, first receive the glucose challenge test. Another name for this test is the glucose screening test. In this test, draw blood 1 hour after drink a sweet liquid containing glucose. no need to fast

for this test. If the blood glucose is too high—135 to 140 or more—we may need to return for an oral glucose tolerance test while fasting.

6.Oral glucose tolerance test (OGTT)

The OGTT measures blood glucose after fast for at least 8 hours. First, blood draw then will drink the liquid containing glucose. For diagnosing gestational diabetes, need blood drawn every hour for 2 to 3 hours.

High blood glucose levels at any two or more blood test times during the OGTT—fasting, 1 hour, 2 hours, or 3 hours—mean gestational diabetes.

The OGTT is used to diagnose type 2 diabetes and prediabetes in people who are not pregnant. The OGTT helps to detect type 2 diabetes and prediabetes better than the FPG test. However, the OGTT is a more expensive test and is not as easy to give. To diagnose type 2 diabetes and prediabetes, a health care professional will need to draw your blood 1 hour after you drink the liquid containing glucose and again after 2 hours.

What test numbers tell me if the patient have diabetes or prediabetes?

Each test to detect diabetes and prediabetes uses a different measurement. Usually, the same test method needs to be repeated on a second day to diagnose diabetes. the doctor may also use a second test method to confirm diabetes. The following table helps to understand what your test numbers mean if you are not pregnant.

Diagnosis	A1C (percent)	Fasting plasma glucose (FPG)a	Oral glucose tolerance test (OGTT)ab	Random plasma glucose test (RPG)a
Normal	below 5.7	99 or below	139 or below	
Prediabetes	5.7 to 6.4	100 to 125	140 to 199	
Diabetes	6.5 or above	126 or above	200 or above	200 or above

a Glucose values are in milligrams per deciliter, or mg/dL.

Even though the tests described here can confirm that the patient have diabetes,but they can’t identify what type. some time unsure if diabetes is type 1

or type 2. A rare type of diabetes that can occur in babies, called **monogenic diabetes**, can also be mistaken for type 1 diabetes. Treatment depends on the type of diabetes, so knowing which type is important.

Note

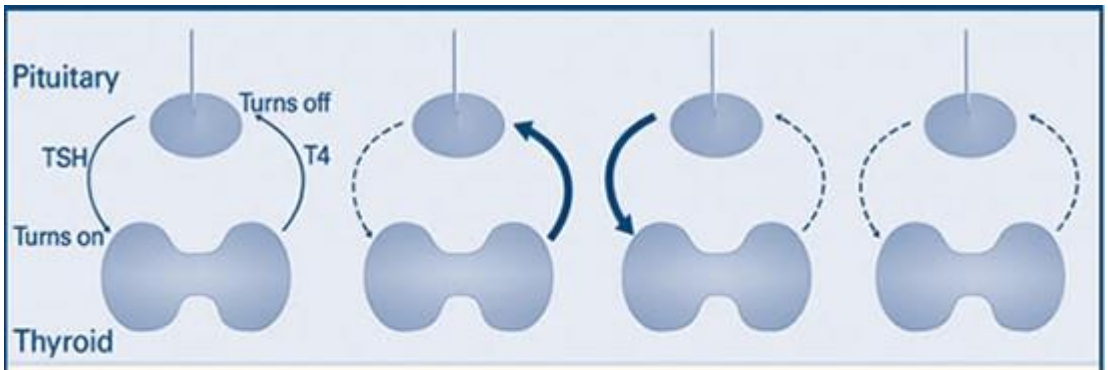
To confirm diabetes is type 1,. The presence of one or more of several types of autoantibodies specific to diabetes is common in type 1 diabetes, but not in type 2 or monogenic diabetes.

If diabetes occur when the patient pregnant, get tested 6 to 12 weeks after baby is born to see if the patient have type 2 diabetes.

The test of the thyroid gland

The major thyroid hormone secreted by the thyroid gland is thyroxine, also called T4 because it contains four iodine atoms. To exert its effects, T4 is converted to triiodothyronine (T3) by the removal of an iodine atom.

The mount of T4 produced by the thyroid gland is controlled by another hormone, which is made in the pituitary gland located at the base of the brain, called thyroid stimulating hormone (abbreviated TSH).



CONDITION:	Normal	Hyperthyroidism	Hypothyroidism Primary	Hypothyroidism Secondary
TSH	Normal	Low	High	Low
T4	Normal	High	Low	Low

T4 and T3 circulate almost entirely bound to specific transport proteins, and there are some situations which these proteins could change their level in the blood, producing also changes in the T4 and T3 levels (it happens frequently during pregnancy, women who take control birth pills, etc).

TESTS

Blood tests to measure TSH, T4, T3 and Free T4 are readily available and widely used. Tests to evaluate thyroid function include the following:

1.TSH TESTS

The best way to initially test thyroid function is to measure the TSH level in a blood sample. A high TSH level indicates that the thyroid gland is failing because of a problem that is directly affecting the thyroid (primary hypothyroidism). The opposite situation, in which the TSH level is low, usually indicates that the person has an overactive thyroid that is producing too much thyroid hormone (hyperthyroidism). Occasionally, a low TSH may result from an abnormality in the pituitary gland, which prevents it from making enough TSH to stimulate the thyroid (secondary hypothyroidism). In most healthy individuals, a normal TSH value means that the thyroid is functioning normally.

2.T4 TESTS

T4 circulates in the blood in two forms:

A.) T4 bound to proteins that prevent the T4 from entering the various tissues that need thyroid hormone.

B.)Free T4, which does enter the various target tissues to exert its effects. The free T4 fraction is the most important to determine how the thyroid is functioning, and tests to measure this are called the Free T4 (FT4) and the Free T4 Index (FT4I or FTI). Individuals who have hyperthyroidism will have an elevated FT4 or FTI, whereas patients with hypothyroidism will have a low level of FT4 or FTI.

Combining the TSH test with the FT4 or FTI accurately determines how the thyroid gland is functioning.

The finding of an elevated TSH and low FT4 or FTI indicates primary hypothyroidism due to disease in the thyroid gland. A low TSH and low FT4 or FTI indicates hypothyroidism due to a problem involving the pituitary gland. A low TSH with an elevated FT4 or FTI is found in individuals who have hyperthyroidism.

3.T3 TESTS

T3 tests are often useful to diagnosis hyperthyroidism or to determine the severity of the hyperthyroidism. Patients who are hyperthyroid will have an elevated T3 level. In some individuals with a low TSH, only the T3 is elevated and the FT4 or FTI is normal. T3 testing rarely is helpful in the hypothyroid patient, since it is the last test to become abnormal.

Patients can be severely hypothyroid with a high TSH and low FT4 or FTI, but have a normal T3. In some situations, such as during pregnancy or while taking birth control pills, high levels of total T4 and T3 can exist. This is because the estrogens increase the level of the binding proteins. In these situations, it is better to ask both for TSH and free T4 for thyroid evaluation.

4.THYROID ANTIBODY TESTS.

Two common antibodies that cause thyroid problems are directed against thyroid cell proteins: thyroid peroxidase and thyroglobulin. Measuring levels of thyroid antibodies may help diagnose the cause of the thyroid problems. For example, positive anti-thyroid peroxidase and/or anti-thyroglobulin antibodies in a patient with hypothyroidism make a diagnosis of Hashimoto's thyroiditis. If the antibodies are positive in a hyperthyroid patient, the most likely diagnosis is autoimmune thyroid disease.

NON-BLOOD TESTS

RADIOACTIVE IODINE UPTAKE. By measuring the amount of radioactivity that is taken up by the thyroid gland (radioactive iodine uptake, RAIU), doctors may determine whether the gland is functioning normally. A very high RAIU is seen in individuals whose thyroid gland is overactive (hyperthyroidism), while a low RAIU is seen when the thyroid gland is underactive (hypothyroidism).

In addition to the radioactive iodine uptake, a thyroid scan may be obtained.

Tests for the liver:

- **Alanine transaminase (ALT) test.** ALT is an enzyme that helps break down proteins and is found mainly in the liver. High levels in blood could mean liver damage.
- **Alkaline phosphatase (ALP) test.** ALP is an enzyme have in the liver, bile ducts, and bone. the patient might have high levels if have liver damage or disease, a blocked bile duct, or bone disease.
- **Albumin and total protein test.** Two main proteins: albumin and globulin. Low levels can mean damage or disease.
- **Aspartate transaminase (AST) test.** AST is another enzyme found in the liver. High blood levels could be a sign of damage or disease.
- **Bilirubin test.** Bilirubin is made when red blood cells break down. Usually, the liver cleans bilirubin out of the body. If high levels in blood, a problem called jaundice, mean liver damage.
- **Gamma-glutamyltransferase (GGT) test.** High levels of the GGT enzyme could point to liver or bile duct damage.
- **L-lactate dehydrogenase (LD) test.** LD is another enzyme that's high when have liver damage, but other conditions can raise its level, as well.
- **Prothrombin time (PT) test.** This test measures how long it takes blood to clot. If it takes a long time, that could be a sign of liver damage. Medications that thin blood, such as warfarin (Coumadin), can also lead to a longer PT.

Another name for AST is serum glutamic oxaloacetic transaminase (SGOT). Similarly another name for ALT is serum glutamic pyruvic transaminase (SGPT). Hence, AST is also referred to as SGOT and ALT is also referred to as SGPT

The Diagnosis of Hepatitis

There are a number of reasons why people may want to consider talking to their doctors about a hepatitis screening, which includes:

• Being born to a mother who has hepatitis.

- Any emergency or health care providers who may have come into contact with contaminated blood or accidently pricked with a needle
- Anyone who has undergone long term hemodialysis treatment
- Any individual who has ever used a needle to inject illegal drugs
- Anyone who received a organ transplant or blood diffusion before
- Anyone who has had sexual intercourse with a HCV infected person

Clinical manifestations vary widely between different forms of viral hepatitis, as summarized below.

- HAV is highly contagious and usually manifests as acute infection in adults but is usually asymptomatic in children. It is a self-limiting disease, has no chronic carrier state, and seldom causes serious sequelae, although some patients may develop acute fulminant liver failure.
- HBV and HCV manifest as acute or asymptomatic disease, but often establish chronic infection resulting in substantial morbidity and mortality. Chronic infection with HBV or HCV may lead to liver cirrhosis and hepatocellular carcinoma (HCC).

HDV is a "defective" virus in that it can replicate only in the presence of HBV. HBV/HDV coinfection (simultaneous acquisition of HBV and HDV) and superinfection (acquisition of HDV by a person with chronic HBV infection) significantly increase the severity of disease relative to HBV infection alone.

Acute HBV/HDV coinfection may be severe, but it tends to resolve spontaneously. In contrast, HBV/HDV superinfection has a high likelihood of progressing to chronic infection

Interpretation of Individual Test Results in the Diagnosis of Acute and Chronic Viral Hepatitis

Marker	Interpretation
HAV	
HAV IgM	Presence indicates current or recent infection. A negative result indicates absence of infection.
HAV total Ab	Presence of total (IgM and IgG) HAV antibody in the absence of HAV IgM antibody indicates immunity against HAV infection.
HBV	
HBsAg	Presence indicates that a person has HBV infection and is infectious.
HBcAb, total	Presence indicates past or current HBV infection.
HBcAbIgM	Presence usually indicates HBV infection within the preceding 4 to 6 months (ie, acute infection).
HBeAb	Presence indicates resolving infection or response to therapy.
HBeAg	Presence indicates active viral replication and high infectivity
HBsAb	Presence indicates resolution and immunity against HBV infection or response to vaccination.
HBV DNA	•
HDV	
	Presence indicates current infection.
HDV Ab, total	Presence coincident with the presence of HBsAg indicates past or current HBV/HDV coinfection or superinfection.

	HDV IgM	Presence coincident with the presence of HBsAg indicates past or current HBV/HDV coinfection or superinfection. A negative result coincident with the presence of HDV total antibody indicates resolved infection.
HCV		
	HCV Ab	Presence (with detectable HCV RNA) indicates current infection. A positive result coincident with a negative HCV RNA test may indicate a resolved infection or a false-positive antibody screening test.
	HCV RNA	Presence indicates current infection. A negative result indicates absence of current infection.

Routine blood test of kidney function

The usual blood test which checks that the kidneys are working properly measures the level of urea, creatinine and certain dissolved salts.

1.Urea is a waste product formed from the breakdown of proteins. Urea is usually passed out in the urine. A high blood level of urea ('uraemia') indicates that the kidneys may not be working properly, or that you have a low body water content (are dehydrated).

2. Creatinine is a waste product made by the muscles. Creatinine passes into the bloodstream, and is usually passed out in urine. A high blood level of creatinine indicates that the kidneys may not be working properly. Creatinine is usually a more accurate marker of kidney function than urea. The effect of muscle mass needs to be taken into account. A person with a lot of muscle and little fat on their body is likely to have a higher creatinine than a person who has a lot of fat and little muscle.

3.Estimated glomerular filtration rate (eGFR) provides a guide to kidney function. Although the level of creatinine in the blood is a useful guide to kidney function, the eGFR is a more accurate measure. Blood creatinine can be used to estimate the eGFR using age, sex and race.. The normal value for eGFR is 90-120 ml/min. An eGFR below 60 ml/min suggests that some kidney damage has occurred. The value becomes lower with increasing severity of kidney damage.

4.Dissolved Saltsthat are routinely measured are sodium, potassium, chloride and bicarbonate. They are sometimes referred to as 'electrolytes'. Abnormal blood levels of any of these may be due to a kidney problem. (Some other conditions may also alter the salt balance in the blood).

Lecture 6.

THE HEMOTOLGIACL EXAMINATION

The complete blood count (CBC) is often used as a broad screening test to determine an individual's general health status. It can be used to:

1. Screen for a wide range of conditions and diseases
2. Help diagnose various conditions, such as anemia, infection, inflammation, bleeding disorder or leukemia
3. Monitor the condition and/or effectiveness of treatment after a diagnosis is established
4. Monitor treatment that is known to affect blood cells, such as chemotherapy or radiation therapy

A CBC is a panel of tests that evaluates the three types of cells that circulate in the blood

1. Evaluation of white blood cells, the cells that are part of the body's defense system against infections and cancer and also play a role in allergies and inflammation: White blood cell (WBC) count is a count of the total number of white blood cells in a person's sample of blood.

White blood cell differential may or may not be included as part of the panel of tests. It identifies and counts the number of the various types of white blood cells present. The five types include neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

2.Evaluation of red blood cells, the cells that transport oxygen throughout the body: Red blood cell (RBC) count is a count of the actual number of red blood cells in a person's sample of blood.

Hemoglobin measures the total amount of the oxygen-carrying protein in the blood, which generally reflects the number of red blood cells in the blood.

Hematocrit measures the percentage of a person's total blood volume that consists of red blood cells. In general the hematocrit mirror the result of the RBC count and hemoglobin a low hematocrit and low RBC indicate anemia some other causes:

Excessive loss of the blood for ex ,trauma, chronic bleeding like bleeding from digestive tract e.g ulcer polyps, colon cancer, ,heavy menstrual bleeding ,nutritional deficiencies such as iron ,folate or vit B12 deficiency, damage to the bone marrow ,aplastic anemia ,.leukemia, lymphoma ,multiple myeloma ,kidney disease ,erythropoietin production ,chronic inflammatory diseases ,thalassemia and ,hemolytic anemia caused by autoimmunity or defect in the red blood cell itself. While, high hematocrit indicate Dehydration .

- lung pulmonary disease
- congenital heart disease
- kidney tumor
- smoking and living at a high altitudes a compensation for decrease O2 in the air polycythemia vera

Red blood cell indices are calculations that provide information on the physical characteristics of the RBCs:

Mean corpuscular volume (MCV) is a measurement of the average size of a single red blood cell.

Mean corpuscular hemoglobin (MCH) is a calculation of the average amount of hemoglobin inside a single red blood cell.

Mean corpuscular hemoglobin concentration (MCHC) is a calculation of the average concentration of hemoglobin inside a single red blood cell.

Red cell distribution width (RDW) is a calculation of the variation in the size of RBCs.

The CBC may also include reticulocyte count, which is a measurement of the absolute count or percentage of young red blood cells in blood.

Evaluation of platelets, cell fragments that are vital for normal blood clotting:

3.. The platelet count is the number of platelets in a person's sample of blood.

Mean platelet volume (MPV) may be reported with a CBC. It is a calculation of the average size of platelets.

Platelet distribution width (PDW) may also be reported with a CBC. It reflects how uniform platelets are in size.

Note

The CBC is a very common test. Many people have a CBC performed when they have a routine health examination. If a person is healthy and has results that are within normal limits, then that person may not require another CBC until their health status changes or until their healthcare provider feels that it is necessary.ist When the dentist is used complete blood picture?

A CBC may be ordered when

1. a person has any number of signs and symptoms that may be related to disorders that affect blood cells.
2. When an individual has fatigue or weakness or has an infection, inflammation, bruising, or bleeding,
3. When a person has been diagnosed with a disease known to affect blood cells,
4. CBC will often be ordered on a regular basis to monitor their condition. Likewise, if someone is receiving treatment for a blood-related disorder, then a CBC may be performed frequently to determine if the treatment is effective.
5. Some therapies, such as chemotherapy, can affect bone marrow production of cells. Some medications can decrease WBC counts overall. A CBC may be ordered on a regular basis to monitor these drug treatments.

What does the test result mean?

A health practitioner typically evaluates and interprets results from the components of the CBC together. Depending on the purpose of the test, a number of additional or follow-up tests may be ordered for further investigation.

The following tables briefly and generally explain what the result for each component of the CBC may mean.

WBC evaluation , RBC evaluation, Platelet evaluation

Test	FUll Name	examples of causes of a low count	examples of causes of a high count
WBC	White Blood Cell Count	Known as leukopenia Bone marrow disorders or damage Autoimmune conditions Severe infections (sepsis) Lymphoma or other cancer that spread to the bone marrow Dietary deficiencies Diseases of immune system (e.g., HIV/AIDS)	Known as leukocytosis Infection, most commonly bacterial or viral Inflammation Leukemia, myeloproliferative disorders Allergies, asthma Tissue death (trauma, burns, heart attack) Intense exercise or severe stress
Diff	White Blood Cell Differential (Not always performed; may be done as part of or in follow up to CBC;		
Neu, PMN, polys	Absolute neutrophil count, % neutrophils)	Known as neutropenia Severe, overwhelming infection (sepsis) Autoimmune disorders Dietary deficiencies Reaction to drugs, chemotherapy Immunodeficiency Myelodysplasia Bone marrow damage (e.g., chemotherapy, radiation therapy) Cancer that spreads to the bone marrow	Known as neutrophilia Acute bacterial infections Inflammation Trauma, heart attack, or burns Stress, rigorous exercise Certain leukemias (e.g., chronic myeloid leukemia) Cushing syndrome

Lymph	Absolute lymphocyte	Known as lymphocytopenia Autoimmune disorders (e.g.,	Known as lymphocytosis Acute viral infections (e.g., chicken

	count, % lymphocytes	lupus, rheumatoid arthritis) Infections (e.g., HIV, viral hepatitis, typhoid fever, influenza) Bone marrow damage (e.g., chemotherapy, radiation therapy) Corticosteroids	pox, cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes, rubella) Certain bacterial infections (e.g., pertussis (whooping cough), tuberculosis (TB)) Toxoplasmosis Chronic inflammatory disorder (e.g., ulcerative colitis) Lymphocytic leukemia, lymphoma Stress (acute)
Mono	Absolute monocyte count, % monocytes	Usually, one low count is not medically significant. Repeated low counts can indicate: Bone marrow damage or failure Hairy cell leukemia Aplastic anemia	Chronic infections (e.g., tuberculosis, fungal infection) Infection within the heart (bacterial endocarditis) Collagen vascular diseases (e.g., lupus, scleroderma, rheumatoid arthritis, vasculitis) Monocytic or myelomonocytic leukemia (acute or chronic)
Eos	Absolute eosinophil count, % eosinophils	Numbers are normally low in the blood. One or an occasional low number is usually not medically significant	Asthma, allergies such as hay fever Drug reactions Parasitic infections Inflammatory disorders (celiac disease, inflammatory bowel disease) Some cancers, leukemias or lymphomas Addison disease

Baso	Absolute basophil count, % basophils	As with eosinophils, numbers are normally low in the blood; usually not medically significant	Rare allergic reactions (hives, food allergy) Inflammation (rheumatoid arthritis, ulcerative colitis) Some leukemias Uremia
Test	Full Name	examples of causes of low result	examples of causes of high result
RBC	Red Blood Cell Count	Known as anemia Acute or chronic bleeding RBC destruction (e.g., hemolytic anemia, etc.) Nutritional deficiency (e.g., iron deficiency, vitamin B12 or folate deficiency) Bone marrow disorders or damage Chronic inflammatory disease Chronic kidney disease	Known as polycythemia Dehydration Lung (pulmonary) disease Kidney or other tumor that produces excess erythropoietin Smoking Living at high altitude Genetic causes (altered oxygen sensing, abnormality in hemoglobin oxygen release) Polycythemia vera—a rare disease
Hb	Hemoglobin	Usually mirrors RBC results, provides added information	Usually mirrors RBC results
Hct	Hematocrit	Usually mirrors RBC results	Usually mirrors RBC results; most common cause is dehydration
RBC indices			
MCV	Mean Corpuscular Volume	Indicates RBCs are smaller than normal (microcytic); caused by iron deficiency anemia or thalassemias, for example.	Indicates RBCs are larger than normal (macrocytic), for example in anemia caused by vitamin B12 or folate deficiency, myelodysplasia, liver disease, hypothyroidism

MCH	Mean Corpuscular Hemoglobin	Mirrors MCV results; small red cells would have a lower value.	Mirrors MCV results; macrocytic RBCs are large so tend to have a higher MCH.
MCHC	Mean Corpuscular Hemoglobin Concentration	May be low when MCV is low; decreased MCHC values (hypochromia) are seen in conditions such as iron deficiency anemia and thalassemia.	Increased MCHC values (hyperchromia) are seen in conditions where the hemoglobin is more concentrated inside the red cells, such as autoimmune hemolytic anemia, in burn patients, and hereditary spherocytosis, a rare congenital disorder.
RDW (Not always reported)	RBC Distribution Width	Low value indicates uniformity in size of RBCs.	Indicates mixed population of small and large RBCs; young RBCs tend to be larger. For example, in iron deficiency anemia or pernicious anemia, there is high variation (anisocytosis) in RBC size (along with variation in shape – poikilocytosis), causing an increase in the RDW.
Reticulocyte Count (Not always done)	Reticulocytes (absolute count or %)	In the setting of anemia, a low reticulocyte count indicates a condition is affecting the production of red blood cells, such as bone marrow disorder or damage, or a nutritional deficiency (iron, B12 or folate).	In the setting of anemia, a high reticulocyte count generally indicates peripheral cause, such as bleeding or hemolysis, or response to treatment (e.g., iron supplementation for iron deficiency anemia).

Plt	Count Platelet reference (See range)	Known as thrombocytopenia: Viral infection (mononucleosis, measles, hepatitis) Rocky mountain spotted fever Platelet autoantibody Drugs (acetaminophen, quinidine, sulfa drugs) Cirrhosis Autoimmune disorders Sepsis Leukemia, lymphoma Myelodysplasia Chemo or radiation therapy	Known as thrombocytosis: Cancer (lung, gastrointestinal, breast, ovarian, lymphoma) Rheumatoid arthritis, inflammatory bowel disease, lupus Iron deficiency anemia Hemolytic anemia Myeloproliferative disorder (e.g., essential thrombocythemia)
MPV (Not always reported)	Mean Platelet Volume	Indicates average size of platelets is small; older platelets are generally smaller than younger ones and a low MPV may mean that a condition is affecting	Indicates a high number of larger, younger platelets in the blood; this may be due to the bone marrow producing and releasing platelets rapidly into circulation.
		the production of platelets by the bone marrow.	
PDW (Not always reported)	Platelet Distribution Width	Indicates uniformity in size of platelets	Indicates increased variation in the size of the platelets, which may mean that a condition is present that is affecting platelets

Many different conditions can result in increases or decreases in blood cell populations. Some of these conditions may require treatment, while others may resolve on their own. Recent blood transfusions affect the results of the CBC.

Normal CBC values for babies and children are different from adults. The laboratory will supply the reference ranges for various age groups, and a health practitioner will take these into consideration when interpreting data.

There are many types of anemia, including :

1- Iron deficiency anemia

Is a very common cause of anemia . This is because iron is major component of hemoglobin and essential for its proper function.

Chronic blood loss due to any reason is the main cause of low iron level in the body as it depletes the body's iron stores to compensate for the ongoing loss of iron. Anemia that is due to low iron levels is called iron deficiency anemia.

1- Young women are likely to have low grade iron deficiency anemia because of the loss of blood each month through normal menstruation .This is generally without any major symptoms as the blood loss is relatively small and temporary

2- Another common reason for iron deficiency anemia can be due to recurring or small ongoing bleeding, for instance from colon cancer or from stomach ulcers. Stomach ulcer bleeding may be induced by medications, even very common over-the-counter drugs such as aspirin and ibuprofen. Slow and chronic oozing from these ulcers can lead to loss of iron. Gradually, this could result in anemia.

3- In infants and young children, iron deficiency anemia is most often due to a diet lacking iron.

Interpretation of CBC may lead to clues to suggest this type of anemia. For instance, iron deficiency anemia usually presents with low mean corpuscular volume (microcytic anemia) in addition to low hemoglobin (microcytic hypochromic anemia).

2- Pernicious Anemia

Pernicious anemia is a condition in which the body can't make enough healthy red blood cells because it doesn't have enough vitamin B12.

People who have pernicious anemia can't absorb enough vitamin B12 due to a lack of intrinsic factor (a protein made in the stomach)..

This typically causes of macrocytic (large blood cell volume) anemia.

Vitamin B12, along with folate, is involved in making the heme molecule that is an integral part of hemoglobin.

Folate deficiency can be the cause of anemia as well. This may also be caused by inadequate absorption, and also long-term heavy alcohol use. However, other conditions and factors can also cause vitamin B12 deficiency.

Causes:

1- A lack of intrinsic factor is a common cause of pernicious anemia as the body can't absorb enough vitamin B12.

2- Some pernicious anemia occurs because the body's small intestine can't properly absorb vitamin B12 which may be due to the wrong bacteria in the small intestines;

3- Certain diseases that interfere with vitamin B12 absorption , 4-certain medicines

5- Surgical removal of part of the small intestine , 6- Tapeworm infection .

7 - Strict vegetarians are at risk if they do not take adequate vitamin supplement.

8- Under-consumption of green, leafy vegetables , 9- Long-term alcoholics.

Signs and symptoms

Apart from the symptoms of anemia (fatigue, dizziness, etc.), the vitamin B12 deficiency may also have some serious symptoms like Nerve damage, Neurological problems such as confusion, dementia, depression, and memory loss.

Symptoms in the digestive tract include nausea and vomiting, heartburn, abdominal bloating and gas, constipation or diarrhea, loss of appetite, and weight loss .An enlarged liver, A smooth, beefy red tongue. Infants who have vitamin B12 deficiency may have poor reflexes or unusual movements, such as face tremors.

Treatment

Pernicious anemia is treated by replacing the missing vitamin B12 in the body. People who have this disease may need Lifelong treatment.

3- Aplastic Anemia

Aplastic anemia is a blood disorder in which the body's bone marrow doesn't make enough new blood cells. This may result in a number of health problems including arrhythmias, an enlarged heart, heart failure, infections and bleeding .

Aplastic anemia is a rare but serious condition. It can develop suddenly or slowly and tends to worsen with time, unless the cause is found and treated .

Causes

Damage to the bone marrow's stem cells causes aplastic anemia. In more than half of people who have aplastic anemia, the cause of the disorder is unknown.

1- A number of acquired diseases, conditions, and factors can cause aplastic anemia including: Toxins, such as arsenic, and benzene, Radiation and chemotherapy, Medicines such as chloramphenicol, Infectious diseases such as hepatitis, Epstein-Barr virus, cytomegalovirus, parvovirus B19, and HIV

Autoimmune disorders such as lupus and rheumatoid arthritis

2- Inherited conditions, such as Fanconi anemia, Shwachman-Diamond syndrome, dyskeratosis congenital.

Signs and symptoms

The most common symptoms of aplastic anemia are Fatigue, Shortness of breath , Dizziness , Headache, Coldness in hands or feet, Pale skin, gums and nail beds,

Chest pain

Treatment

Treatment of aplastic anemia includes blood transfusions, blood and marrow stem cell transplants, and medication. These treatments can prevent or limit complications, relieve symptoms, and improve quality of life.

In some cases, a cure may be possible. Blood and marrow stem cell transplants may cure the disorder. Removing a known cause of aplastic anemia, such as exposure to a toxin, may also cure the condition.

4- Hemolytic Anemia

Hemolytic anemia is a condition in which red blood cells are destroyed and removed from the blood stream before their normal lifespan is up. A number of diseases, conditions and factors can cause the body to destroy its red blood cells. Hemolytic anemia can lead to various health problems such as fatigue, pain, arrhythmias, an enlarged heart and heart failure.

There are many types of hemolytic anemia's – some of which are inherited and others that are acquired.

1- Inherited hemolytic anemia's include:

Sickle cell anemia, Thalassaemias, Hereditary spherocytosis,

Glucose-6-phosphate dehydrogenase (G6PD) deficiency, Pyruvate kinase deficiency

2- Acquired hemolytic anemia include:

Autoimmune hemolytic anemia, Drug-induced hemolytic anemia

Mechanical hemolytic anemia, certain infections and substances can also damage red blood cells and lead to hemolytic anemia.

Causes

The immediate cause of hemolytic anemia is the early destruction of red blood cells. A number of diseases, conditions, and factors can cause the body to destroy its red blood cells. These causes can be inherited or acquired.

In **inherited hemolytic anemia** , this is due to affected genes .In each type of inherited hemolytic anemia the body makes abnormal red blood cells. The problem with the red blood cells may involve the hemoglobin, cell membrane, or enzymes that maintain healthy red blood cells.

In **acquired hemolytic anemia,** the body makes normal redblood cells , however, some disease, condition, or factor destroys the cells too early. Examples include immune disorders, infections and reactions to medicines or blood transfusions.

5-Thalassaemia

Thalassaemias are inherited blood disorders which cause the body to make fewer healthy red blood cells and less hemoglobin. The two major types of thalassaemia are: alpha- and beta thalassaemia.

•The most severe form of alpha thalassaemia is known as alpha thalassaemia major or hydrops fetalis

• the severe form of beta thalassaemia is known as thalassaemia major or Cooley's anemia.

Thalassaemias affect both males and females. Severe forms are usually diagnosed in early childhood and are lifelong conditions.

Hemoglobin in red blood cells has two kinds of protein chains:

alpha globin and beta globin. If the body doesn't make enough of these protein chains, red blood cells don't form properly and can't carry enough oxygen.

Genes control how the body makes hemoglobin protein chains. When these genes are missing or altered, thalassaemias occur.

Thalassaemias are inherited disorders. People who get abnormal hemoglobin genes from one parent but normal genes from the other are carriers. Carriers often have no signs of illness other than mild anemia. However, they can pass the abnormal genes on to their children.

Signs and symptoms

Symptoms of thalassaemias are caused by a lack of oxygen in the blood stream. This occurs because the body doesn't make enough healthy red blood cells and hemoglobin.

The severity of symptoms depends on the severity of the disorder: People who have alpha or beta thalassaemia can have mild anemia.

People with beta thalassaemia intermedia have mild to moderate anemia. They may also have other health problems including: slowed growth and delayed puberty; bone problems; and an enlarged spleen.

People with beta thalassaemia major have severe thalassaemia. Symptoms occur within the first two years of life and include severe anemia and other serious health problems. Pale

and listless appearance, Poor appetite, Dark urine, Slowed growth and delayed puberty, Jaundice, Enlarged spleen, liver and heart, Bone problems.

Treatment

Treatment for thalassaemias depends on the type and severity of the disorder. People who are carriers need little or no treatment.

Three standard treatments are used to treat moderate and severe forms of thalassaemia, these include blood transfusions, iron chelation therapy, and folic acid supplements.

6- Sickle Cell Anemia

Sickle cell anemia is a serious disease in which the body makes sickleshaped ("C"-shaped) red blood cells. Normal red blood cells are diskshaped and move easily through blood vessels.

Sickle cells contain abnormal hemoglobin that causes the cells to have a sickle shape, which don’t move easily through the blood vessels –they are stiff and sticky and tend to form clumps and get stuck in the blood vessels.

The clumps of sickle cells block blood flow in the blood vessels that lead to the limbs and organs. Blocked blood vessels can cause pain, serious infections, and organ damage.

In sickle cell anemia, a lower-than-normal number of red blood cells occur because sickle cells don't last very long.

Sickle cells usually die after about 10 to 20 days and the body can't reproduce red blood cells fast enough to replace the dying ones, which causes anemia.

Causes

Sickle cell anemia is an inherited, lifelong disease. People who have the disease inherit two copies of the sickle cell gene – one from each parent.

Signs and Symptoms

The most common symptoms of sickle cell anemia are linked to anemia and pain .Sudden pain throughout the body is a common symptom of sickle cell anemia.

This pain is called a "sickle cell crisis", and often affects the bones, lungs, abdomen, and joints.

Treatment

Sickle cell anemia has no widely-available cure. However, treatments can help relieve symptoms and treat complications.

The goals of treating sickle cell anemia are to relieve pain, prevent infections, eye damage and strokes, and control complications.

Bone marrow transplants may offer a cure in a small number of sickle cell anemia cases.

Diagnosis of iron deficiency anemia

1- CBC : **Red blood cell size and color (blood film) .**In iron deficiency anemia, red blood cells are smaller and paler in color than normal(.Microcytic,hypochromic)

Hematocrit(pcv). This is the percentage of blood volume made up by red blood cells. Normal levels are generally between 36-47 percent for adult women and 40-50 percent for adult men. These values may change depending on age .

Hemoglobin . Lower than normal hemoglobin levels indicate anemia.

2- **Ferritin** This protein helps store iron in the body, and a low level of ferritin usually indicates a low level of stored iron .

3- Total iron binding capacity

Total iron binding capacity (TIBC) is a blood test to see if there is too much or too little iron in blood. Iron moves through the blood attached to a protein called transferrin. 4-

Serum iron test

• Normal value range is: • Iron: 60 to 170 micrograms per deciliter (mcg/dL)

• TIBC: 240 to 450 mcg/dL, • Transferrin saturation: 20% to 50%

Other investigation that may be required by the dentist

Bleeding time is a medical test done on someone to assess their platelets function. It involves making a patient bleed then timing how long it takes for them to stop bleeding

Interpretation

Bleeding time is affected by platelet function, Certain vascular disorders and von Willebrand Disease—not by other coagulation factors such as haemophilia. Diseases that cause prolonged bleeding time include thrombocytopenia , disseminated intravascular coagulation (DIC),Glanzmanns thrombasthenia and Bernard-Soulier disease.

Asprin and other cyclooxygenase inhibitors can affect bleeding time

Other medication like wafarin and heparin also increase bleeding time .

It is also prolonged in hypofibrinogenemia

Clotting time : is the time required for a sample of blood to coagulate in vitro under standard conditions.

There are various methods for determining the clotting time, the most common being the capillary tube method. It is affected by calcium ion levels and many diseases. Normal value of clotting time is 8 to 15 minutes

A prothrombin time (pt) . this test used to detect and diagnosis a bleeding disorder or excessive clotting disorder ,used when the patient taking warfarin or when the patient have unexplained or prolonged bleeding or inappropriate blood clotting prolong in the pt may indicate decrease in the vitamine K or defective in factor VII ,or chronic low grade disseminated intravascular coagulation (DIC)

The **partial thromboplastin time** (**PTT**) or **activated partial thromboplastin time** (**aPTT** or **APTT**) is a medical test that characterizes blood coagulation .the typical reference range is betwen 30-50 sec. te prolong APTT may indicate the use of heparin or the antiphospholipid antibody especially lupus anticoagulant also the coagulation factor deficiency e.g hemophilia (very important).

also sepsis-coagulation factor consumption .sometimes the presence of antibodies against coagulation factor(factor inhibitors)

Deficiency of factors factors VIII, IX, XI and XII and rarely caused , von Willebrand factor (if causing a low factor VIII level) may lead to a prolonged aPTT

Erythrocyte Sedimentation Rate (ESR)

An erythrocyte sedimentation rate (ESR) is a type of blood test that measures how quickly erythrocytes (red blood cells) settle at the bottom of a test tube that contains a blood sample. Normally, red blood cells settle relatively slowly. A faster-than-normal rate may indicate inflammation in the body. Inflammation is part of the immune response system. It can be a reaction to an infection or injury. Inflammation may also be a sign of a chronic disease, an immune disorder, or other medical condition.

Other names: ESR, SED rate sedimentation rate; Westergren sedimentation rate

An ESR test can help determine if you have a condition that causes inflammation. These include arthritis, vasculitis, or inflammatory bowel disease. An ESR may also be used to monitor an existing condition.

- Headaches, Fever
- Weight loss, Joint stiffness
- Neck or shoulder pain, Loss of appetite
- Anemia

What do the results mean to the dentist?

- Infection, Rheumatoid arthritis
- Rheumatic fever, Vascular disease
- Inflammatory bowel disease, Heart disease
- Kidney disease , Certain cancers

Sometimes the ESR can be slower than normal. A slow ESR may indicate a blood disorder, such as:

- Polycythemia
- Sickle cell anemia
- Leukocytosis, an abnormal increase in white blood cells

If the results are not in the normal range, it doesn't necessarily mean that the patient have a medical condition that requires treatment. A moderate ESR may indicate pregnancy, menstruation, or anemia, rather than an inflammatory

disease. Certain medicines and supplements can also affect the results. These include oral contraceptives, aspirin, cortisone, and vitamin A.

Note

An ESR does not specifically diagnose any diseases, but it can provide information about whether or not there is inflammation in the body.

INR

INR stands for International Normalised Ratio, also referred to as Prothrombin time (PT), and is a standardised measurement of the time it takes for blood to clot.

What is an INR test?

An INR test measures how long it takes for the blood to clot. It is primarily used to diagnose unusual bleeding, blood clots, and monitoring people being treated with warfarin (an anti-clotting treatment).

The most common reasons for an INR test are:

- Monitoring as a part of warfarin therapy
- In relation to liver function tests - liver dysfunction can lead to decreased production of certain clotting factors
- Deep Vein Thrombosis (DVT) – a clot in a deep vein, commonly of the leg
- Pulmonary Embolism (PE) –Atrial Fibrillation (AF) Some cases of Heart failure (Left Ventricular, and Congestive Cardiac Failure), Artificial heart valves of the mechanical type

INR test results explained

The INR test result is given as a number, which is a ratio of:

- The test sample's Prothrombin time (a protein made by the liver and the time it takes to clot the blood) .
- The Prothrombin time of a normal sample of blood A result of 1.0, up to 1.5, is therefore normal.

A low INR result means the blood is 'not thin enough' or coagulates too easily and puts the patient at risk of developing a blood clot.

A high INR result means that the blood coagulates too slowly and you risk bleeding..

●Biopsy

A biopsy is a way of diagnosing diseases. A doctor removes a sample of tissue or cells to be examined by a pathologist, usually under a microscope.

A pathologist is a specialist who is trained to examine a sample of tissue for signs and extent of disease under a microscope. Tissue for a biopsy is normally taken from a living subject. Examining tissue under a microscope can provide information about various conditions.

Types of biopsy:-

1-Excisional

2-Incisional

3-FNA

4- Thick (core) needle biopsy

5- Exfoliative cytology

6-Frozen section

7-Oral brush biopsy

Depending on the aim, a biopsy may be excisional or incisional:

An excisional biopsy is when a whole lump or targeted area is surgically removed.

An incisional biopsy, or core biopsy, involves taking a sample of tissue

●cytology mean the study of the microscopic appearance of cells, esp. for the diagnosis of abnormalities and malignancies.

Fine needle aspiration (FNA)

is sometimes considered a cytology test and is sometimes considered a biopsy. During fine-needle aspiration, a long, thin needle is inserted into the suspicious area.

A syringe is used to draw out fluid and cells for analysis & smeared on slide, it is rapid & usually effective to diagnose of malignant from benign neoplasm although it is not completely conclusive.

Small size of the needle avoid damage to vital structure & it is valuable in case when incisional biopsy contra indicated as in pleomorphic adenoma or other types of malignant lesions in parotid gland

Disadvantage: it requires experience, small specimen may be unrepresentative, definitive diagnosis is not always possible.

Core needle biopsy

A larger needle with a cutting tip is used during core needle biopsy to draw a column of tissue out of a suspicious area.

The sample are larger than FNA & preserve architecture of tissue ,give more definitive diagnosis than FNA , but there is increase of the risk of seeding of neoplasm into the tissue & risk of damaging vital structures. It is used when incisional biopsy is inaccessible e.g. laryngeal tumor.

Exfoliative cytology

which is the examination of cells scraped from the surface of a lesion , it is quick & easy ,no local anesthesia is required also special techniques such as immune-staining can be applied.

It is useful in detection of virally damaged cells, acantholytic cells of pemphigues & candidal hyphae. But it provides no information on deeper tissue & has no value in diagnosis of cancer.

Frozen sections

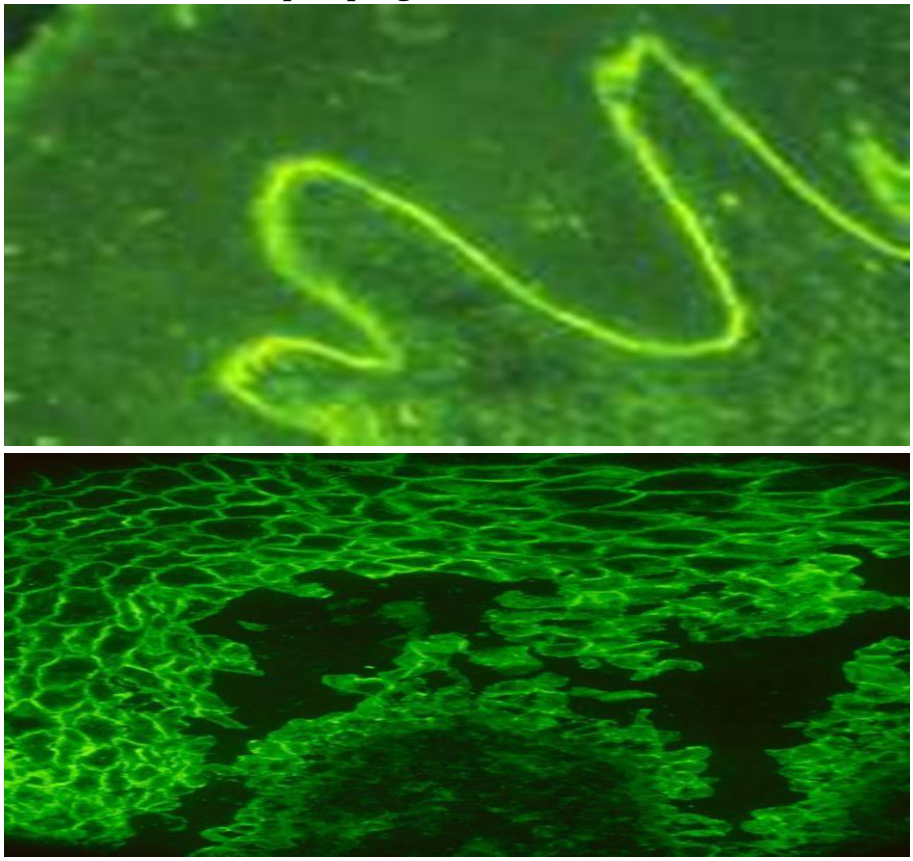
Frozen sections allows a stained slide to examined within 10 min of taking the specimen , the tissue is send fresh to lab. To be quickly frozen to about -70 c by liquid nitrogen or dry ice. Section is cut on refrigerated microtome and stained

The main advantage: is the time is too little so frozen section can be established at operation to determine whether tumor benign or malignant, but the section appear different from fixed material , also freezing artifacts can distort the cellular picture ,and definitive diagnosis sometimes impossible.

Immunofluorecent

Immunofluorecent staining. e.g used to identify pemphigus vulgaris asautoantibodybound to epithelial prickle cells (to desmosomes) & in mucous membrane pemphigoid autoantibodies bond to the basement membrane.

Mucous membrane pemphigoid



Pemphigus vulgaris

●Diagnostic ultrasound used in the soft tissue lumps and salivary gland

●Radioisotope imaging (nuclear scaning) very small quantities of radioactive materials called radioisotopes to image parts of the body may be used in salivary gland scanning like in the sjogrens or in the bone scanning

Imaging

Conventional radiography example (bitwing ,periapical)….

Computed tomography .in CT the dense bone is whit , soft tissue is present mid gray ,fat is dark gray and air is black and the dental filling may cause artifact

Magnetic resonance imaging (MRI) : for the soft tissue salivary gland and TMJ

●molecular –biological test

- chromosome studies
- comparative genomic hybridization
- DNA microarrays
- fluorescence in situ hybridization (FISH)
- polymerase chain reaction
- gene map

Culture and Sensitivity Testing if the body has an infection of any kind--from an upper respiratory infection ,to a jaw abscess to a urinary tract infection--it's critical to know which antibiotics will be effective against the particular pathogen (i.e., disease-causing agent) causing the problem. This means that (1) the species and strain of bacteria (or other pathogen) must be identified and (2) the drugs most effective at inhibiting their growth must be determined. The only reliable way this can be done is a culture and sensitivity test. The microbiological test which is used for the detection of the infection and also for the Bacterial study to determine the sensitivity of the infection agent for the treatment by the antibiotic sensitivity test .ex .in pus salivary gland …

Fungi by the direct smear from the area stained by the periodic acid shift or gram stain and the presence of the typical hyphae indicate the Candida proliferation.

Isolation and identification of candida albicans

Specimen collection

Samples were taken by a sterile swab, which rubbed and rotated vigorously over the mucosa, pressure put on the swabs in an attempt to pick up deeply seated microorganism. e.g. Swab was taken from the mucosa of palate beneath the upper complete denture.

Cultivation of candida albicans

The sample that collected was cultured on sabouraud dextrose agar (SD) for the growth of candida albicans, and then the plates were incubated aerobically for 48-72 hrs at 37C.

Identification Colony morphology:

The Candida species was identified according to the following morphological appearance on sabouraud dextrose agar. The colonies appeared medium size, moist, creamy, having a yeasty like odor, whitish cottony colonies

Viruses: the use of the virology lab from the fresh vesicle or by the titer of the antibody in the patient serum

●IMMUNOLOGIGICAL TESTS

Immunoglobulin's rheumatoid factor

HLA(human leukocyte antigens)

type antinuclear antibody anti-

DNA-antibody anti double strand

DNA test ant-Ro-ssa and anti-la-ssb

Oral Medicine

Lec.3 أ.م.رائدة نوري حامد

Pain: - Pain is, an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Acute pain resulting from injury will generally initiate a reflex withdrawal thus ensuring minimal or no tissue damage (nociceptive pain).

Allodynia: the injured region becomes sensitive to even light touch it refers to central pain sensitization (increased response of neurons) following normally non-painful, often repetitive, stimulation.

Hyperalgesia: over reactive to painful stimuli .An increased response to a stimulus that is normally painful, at the site of injury or inflammation. Primary hyperalgesia results from the direct effects of injury to skin and nerve tissue, whereas secondary hyperalgesia involves the increased pain sensitivity of the surrounding tissue.

What are the four phases of the pain pathway?

Nociceptive pain occurs in 5 phases: **1) Transduction, 2) Conduction, 3) Transmission, 4) Modulation, 5) Perception.** Transduction begins when peripheral terminals of nociceptive C fibers and A-delta (Aδ) fibers are depolarized by noxious mechanical, thermal, or chemical energy. The spinal cord carries the pain message from its receptors all the way up to the brain, where it is received by the thalamus and sent to the cerebral cortex, the part of the brain that processes the message.

Cellular damage and inflammation increase concentrations of other chemical mediators such as **histamine, bradykinin**, and **prostaglandins** in the area surrounding functional pain units. Endorphin and enkephalin are the body's natural painkillers. ... Enkephalins block pain signals in the spinal cord. Endorphins are thought to block pain principally at the brain stem. Both are morphine-like substances whose functions are similar to those of opium-based drugs.

Orofacial Pain.

Acute OFP: is primarily associated with the teeth and their supporting structures. Most frequently, dental pain is due to dental caries, although a broken filling or tooth- abrasion may also cause dental sensitivity.

Chronic orofacial pain (COFP): is a term used to describe painful regional syndromes with a chronic, unremitting pattern.

Anatomic consideration

• Cranial nerve V (CN V), the trigeminal nerve, is the dominant nerve that relays sensory impulses from the orofacial area to the central nervous system

• The facial (CN VII), glossopharyngeal (CNIX), and vagus (CN X) nerves and the upper cervical nerves (C2 and C3) also relay sensory information from the face and surrounding area.

By intense or noxious stimuli. Some are unimodal and respond only to thermal or mechanical stimuli; others are polymodal and respond to mechanical, thermal, and chemical stimuli. Nociceptors encode the intensity, duration, and quality of a noxious stimulus.

Clinically COFP may be subdivided into three main symptomatic classes

1- Musculoskeletal 2- neuropathic 3- Neurovascular .

Musculoskeletal entities are dealt with Temporomandibular Disorders. Possible causes of Facial Pain: • Dental pain • TMJ • Neuropathic pain (neuralgias) • Pathology in related str. (salivary gland , sinus ,eyes , cervical spine, nasopharyns) • Vascular disorder (headaches) • Intracranial lesions (neoplasm)• Referred pain (angina pect.) • Psychogenic facial pain.

2.Neuropathic pain is pain caused by damage or disease affecting the somatosensory nervous system. Neuropathic pain may be associated with abnormal sensations called dysesthesia or pain from normally non-painful stimuli (allodynia).

Neuropathic OFP includes a number of clinical entities; the most common are :- Trigeminal Neuralgia (TN), glossopharyngeal neuralgia (GN) , geniculate neuralgia,burning mouth syndrome (BMS.

3-Neurovascular Pain includes: Cluster headache (CH), migraine, paroxysmal hemicrania (PH), cranial arteritis , tension-type headache.

Drug therapy:

✓ Non-opioid Analgesics:

This group consists primarily of acetaminophen and the large group of nonsteroidal anti-inflammatory drugs (NSAIDs).

Acetaminophen generally has fewer adverse effects when compared to NSAIDs. It does not affect platelet function, rarely causes gastrointestinal (GI) disturbances, and can be given to patients who are allergic to aspirin or other NSAIDs. Caffeine has been shown to enhance the effectiveness of non-opioid drugs and is often added to the analgesic.

The mechanism of action of acetaminophen is different from that of the NSAIDs but remains unknown; there is some evidence that suggests a central action.
NSAIDs are thought to work primarily at the site of injury by inhibiting the enzyme cyclo-oxygenase (COX), which is required for the synthesis of prostaglandins, substances that sensitize peripheral sensory nerves and contribute to the experience of pain.
The maximum dose for acetaminophen in a 24 hour period is 4 grams.

Opioids:

Their most important effects are on the central nervous system and GI system.

- ✓ These drugs bind to m-opioid receptors, resulting in actions that lead to the analgesic effects. Effects at the membrane level leading to a decrease in neuronal excitability.
- ✓ Opioids increase activity in some neuronal pathways such as the descending inhibitory pathways.
- ✓ The use of opioid therapy in moderate to severe acute pain and cancer pain is well established.
- ✓ **Adjuvant Drugs:**
- ✓ This group of drugs has been approved for use in conditions other than pain. They have been found to be of value in pain management.
- ✓ Amitriptyline (a tricyclic antidepressant), the antidepressant that has been most frequently studied in clinical trials, has been proven to be effective in chronic orofacial pain treatment.
- ✓ The neurotransmitters serotonin and norepinephrine are thought to play a role in the descending inhibitory transmissions from the brain to the dorsal horn, modulating nociceptive impulses. Tricyclic antidepressants (TCAs) block the reuptake of serotonin and norepinephrine (NE), and this is thought to enhance the central inhibitory system in pain processing.
- ✓ These effects occur at doses that are lower than those required for an antidepressant effect.

Anticonvulsant drugs are effective in the treatment of trigeminal neuralgia and diabetic neuropathy and for migraine prophylaxis. These drugs

frequently produce side effects (including sedation, dizziness, ataxia, and mood changes) that can limit their usefulness.

Newer anticonvulsant gabapentin is receiving attention as possible therapies for pain.gabapentin has become commonly used in pain management partly because of its relatively few side effects.movement disorders have been reported with gabapentin.the disorders resolve after administration of the drug is stopped.

Topical Medications:

Topical analgesic therapy on the skin or oral mucosa has the advantage of reduced systemic absorption and thus a reduced risk of side effects.

Capsaicin used as a topical cream. It is effective in treating postherpetic neuralgia. Topical application blocks C-fiber conduction, inactivates the release of neuropeptides from peripheral nerve endings.

Facial Neuralgias:

Group of neurologic disorders involving the cranial nerves and are characterized by:

(a) Brief episodes of shooting, often electric shock–like pain along the course of the affected nerve branch.

(b) Trigger zones on the skin or mucosa that precipitate painful attacks when touched.

(c) Pain-free periods between attacks and refractory periods immediately after an attack, during which a new episode cannot be triggered.

These clinical characteristics differ from neuropathic pain, which tends to be;

1- Constant.

2- Burning quality.

3- Absent of trigger zones.

Trigeminal neuralgia:

- 10% of cases have detectable underlying pathology such as a tumor of the cerebellar pontine angle, a demyelinating plaque of multiple sclerosis, or a vascular malformation.

- The remainder of cases of TN are classified as idiopathic.

The most widely accepted theory is that a majority of cases of TN are caused by an atherosclerotic blood vessel pressing on the trigeminal nerve. This pressure results in focal demyelinization and hyperexcitability of nerve fibers, which will then fire in response to light touch, resulting in brief episodes of intense pain.

-evidence for this theory was obtained from a study using tomographic magneyic resonance imaging (MRI), which showed that contactbetween a

blood vessel and the trigeminal nerve root was much greater on the affected side .

Clinical features:

- Episodes of intense shooting stabbing pain that lasts for a few seconds and then completely disappears. The pain characteristically has an electric shock–like quality and is unilateral.
- The maxillary branch is the branch that is most commonly affected, followed by the mandibular branch and (rarely) the ophthalmic branch, involvement of more than one branch occurs in some cases.
- Pain in TN is precipitated by light touch on a "trigger zone" present on the skin or mucosa within the distribution of the involved nerve branch.

Common sites for trigger zones include the nasolabial fold and the corner of the lip. Shaving, showering, eating, speaking, or even exposure to wind can trigger a painful episode.

- Just after an attack, there is a refractory period when touching the trigger zone will not precipitate pain.

The number of attacks may vary from one or two per day to several per minute.

Management

-combinations of drugs should be attempted before surgery is recommended.

-initially drugs that are effective in eliminating the painful attacks.

-anticonvulsant drugs are most frequently used and are most effective.

-Carbamazepine (Tegretol) is the most commonly used drug and is effective therapy for greater than 85%of newly diagnosed cases of TN. The drug is administered in slowly increasing doses until pain relief has been achived.

- Surgery is indicated when the drug is ineffective or the patient cannot tolerate the side effects of the drugs.

Glossopharyngeal neuralgia:

- It is a rare condition that is associated with paroxysmal pain that is similar to, but less intense than, the pain of TN.
- The location of the trigger zone and pain sensation follows the distribution of the glossopharyngeal nerve (the pharynx, posterior tongue and ear).
- Pain is triggered by stimulating the pharyngeal mucosa during chewing, talking, and swallowing.

Glossopharyngeal neuralgia may occur with TN, and when this occurs, a search for a common central lesion is essential.

- Glossopharyngeal neuralgia also may be associated with vagal symptoms, such as syncope and arrhythmia, owing to the close anatomic proximity of the two nerves.

The application of a topical anesthetic to the pharyngeal mucosa eliminates glossopharyngeal nerve pain and can aid in distinguishing it from the pain of other neuralgias.

-the most common causes of glossopharyngeal neuralgia are intracranial or extracranial tumors and vascular abnormalities that compress CN IX.

-TREATMENT is similar to that for TN, with a good response to carbamazepine and baclofen.

Geniculate neuralgia:

- It is an uncommon paroxysmal neuralgia of facial nerve, characterized by pain in the ear and (less frequently) the anterior tongue or soft palate.

There is often some degree of facial paralysis, indicating the involvement of the motor root.

- Geniculate neuralgia commonly results from herpes zoster of the geniculate ganglion, a condition referred to as Ramsay Hunt syndrome. Viral vesicles may be observed in the ear canal or on the tympanic membrane and facial paralysis.

The symptoms result from inflammatory neural degeneration, and a short course (2 to 3 weeks) of high-dose steroid therapy is beneficial. Acyclovir significantly reduces the duration of the pain. Patients with geniculate neuralgia are also treated with carbamazepine and antidepressants.if not responed then undergo surgery.

Occipital neuralgia:

- It is a rare neuralgia in the distribution of the sensory branches of the cervical plexus.

- The most common causes are trauma, neoplasms, infections, and aneurysms involving the affected nerve.

-palpation below the superior nuchal line may reveal a tender spot.

postherpetic neuralgia:

- Herpes zoster (shingles) is caused by the reactivation of latent varicella-zoster virus infection that results in both pain and vesicular lesions along the course of the affected nerve.

- Persistent pain, paresthesia, hyperesthesia, and allodynia months to years after the zoster lesions have healed.

- Approximately 15 to 20% of cases of herpes zoster involve the trigeminal nerve although the majority of these cases affect the ophthalmic division of the fifth nerve, resulting in pain and lesions in the region of the eyes and forehead.

- In a majority of cases, the pain of herpes zoster resolves within a month after the lesions heal. Pain that persists longer than a month is classified as postherpetic neuralgia (PHN) although some authors do not make the diagnosis of PHN until the pain has persisted for longer than 3 or even 6 months.

- The combination of peripheral and central injury by varicella-zoster virus results in the spontaneous discharge of neurons and an exaggerated painful response to nonpainful stimuli.

- Antiviral drugs, particularly famciclovir, along with a short course of systemic corticosteroids during the acute phase of the disease.

- Topical anesthetic agents, such as lidocaine, or analgesics, particularly capsaicin.

- Tricyclic antidepressants such as amitriptyline and nortriptyline.

- Gabapentin, carbamazepine or phenytoin.

Post-traumatic neuropathic pain:

A neuroma is an incomplete or failed attempt at nerve repair following injury to a peripheral nerve, resulting in a disorganized nerve fiber that is focally electrically excitable.

Trigeminal nerve injuries may result from facial trauma or from surgical procedures,such as the removal of impacted third molars,the placement of dental implants ,the removal of cysts or tumors of the jaws, genioplasties, or osteotomies.

-total nerve section (neurotmesis) frequently causes permanent nerve damage, resulting in anesthesia and / or dysthesia.

Clinical manifestations:

The pain associated with peripheral nerve injury may be persistent or may occuer only in response to a stimulus such as light touch.

Patient with nerve damage may experience anesthesia (loss in sensation), paresthesia (a feeling of pins and needles),allodynia,or hyperalgesia.

Management:

Systemic corticosteroids .

- The tricyclic antidepressants (TCAs) such as amitriptyline and nortriptyline.

- Gabapentin, an anticonvulsant drug.

- Topical capsaicin may also be effective in controlling pain.

Atypical Facial Pain:

- One theory considers atypical facial pain to be a form of de-afferentation or phantom tooth pain. Neuropathic pain may result from tissue injury that affects peripheral nerves, resulting in CNS changes, causing persistent pain.
- The effectiveness of tricycle antidepressant medication have been used to support a psychological explanation.
- Others consider that atypical facial pain is a form of sympathetically maintained pain. The pain is worsened during periods of stress.

It is proposed that following injury, sympathetic-sensory coupling occurs in which nociceptors upregulate α-adrenergic receptors and respond to norepinephrine released from sympathetic terminals in the injured region.

Clinical manifestations:

- Most frequently in women in the fourth and fifth decades of life.
- Patients should be reassured
- Constant dull aching pain without an apparent cause that can be detected by examination or laboratory studies.
- The patient frequently reports that the onset of pain coincided with a dental procedure such as oral surgery or an endodontic or restorative procedure.
- Patients will give a history of receiving trials of multiple medications, including antibiotics, corticosteroids, decongestants, or anticonvulsant drugs.
- The pain may remain in one area or may migrate.
- a through history and examination must be performed to rule out organic cause.

Management:

- TCAs such as amitriptyline and nortriptyline
- Gabapentin and clonazepam.
- Topical desensitization with capsaicin.

Lec.4 facial pain أ.م. رائدة نوري الكبيسي

(part 2)

Burning Mouth Syndrome (BMS) Is a poorly understood pain condition that is most probably neuropathic. The condition is also known as stomatodynia and is characterized by a burning mucosal pain with no significant physical signs and is common in postmenopausal women.

BMS may be subclassified into:-

1- "Primary" or idiopathic BMS for which a neuropathological cause is likely and cannot be attributed to any systemic or local cause.

2- "Secondary BMS" (SBMS) resulting from local or systemic pathological conditions.

BMS is characterized by resistance to a wide range of treatments and is one of the most challenging management problems in the field of OFP. Pain is most commonly described as burning or hot and intensity varies from mild to severe.

BMS is typically of spontaneous onset and lasts from months to several years. Spontaneous remission is very rare. Common aggravating factors include personal stressors, fatigue, and specific foods (acidic, hot, or spicy). More than two-thirds of the patients complain of altered taste sensation (dysgeusia) accompanying the burning sensation, in many cases described as a spontaneous metallic taste. Abnormal sensations, such as feeling of dry mouth, are common but true hyposalivation is less common and should be considered under secondary or symptomatic BMS. Oral and perioral burning sensation as a result of local or systemic factors or diseases is classified as SBMS.

1- Local factors and diseases known to induce SBMS include oral candidiasis , lichen planus, and allergies.

2- Systemic disorders that induce SBMS include hormonal changes, deficiencies of vitamin B12, folic acid or iron, diabetes mellitus, side effects of medications, and autoimmune diseases.

Successful treatment of the primary disease will usually alleviate the burning sensation in SBMS patients.

Treatment Topical therapies in elderly, medically compromised patients. The most established is clonazepam (tranquilizers) (1 mg) which should be sucked and subsequently spat out three times daily.

Topical anesthetics may decrease or increase pain and are therefore unpredictable. Systemic therapies include paroxetine (antidepressant) (20 mg/d) and sertraline (50 mg/d) or other selective serotonin reuptake inhibitors (SSRIs).

These may reduce pain and improve anxiety and depression. A two-month course of 600 mg daily of alpha-lipoic acid may be beneficial. A combination of alpha-lipoic acid (600 mg/d) and gabapentin (300 mg/d) results in greater improvement of the burning symptoms compared to these medications taken alone.

Neurovascular pain

Cluster headache (CH) is a distinct pain syndrome characterized by episodes of severe unilateral head pain occurring chiefly around the eye and accompanied by a number of autonomic signs (AS), with severe pain and major autonomic activation. The precise genetics of CH are unclear but is likely to involve an autosomal dominant gene with low penetrance.

CH typically appears between the ages of 20-29 years, is more common than previously thought, and seems to affect men more than women.

Features; Pain in CH is usually periorbital or ocular but varies. In “upper CH” the forehead, temporal, and parietal regions are involved, whereas in “lower CH” the temporal and suboccipital regions are affected with radiation to the teeth, jaws, neck, and cheeks. Pain is unilateral and in 20% of cases may change sides. Severity is excruciating and rated as 8-10 on a visual analog scale. Quality is nonspecific and is variably described as throbbing or boring, burning, stabbing or a “stabbing” feeling in the eye. Individuals with CH frequently describe the pain as a hot metal rod in or around the eye.

. CH active periods are seasonal, occurring around spring or autumn last 15-180 minutes reaching peak intensity very rapidly—within 3 minutes (up to 9-10 minutes). Longer attacks lasting from 3 to 48 hours are rare and frequency is one every other day to 8/d. Pain is most usually accompanied by at least one ipsilateral autonomic sign (AS); conjunctival injection/lacrimation, nasal congestion/rhinorrhea, eyelid edema, forehead/facial sweating, miosis, and ptosis.

The vast majority (>80%) of patients are markedly restless during an attack. Patients appear agitated; continually move around, particularly during more severe attacks; in sharp contrast to the quiet-seeking behavior observed in migraine. The cause of cluster headache is unknown Cluster headaches were historically prsent as dilation of blood vessels which in turn, was thought to create pressure on the trigeminal nerve.

1.Genetics Cluster headache may, but rarely, run in some families in an autosomal dominant inheritance pattern.

2. Tobacco smoking.

3. Hypothalamus.

Pain typically awakens patients within 90 minutes coinciding with the onset of rapid eye movement sleep.

CH prodromes include AS, blurred vision, sensitivity to smells, nausea, dyspepsia, hunger, irritability, tiredness, tenseness, and mild pain or non-painful sensations in the area that subsequently becomes painful.

Migrainous features are common in CH and may confuse diagnosis. Photophobia, phonophobia, nausea, and vomiting are reported in up to half of cases. It is important to note that phono- and photophobia are unilateral while in migraine these are bilateral.

Differential Diagnosis and Secondary CH

CH is often misdiagnosed as dental or maxillary sinus pathology

CH Treatment Based on attack patterns, patients should avoid daytime naps, alcoholic beverages, and other triggers.

Pharmacologic Treatment may be abortive, transitional, or preventative or prophylaxis.

1- Abortive symptomatic relief may be rapidly attained with oxygen inhalation. Subcutaneous sumatriptan (neuro active alkaloids).

2- Rapid transitional prophylaxis may be attained with corticosteroids that may be continued only for a limited period in selected patients.

3- Prophylactic or preventive (In both episodic and chronic CH.) is usually with verapamil (calcium channel blockers) and topiramate (anticonvulsant) as second-line therapy. Remission periods may increase with time beyond the age of 65-75 active CH is rare.

Migraine ; is the most common headaches, which may occasionally also cause pain of the face and jaws. It may be triggered by foods such as nuts, chocolate, and red wine; stress; sleep deprivation; or hunger. Migraine is more common in women. The migraine headache is frequently accompanied by nausea, vomiting, photophobia (aversion to light), phonophobia (aversion to sound), and osmophobia (aversion to odors). It may be preceded by an aura of neurological dysfunction, such as visual disturbances, vertigo, numbness, or weakness. In many patients, migraine is triggered by specific factors, such as menses, weather changes, irregular sleep, alcohol, or certain foods. Migraine is also often relieved by sleep. The life time prevalence of migraine is estimated to be near 35%, and it affects greater than 17% of women and 6% of men.

Etiology and Pathogenesis;

1. family members who suffer from migraine. In addition, specific mutations leading to rare causes of vascular headache have been identified.

2- Vascular Theory The aura of migraine was once thought to be caused by cerebral vasoconstriction and the headache by reactive vasodilation.

3- Neuronal Theory and the Trigeminovascular System Migraine aura is Migraine probably results from pathologic activation of meningeal vessel nociceptors combined with a change in central pain modulation.

4- Role of Serotonin and Dopamine.

Clinical Findings; The clinical features of migraine are separated into two types of headache:

1-Migraine without aura (common migraine).
2- Migraine with aura (classic migraine). Classic migraine starts with a prodromal.

Treatment Generally, migraine management is divided into three specific components:

(1) Prophylactic or preventative therapy.

(2) Abortive therapy.

(3) Palliative or rescue therapy.

Patients experiencing more than three migraines per month are candidates for prophylactic therapy. Patients with migraine should be carefully assessed to determine common food triggers. Attempts to minimize reactions to the stress of everyday living by using relaxation techniques may also be helpful to some patients.

Drugs that are useful in aborting migraine include **ergotamine** and **sumatriptan,** which can be given orally, nasally, rectally or parenterally. Ergotamine Initial dose: Oral, Sublingual: 2 mg ergotamine in fixed combination with caffeine given as quickly as possible after the first symptom of headache. These drugs must be used cautiously since they may cause hypertension and other cardiovascular complications. Drugs that are used to prevent migraine include propranolol, verapimil, and TCAs or monoamine oxidase inhibitors such as phenelzine can be used to manage difficult cases that do not respond to safer drugs.

Other recommended drugs include gabapentin and clonazepam. Some clinicians report benefit from topical desensitization with capsaicin, topical anesthetics, or topical doxepin.

Vascular Pain Pain originating from vascular structures may cause facial pain that can be misdiagnosed and mistaken for other oral disorders, including toothache or TMD. The pain is dull, pressing or throbbing**.**

CRANIAL ARTERITIS Cranial arteritis (temporal arteritis, giant cell arteritis) is an inflammatory disorder involving the medium-sized branches of the carotid arteries. The temporal artery is the most commonly involved branch.

Etiology and Pathogenesis Both cranial arteritis and polymyalgia rheumatica are caused by immune abnormalities that affect cytokines and T -lymphocytes, resulting in inflammatory infiltrates in the walls of arteries. This infiltrate is characterized by the formation of multinucleated giant cells. The underlying trigger of the inflammatory response is unknown.
Clinical Manifestations Cranial arteritis most frequently affects adults above the age of 50 years. Patients have a throbbing headache accompanied by generalized symptoms including fever, malaise, and loss of appetite. Dull temporal pain, fatigue of the masticatory muscles, joint pain, and headache of recent onset that is chronic and possibly progressive .

Moderate-to-severe headache, polymyalgia, and claudication of the masticatory muscles may be present. There may be a swollen and tender scalp artery, usually the superficial temporal artery, pain radiate to face, neck, maxilla and mandible. Blindness may develop in 50% of patients. Examination of the involved temporal artery reveals a thickened vessel with burning sensation over the artery.

Arteritis

Laboratory investigations: Laboratory abnormalities include an elevated erythrocyte sedimentation rate (ESR) and anemia. Abnormal C-reactive protein may also be an important early finding. The most definitive diagnostic test is a biopsy specimen (from the involved temporal artery) that demonstrates the characteristic inflammatory infiltrate.

Treatment Individuals with cranial arteritis should be treated with systemic corticosteroids as soon as the diagnosis is made. The initial dose ranges between 40 to 60 mg of prednisone per day, and the steroid is tapered once the signs of

the disease are controlled. . Steroids may be supplemented by adjuvant therapy with immunosuppressive drugs, such as cyclophosphamide

cardiac Toothache (referred pain);

Angina pectoris or acute myocardial infarction, refer pain to the shoulder, arm, the jaw and to the teeth. Associated with chest pain (substernal), Tooth ache increases with exercises and decreased with medication specific for the heart (nitroglycerin). If patients are experiencing a cardiogenic toothache give them an aspirin, and make sure they get to a hospital emergency room immediately.

Sinusitis and orofacial pain;

Acute sinusitis, is a short-term infection or inflammation of the membranes that line sinuses. It prevents mucus from draining from nose. Symptoms of acute sinusitis include:

• nasal congestion, • thick, yellow, or green mucus discharge from the nose, • sore throat, • a cough (usually worse at night), • drainage of mucus in the back throat (post nasal drip), • headache, • pain, pressure, or tenderness behind eyes, nose, cheeks, or forehead, • earache, • toothache• bad breath, reduced sense of taste, reduced sense of smell, • fever.

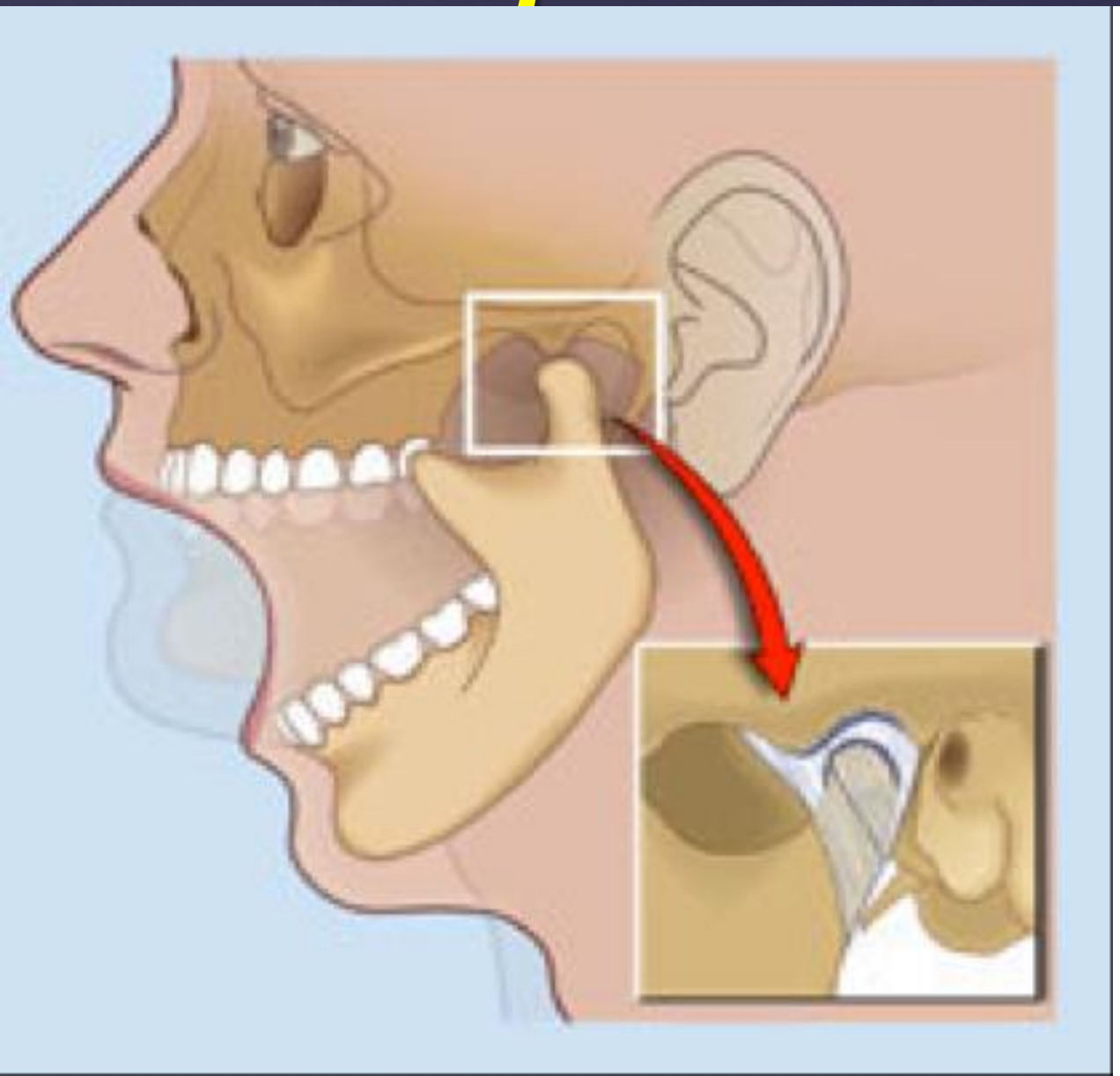
Fatigue: Dull pain, aching or throbbing in several upper teeth, associated with pressure below the eyes and worsen by bending down, applying pressure in the sinuses, coughing, sneezing, Chewing, cold, percussion, worsen the pain, with history of upper respiratory infection, nasal congestion, or sinus problem.

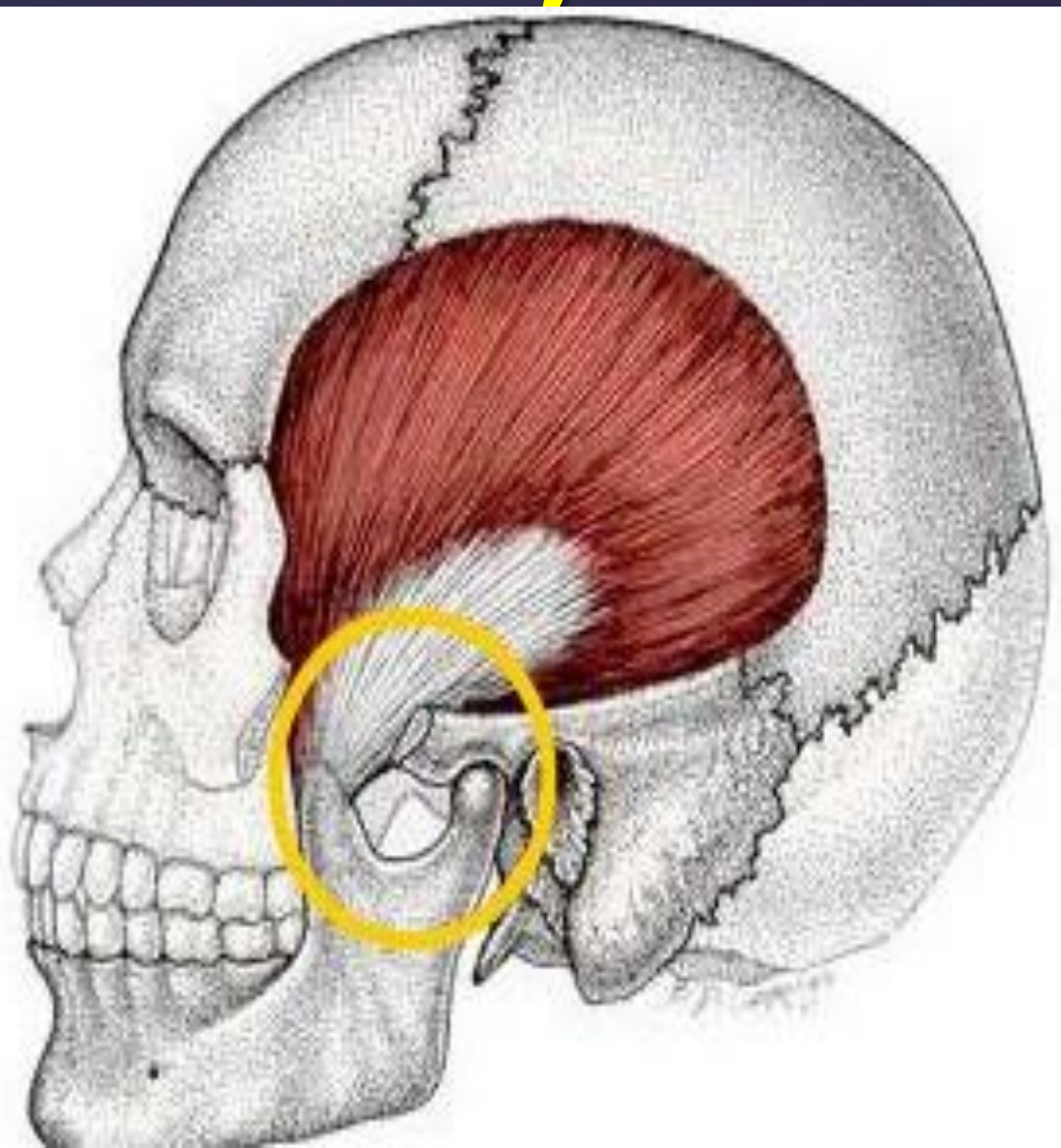
University of Anbar
College of Dentistry

Oral Medicine

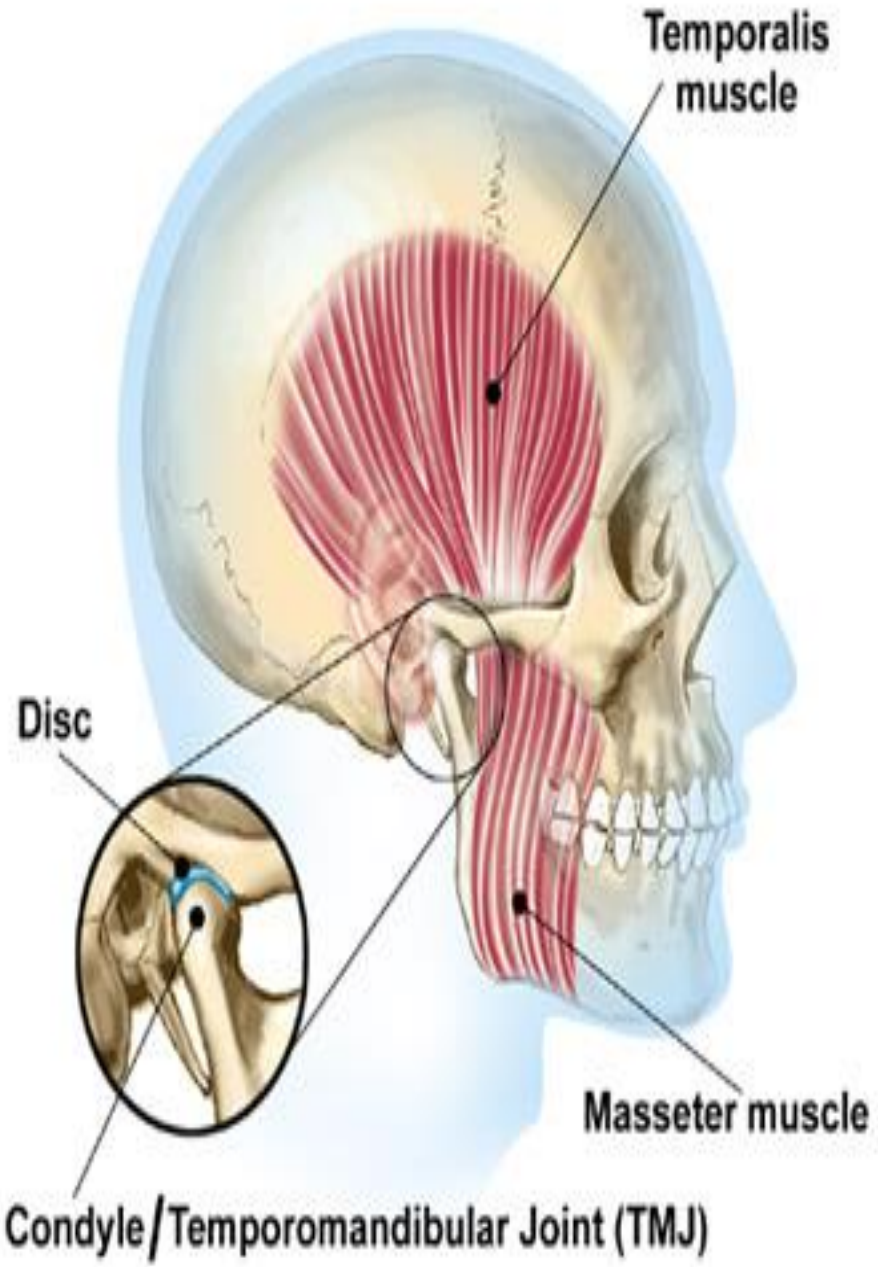
Dr. Shaimaa Hamid
PhD of Oral Medicine

Temporomandibular Joint





Temporomandibular disorders (TMDs) *is a collective term embracing a number of clinical problems that involve* the masticatory muscles, the temporomandibular joints (TMJs) and associated structures, or both.

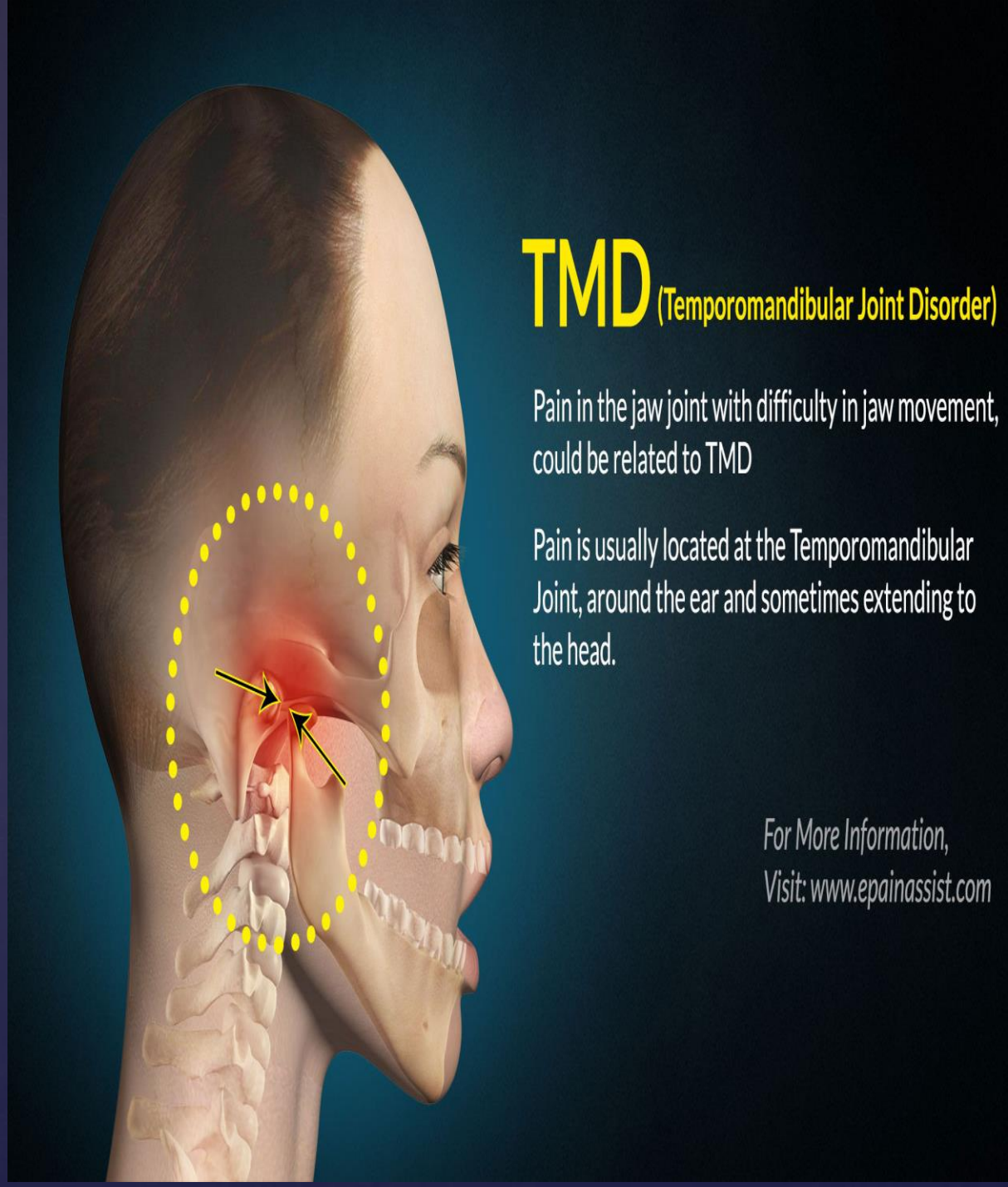


TMD characterized by the presence of one or more of the following signs and symptoms:

(1) facial pain in the region of the TMJs and/or muscles of mastication,

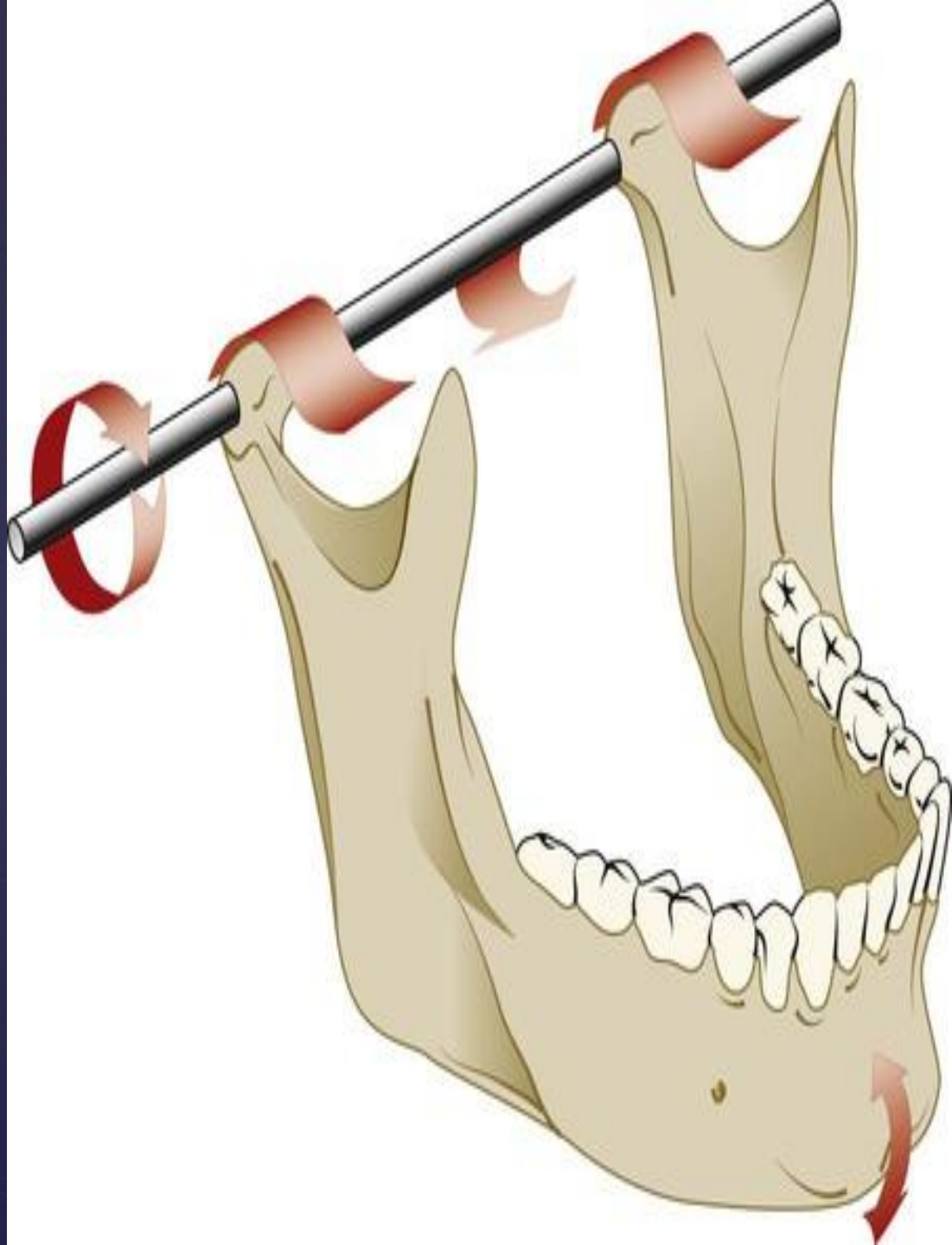
(2) limitation or deviation in mandibular movements,

(3) TMJ sounds during jaw movement and function.

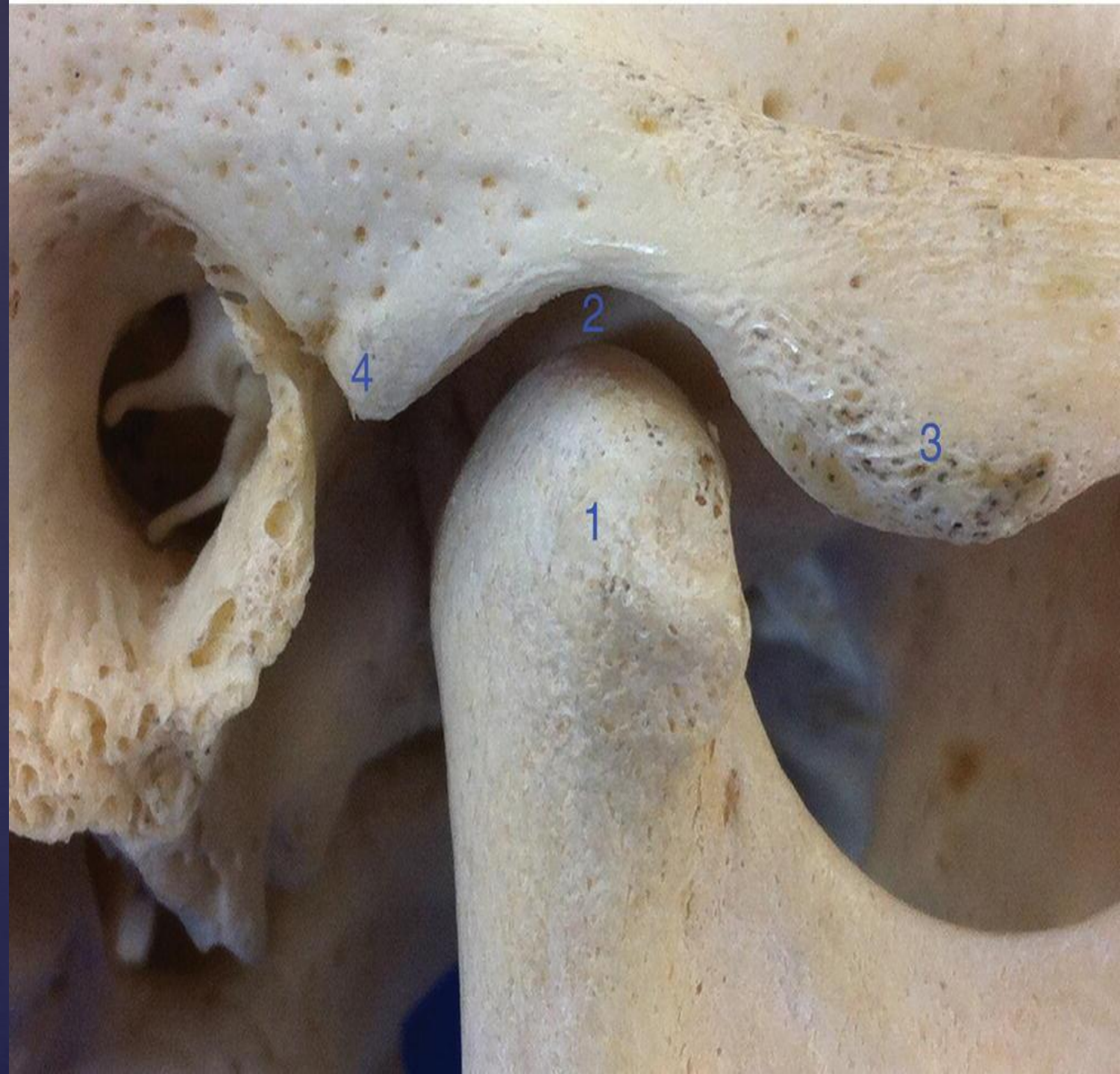


Functional Anatomy

The TMJ articulation is a joint that is capable of hinge-type movements and gliding movements.



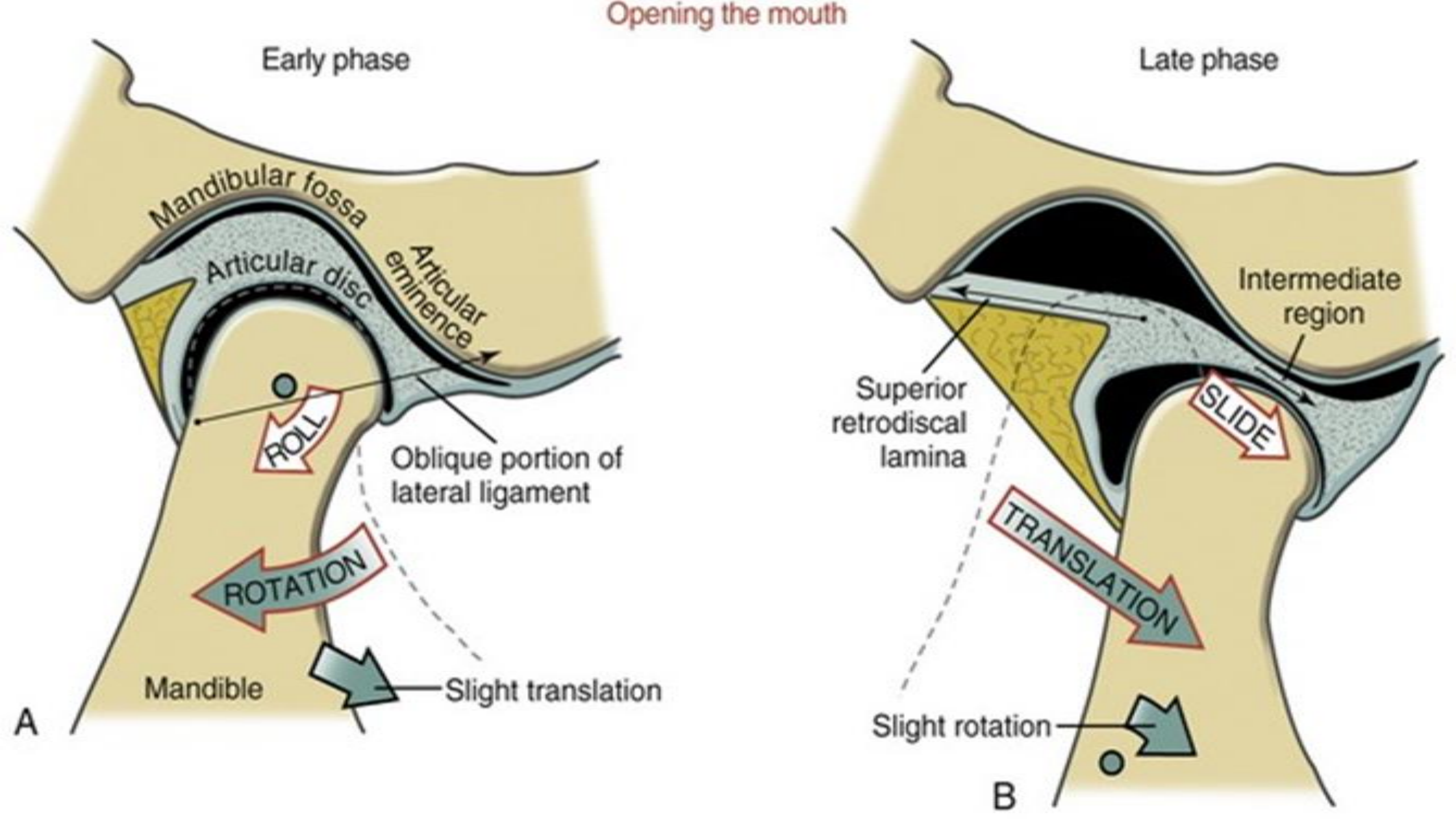
The articulation is formed by the mandibular condyle, which forms the lower part of the bony joint occupying a hollow in the temporal bone (the mandibular or glenoid fossa) which form the upper part of the bony joint.



During wide mouth opening, the condyle rotates around a hinge axis and glides, causing it to move beyond the anterior border of the fossa, identified as the articular eminence.

The TMJ has a rigid end point determined by tooth contact.

Rotation of the condyle contributes more to normal mouth opening than translation.

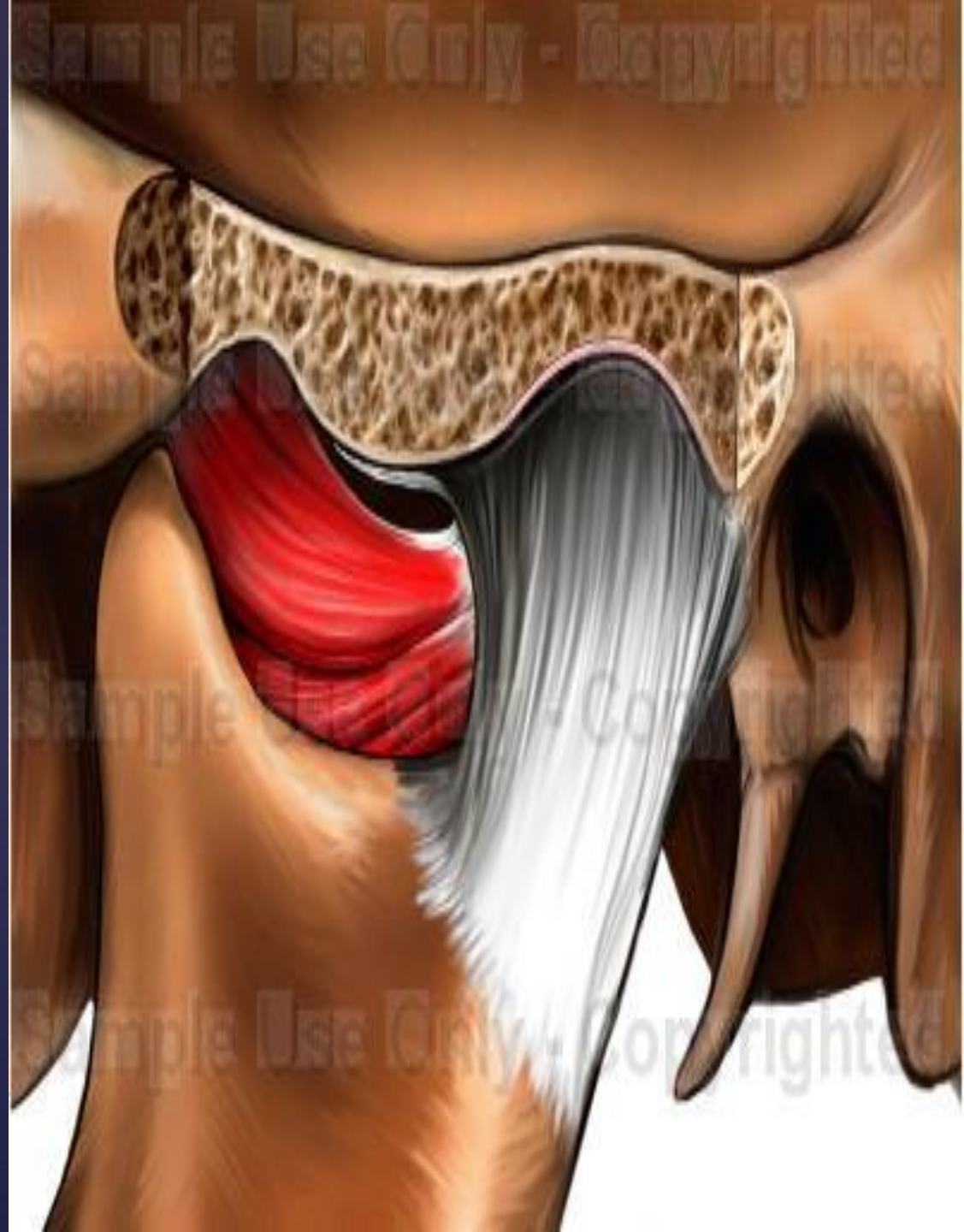

Opening the mouth
Early phase
Late phase
Mandibular fossa
Articular disc
Articular eminence
ROLL
Oblique portion of lateral ligament
ROTATION
Mandible
Slight translation
A
Intermediate region
Superior retrodiscal lamina
SLIDE
TRANSLATION
Slight rotation
B

The bony components are enclosed and connected by a fibrous capsule.

The capsule is lined with synovium and the joint cavity is filled with synovial fluid.

The synovium is a vascular connective tissue lining the fibrous joint capsule and extending to the boundaries of the articulating surfaces.

Synovial fluid is a filtrate of plasma with added mucins and proteins. Fluid forms on the articulating surfaces and decreases friction during joint compression and motion.

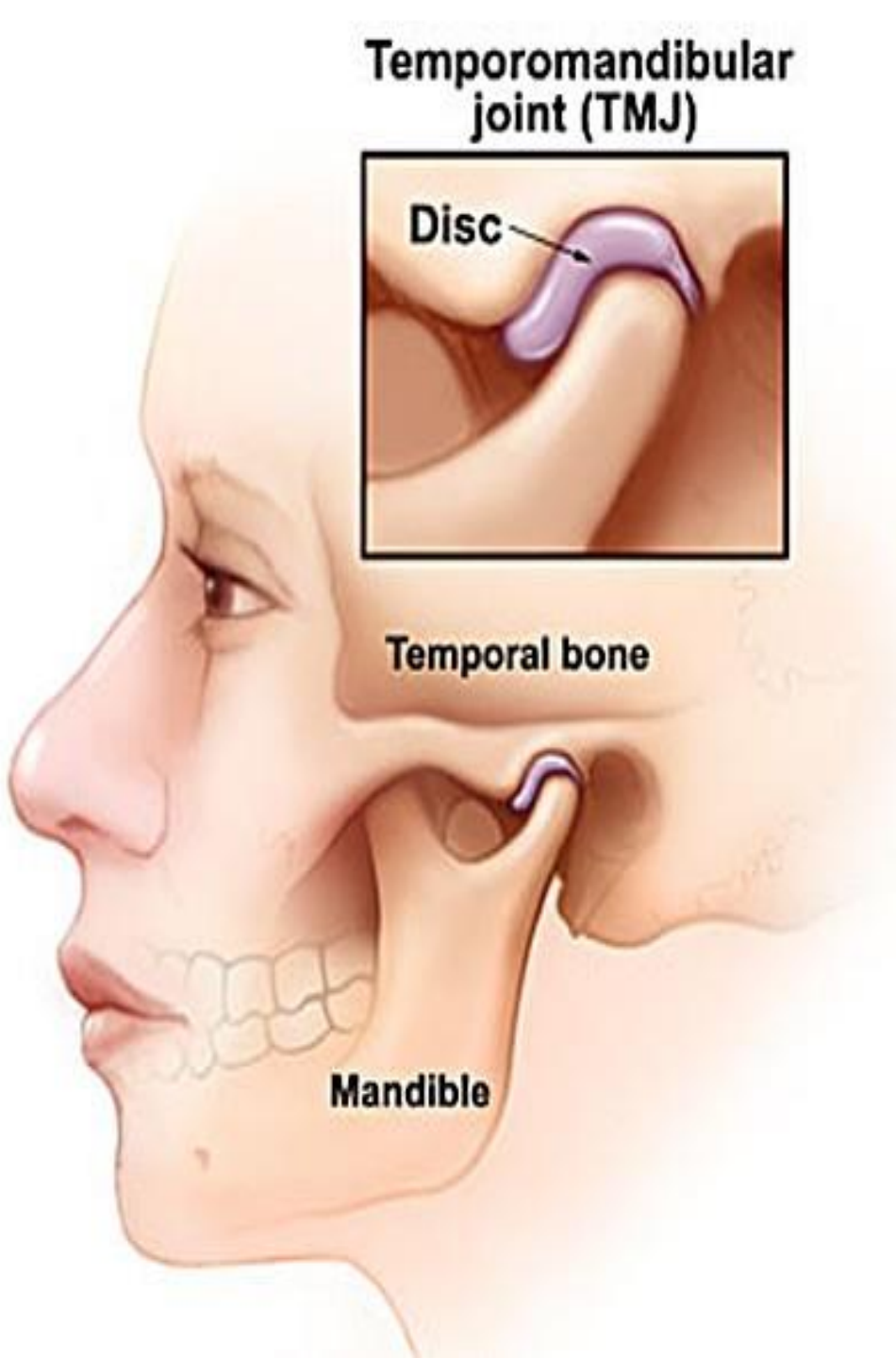


Articular Disc

A fibrocartilage made up primarily of dense collagen of variable thickness and referred to as a disc occupies the space between the condyle and mandibular fossa.

The disc is attached by ligaments to the lateral and medial poles of the condyle.

These ligaments permit rotational movement of the disc on the condyle during mouth opening and closing.

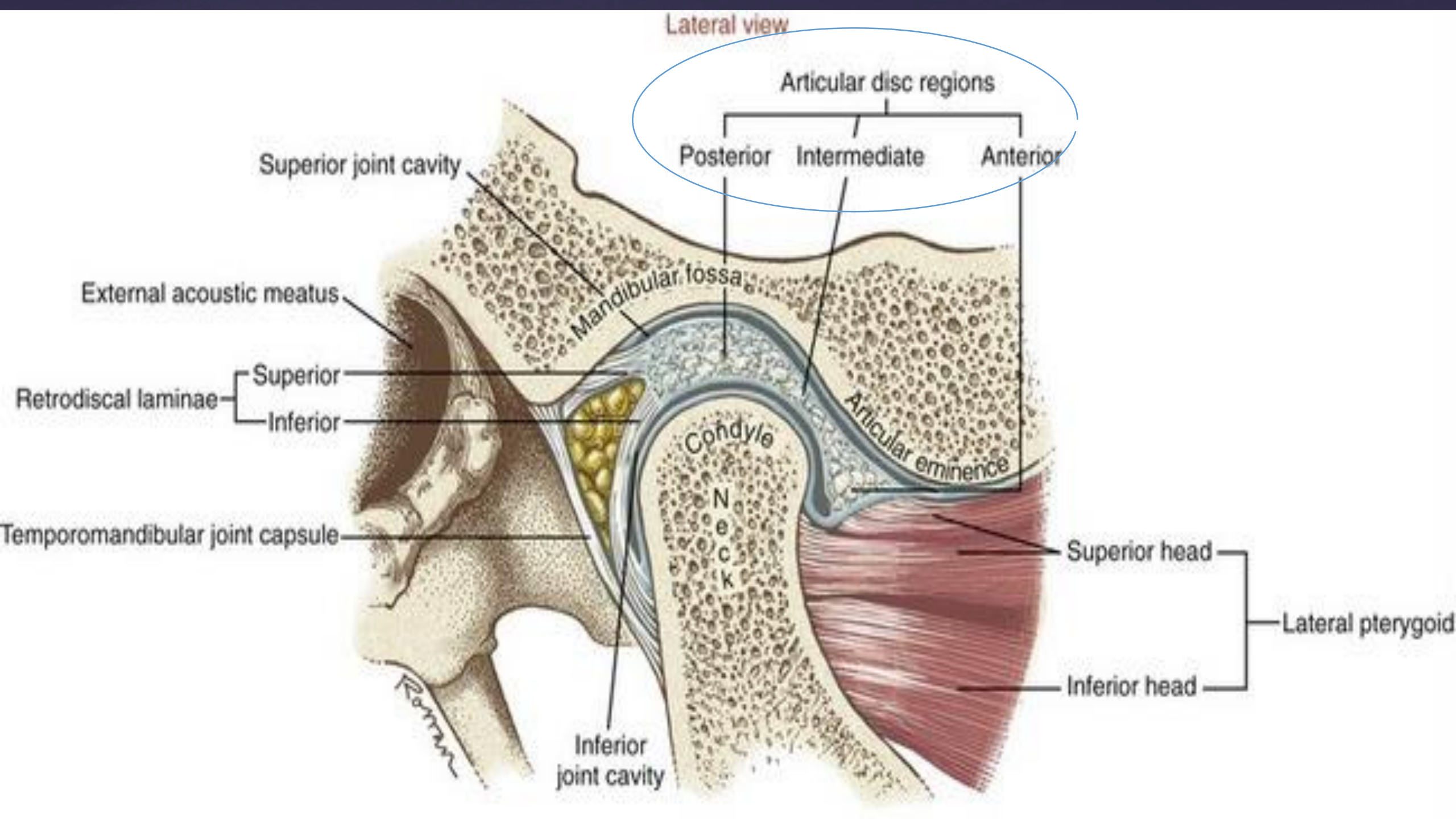


The disc is thinnest in its center and thickens to form anterior and posterior bands.

This arrangement is considered to help stabilize the condyle in the glenoid fossa.

The disc is primarily avascular and has little sensory nerve penetration.

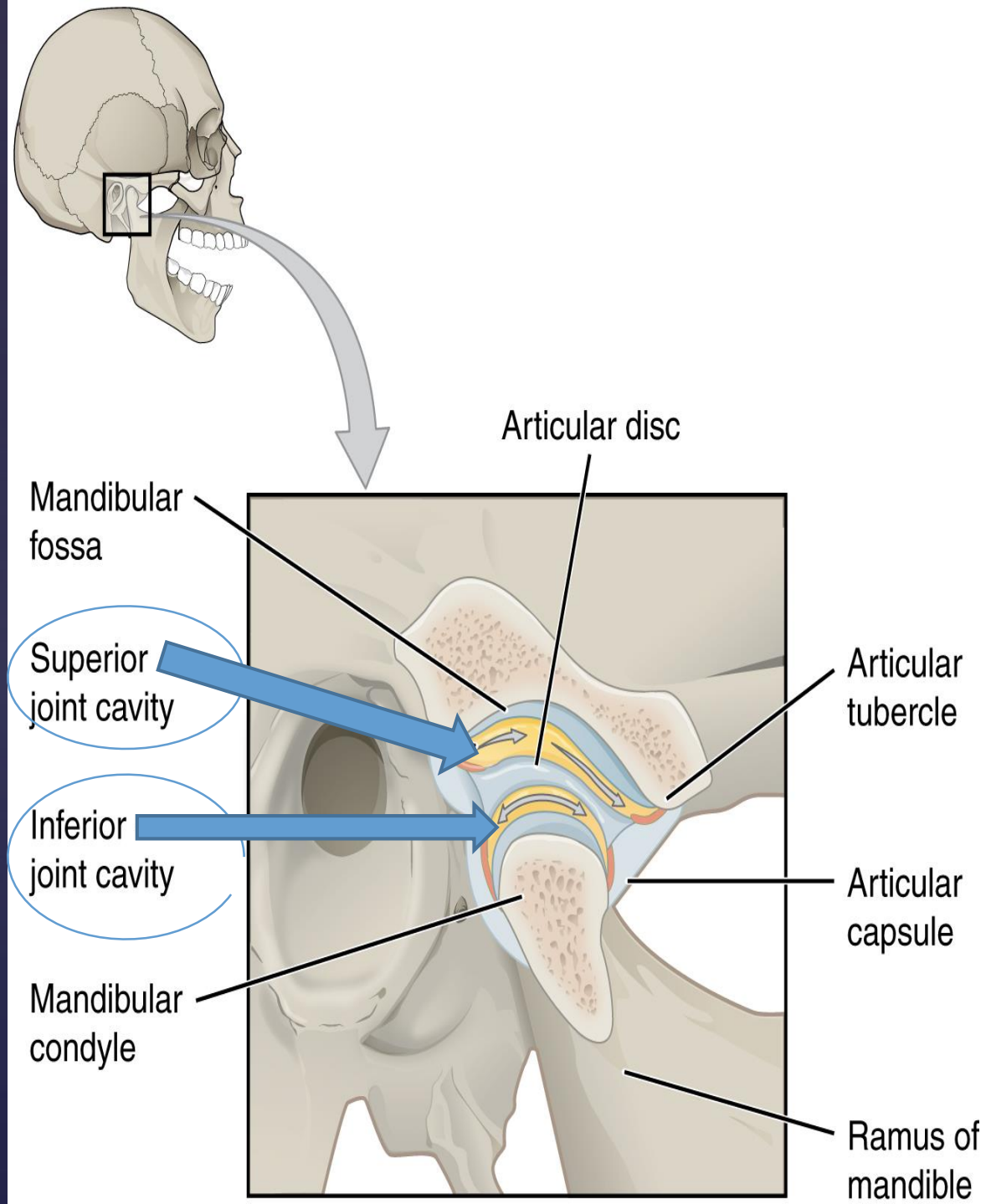
The disc provides an interface for the condyle as it glides across the temporal bone.


Lateral view
Articular disc regions
Posterior
Intermediate
Anterior
Superior joint cavity
External acoustic meatus
Mandibular fossa
Retrodiscal laminae
Superior
Inferior
Articular eminence
Condyle
Neck
Temporomandibular joint capsule
Superior head
Lateral pterygoid
Inferior head
Inferior
joint cavity

The disc and its attachments divide the joint into upper and lower compartments that normally do not communicate.

The roof of the superior compartment is the mandibular fossa, whereas the floor is the superior surface of the disc.

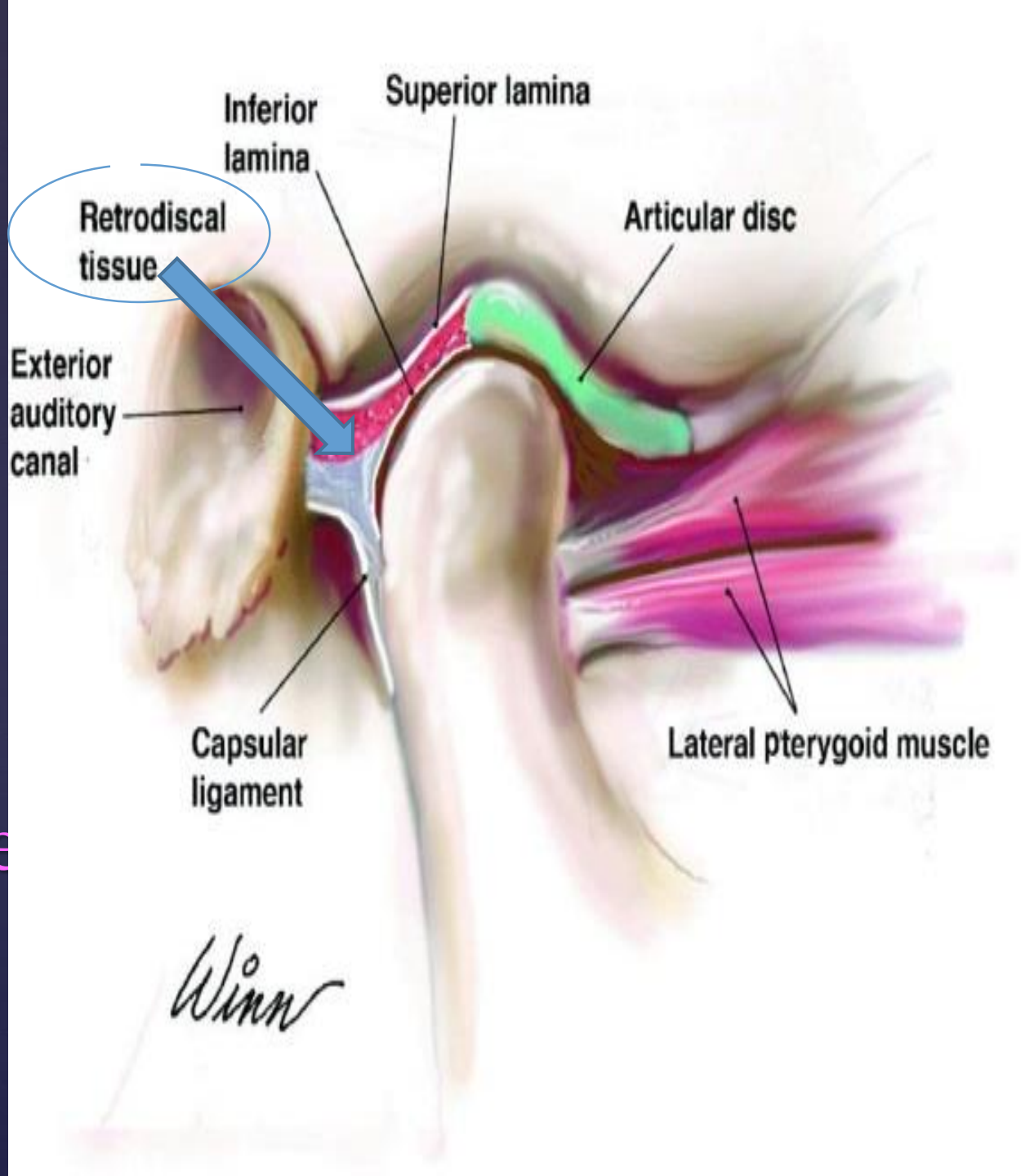
The roof of the inferior compartment is the inferior surface of the disc and the floor is the articulating surface of the mandibular condyle.

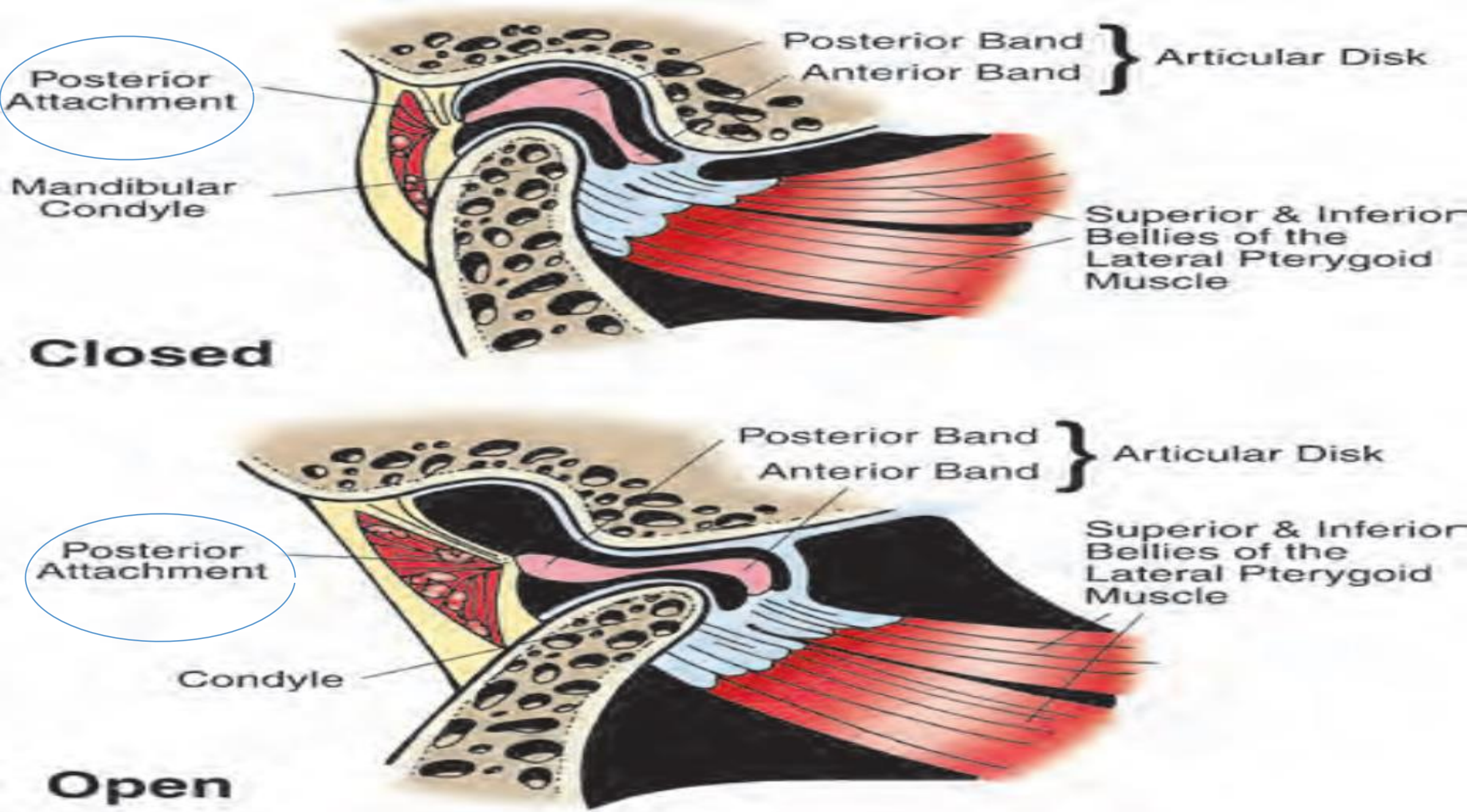


Retrodiscal Tissue

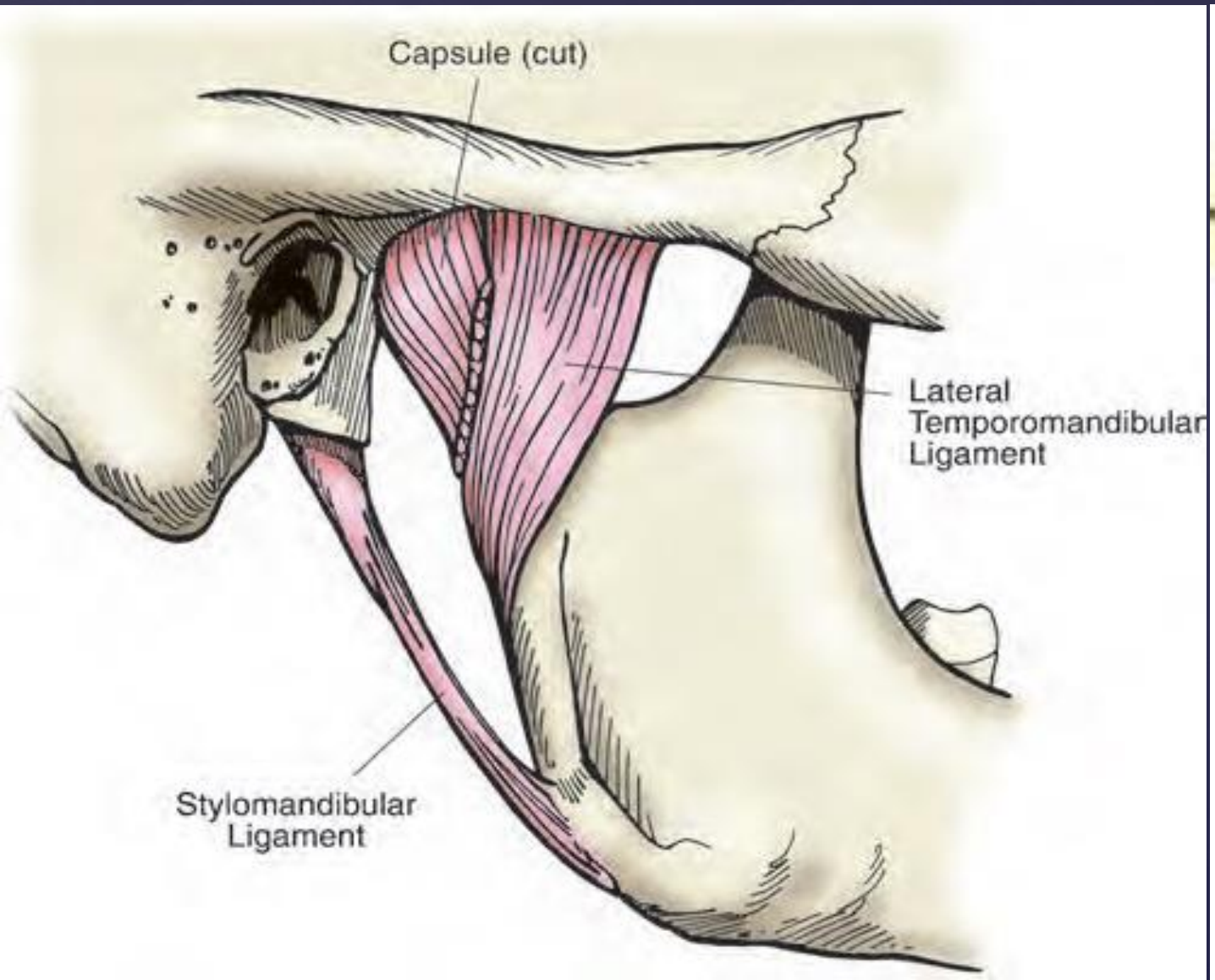
A mass of soft tissue occupies the space behind the disc and condyle. It is often referred to as the posterior attachment.

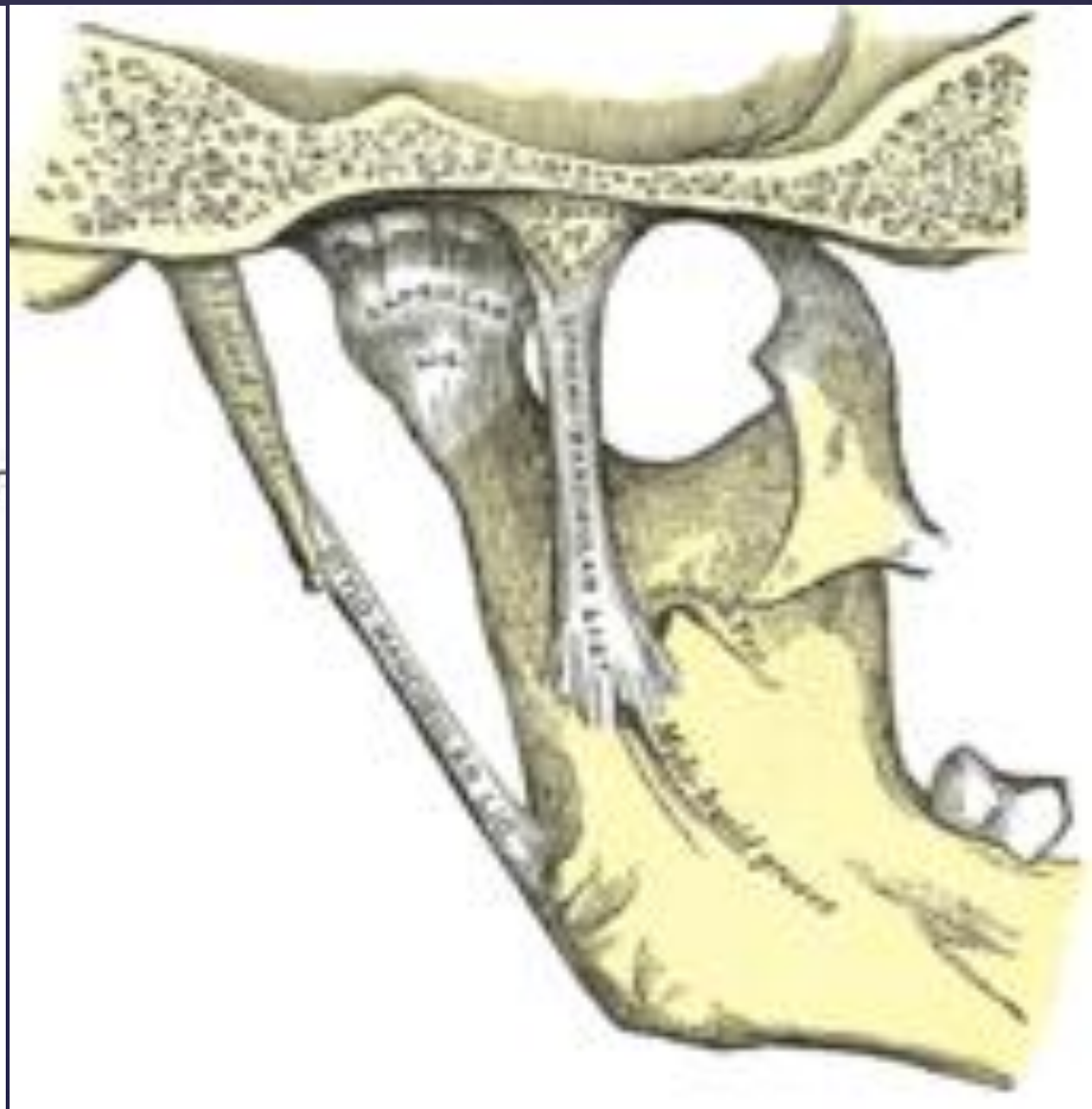
The attachment has been described as being arranged in two lamina of dense connective tissue (superior and inferior lamina).




Posterior Band
Anterior Band
Articular Disk
Posterior Attachment
Mandibular Condyle
Superior & Inferior Bellies of the Lateral Pterygoid Muscle
Closed
Posterior Band
Anterior Band
Articular Disk
Posterior Attachment
Condyle
Superior & Inferior Bellies of the Lateral Pterygoid Muscle
Open

Temporomandibular Ligaments





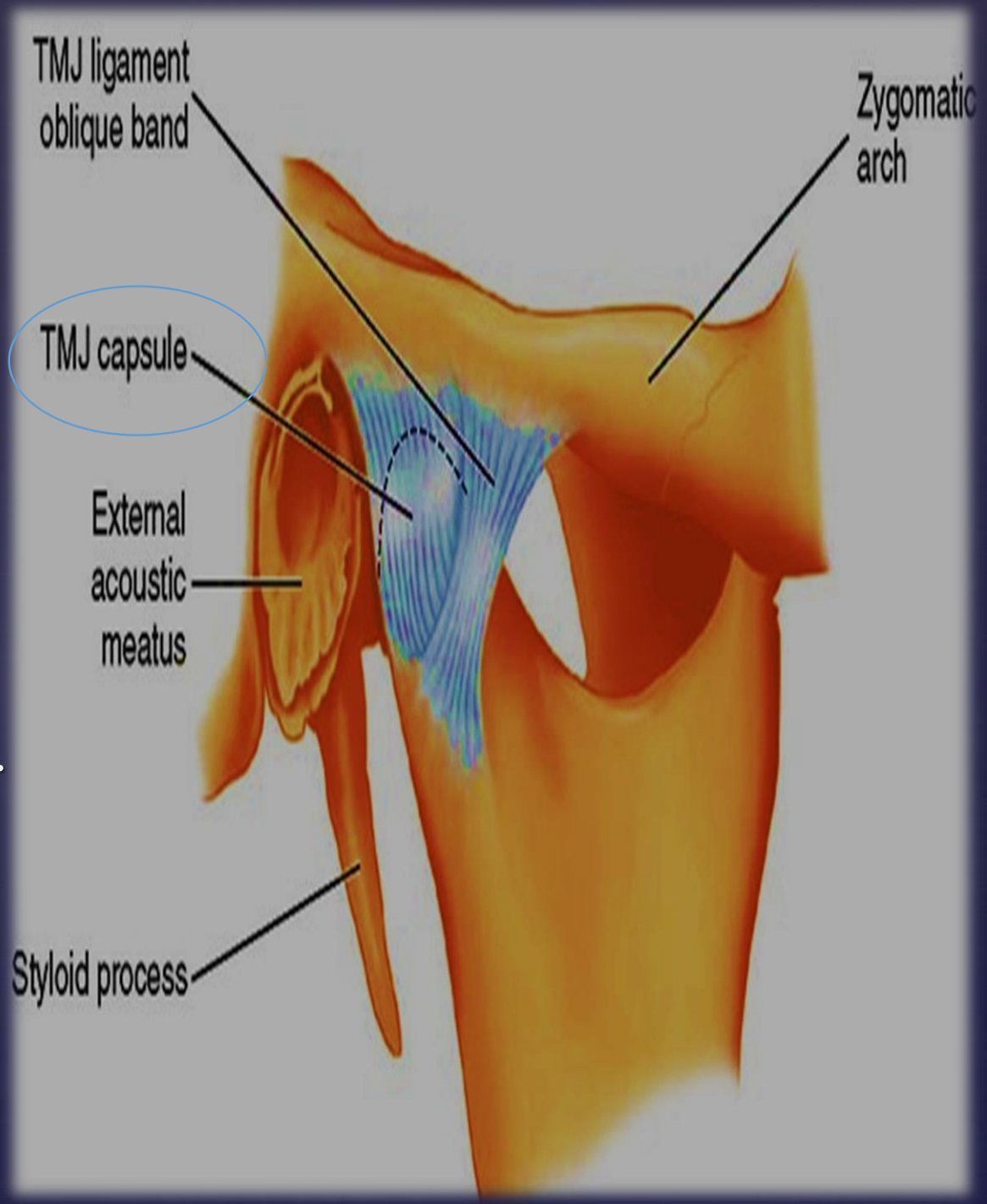
Capsular Ligament

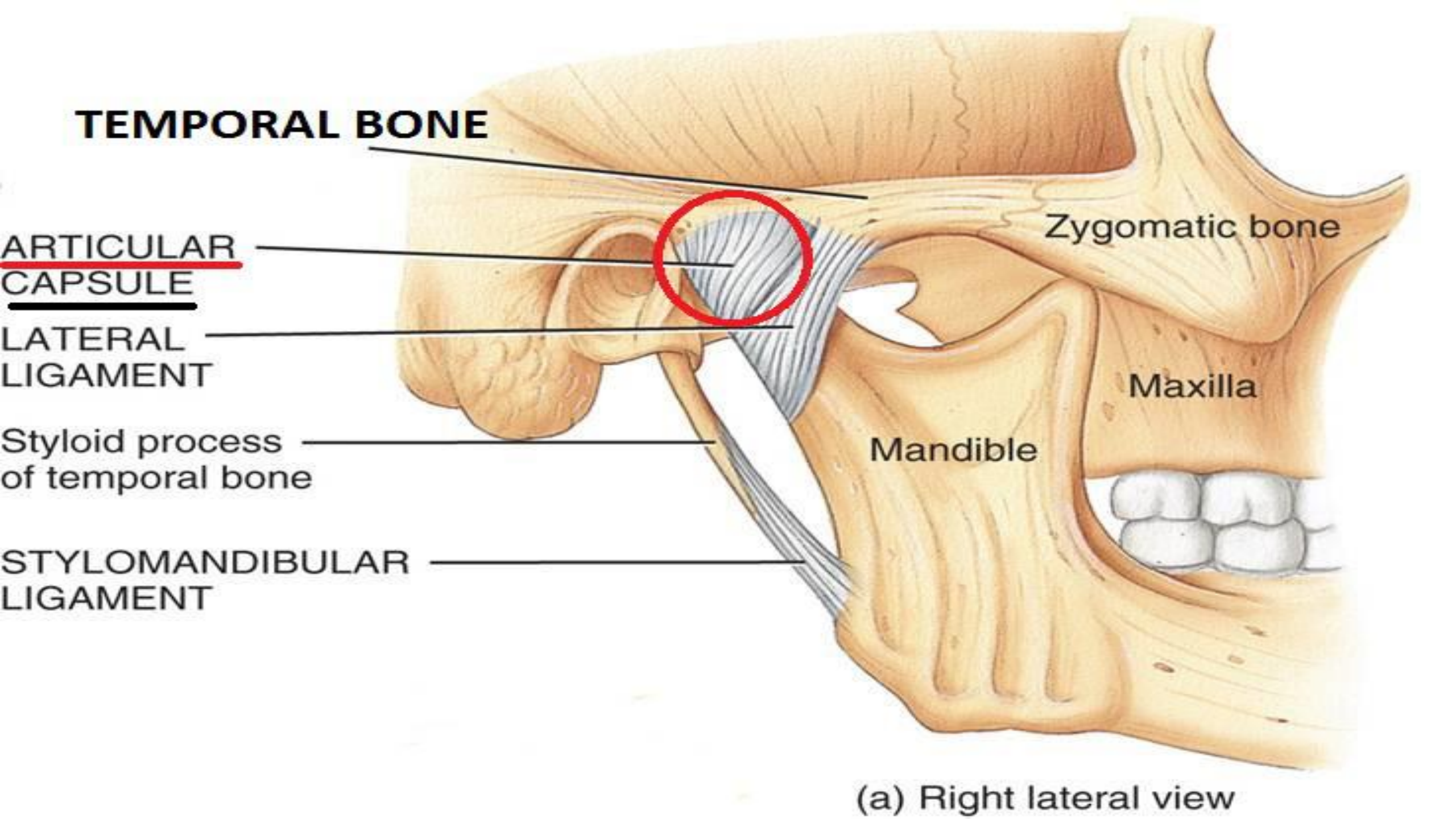
the entire TMJ is surrounded and encompassed by the capsular ligament.

The fibers of the capsular ligament are attached superiorly to the temporal bone and inferiorly, the fibers are attached to the neck of the condyle.

It acts to resist any medial, lateral or inferior forces that tend to separate or dislocate the articular surface.

Another function is to encompass the joint, thus retaining the synovial fluid.





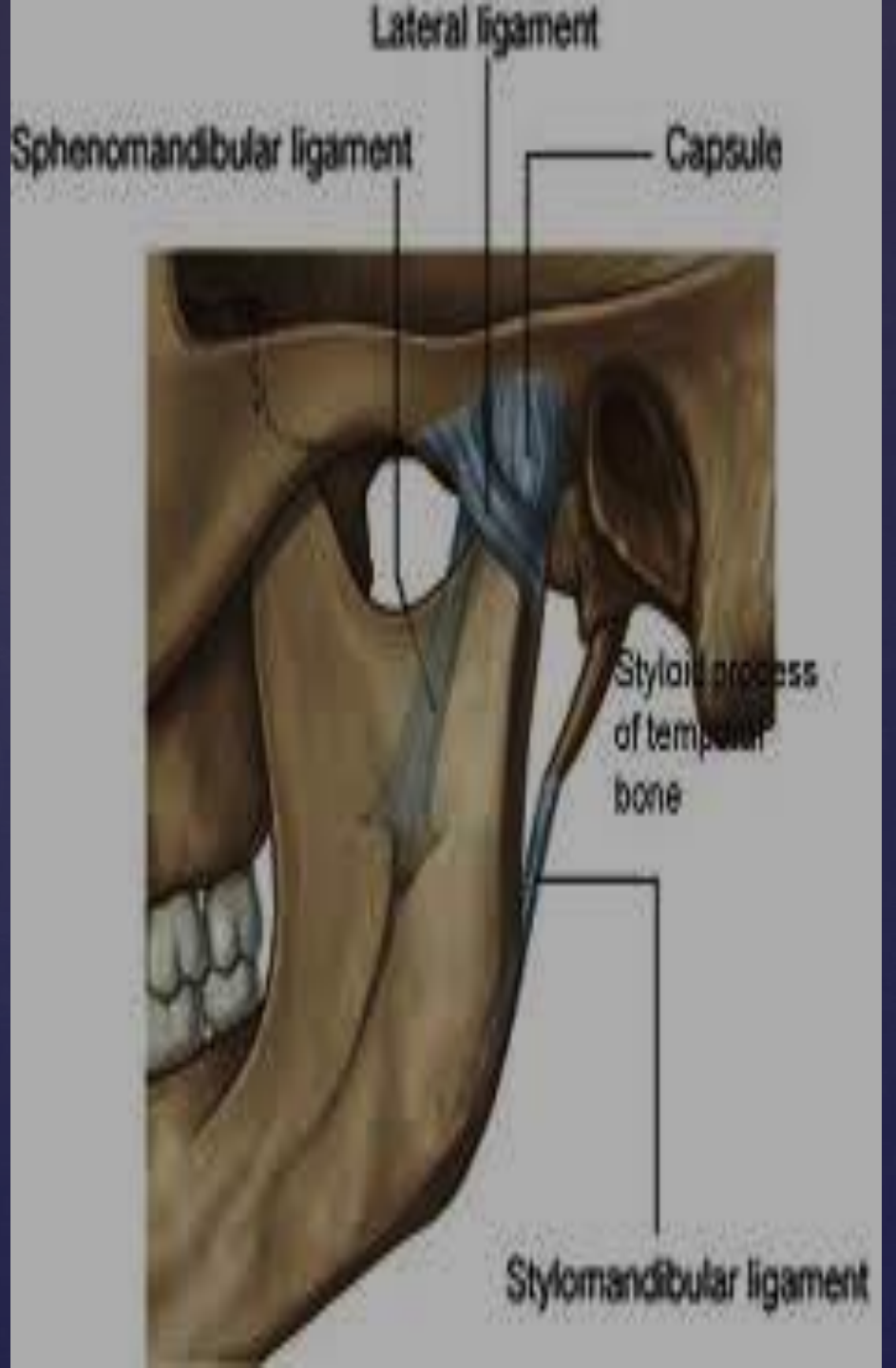
(a) Right lateral view

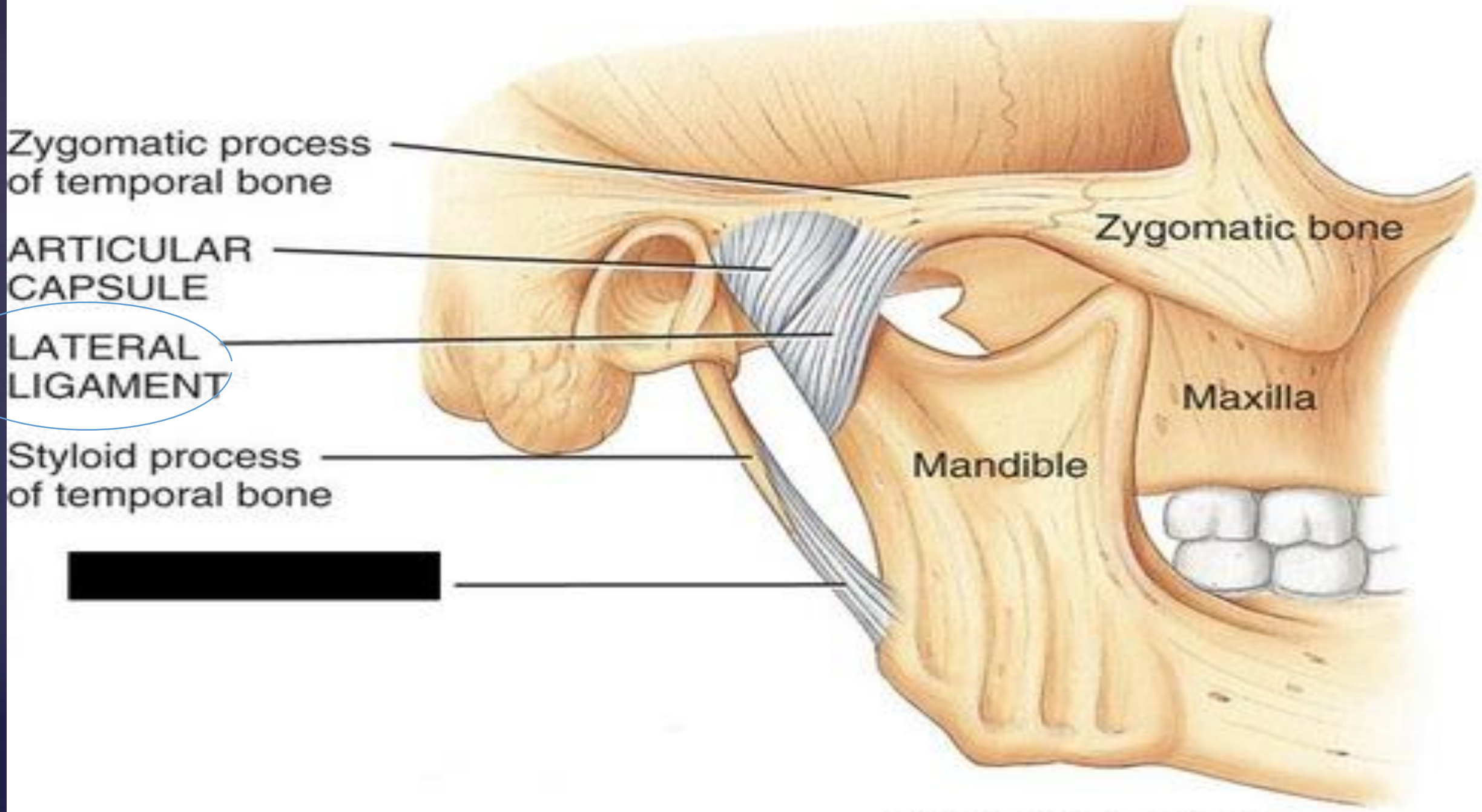
Lateral Temporomandibular Ligament

Is the main ligament of the joint, lateral to the capsule but not easily separated from it by dissection.

It is composed of two parts,
an outer oblique portion and
an inner horizontal portion.

The oblique portion of the ligament resists excessive dropping of the condyle and therefore acts to limit the extent of mouth opening.

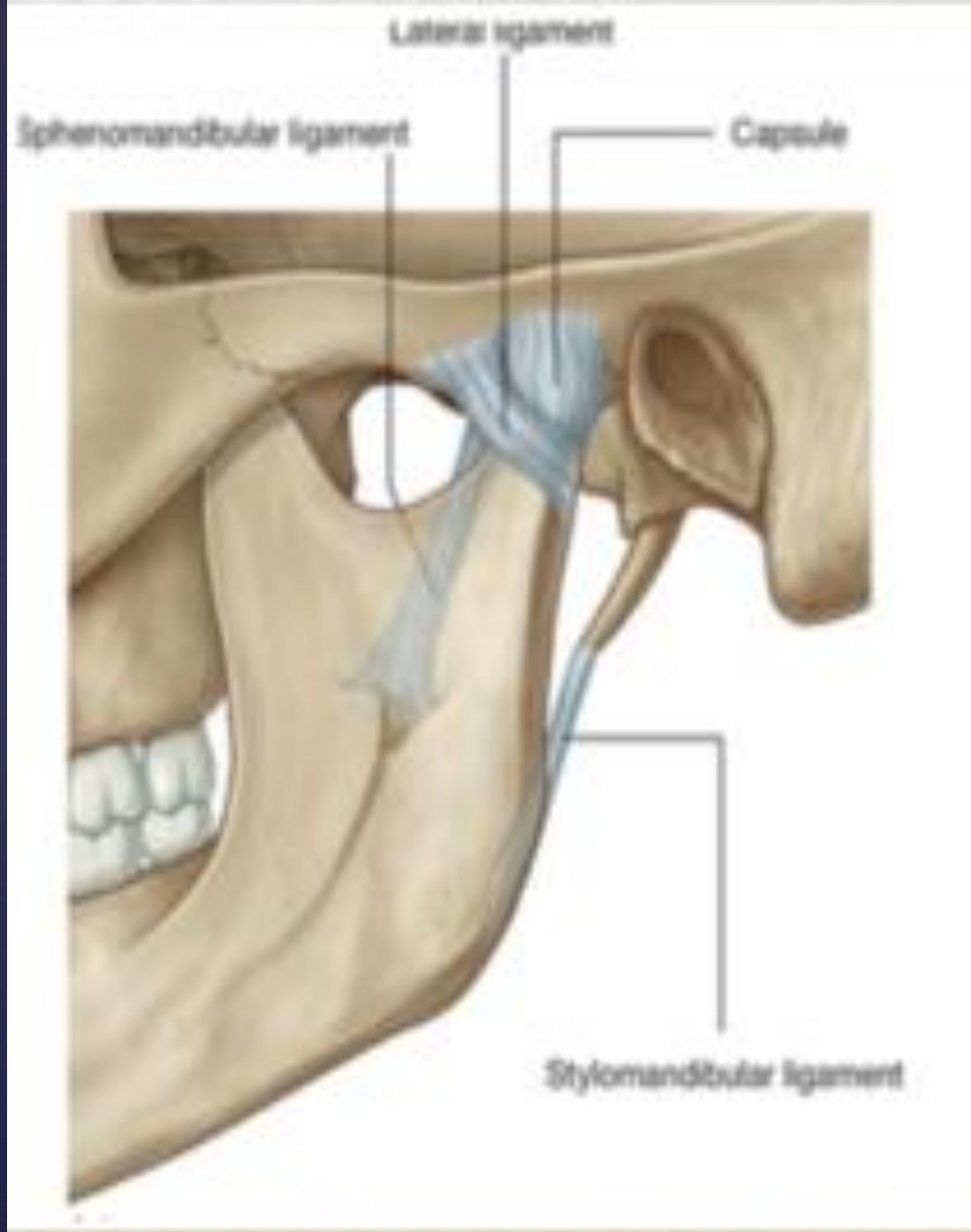


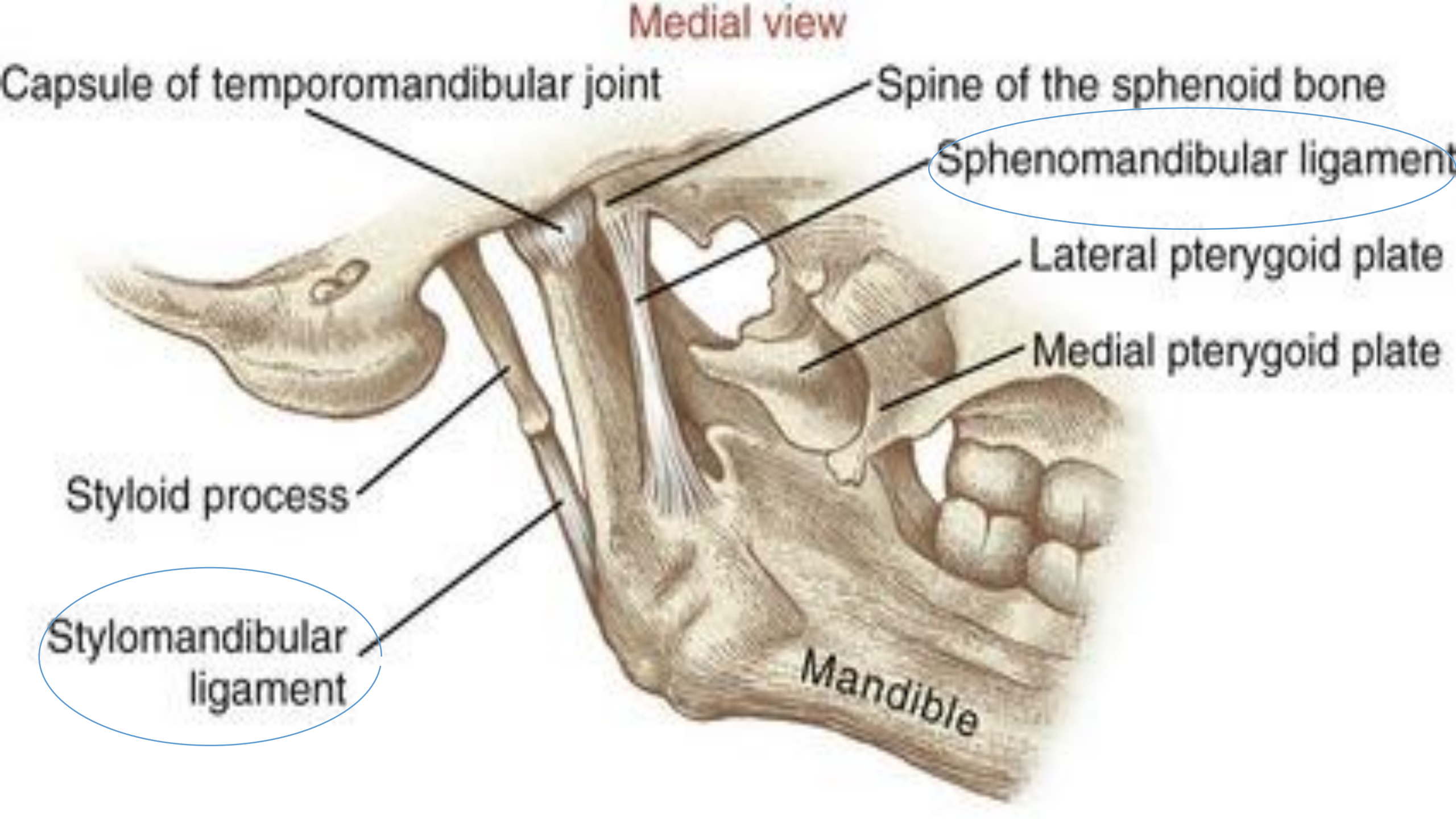

Zygomatic process of temporal bone
ARTICULAR CAPSULE
LATERAL LIGAMENT
Styloid process of temporal bone
[redacted]
Zygomatic bone
Maxilla
Mandible
(a) Right lateral view

Accessory Ligaments

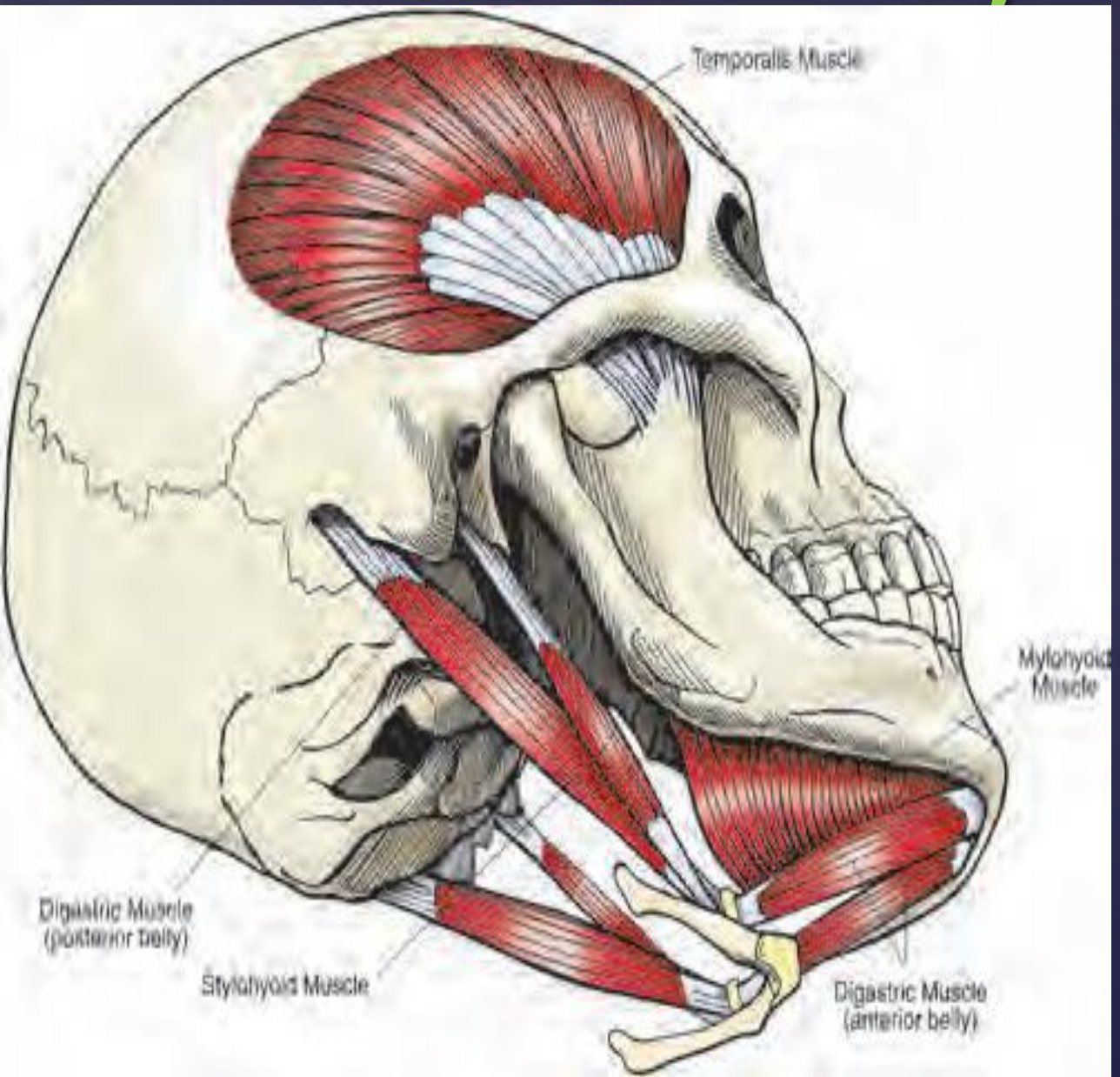
- The sphenomandibular ligament arises from the sphenoid bone and inserts on the medial aspect of the mandible at the lingula. It is not considered to limit or affect mandibular movement.

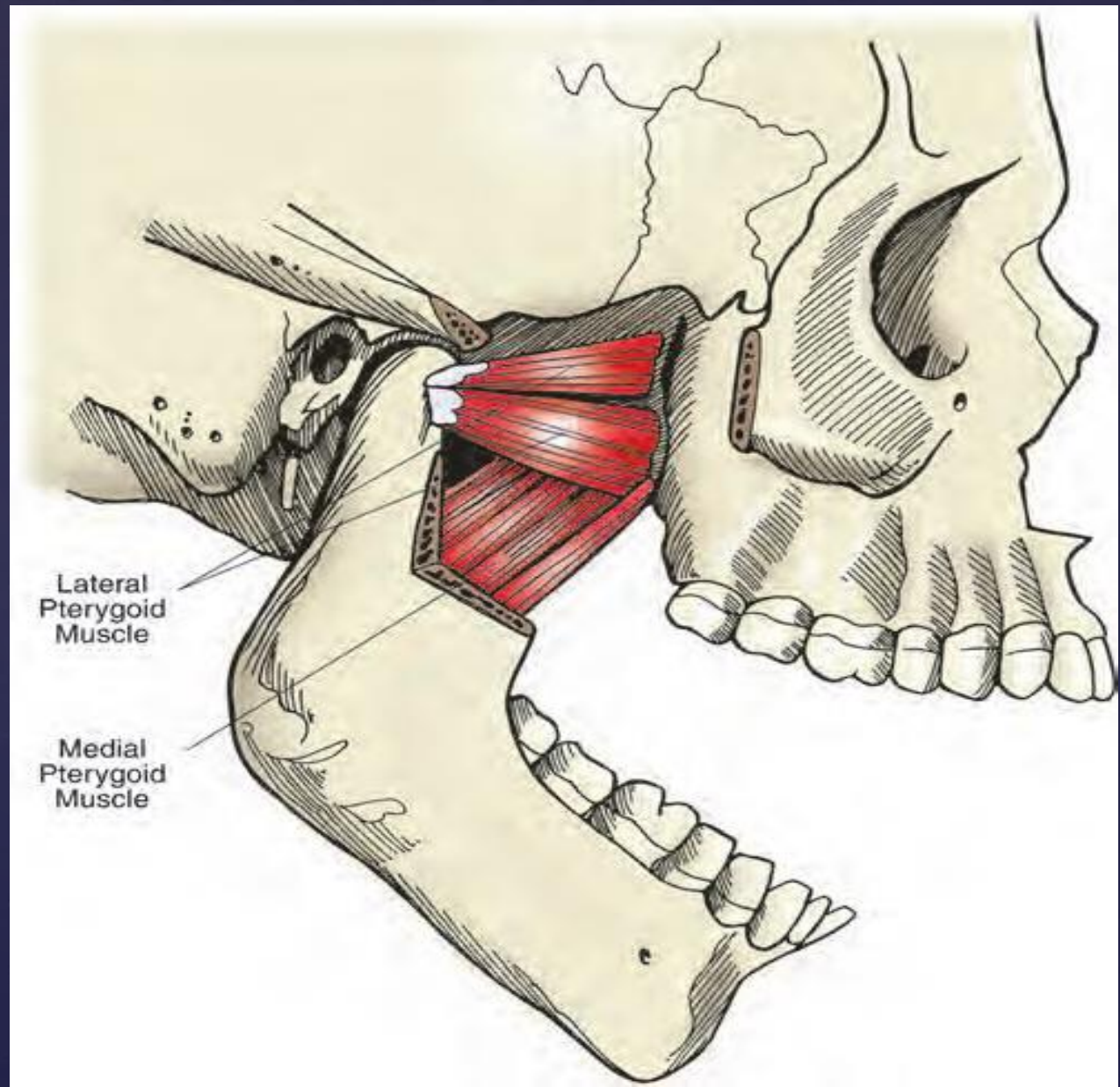
- The stylomandibular ligament extends from the styloid process to the deep fascia of the medial pterygoid muscle. It is thought to become tense during protrusive movement of the mandible and may contribute to limiting protrusive movement.




Medial view
Capsule of temporomandibular joint
Spine of the sphenoid bone
Sphenomandibular ligament
Lateral pterygoid plate
Medial pterygoid plate
Styloid process
Stylomandibular ligament
Mandible

Muscles of mastication



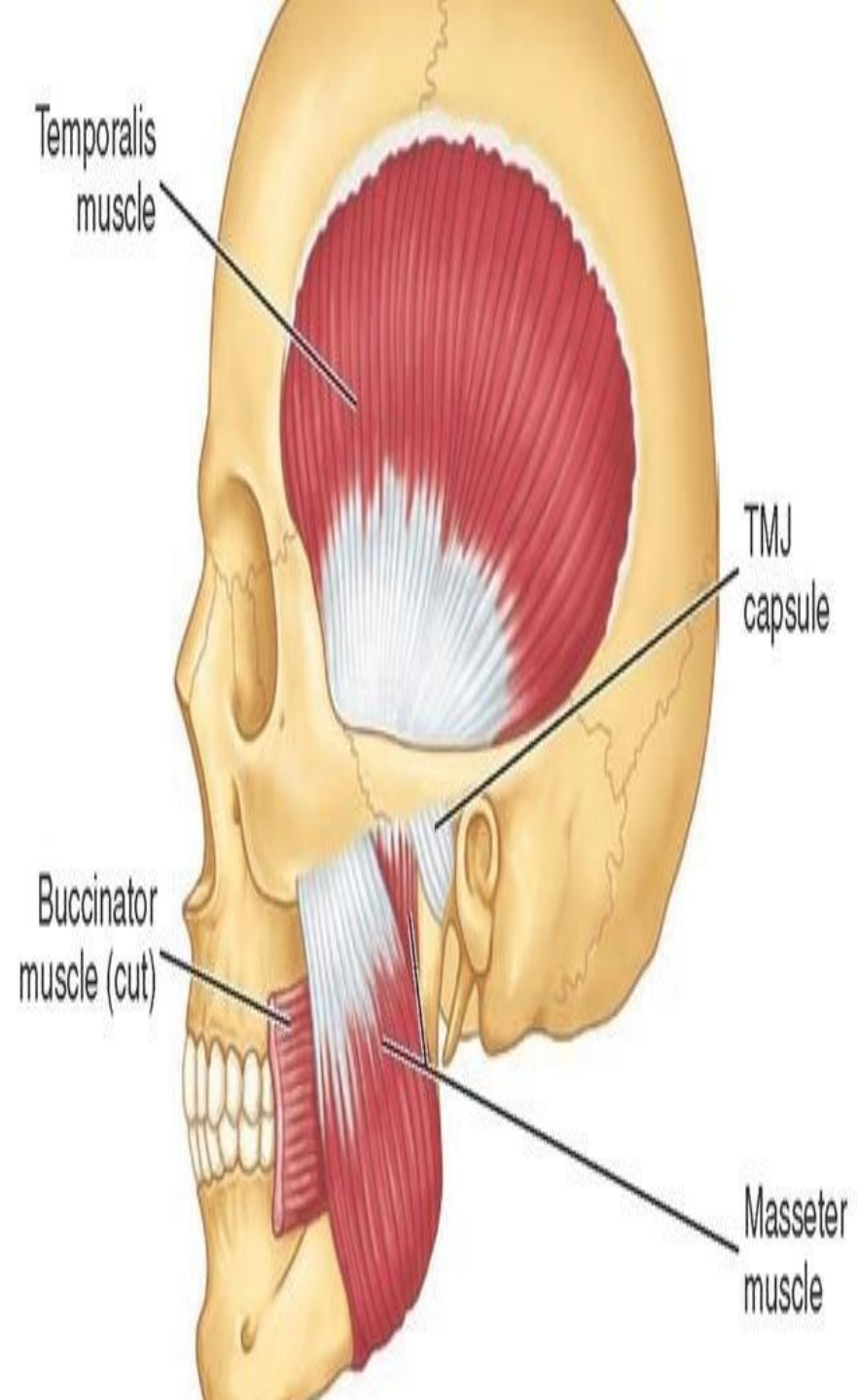


Masseter

It is the most powerful muscle of mastication. It is quadrangular in shape, and can be split into two parts; deep and superficial.

Attachments: The superficial part originates from maxillary process of the zygomatic bone. The deep part originates from the zygomatic arch of the temporal bone. Both parts attach to the ramus of the mandible.

Actions: Elevates the mandible, closing the mouth and retraction of the mandible.
Innervation: Mandibular nerve (V3).



Primary Muscles

- Masseter Muscle
- Temporalis Muscle
- Lateral Pterygoid Muscle
- Medial Pterygoid Muscle

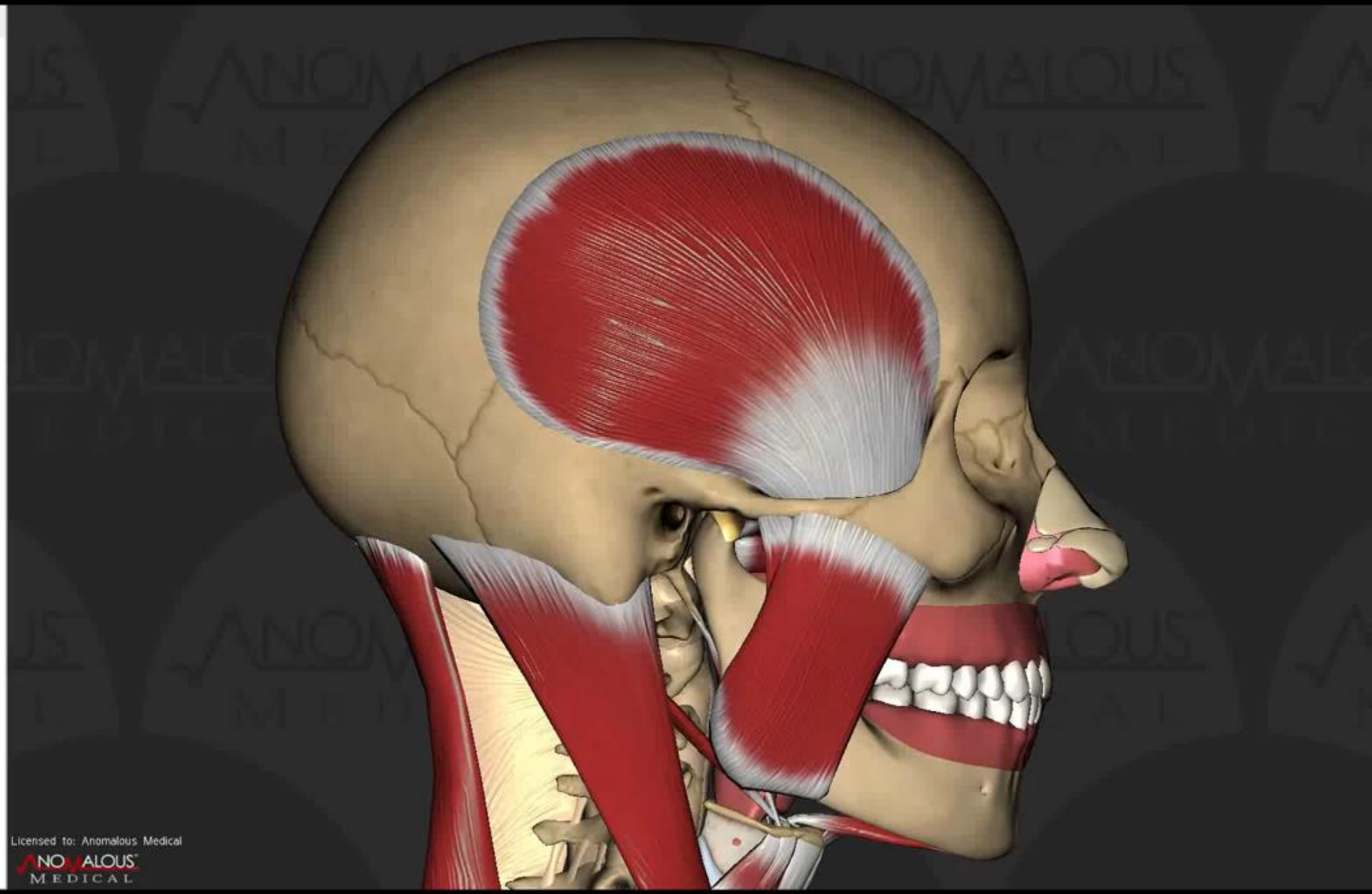
Accessory Muscles

Suprahyoid Muscles

- Digastric Muscle
- Stylohyoid Muscle
- Mylohyoid Muscle
- Geniohyoid Muscle

Infrahyoid Muscles

- Sternohyoid Muscle
- Thyrohyoid Muscle
- Omohyoid Muscle



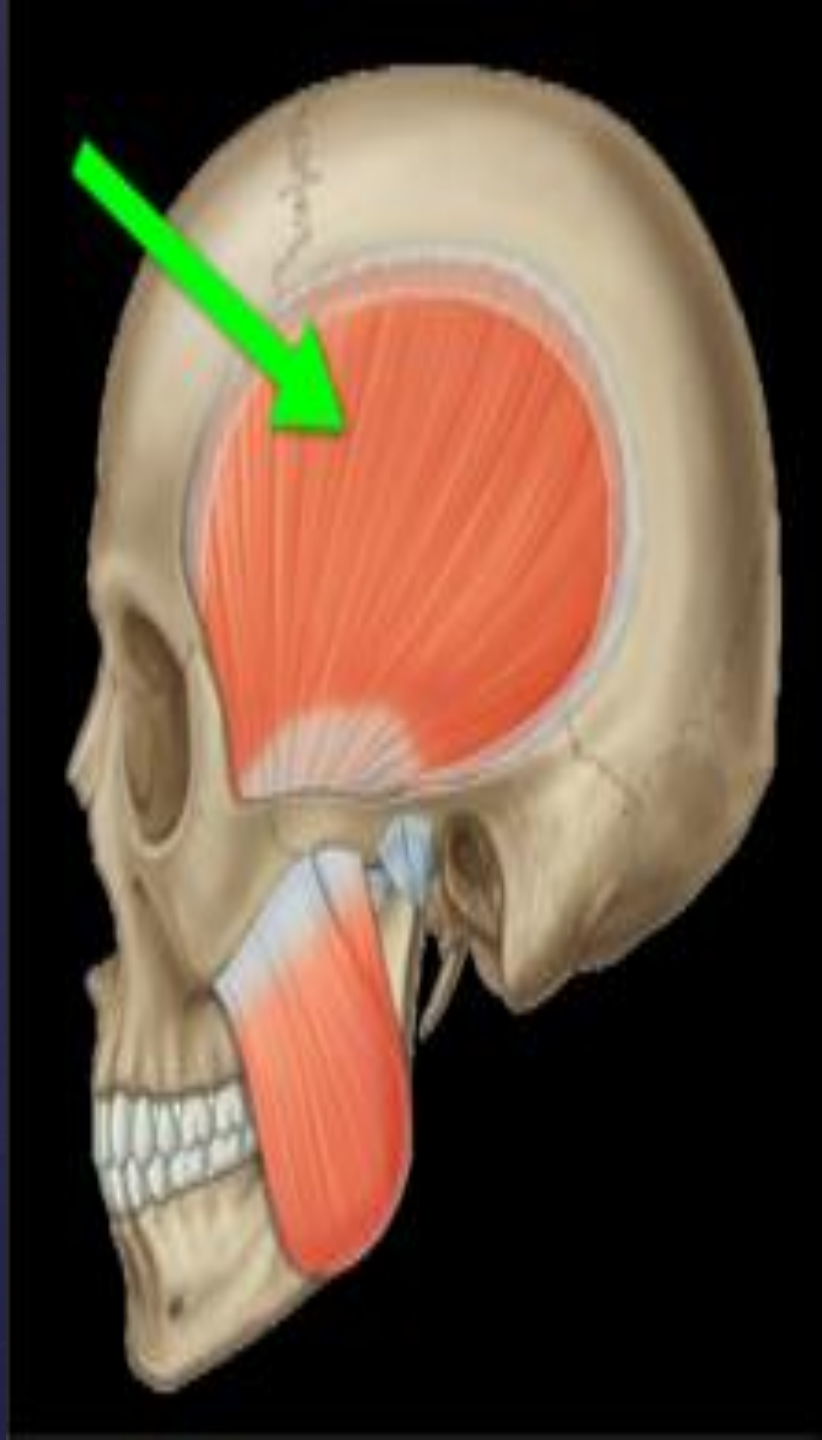
Temporalis

It is broadly attached to the lateral skull and has been divided into anterior, middle, and posterior parts.

Attachments: Originates from the temporal fossa. It condenses into a tendon, which inserts onto the coronoid process of the mandible.

Actions: Elevates the mandible, closing the mouth. Also retracts the mandible, pulling the jaw posteriorly.

Innervation: Mandibular nerve (V3).



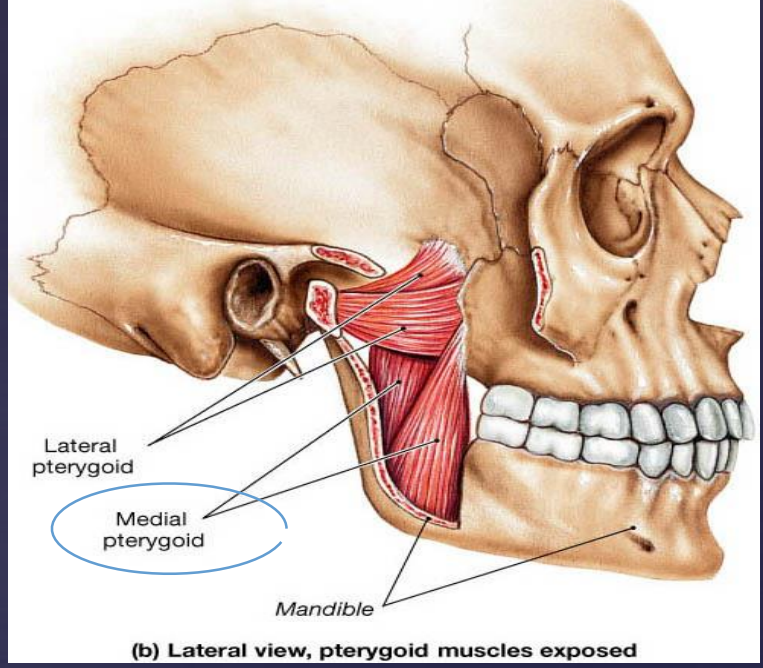
Medial Pterygoid

It has a quadrangular shape, with two heads; deep and superficial. It is located inferiorly to the lateral pterygoid.

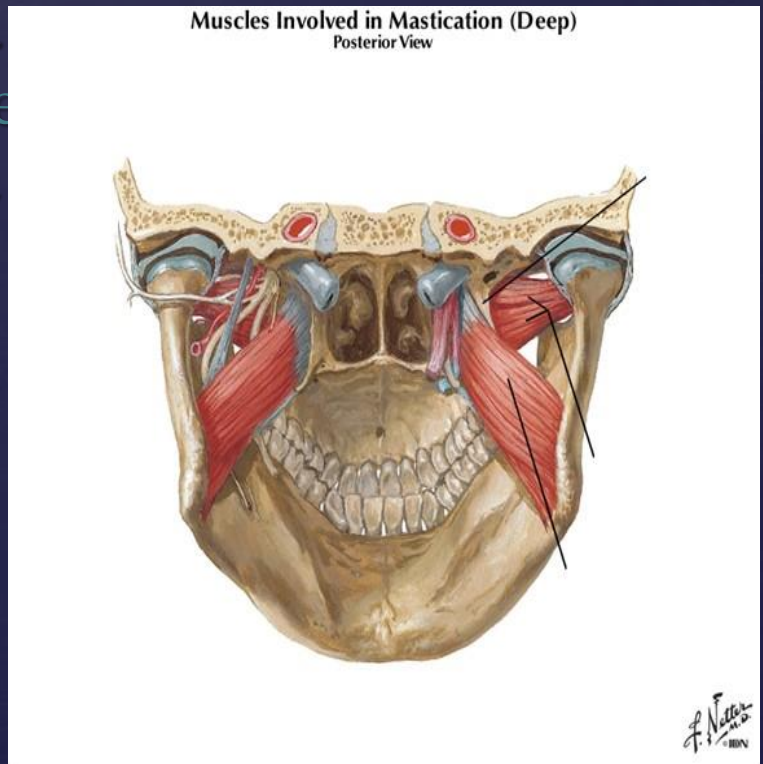
Attachments: The superficial head originates from the maxilla. The deep head originates from the lateral pterygoid plate of the sphenoid bone. Both parts attach to the ramus of the mandible, near the angle of mandible.

Actions: Elevates the mandible, closing the mouth, protrusion of the mandible and lateral deviation of the mandible.

Innervation: Mandibular nerve (V3).



(b) Lateral view, pterygoid muscles exposed



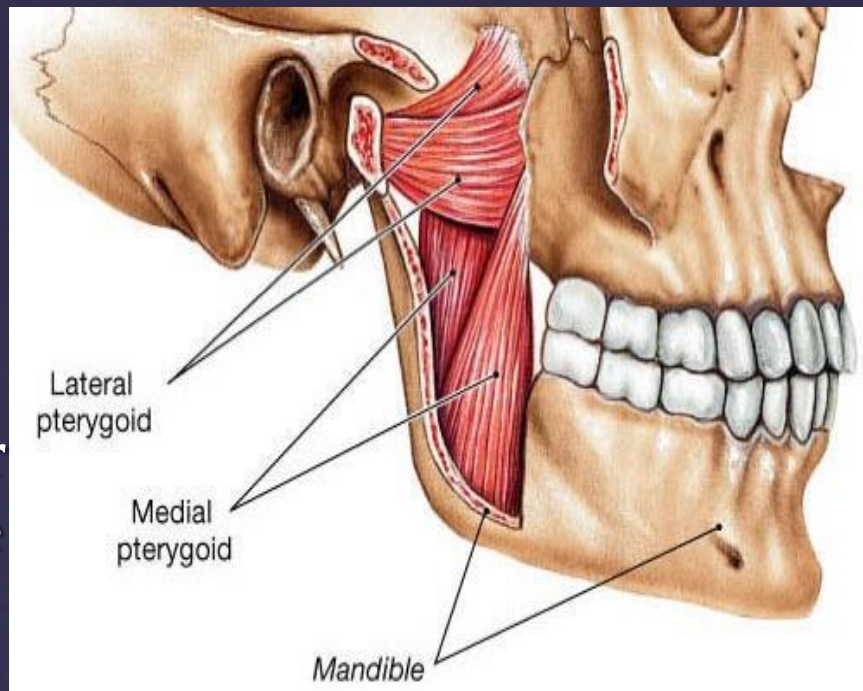
Lateral Pterygoid

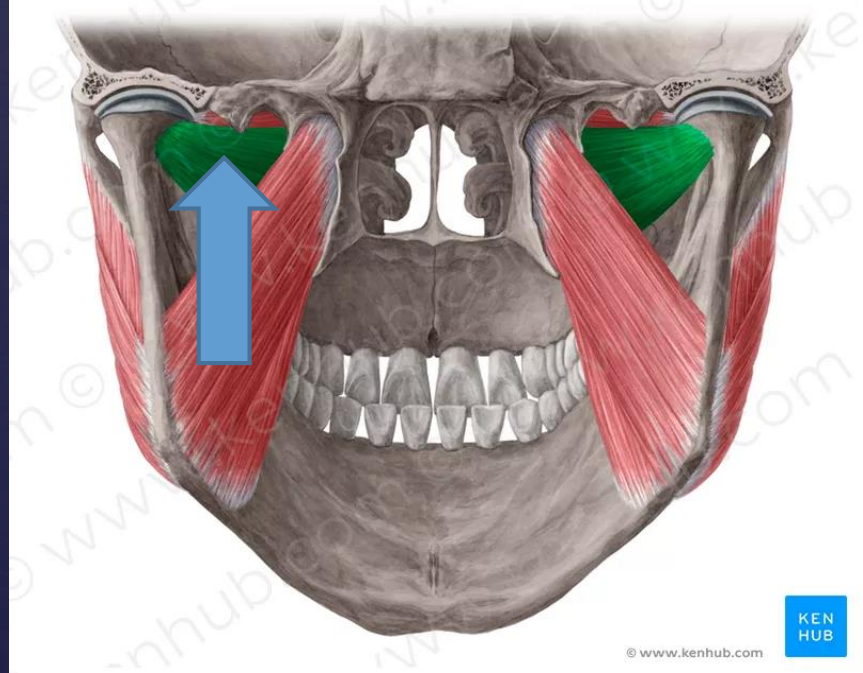
It has a triangular shape, with two heads; superior and inferior. It has horizontally orientated muscle fibres, and thus is the major protractor of the mandible.

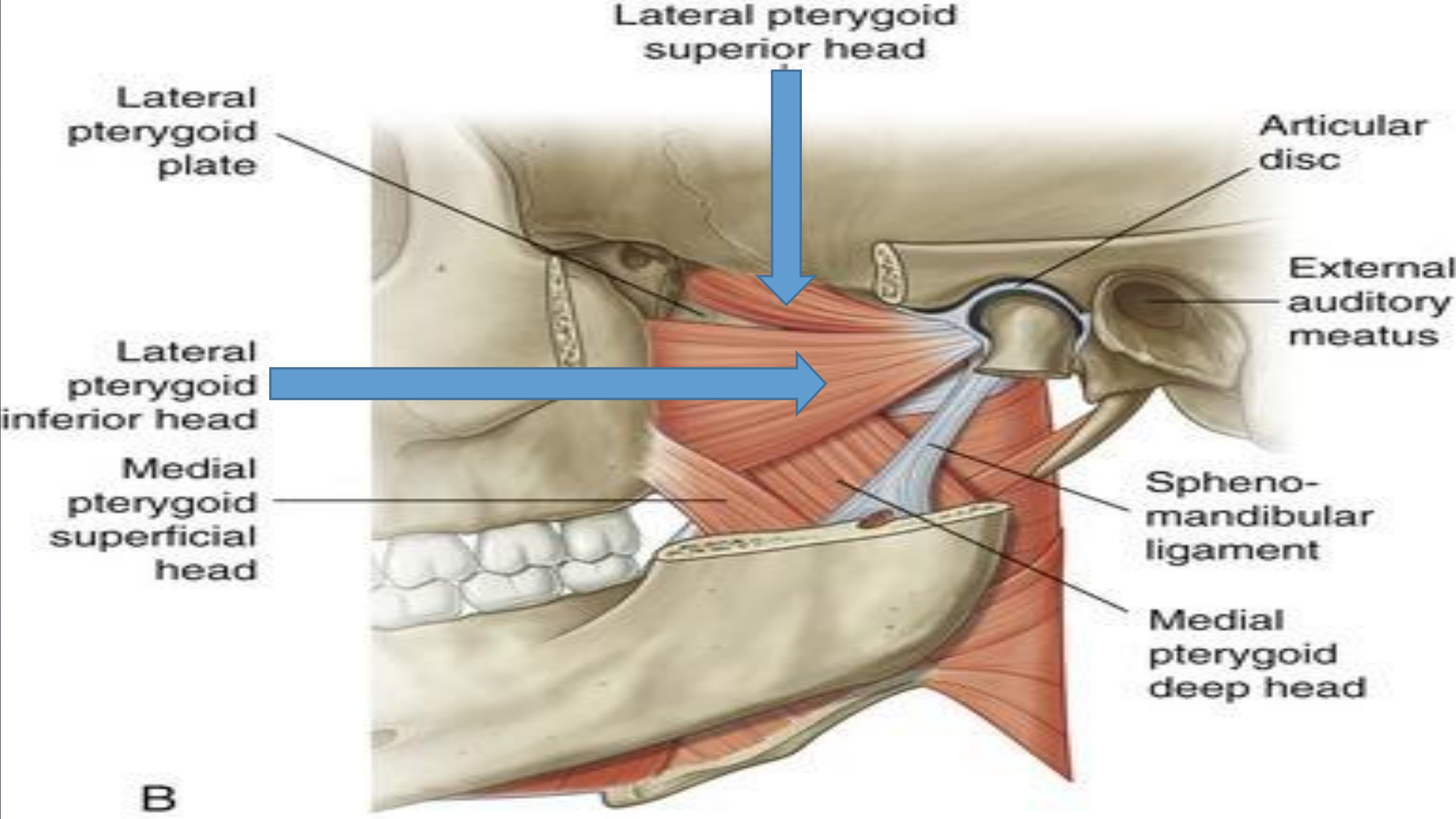
Attachments: The superior head originates from the greater wing of the sphenoid. The inferior head originates from the lateral pterygoid plate of the sphenoid. The two heads converge into a tendon, which attaches to the neck of the mandible.

Actions: Acting bilaterally, the lateral pterygoids protract the mandible, pushing the jaw forwards. Unilateral action produces the 'side to side' movement of the jaw.

Innervation: Mandibular nerve (V3).





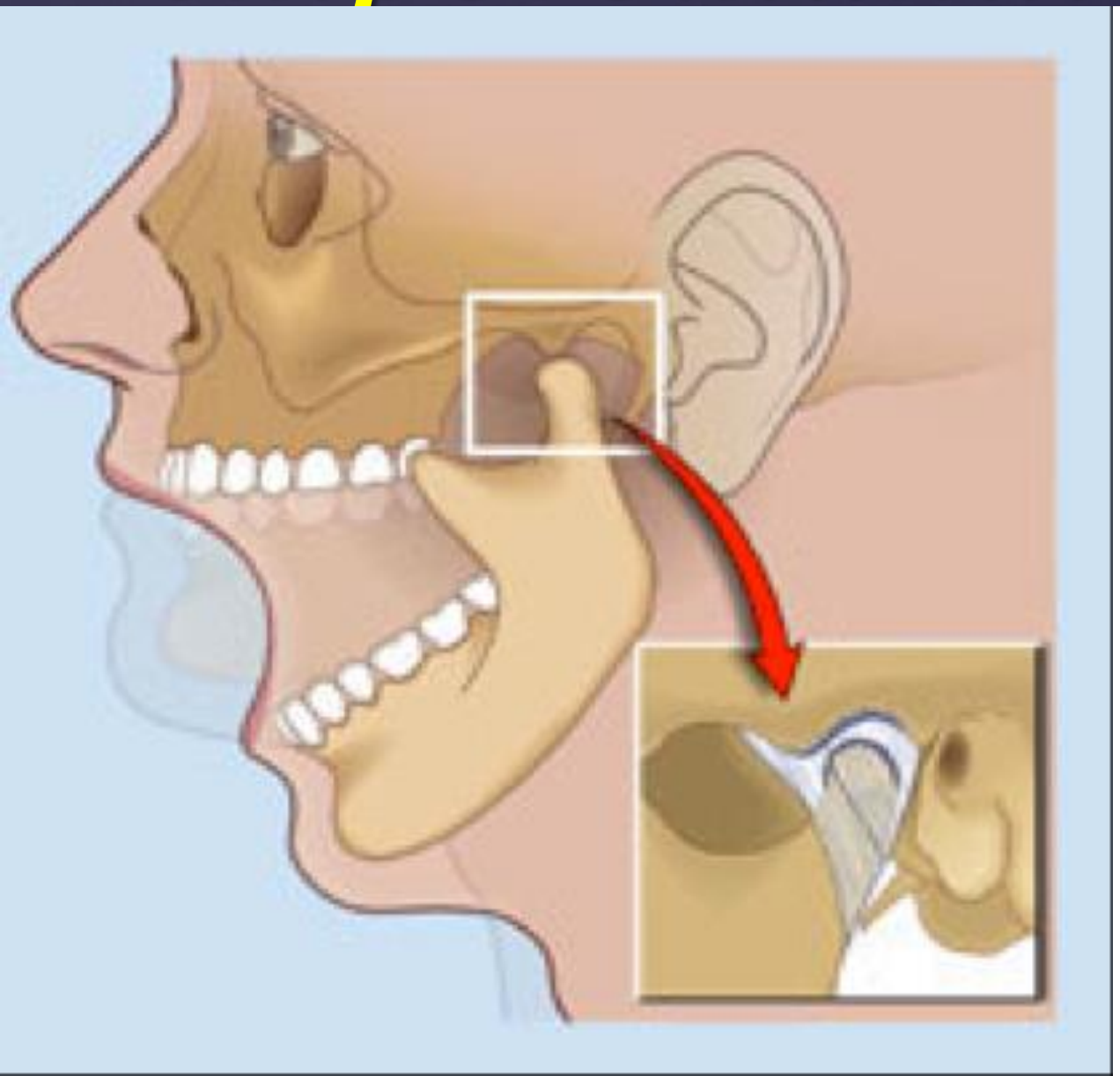

Lateral pterygoid superior head
Lateral pterygoid plate
Articular disc
External auditory meatus
Lateral pterygoid inferior head
Medial pterygoid superficial head
Spheno-mandibular ligament
Medial pterygoid deep head
B

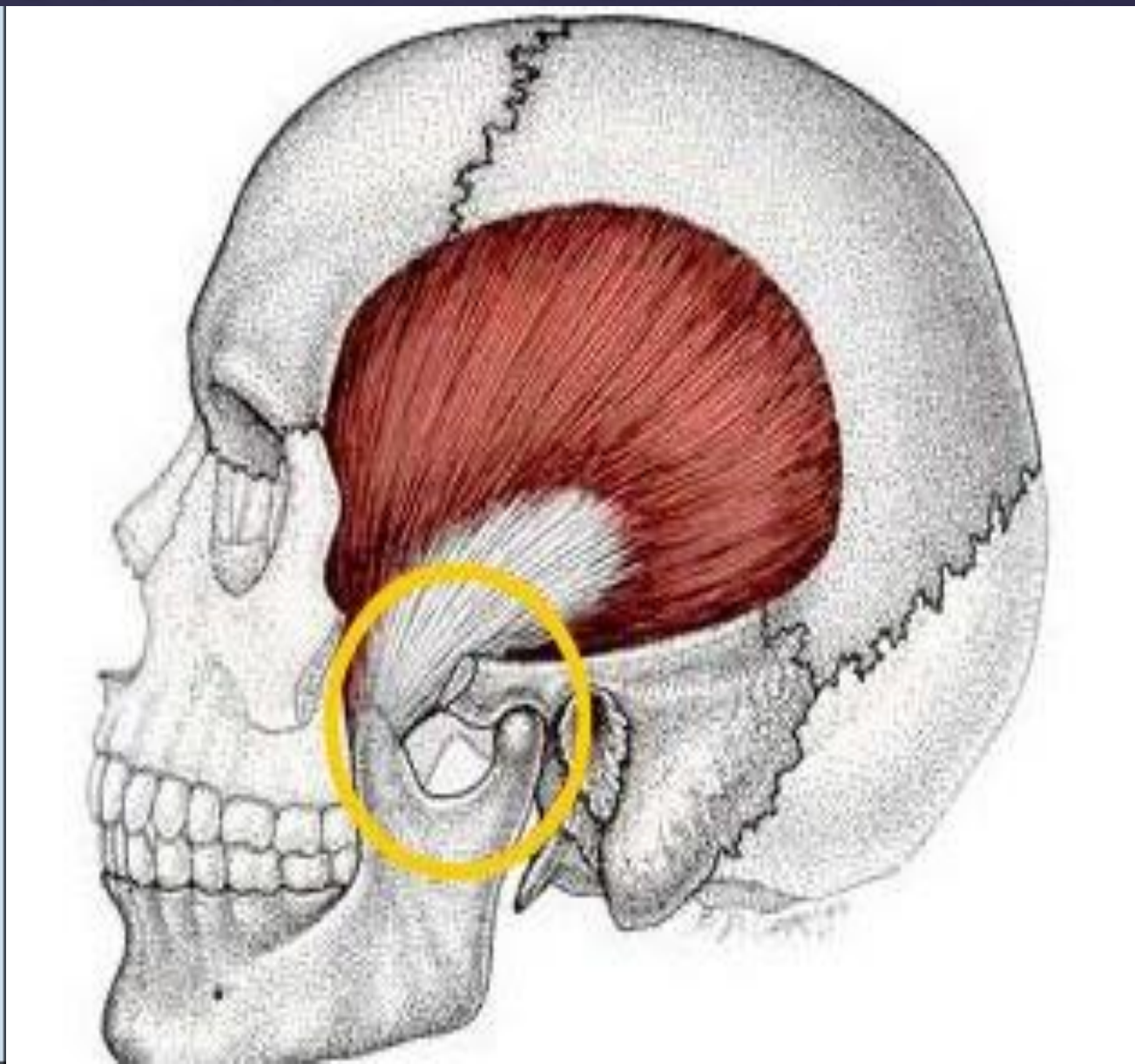
University of Anbar
College of Dentistry

Oral Medicine

Dr. Shaimaa Hamid
PhD of Oral Medicine

Temporomandibular Disorders





Etiological factors in Temporomandibular Joint Disorders (TMDs)

1. Parafunctional habits (eg, nocturnal bruxing, tooth clenching, lip or cheek biting)
2. Emotional distress
3. Acute trauma to the jaw
4. Trauma from hyperextension (eg, dental procedures, oral intubations for general anesthesia, yawning, hyperextension associated with cervical trauma)
5. Instability of maxillomandibular relationships
6. Laxity of the joint
7. Comorbidity of other rheumatic or musculoskeletal disorders
8. Poor general health and an unhealthy lifestyle.

Diagnosis of temporomadibular joint disorders:

1. History taking

*past history of the diseases include; the onset of the illness, duration, frequency, initiating or relieving factors.

*social and family history

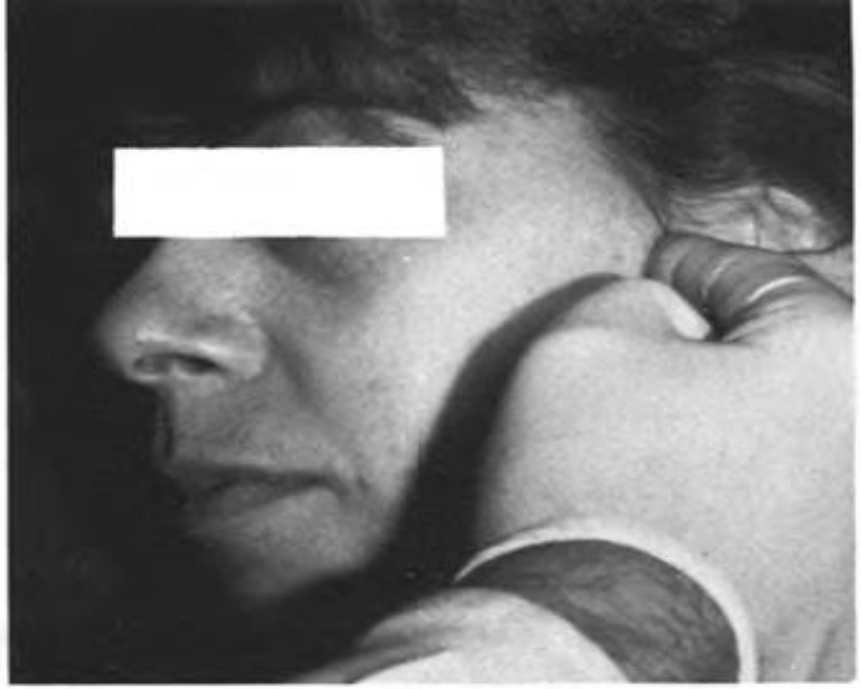
*past dental and medical history and hospitalization.

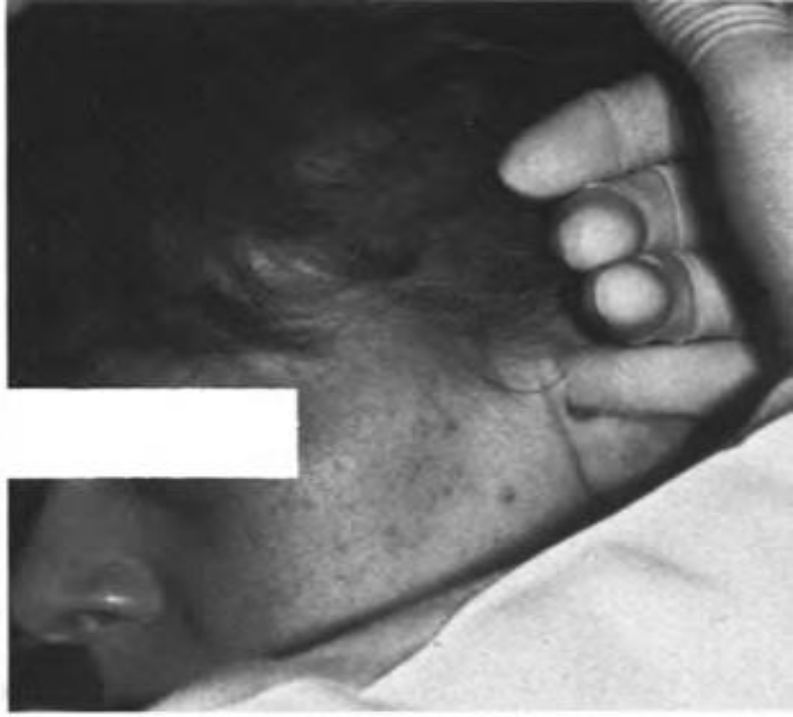
2. Clinical examination

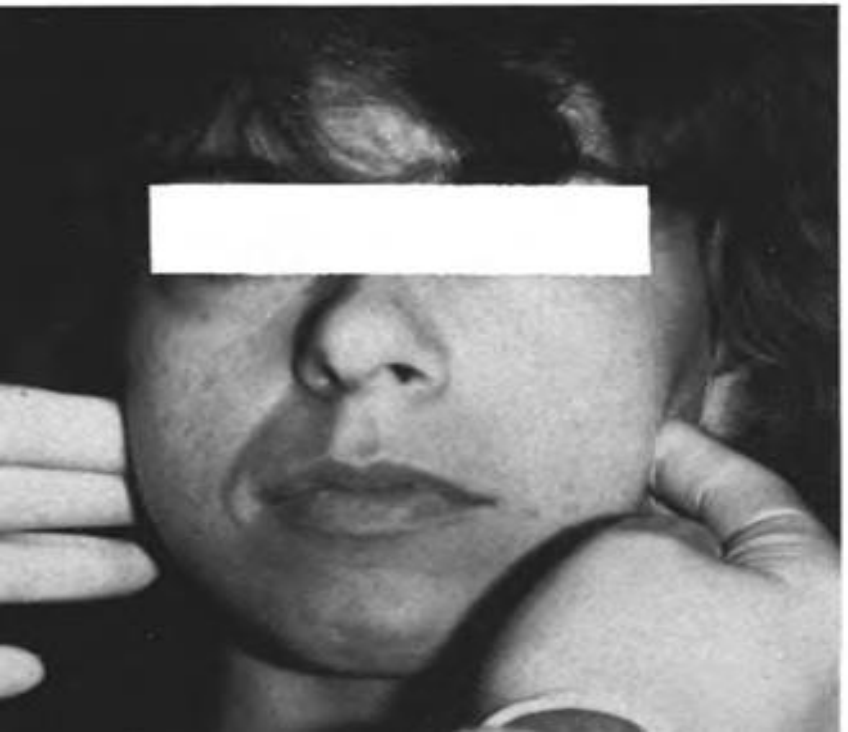
*Extra oral examination

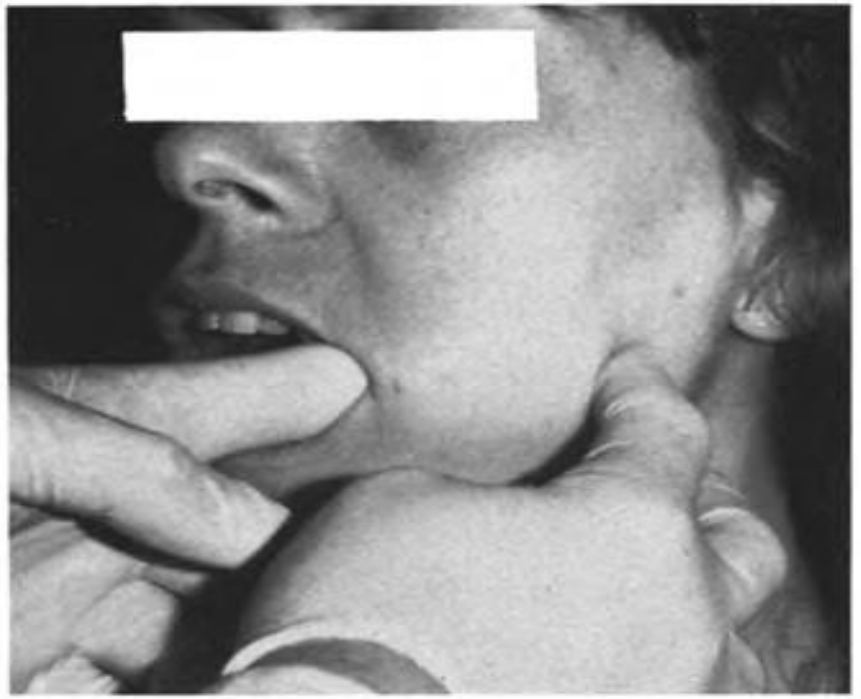
-Asymmetry
-Color of the face
-Presence of scar…..etc

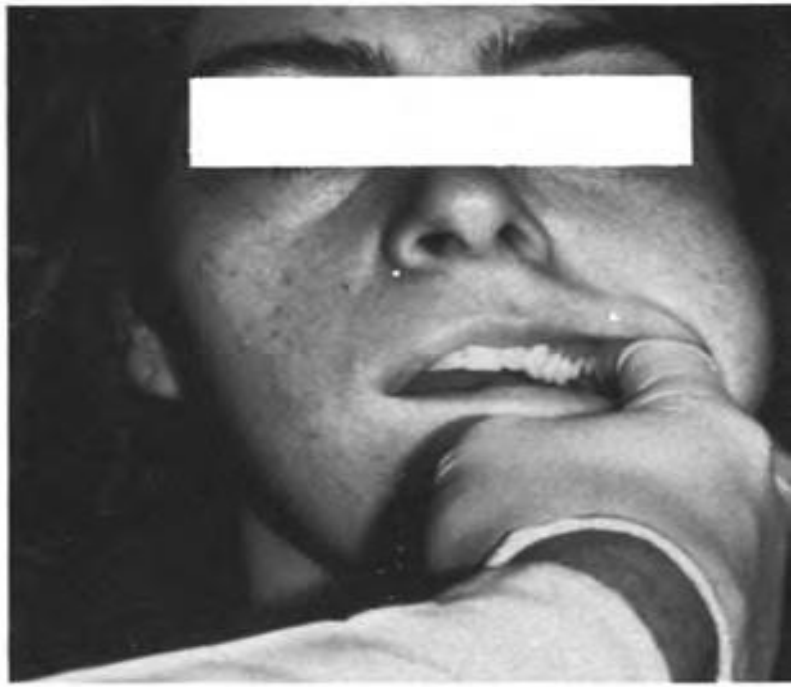
-Palpation of the muscles of mastication
-Digital examination of the TMJ
-Auscultation of the joint

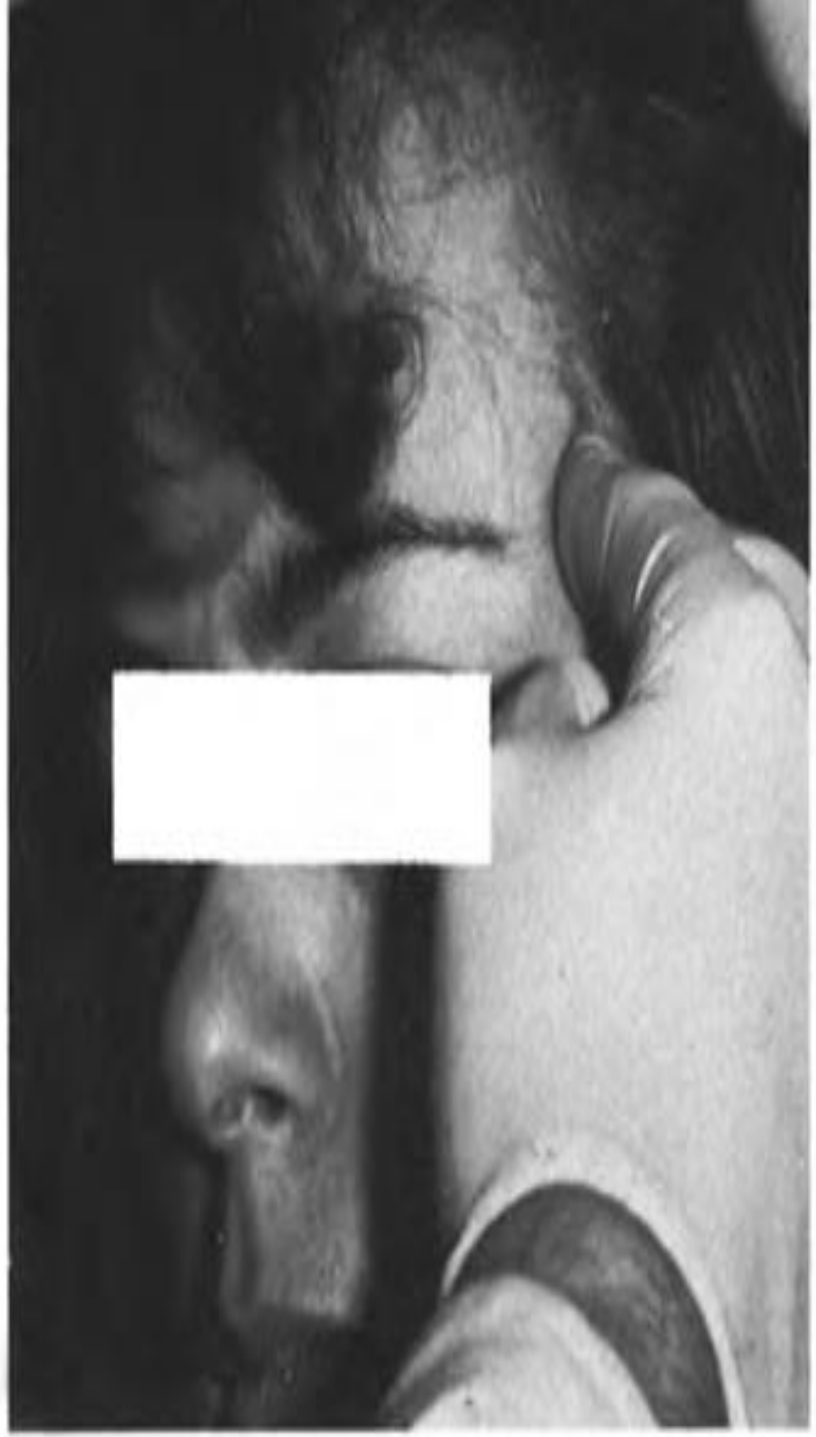


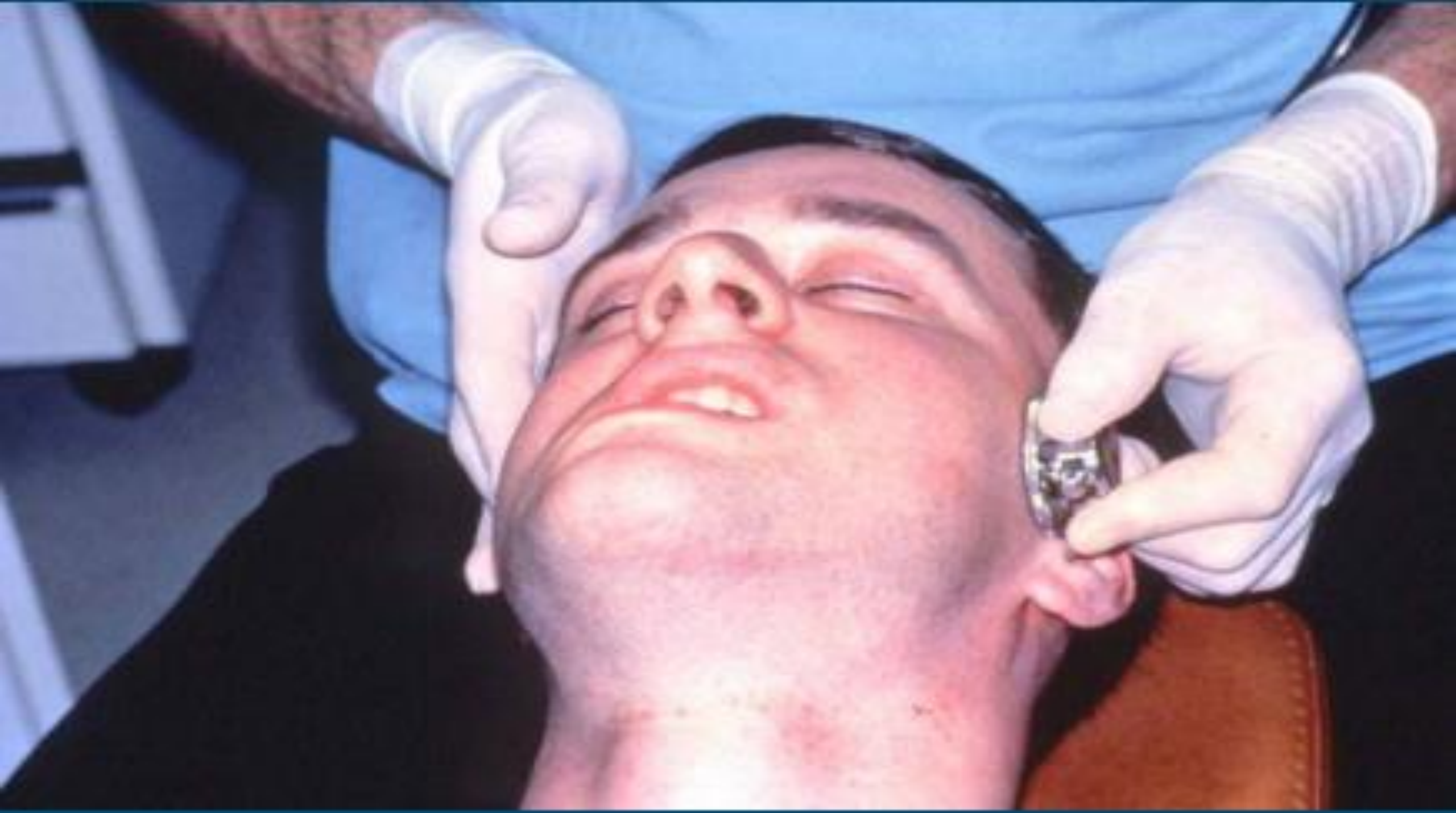












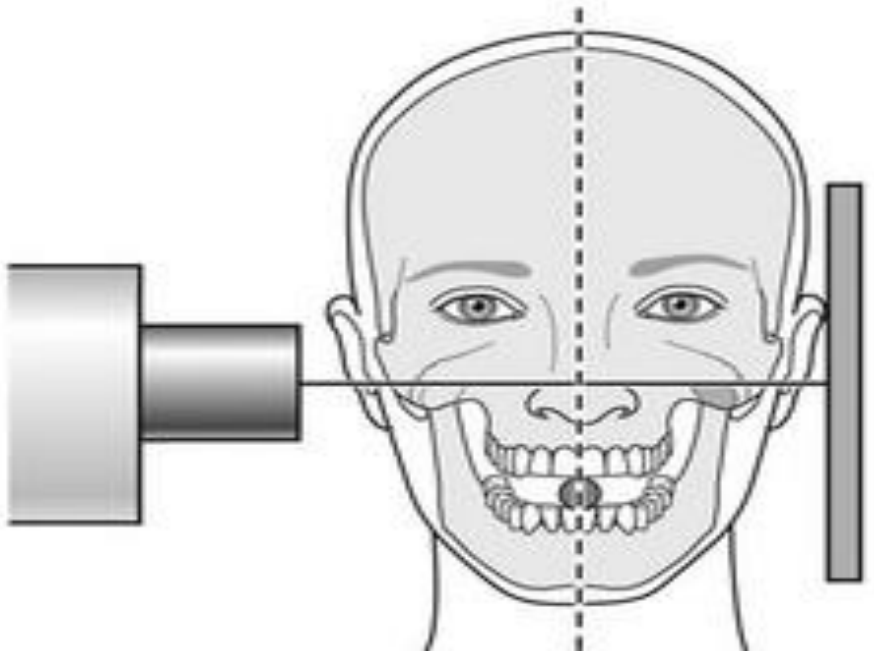
*Intra oral examination
-Soft tissue condition
-Teeth and jaw relation
-Mouth opening
-Para functional movement

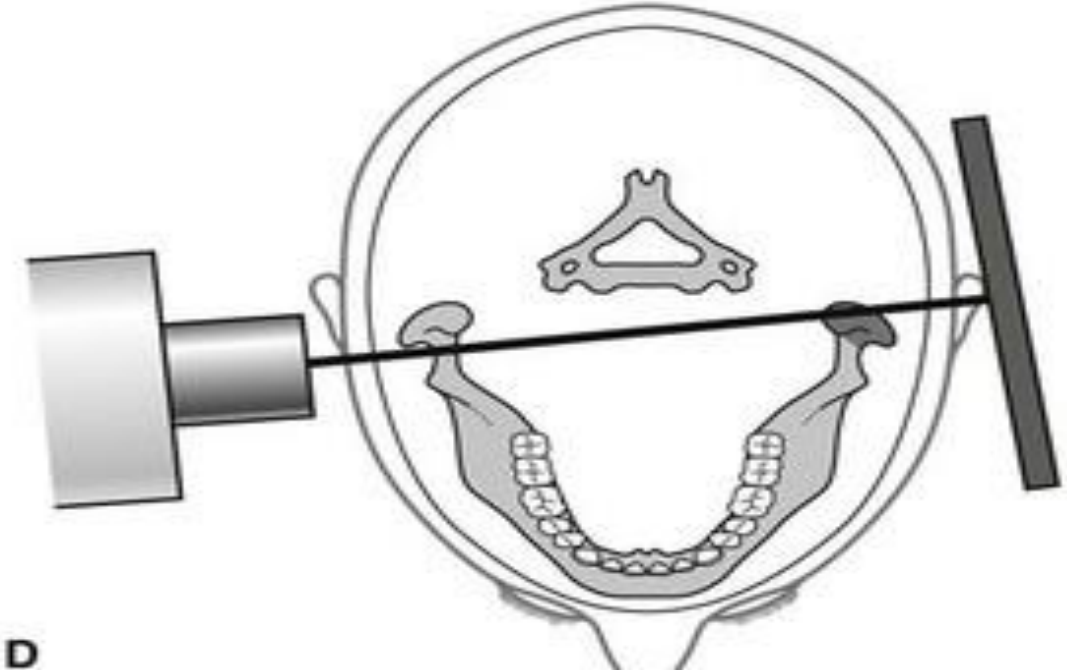
3. Radiographic examination

*Orthopantomograph
*Transcranial or transpharangial
*Tomograph
*Arthrograph
*CT scan

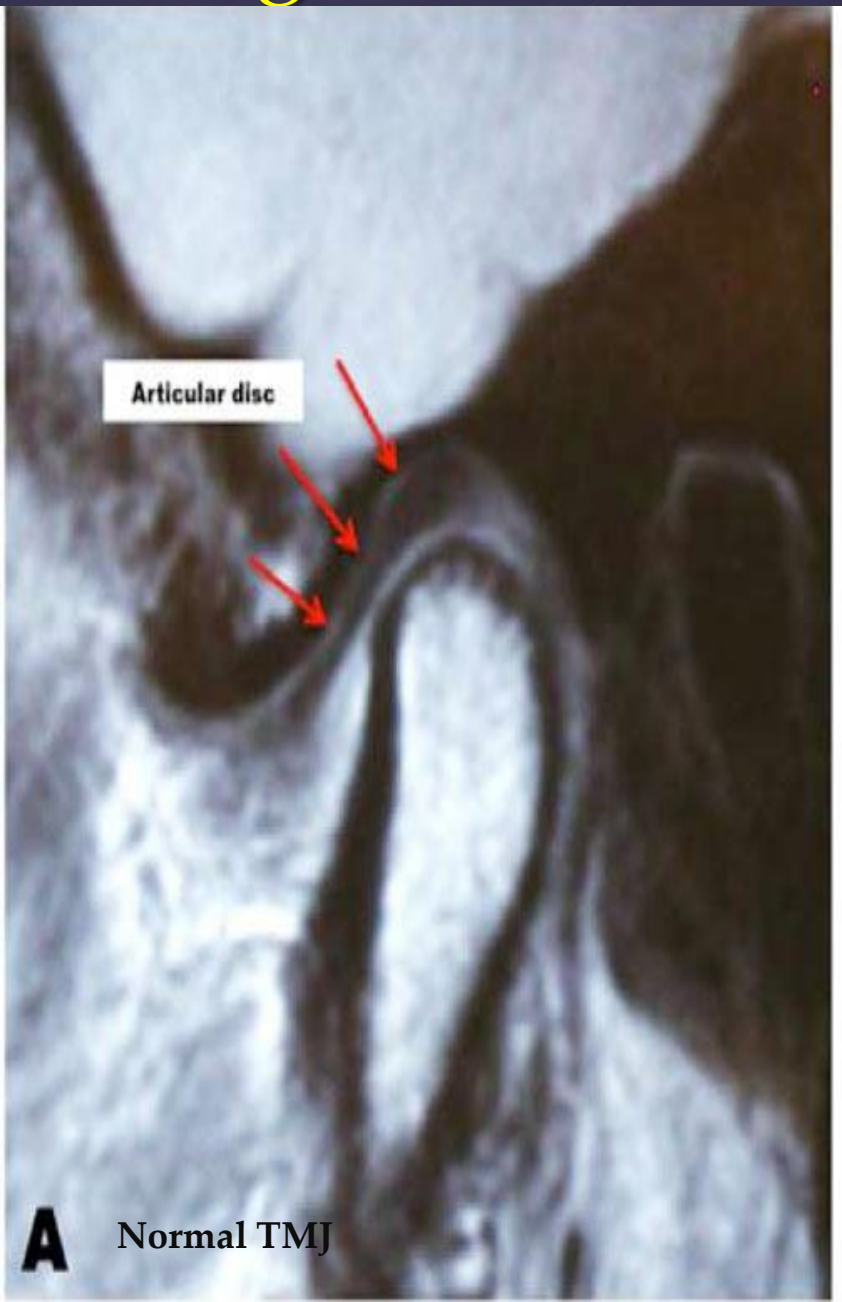

A


B
L

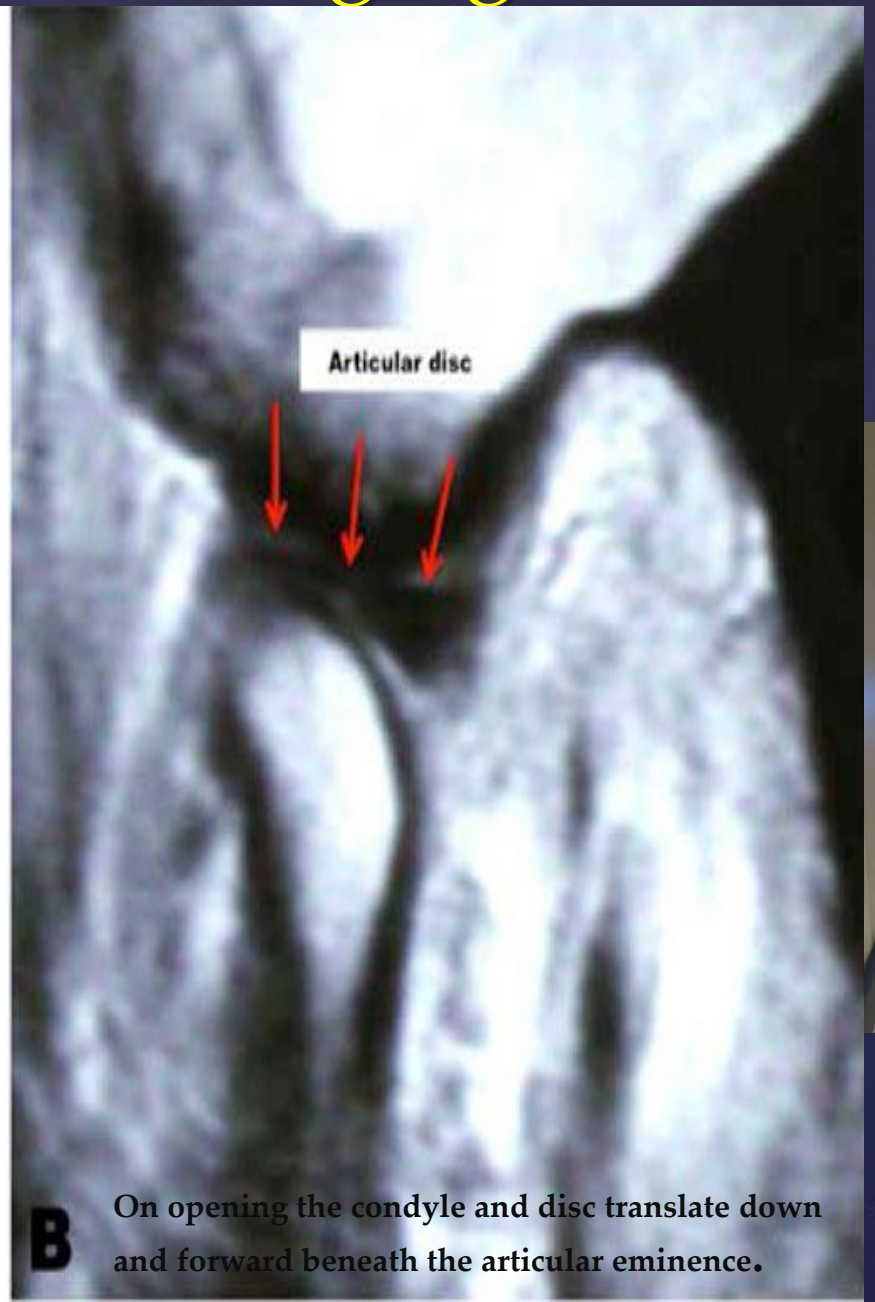

C


D

4. Magnetic Resonance Imaging



A Normal TMJ



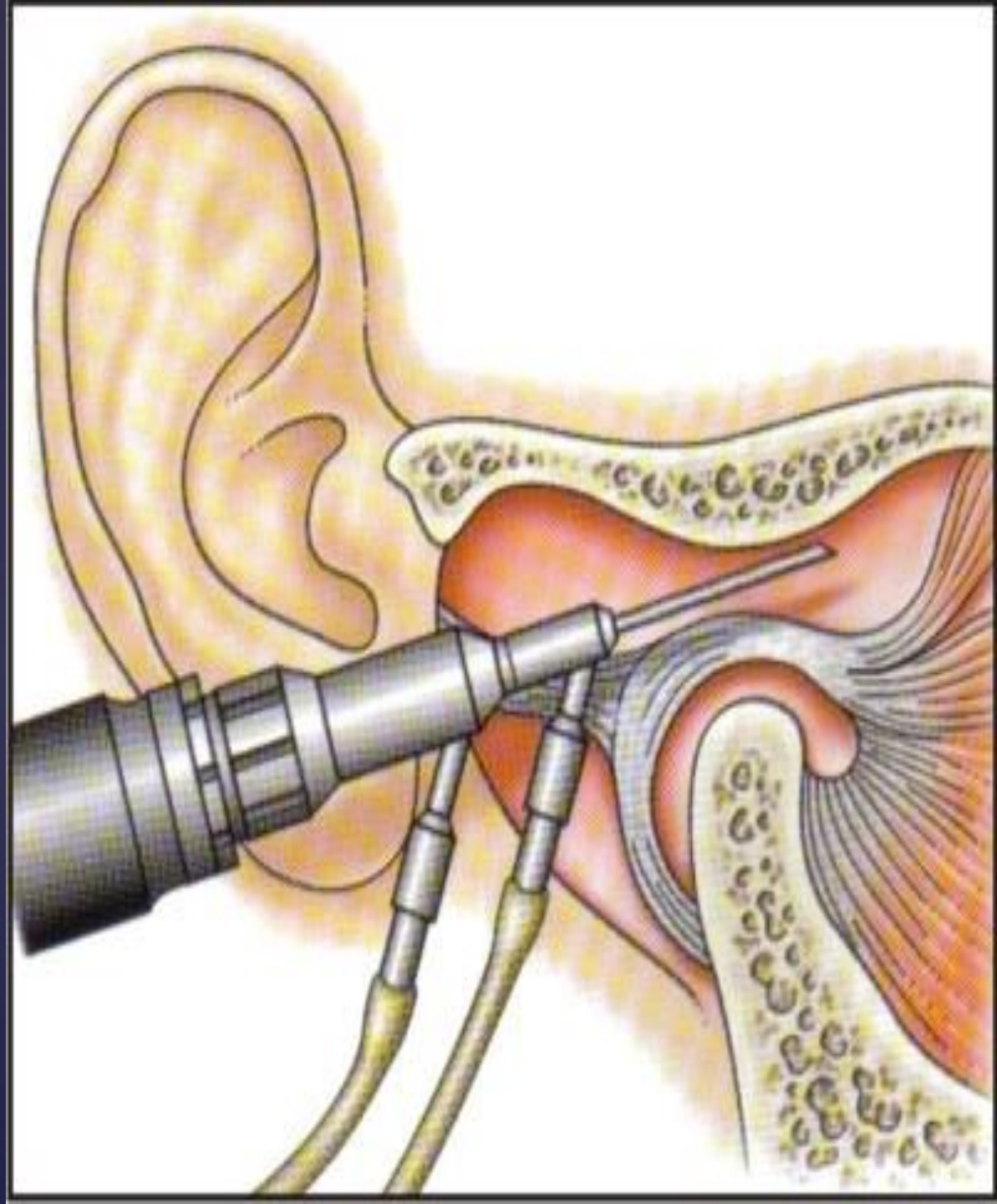
B On opening the condyle and disc translate down and forward beneath the articular eminence.

5. Arthroscope

A device used by inserting a tube into the joint space for:

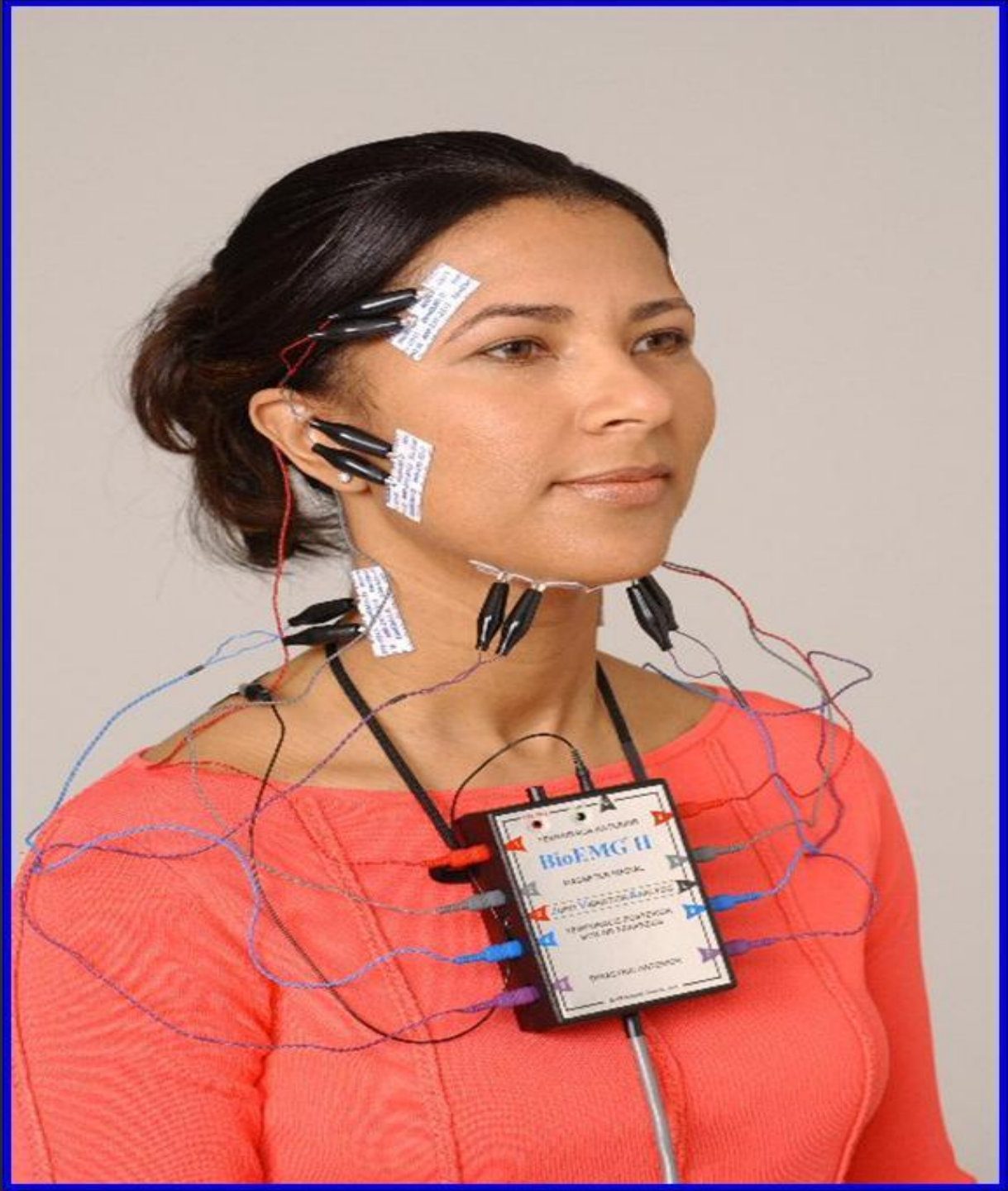
- The diagnosis of the joint diseases to visualize the surfaces of the disc, bones and lesions of the joint.

- The treatment is by injecting a fluid for debridment of the waste products out of the synovial spaces.



6. Electromyograph

A device used to detect the action of the muscles by inserting two electrodes in the muscle affected by spasm and drawing a line on a paper or on the screen to monitor changes activity and the response to the therapy.



Myofascial Pain of the Masticatory Muscles

The term most commonly used for muscle pain produced on palpation is myofascial pain.

The term myofascial pain has also been characterized by muscle pain that also radiates or is referred when the muscle is stimulated during palpation examination.

Clinical Features

- Age and sex distribution—it is seen in middle age group with more predilections for women.
- Onset—it occurs in episodes of several times a day, at times, with extended symptom free intervals. Usually episodes are seen during increased emotional tension, resulting in increased intra-articular pressure in the joint.
- Symptoms— Pain is localized to preauricular area but can be radiated to temporal, frontal, and occipital region. There is difficulty in chewing and restriction of mandibular excursion. Patient also complaint of noise on rubbing, grinding, clicking, and popping snapping sounds on mandibular movement.

- Tinnitus—patient may complaint of tinnitus (ringing in ear) or otalgia (pain in ear) or toothache.

- Hearing loss—it may cause irritation of the chorda tympani nerve, resulting in partial or total hearing loss.

- Signs—restriction of opening and protrusion may be accompanied by deflection of the mandibular incisal pathway. There is also soreness of muscle, when palpated. Myofacial trigger zones are stimulated by pressure and produce referred pain

- Other features—oral or para-functional habits, such as bruxism, present as indentation on lateral borders of the tongue, ridging of the buccal mucosa and extensive attrition of teeth.

Initial Treatment of Myofascial Pain

- Education

-Explanation of the diagnosis and treatment

-Reassurance about the generally good prognosis for recovery and natural course

-Explanation of patient's and doctor's roles in therapy Information to enable patient to perform self-care

- Self-care

-Eliminate oral habits (eg, tooth clenching, chewing gum)
-Provide information on jaw care associated with daily activities

- Physical therapy

-Education regarding biomechanics of jaw, neck, and head posture

-Passive modalities [heat and cold therapy, ultrasound, laser, and transcutaneous electrical nerve stimulation (TENS)]

Cold laser for TMD

TENS unit electronically massages and stimulates the muscles with low frequency pulses to help the muscle find its most relaxed state.

-Range of motion exercises (active and passive)
-Posture therapy
-Passive stretching, general exercise and conditioning program

- **Intraoral appliance therapy**

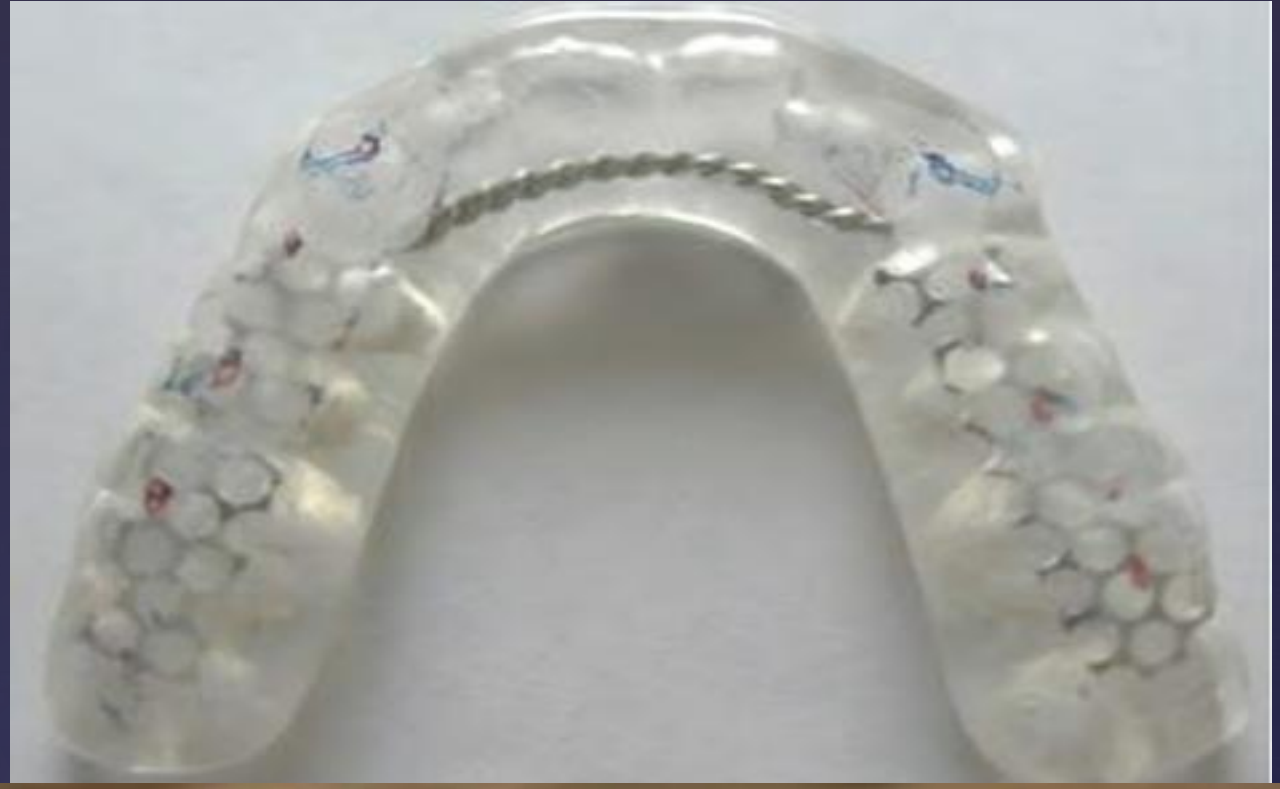
-Cover all the teeth on the arch the appliance is seated on

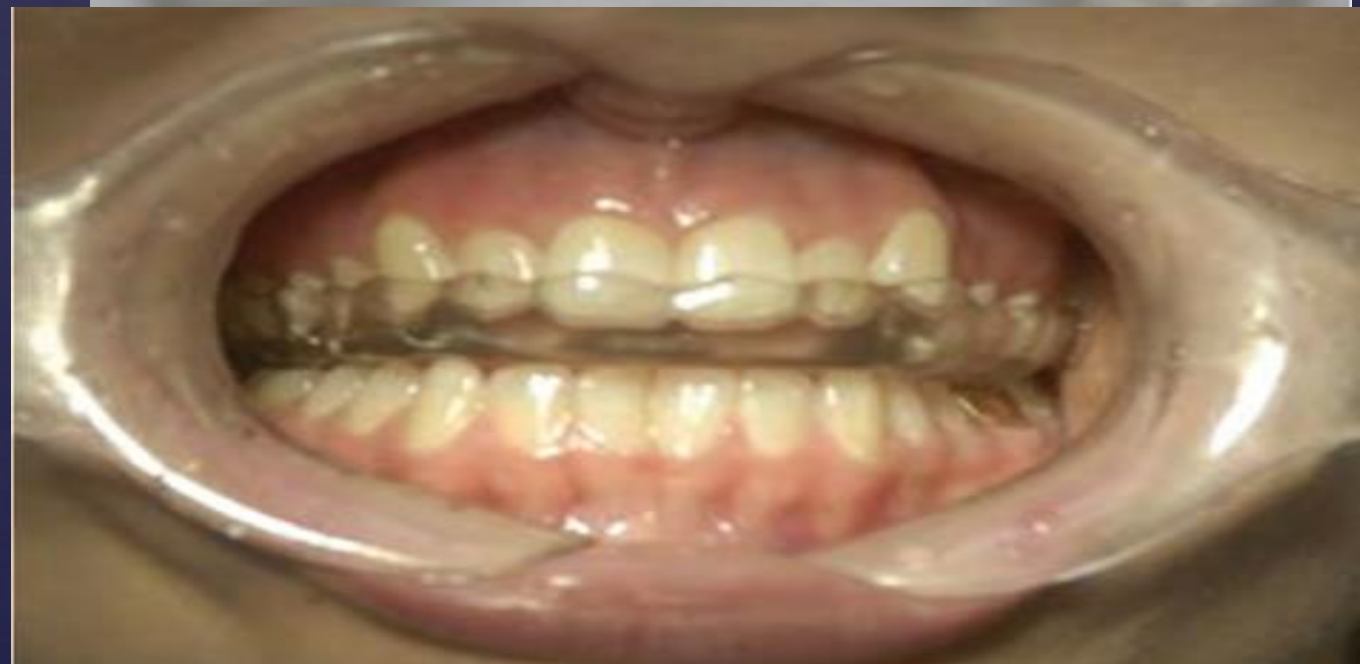
-Adjust to achieve simultaneous contact against opposing teeth

-Adjust to a stable comfortable mandibular posture

-Avoid changing mandibular position

-Avoid long-term continuous use





- Pharmacotherapy

NSAIDs, acetaminophen, muscle relaxants, antianxiety agents, tricyclic antidepressants

- Behavioral/relaxation techniques

-Relaxation therapy
-Hypnosis
-Biofeedback
-Cognitive-behavioral therapy

Articular Disc Disorders of the TMJ

ADD is an abnormal relationship between the disc, the mandibular condyle, and the articular eminence, resulting from the *elongation or tearing of the attachment of the disc to the condyle and glenoid fossa.*

ADD may result in abnormal joint sounds, limitation and deviation of mandibular motion, and pain. The majority of cases of ADD occur without significant pain or joint dysfunction.

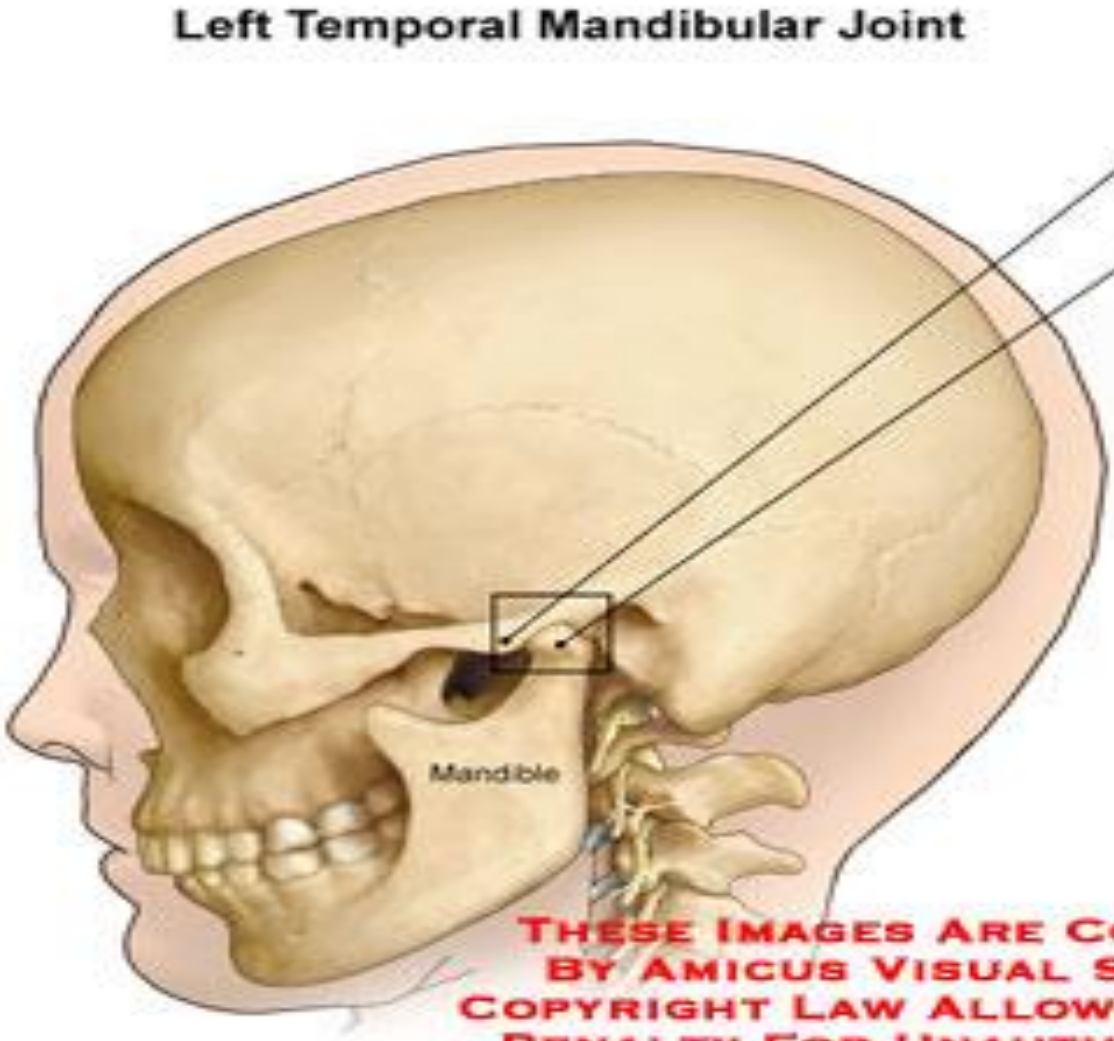
elongation or tearing of the attachment of the disc to the condyle and glenoid fossa.

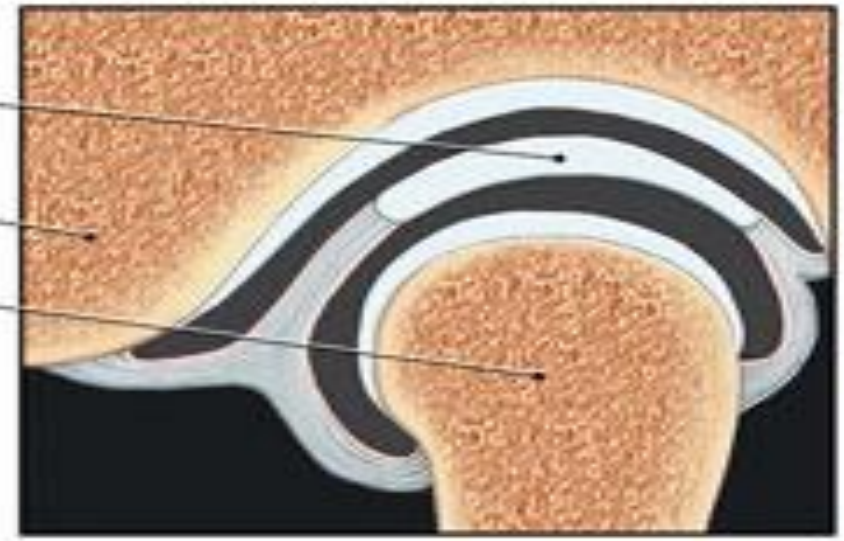
abnormal relationship between the disc, the mandibular condyle, and the articular eminence .(ADD)

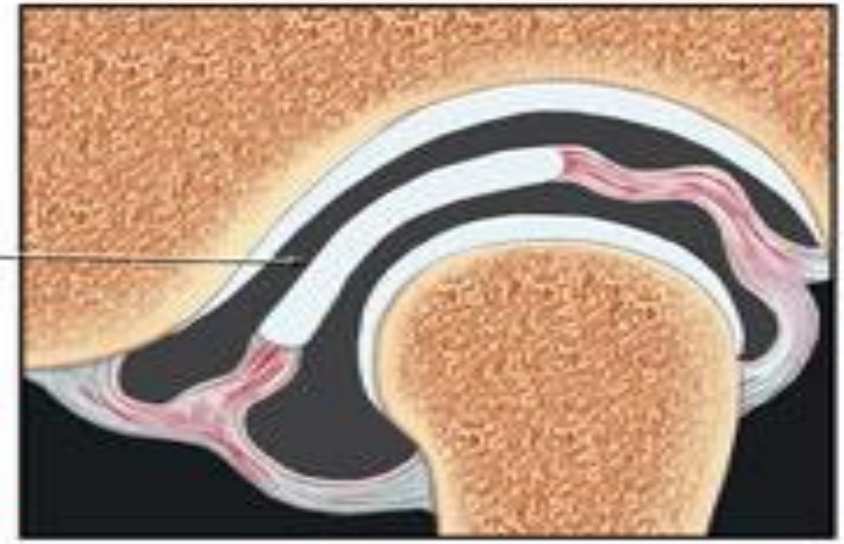
Clinicall y

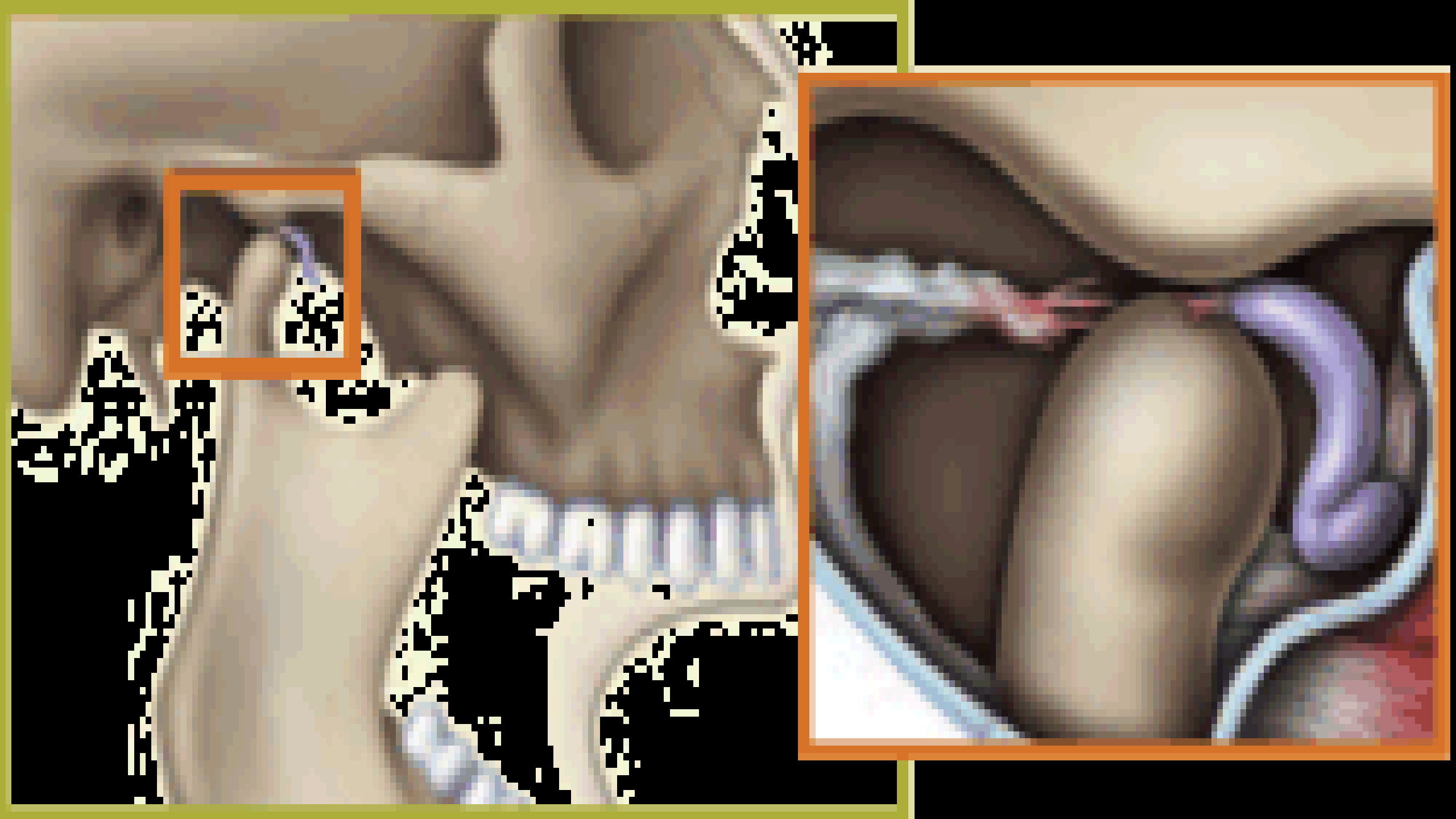
abnormal joint sounds, limitation and deviation of mandibular motion, and pain.

Internal Derangment of the Left TMJ









A specific etiology in the majority of cases of disc displacement is poorly understood.

Some cases result from direct trauma to the joint from a blow to the mandible.

It is also generally believed that chronic low-grade microtrauma resulting from long-term bruxism or clenching of the teeth is a major cause of ADD.

Clinical Manifestations

Disc displacement is divided into stages based on

signs and symptoms
combined with the results of diagnostic imaging.

A simple classification system divides ADD into:

1. Anterior Disc Displacement **with** Reduction.
2. Anterior Disc Displacement **without** Reduction (Closed Lock).
3. Posterior Disc Displacement.

Anterior Disc Displacement with Reduction.

This condition is caused by

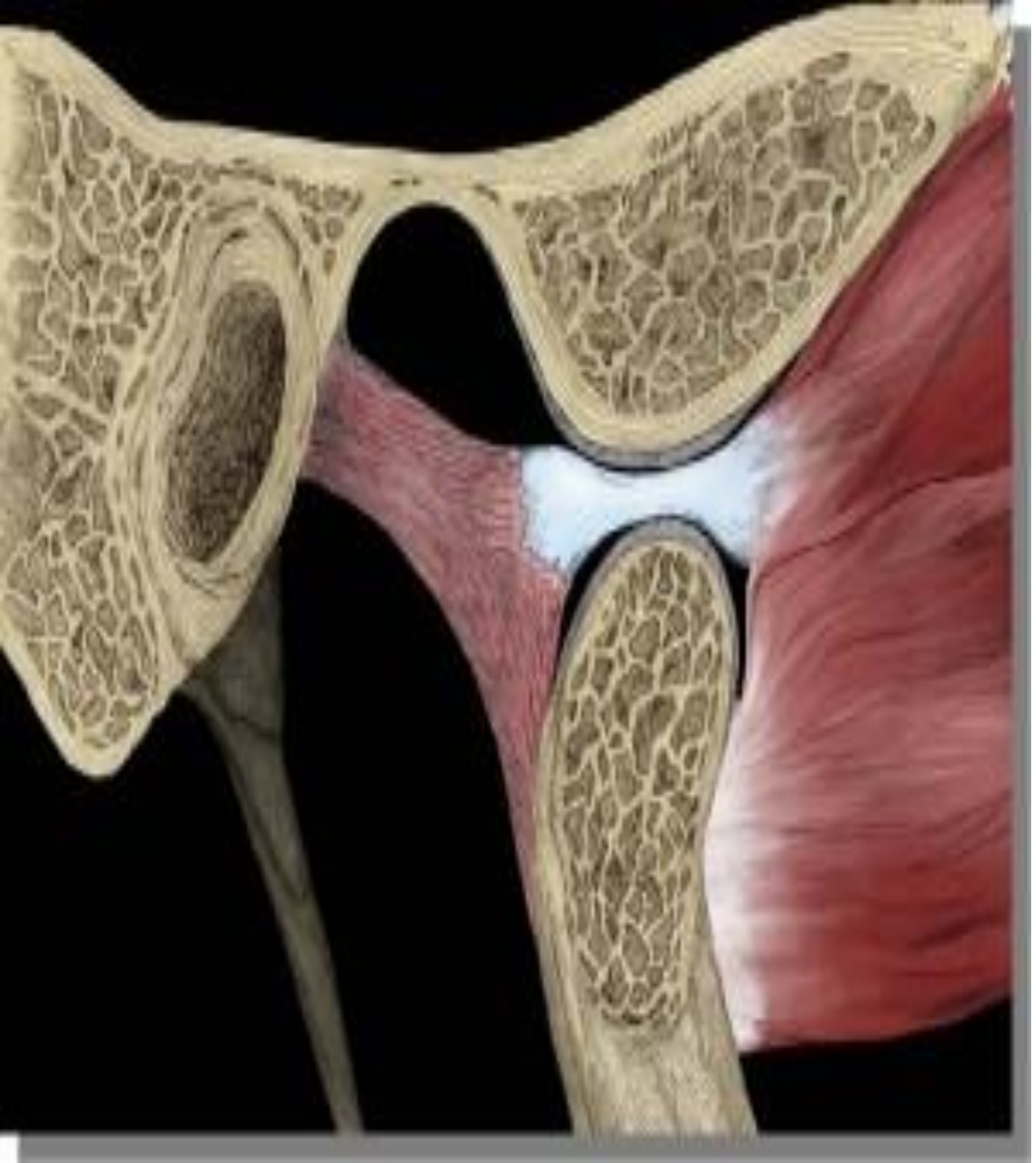
*An articular disc that has been displaced from its position on top of the condyle due to elongation or tearing of the restraining ligaments.

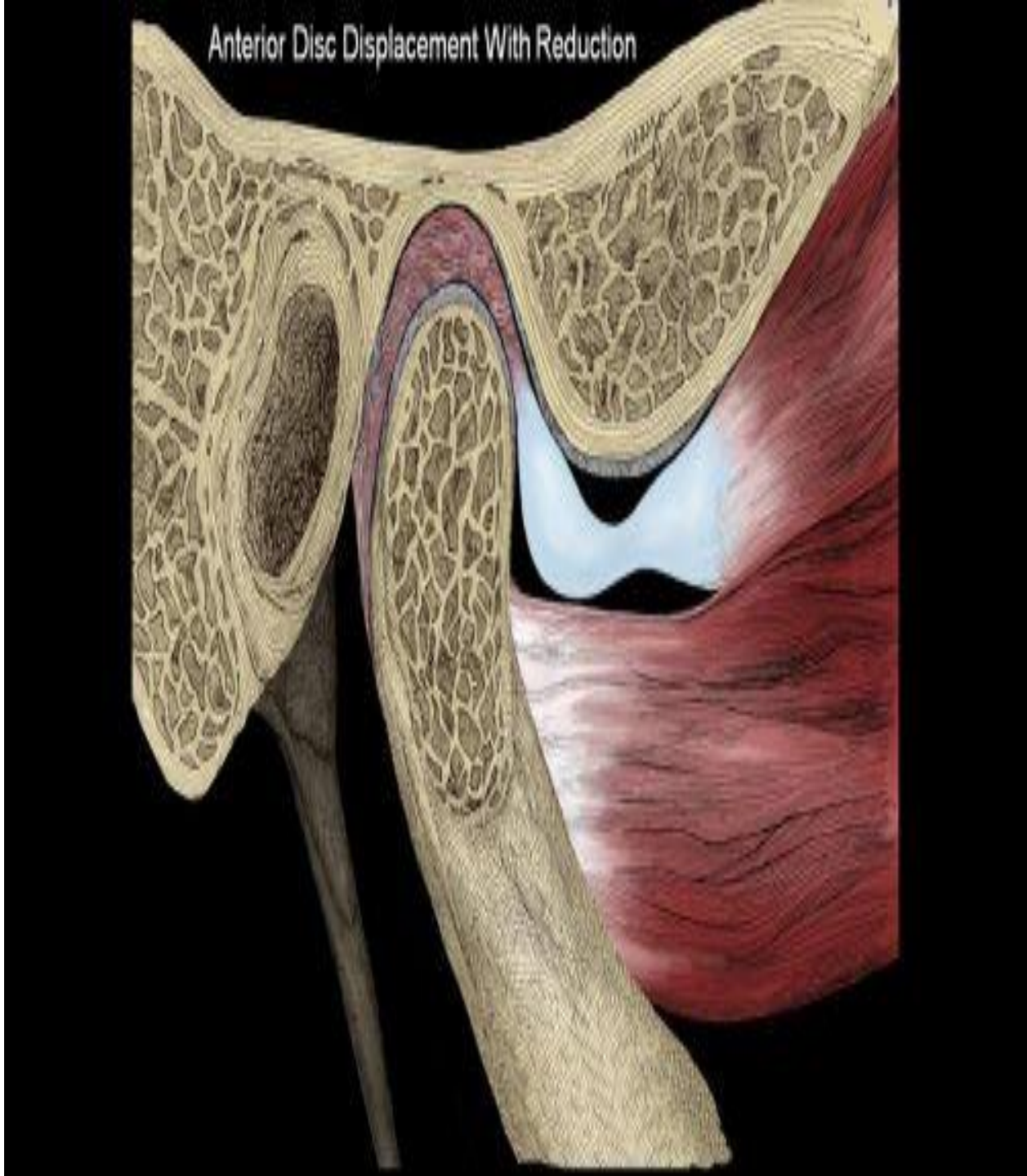
*An alteration in the form of the disc has also been proposed as a possible factor.

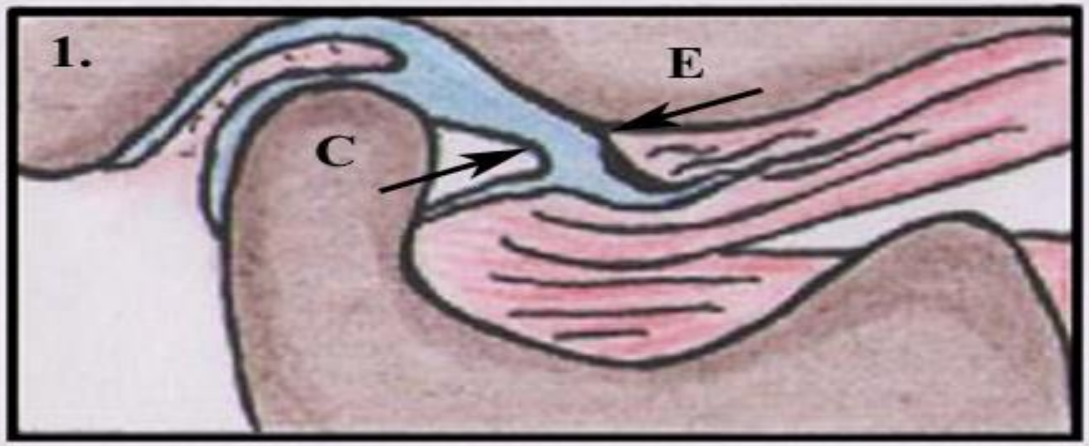
A reducing disc displacement is common in the general population, and a clicking or popping joint is of little clinical significance unless it is accompanied by pain, loss of function, and/or intermittent locking.

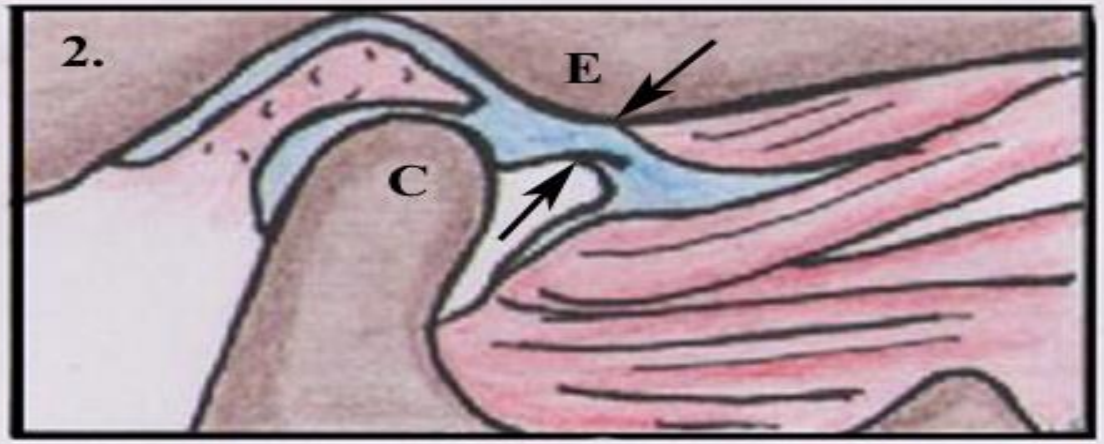
Palpation and auscultation of the TMJ will reveal a clicking or popping sound during both opening and closing mandibular movements (reciprocal click).

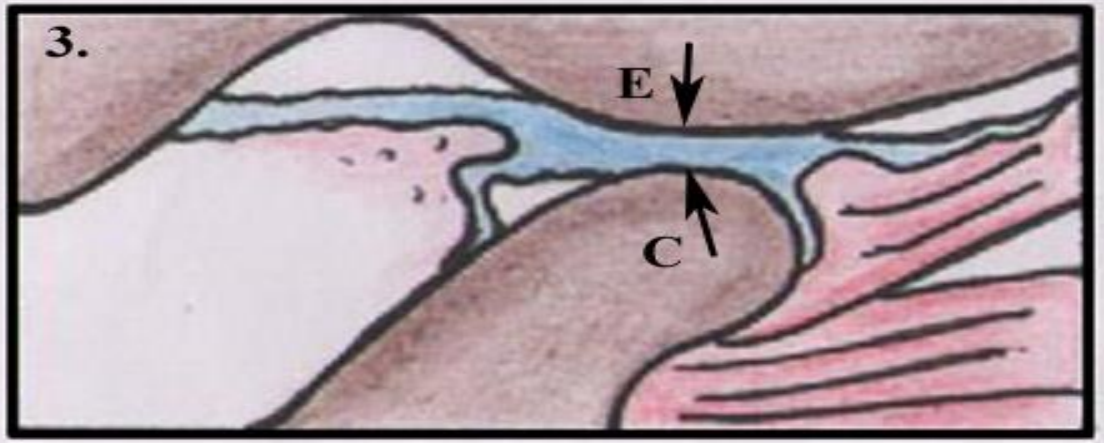
The clicking or popping sound due to anterior disc displacement with reduction is characterized by a click that may occur on opening in the early, middle, or late movement and in the closing movement just before the teeth come in contact.
This is due to movement of the disc as the condyle translates.




Anterior Disc Displacement With Reduction







ADDR, the disc (black arrows) lies anterior to the condyle (C) in closed mouth position (1). On mouth opening the disc moves posteriorly over the head of the condyle (2) and finally rests over the condylar head in maximal open mouth position(3). Thus, the disc which was anteriorly positioned, is now reduced back to its normal position on mouth opening.

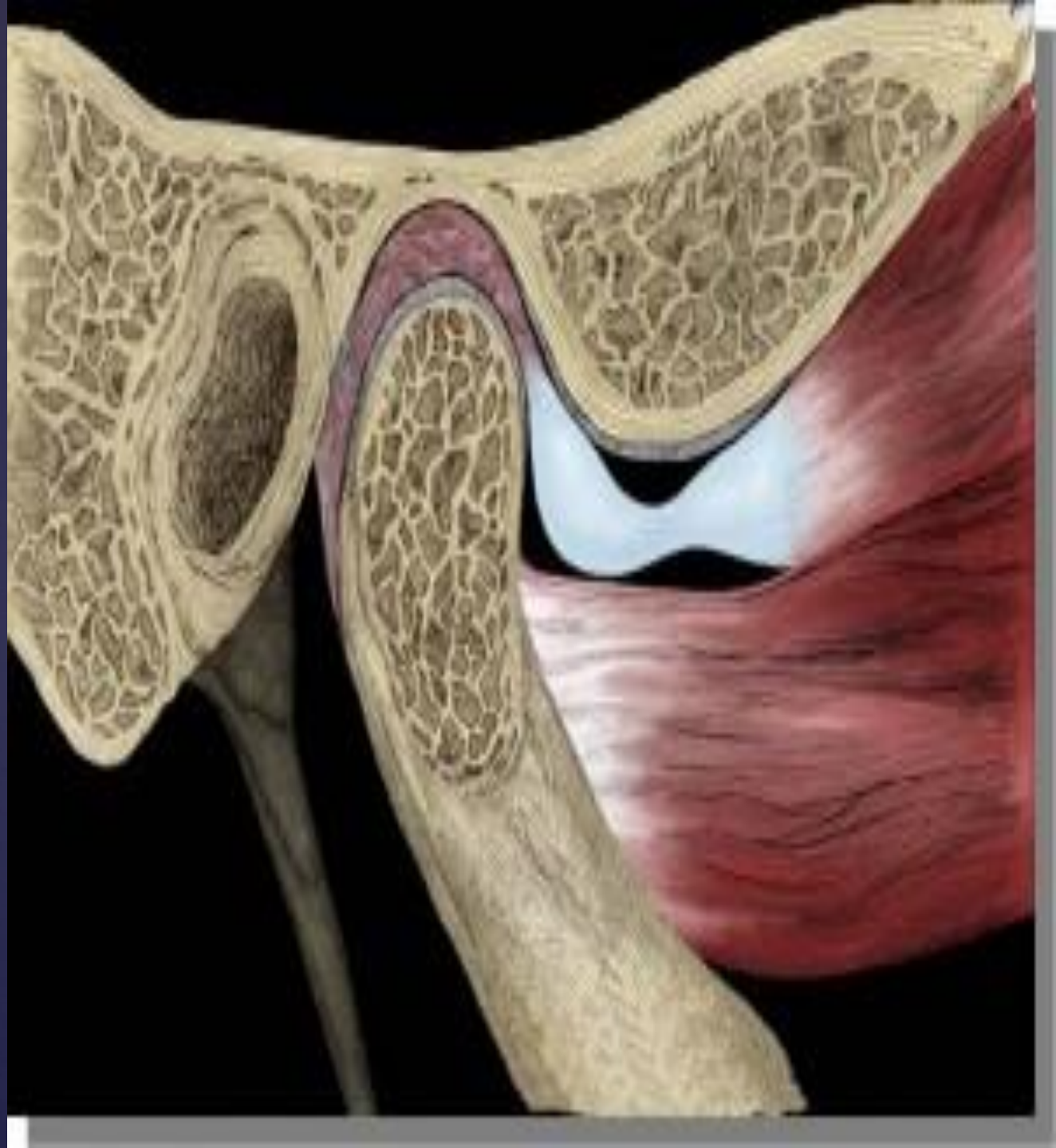
Anterior Disc Displacement without Reduction (Closed Lock):

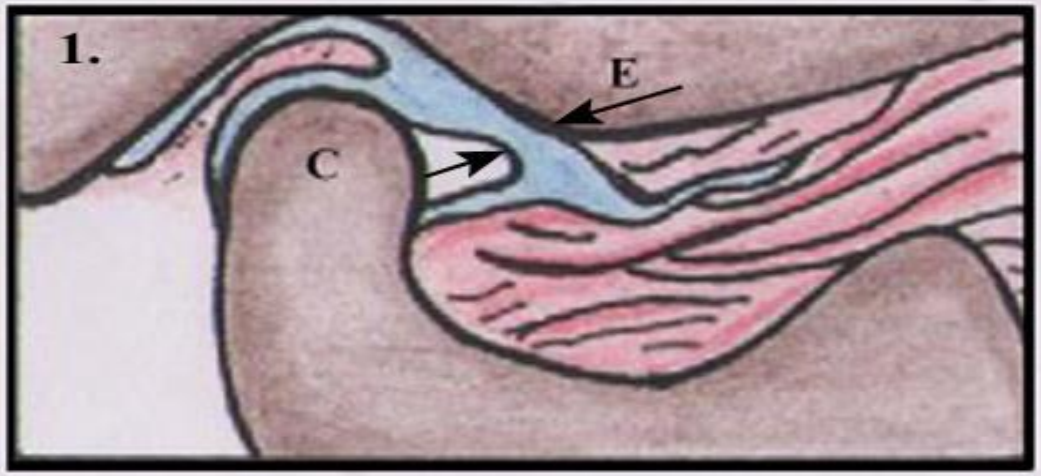
Closed lock may be the first sign of TMD occurring after trauma or severe long-term nocturnal bruxism.

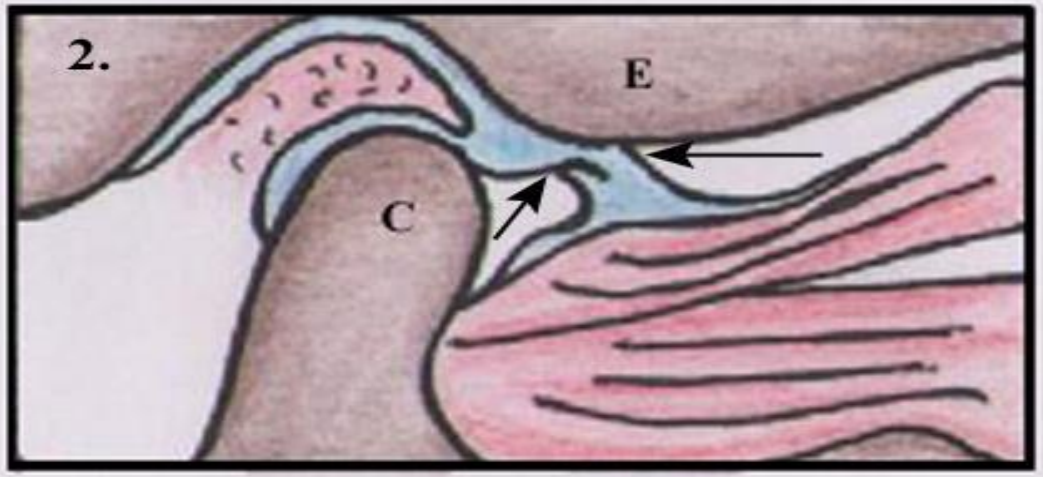
It is detected more frequently in patients with clicking joints that progress to intermittent brief locking and then permanent locking.

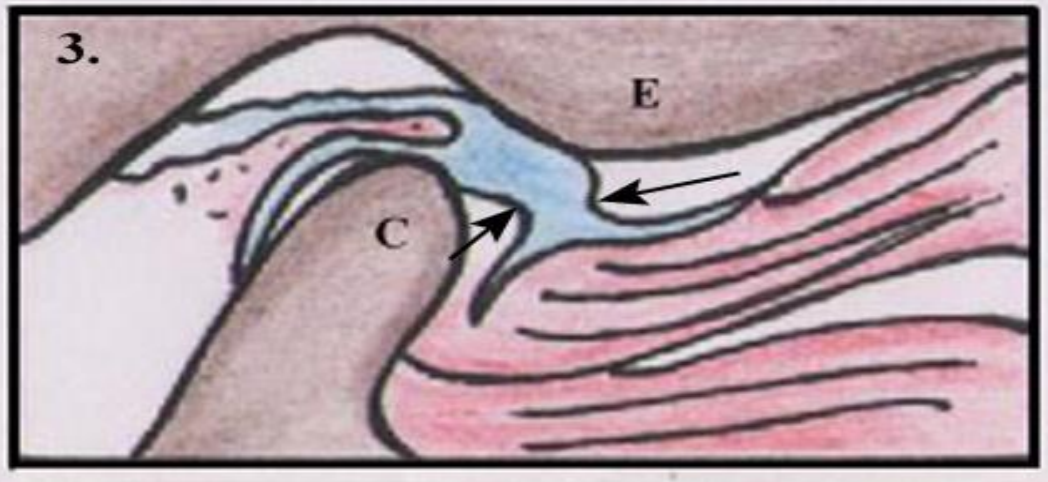
A patient with an acute closed lock will often have a history of a long-standing TMJ click that abruptly disappears followed by a sudden restriction in mandibular opening.

This limited mandibular opening occurs due to disc interference with the normal translation of the condyle.





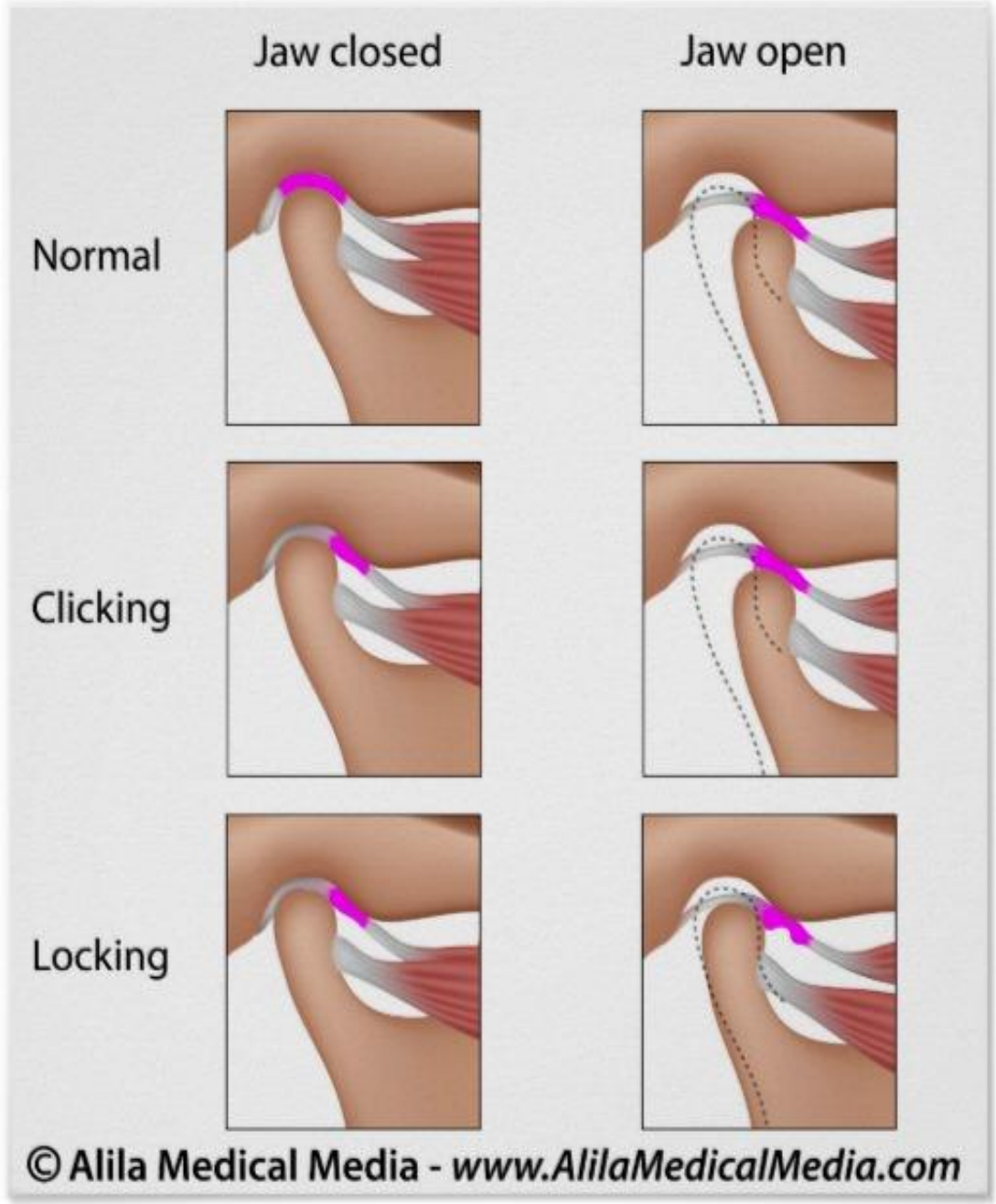




ADDWR,the disc (black arrows) remains persistently anterior to the condyle (C) as the condyle translates from closed mouth position (1) to maximal open mouth position (3).

Other findings include
pain directly over the joint during mandibular opening (especially at maximum opening) and

limited lateral movement to the side away from the affected joint.


Jaw closed
Jaw open
Normal
Clicking
Locking
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Posterior Disc Displacement:

Posterior disc displacement has been described as the condyle slipping over the anterior rim of the disc during opening,
with the disc being caught and brought backward in an abnormal relationship to the condyle when the mouth is closed.
The disc is folded in the dorsal part of the joint space, preventing full mouth closure.

The clinical features are

(1) a sudden inability to bring the upper and lower teeth together in maximal occlusion,

(2) pain in the affected joint when trying to bring the teeth firmly together,

(3) displacement forward of the mandible on the affected side,

(4) restricted lateral movement to the affected side, and

(5) no restriction of mouth opening.

Management

Most symptoms associated with ADD resolve over time either with no treatment or with minimal conservative therapy.

Recommended treatments for symptomatic ADD include splint therapy, physical therapy including manual manipulation, anti-inflammatory drugs, arthrocentesis, arthroscopic lysis and lavage, arthroplasty, and vertical ramus osteotomy.

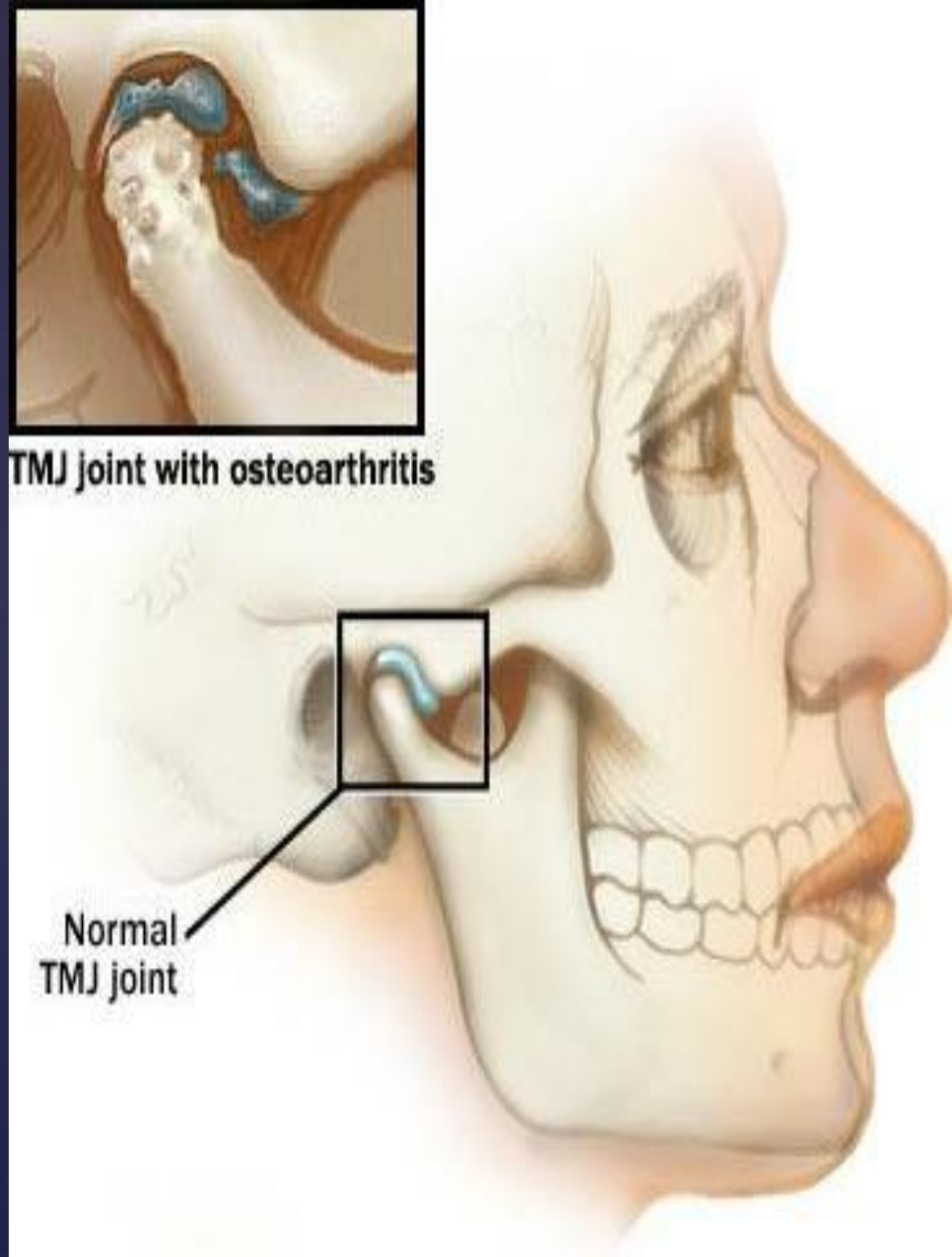
Many of these nonsurgical and surgical techniques are effective in decreasing pain and in increasing the range of mandibular motion, although the abnormal position of the disc is not usually corrected.

Temporomandibular Joint Arthritis Osteoarthritis (Degenerative Joint Disease)

Degenerative joint disease (DJD), also referred to as osteoarthrosis, osteoarthritis, and degenerative arthritis,

is primarily a disorder of articular cartilage and subchondral bone, with secondary inflammation of the synovial membrane.

It is a localized joint disease without systemic manifestations.



DJD may be categorized as

Primary DJD is of unknown origin, but genetic factors play an important role. It is often asymptomatic and is most commonly seen in patients above the age of 50 years.

Secondary DJD results from a known underlying cause, such as trauma, congenital dysplasia, or metabolic disease. Risk factors include gender, diet, genetics, and psychological stress.

Clinical Manifestations:

The incidence of degenerative changes increases with age. Patients with symptomatic DJD of the TMJ experience pain directly over the affected condyle, limitation of mandibular opening, crepitus, and a feeling of stiffness after a period of inactivity.

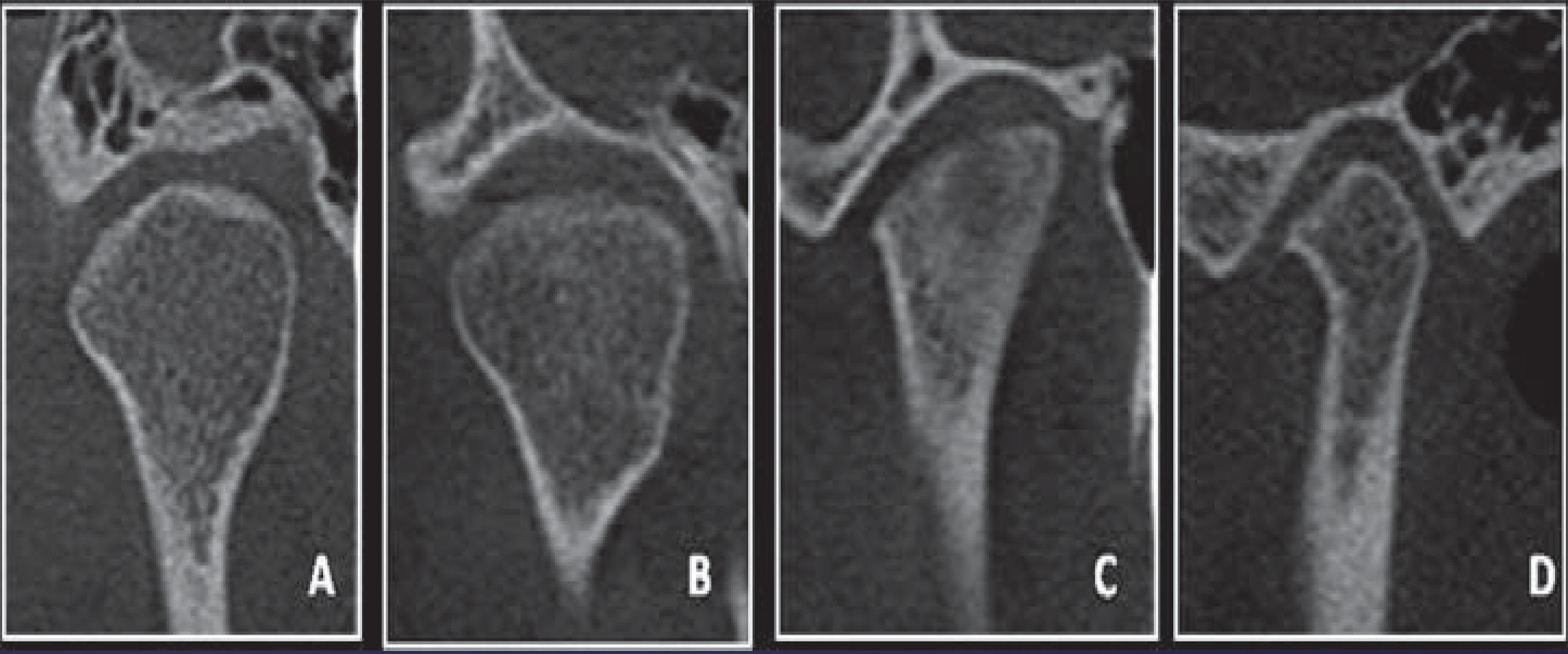
Examination reveals tenderness and crepitus on intra-auricular and pretragus palpation.

.

Radiographic findings in DJD may include

*narrowing of the joint space,
*irregular joint space,
*flattening of the articular surfaces,
*osteophyte formation,
*anterior lipping of the condyle,
*presence of subchondral cysts.

These changes may be seen best on tomograms or CT scans.



Cone-beam computed tomography images of TMJ showing morphological variation of the mandibular condyle.

A- Normal (coronal view)

B- Flattening (coronal view)

C- Erosion (coronal view)

D- Osteophyte (sagittal view)

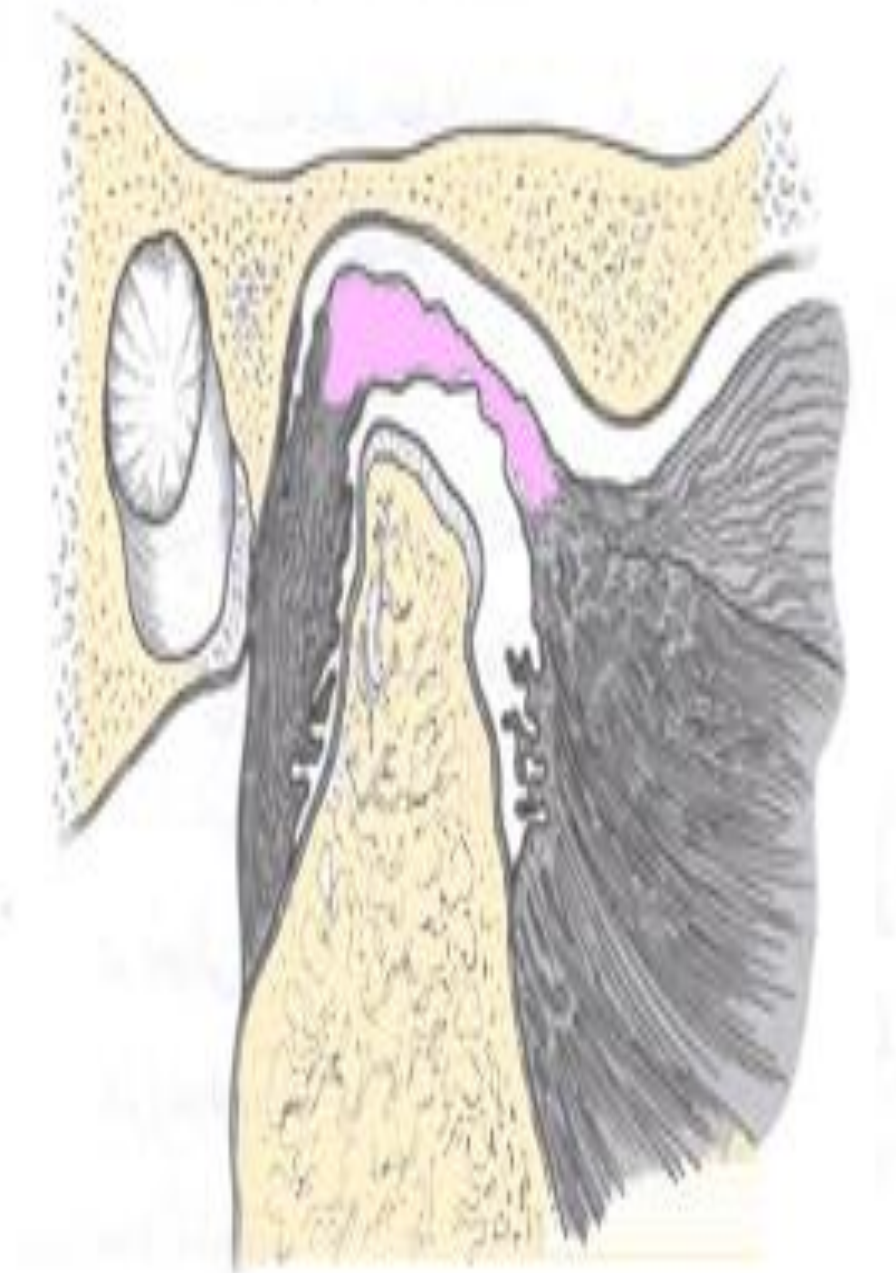
Rheumatoid Arthritis (RA)

RA is an inflammatory disease affecting periarticular tissue and secondarily bone.

The disease process starts as a vasculitis of the synovial membrane.

It progresses to chronic inflammation marked by an intense round cell infiltrate and subsequent formation of granulation tissue.

The cellular infiltrate spreads from the articular surfaces eventually to cause an erosion of the underlying bone.



Degenerative changes in rheumatoid arthritis-attenuation of the condyle.

Clinical Manifestations:

The TMJs in RA are usually involved bilaterally.

Pain is usually associated with the early acute phase of the disease but is not a common complaint in later stages.

Other symptoms often noted include morning stiffness, joint sounds, and tenderness and swelling over the joint area.

The most consistent clinical findings include pain on joint palpation, limited mouth opening, and crepitus.

Micrognathia and an anterior open bite are commonly seen in patients with juvenile idiopathic arthritis.

Radiographic changes in the TMJ associated with RA may include a narrow joint space, destructive lesions of the condyle, and limited condylar movement.

Treatment:

Involvement of the TMJ in RA is usually treated with anti-inflammatory drugs in conjunction with the therapy for the systemic disease.

The patient should be placed on a soft diet during the acute exacerbation.

Use of a flat-plane occlusal appliance may be helpful, particularly if parafunctional habits are present.

An exercise program to increase mandibular movement should be instituted as soon as possible after the acute symptoms subside.

Intra-articular steroids should be considered.

Prostheses appear to decrease symptoms in fully or partially edentulous patients.

Surgical treatment of the joints, including placement of prosthetic joints, is indicated in patients who have severe functional impairment or intractable pain not successfully managed by other means.

Orthognathic surgery and orthodontics are required for correction of facial deformity resulting from arthritis during growth.

Developmental Defects

Developmental disturbances involving the TMJ may result in anomalies in the size and shape of the condyle.

Hyperplasia, hypoplasia, agenesis, and the formation of a bifid condyle may be evident on radiographic examination of the joint.

Local factors, such as trauma or infection, can initiate condylar growth disturbances.

Facial asymmetry often results from disturbances in condylar growth because the condyle is a site for compensatory growth and adaptive remodeling.

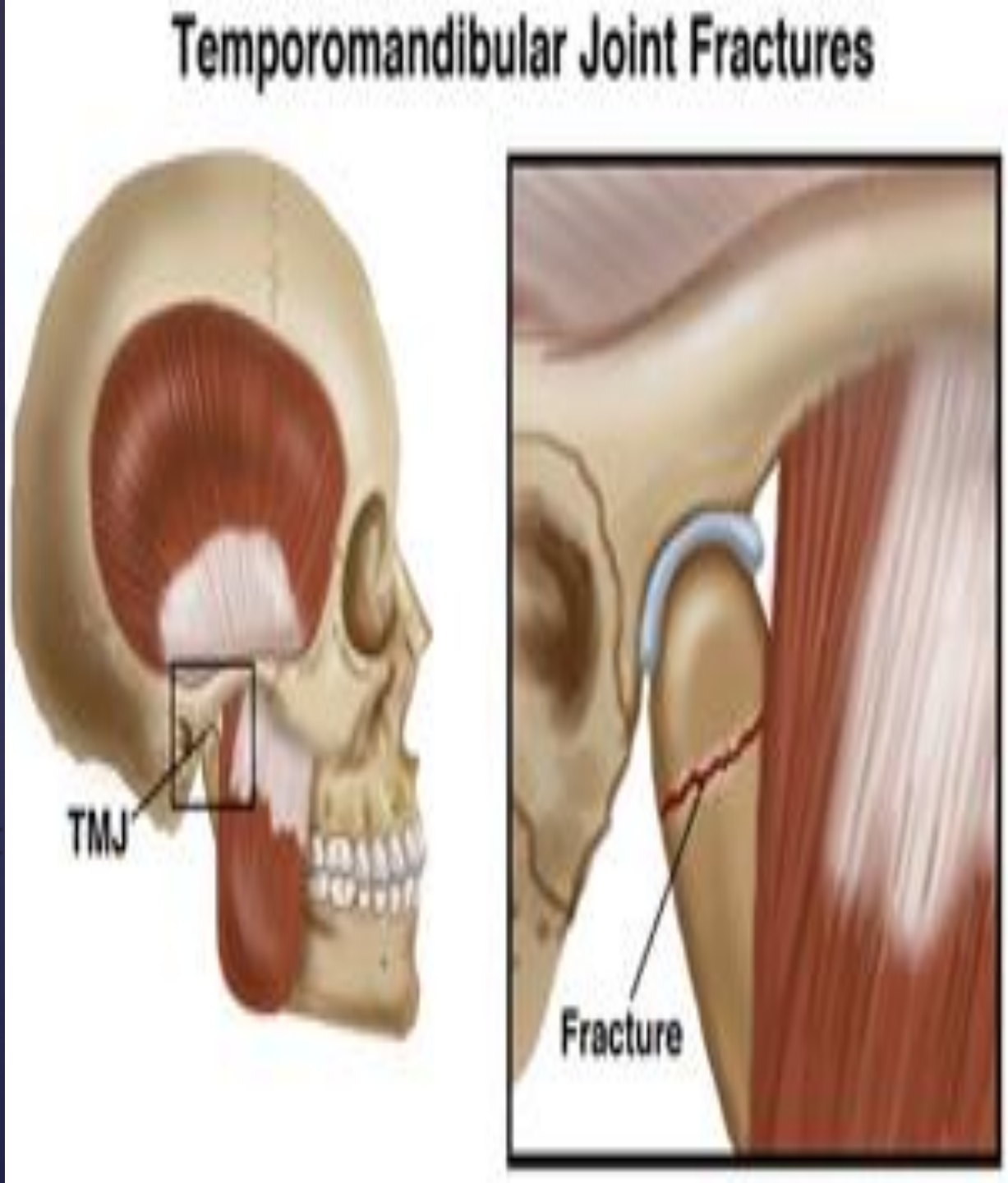
Fractures

Fractures of the condylar head and neck often result from a blow to the chin.

The patient with a condylar fracture usually presents with pain and edema over the joint area and limitation and deviation of the mandible to the injured side on opening.

Bilateral condylar fractures may result in an anterior open bite.

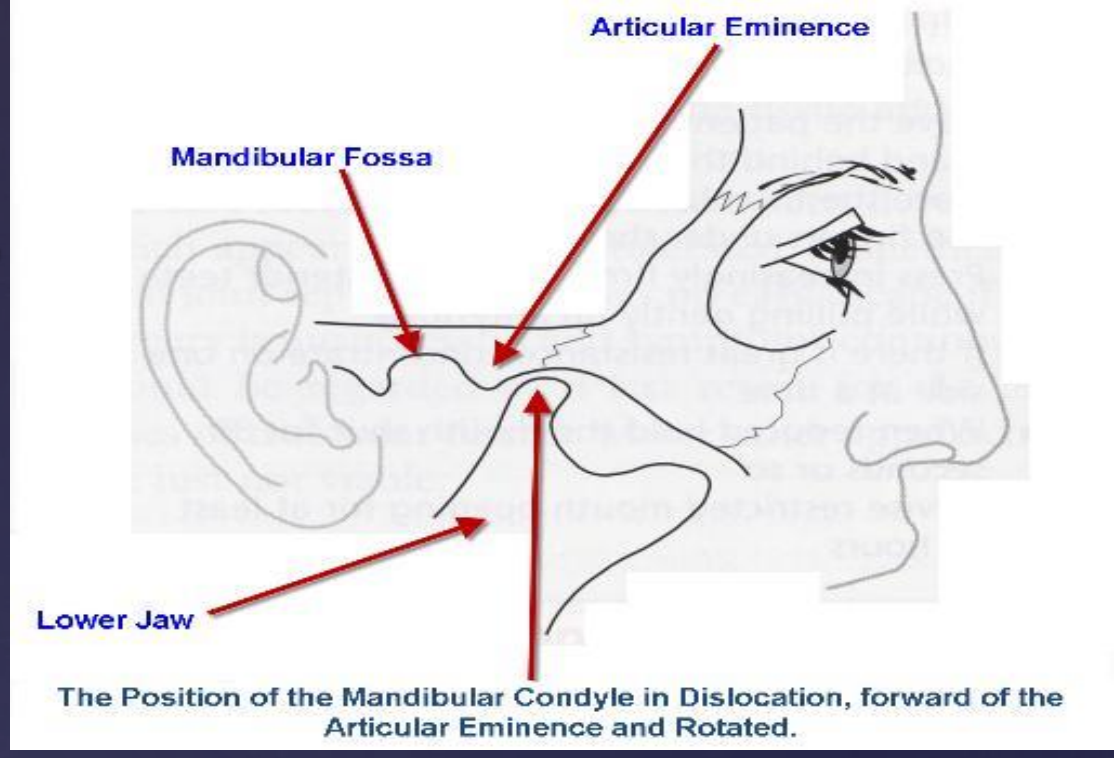
The diagnosis of a condylar fracture is confirmed by diagnostic imaging.



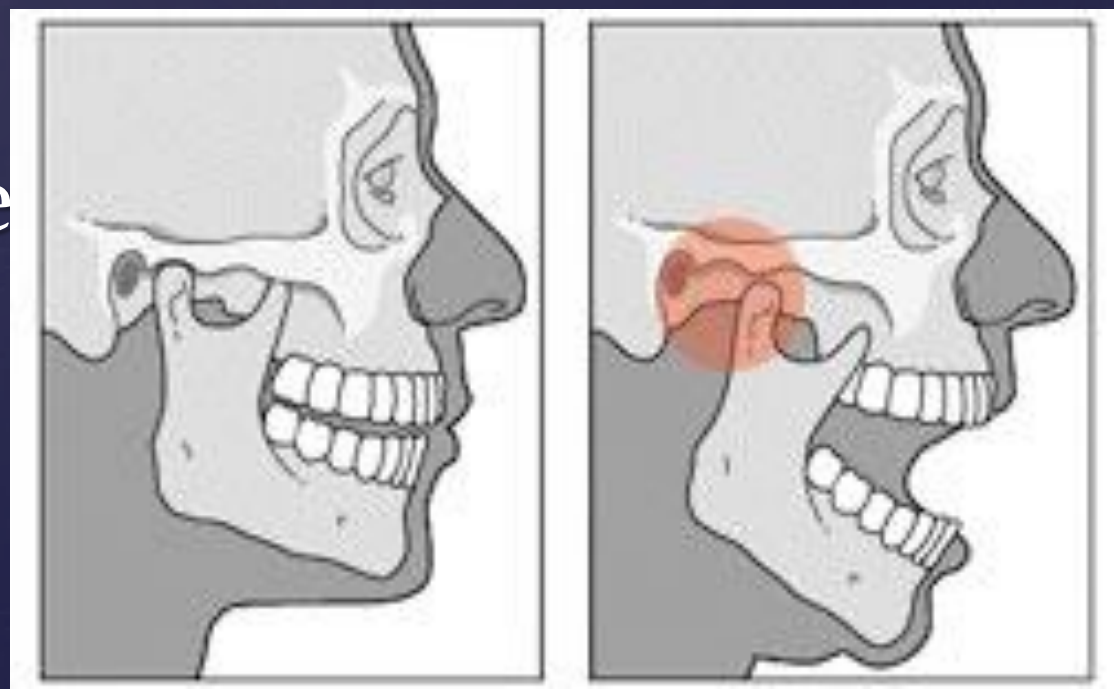
Dislocation

In dislocation of the mandible, the condyle is positioned anterior to the articular eminence and cannot return to its normal position without assistance.

This disorder contrasts with subluxation, in which the condyle moves anterior to the eminence during wide opening but is able to return to the resting position without manipulation.



The Position of the Mandibular Condyle in Dislocation, forward of the Articular Eminence and Rotated.



Dislocations of the mandible usually result from muscular incoordination in wide opening during eating or yawning and less commonly from trauma;
they may be unilateral or bilateral.
The typical complaints of the patient are an inability to close the jaws and pain related to muscle spasm.

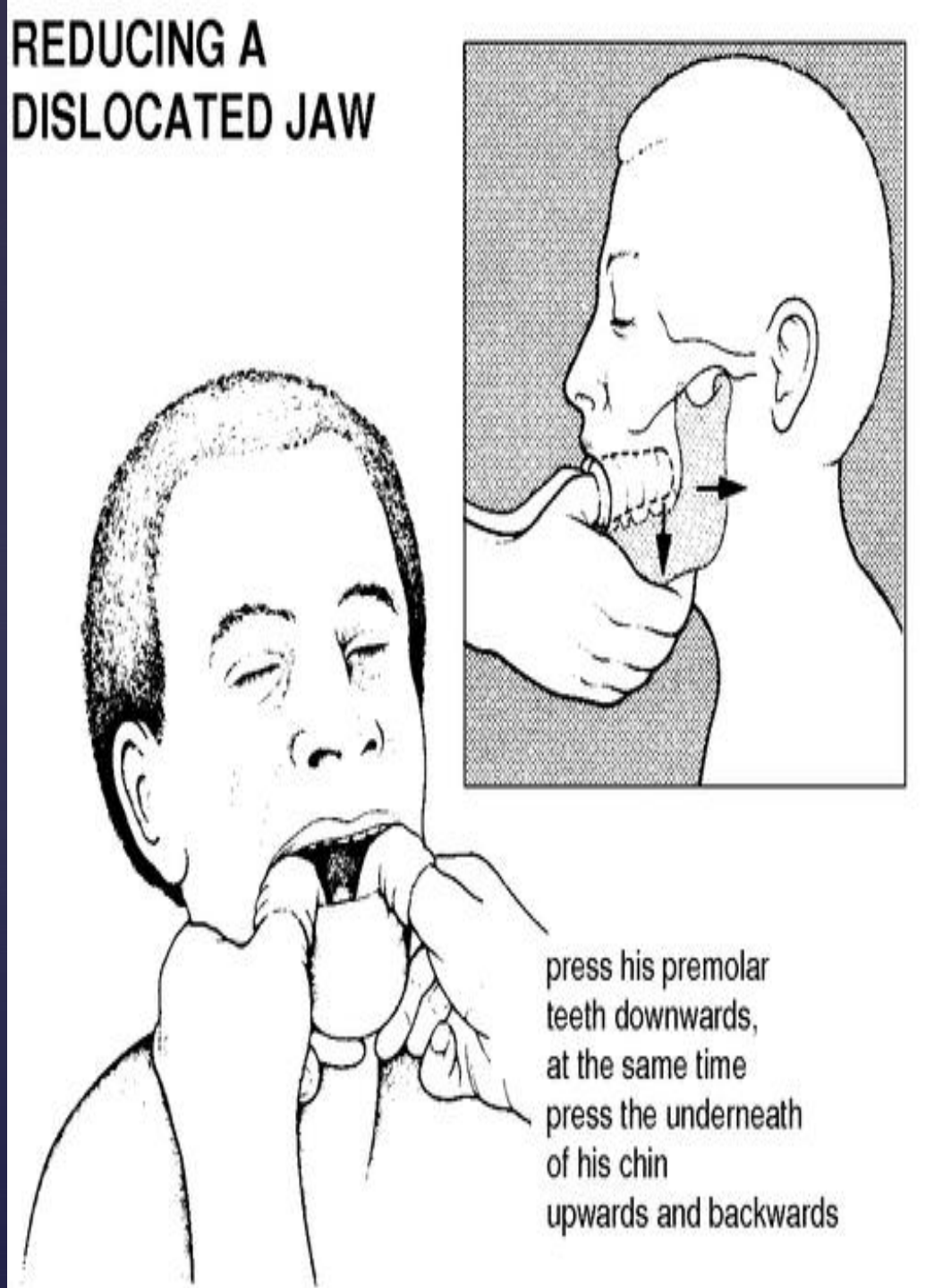
The condyle can usually be repositioned without the use of muscle relaxants or general anesthetics.

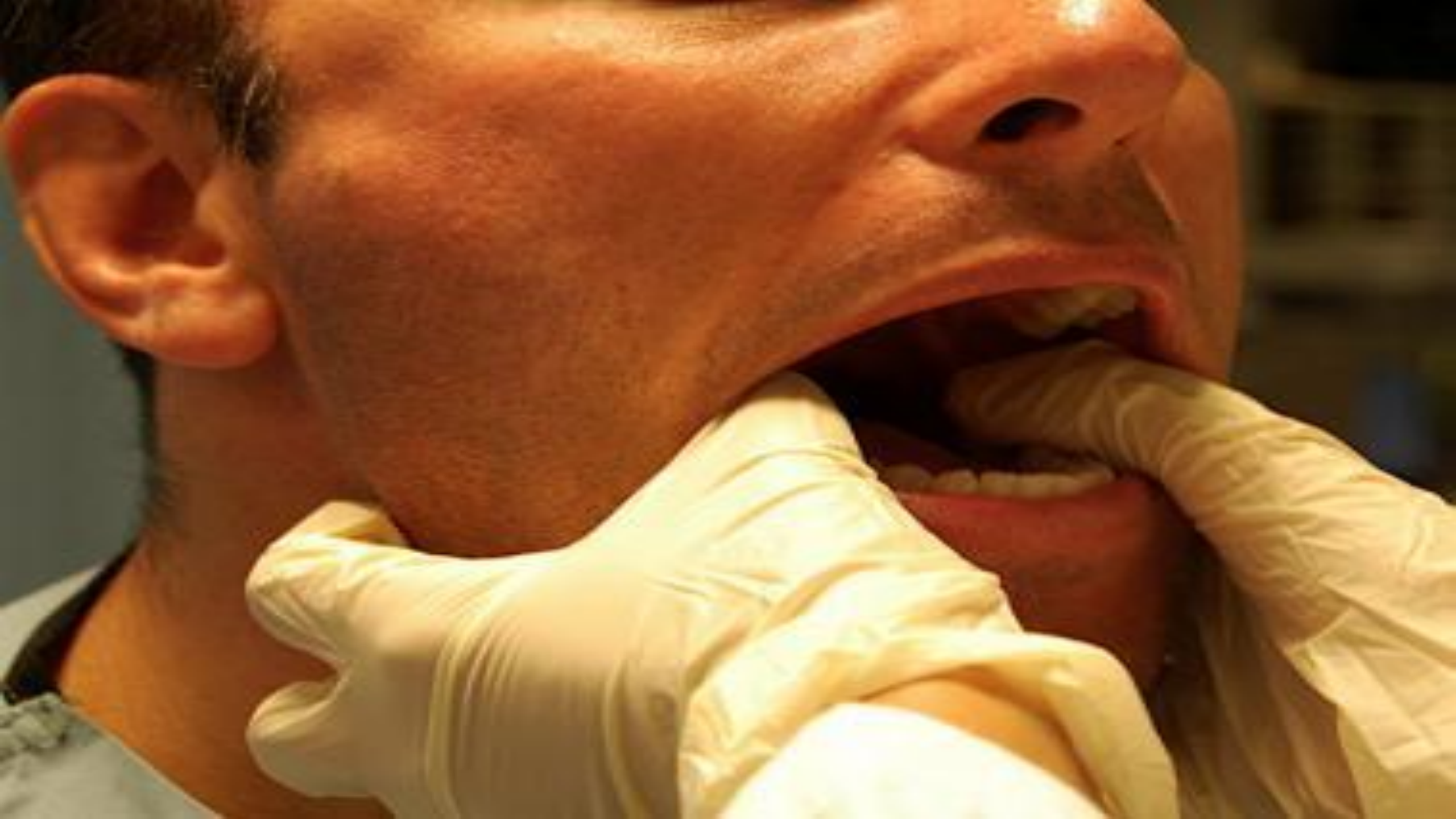
If muscle spasms are severe and reduction is difficult, the use of intravenous diazepam (approximately 10 mg) can be beneficial.

The practitioner who is repositioning the mandible should stand in front of the seated patient and place his or her thumbs lateral to the mandibular molars on the buccal shelf of bone; the remaining fingers of each hand should be placed under the chin.

The condyle is repositioned by a downward and backward movement. This is achieved by simultaneously pressing down on the posterior part of the mandible while raising the chin.

As the condyle reaches the height of the eminence, it can usually be guided posteriorly to its normal position.





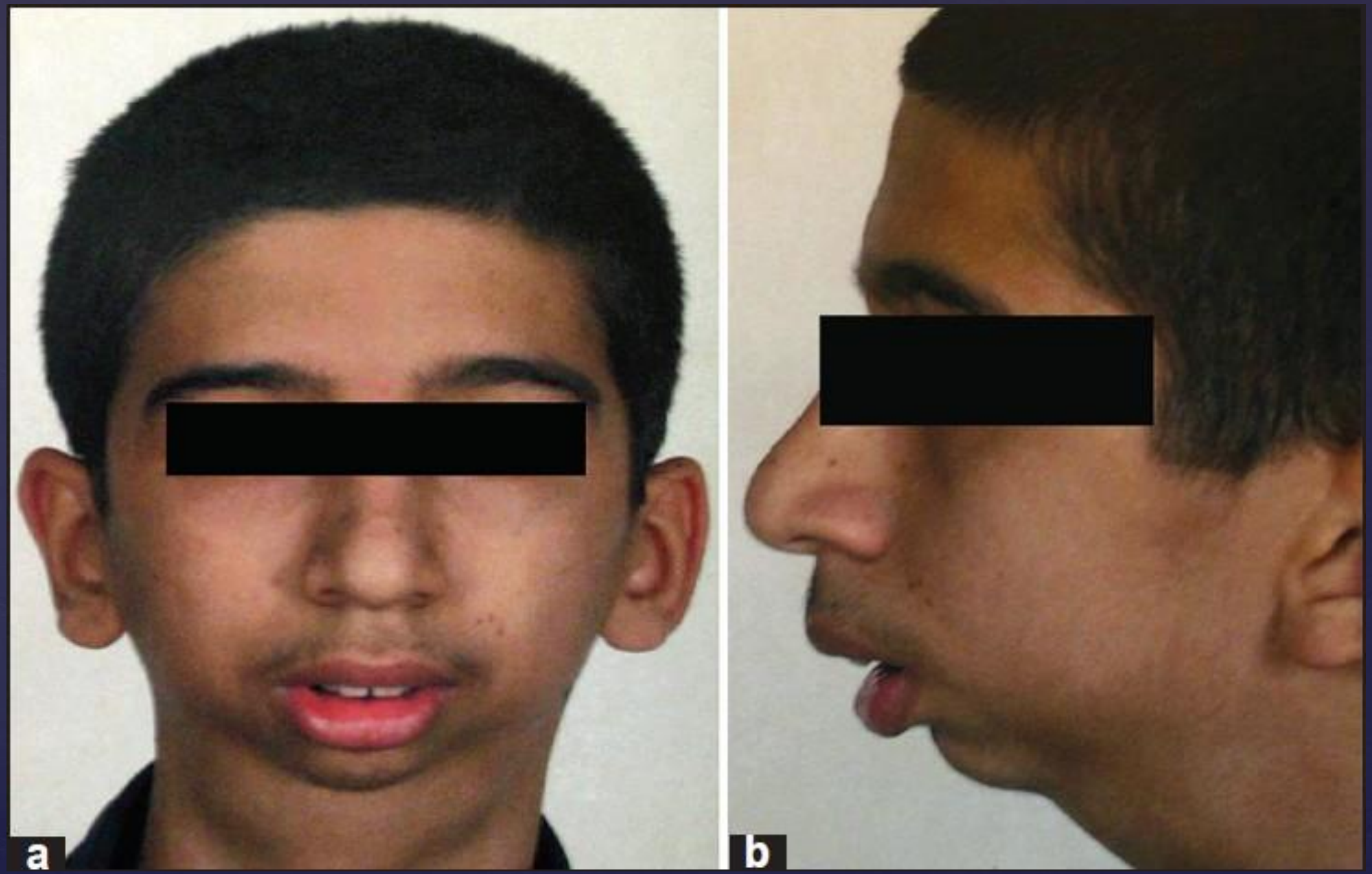
Ankylosis

True bony ankylosis of the TMJ involves fusion of the head of the condyle to the temporal bone.

Trauma to the chin is the most common cause of TMJ ankylosis, although infections also may be involved.

Ankylosis frequently results from prolonged immobilization following condylar fracture.

Limited mandibular movement, deviation of the mandible to the affected side on opening, and facial asymmetry may be observed in TMJ ankylosis.


a
b

Bruxism

Nocturnal bruxing is thought to aggravate or contribute to the persistence of pain symptoms associated with TMD. Occlusal appliances may protect the teeth from the effects of bruxism but cannot be expected to prevent or decrease the bruxing activity. When bruxing is considered to be the cause or a factor of TMD symptoms, oral appliance therapy is effective, but symptoms are likely to return when appliance therapy is withdrawn. Occlusal splints worn during sleep have not been found to stop bruxing but do reduce the signs of bruxing.

Red and White Lesions of the Oral Mucosa Dr. Rehab Faisal

Oral mucosal lesions may be classified according to different characteristics

-**INFECTIOUS DISEASES:** Oral Candidiasis **and** Hairy Leukoplakia

- PREMALIGNANT LESIONS

Oral Leukoplakia and oral Erythroplakia

Oral Submucous Fibrosis

- IMMUNOPATHOLOGIC DISEASES

Oral Lichen Planus

Drug-Induced Lichenoid Reactions

Lichenoid reactions of Graft-versus-Host Disease

Lupus Erythematosus

- ALLERGIC REACTIONS

Lichenoid Contact Reactions

Reactions to Dentifrice and Chlorhexidine

- TOXIC REACTIONS

Reactions to Smokeless Tobacco Smoker's Palate

- REACTIONS TO TRAUMA

Mechanical, chemical **and** thermal

- OTHER RED AND WHITE LESIONS:

Benign Migratory Glossitis (Geographic Tongue)

Leukoedema

White Sponge Nevus **and** Hairy tongue

A white appearance of the oral mucosa may be caused by a variety of factors.

-Hyperkeratosis: an increased production of keratin.

-Keratosis: keratinization of epithelium that is not normally keratinized.

-Acanthosis: is a benign thickening of stratum spinosum.

-Intra and extracellular: accumulation of fluid in the epithelium may also result in clinical whitening.

-Necrosis: of the oral epithelium may occur when the oral mucosa is exposed to toxic chemicals, microbes (particularly fungi can produce whitish pseudomembranes consisting of sloughed epithelial cells) and neutrophils, which are loosely attached to the oral mucosa.

•**The term white patch**: is often used clinically to describe the appearance of lesion presenting as white areas on the oral mucosa without evidence of significant enlargement, erythema or ulceration. Like the Leukoplakia which is defined as a predominately white lesion that cannot be characterized as any other definable lesion. Two types:

- Homogenous leukoplakia.

- Non homogenous leukoplakia

The White lesions appear white due to the following:

1. Hyperkeratosis (the ability of abnormal keratin to evenly reflect the visible light spectrum) because of hydration or water imbibtion in a manner similar to the reaction seen in the stratum corneum of epidermis following prolonged soaking in water.

2. Superficial materials: necrosis of epithelium, food remnants, plaque & inflammatory exudates.

3. Sub-mucosal changes which are diminished vascularity & covered by normal epithelium.

•**Erythroplakia (red lesion):** is defined as a red lesion of the oral mucosa that cannot be characterized as any other definable lesion. The lesion comprises an eroded red lesion that is frequently observed with a distinct demarcation against the normal-appearing mucosa.

Red lesions or red patch appear so due to:-

1. Thin epithelium (atrophy), so underlying vessels become closer to the surface.

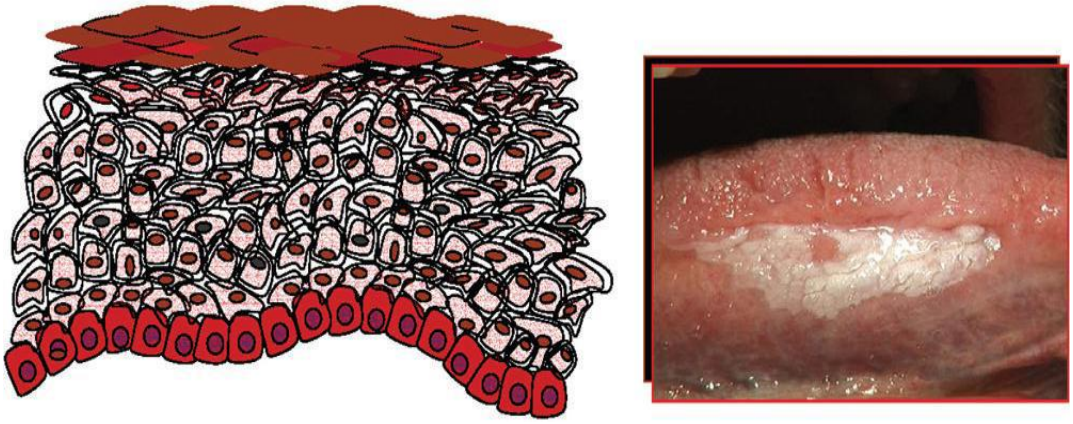
2. Loss of keratin layer.

3. Increased no. or dilated blood vessels (inflamed).

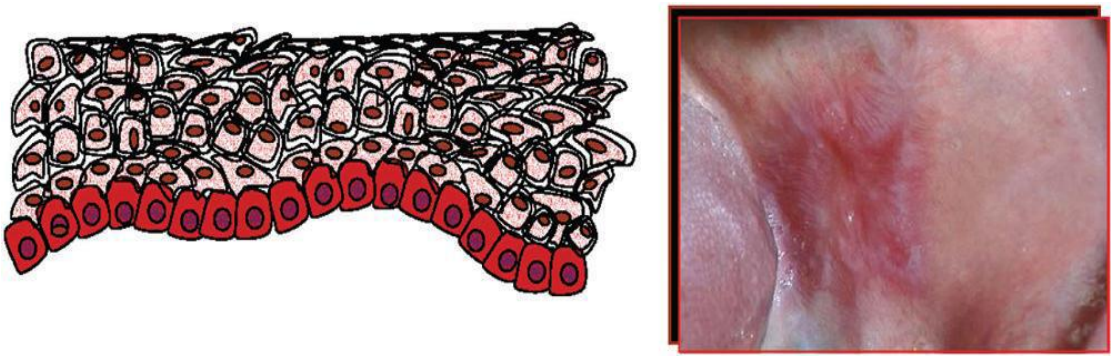
4. Change in the intrinsic nature of the epithelium such as epithelium dysplasia

Main clinical characteristics of red or white lesions.

- Is pain present?
- Are lesions single or multiple?
- Are lesions bilateral or unilateral?
- Is the distribution of lesions linked to mucosal type?
- Are lesion borders defined or indistinct?
- Date of onset
- Are lesions associated with changes of the skin?
- Duration of lesion
- Any changes in shape, size, or texture with time?
- Any previous response to therapy?
- What makes the pain or the lesions worse?
- Have lesions healed and recurred?



Mechanisms leading to a white appearance of the oral mucosa due to an increased production of keratin (hyperkeratosis)



Mechanisms leading to a red appearance of the oral mucosa; a red lesion of the oral mucosa may develop as the result of an atrophic epithelium (atrophy)

Cellular atypia: cellular changes with cytologically characterized malignant and premalignant lesion.

Epithelial dysplasia is defined in general terms as a precancerous lesion of stratified squamous epithelium characterized by cellular atypia and loss of normal maturation short of carcinoma in situ.

Carcinoma in situ is defined as a lesion in which the full thickness of squamous epithelium shows the cellular features of carcinoma without stromal invasion.

Criteria Used for Diagnosing Epithelial Dysplasia

1. Cellular and nuclear pleomorphism (different size and shape).
2. Increased nuclear-cytoplasmic ratio.
3. Loss of polarity of basal cells.
4. Nuclear hyperchromatism and prominent nucleoli.
5. Enlarged nuclei
6. Basal cell hyperplasia.
7. Drop-shaped rete ridges.
8. Irregular epithelial stratification
9. Increased and abnormal mitosis.
10. Loss of intercellular adherence.
11. Abnormal keratinization**.**

Note: atypia refers to cells while the dysplasia refers to tissue.

Oral candidiasis:

C. albicans, C. tropicalis, and yeast like fungus are comprised together over 80% of the species isolated from human Candida infections. It is opportunistic infection. The C. albicans is usually a weak pathogen, and candidiasis is said to affect the very young, the very old, and the very sick. Oral candidiasis is divided into primary and secondary infections. The primary infections are restricted to the oral and perioral sites, whereas secondary infections are accompanied by systemic mucocutaneous manifestations

Pathogenesis:

To invade the mucosal lining, the microorganisms must adhere to the epithelial surface; therefore, candidal strains with better adhesion potential are more virulent than strains with poorer adhesion ability.The yeasts' penetration of the epithelial cells is facilitated by their production of lipases and for the yeasts to remain within the epithelium, they must overcome constant desquamation of surface epithelial cells.

Predisposing factors for Oral Candidiasis and Candida-Associated Lesions

• Local predisposing factors:

-Denture wearing.

-Smoking.

-Topical and inhalation steroid.

-Xerostomia.

-Poor oral hygiene.

-Imbalance of the oral microflora

-Quality and quantity of saliva

• General predisposing factors:

-Immunosuppressive diseases.

-Immunosuppressive drugs.

- Impaired health status

-Chemotherapy.

-Endocrine disorder.

-Debilitated patients (diabetes mellitus, anemia, malnutrition, leukemia and bone marrow transplantation).

Diagnosis of oral candidiasis:

1. on clinical appearance.

2. Smear from the infected area, which comprises epithelial cells.

3. Culture on Sabouraud agar medium.(more sensitive).

Classification of oral candidiasis:

■ Acute:

*Acute pseudo-membranous candidiasis (thrush).

*Acute atrophic candidiasis (antibiotic sore-mouth).

■Chronic: Chronic Plaque-Type and Nodular Candidiasis. (Candidal leukoplakia)(Chronic hyperplastic candidiasis).

■ Candida -associated lesions:

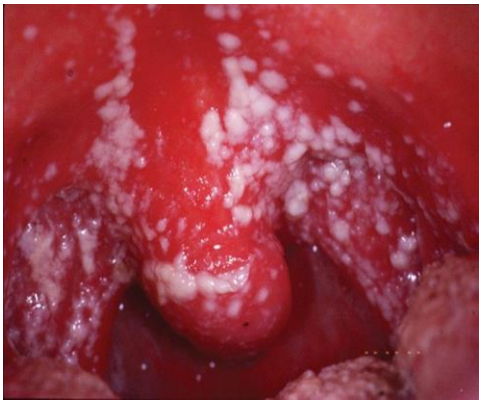
*Denture stomatitis

*Angular cheilitis

*Median rhomboid glossitis.

* Oral Candidiasis Associated with HIV.

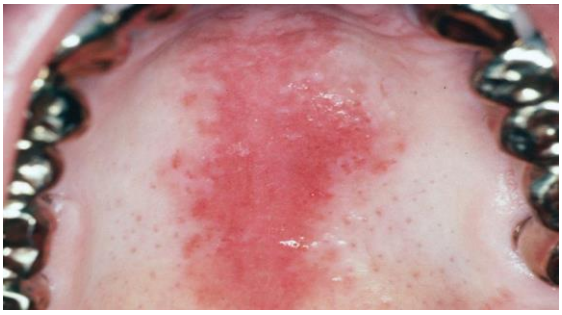
1. Oral thrush or acute pseudomembranous candidiasis: It is a superficial infection of the upper layers of the mucosal epithelium and presents with loosely attached membranes comprising fungal organisms and cellular debris, which leaves an inflamed, sometimes bleeding area if the pseudomembrance is removed. The infection predominantly affects patients taking antibiotics, immunosuppressant drugs, or having a disease that suppresses the immune system.



Diagnosis: by clinical appearance & confirmation by smear or culture.

2. **Acute atrophic candidiasis (antibiotic sore-mouth):**

An erythematous surface may not just reflect atrophy but can also be explained by increased vascularization. The lesion has a diffuse border which helps distinguish it from erythroplakia which usually has a sharper demarcation. It is affect the dorsum of tongue and palate in patient who are using inhalation steroid, smoking and treatment with broad-spectrum antibiotics.



-**Diagnosis:** by history and smear.

-Chronic plaque type and Nodular Candidiasis: (Replaces the older term, candidal leukoplakia), the typical clinical presentation is characterized by a white irremovable plaque, which may be indistinguishable from an oral leukoplakia. The chronic plaque type and nodular candidasis have been associated with malignant transformation, but the possible role of yeasts in oral carcinogenesis is unclear.

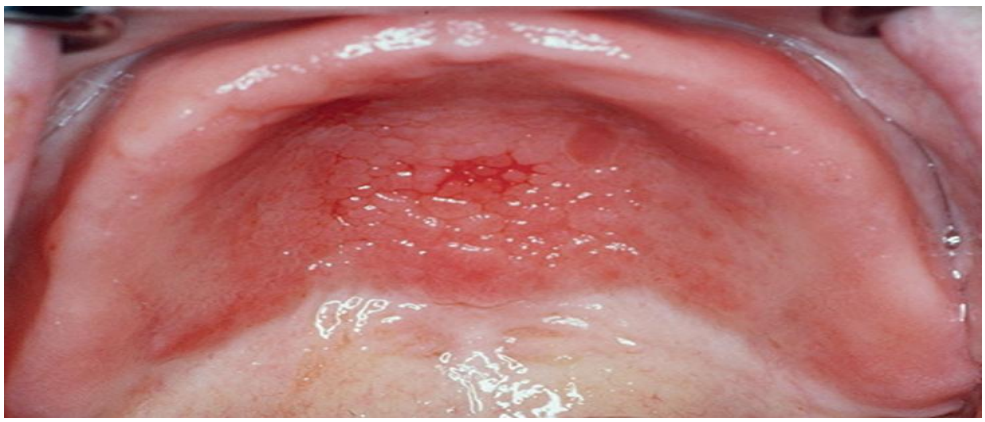
It has been hypothesized that it may act through its capacity to catalyze nitrosamin production

Candida –associated lesions:

***Denture stomatitis:-** diffuse inflammation of the maxillary denture- bearing area, sometime with angular chelilitis. The denture serves as a vehicle that protects the microorganisms from physical influences such as salivary flow. **Clinically** it is appear as patchy red, thin surface with pain and burning.

The denture stomatitis is classified into three different types:

Type I is limited to minor erythematous sites caused by trauma from the denture. **Type II** affects a major part of the denture-covered mucosa In addition to the features of type II; **Type III** has a granular mucosa ((reactive proliferation of underlying fibrous tissue))



Chronic atrophic candidiasis (denture stomatitis) type III with a granular mucosa in the central part of the palate

***Angular cheilitis:-** Its infected fissures of the commissures of the mouth, often surrounded by erythema. The lesions are frequently coinfected with both Candida and Staphylococcus aureus. Dry skin may promote the development of fissures in the commissures, allowing invasion by the microorganisms, 30% of patients with denture stomatitis also have angular cheilitis, but this infection is only seen in 10% of denture-wearing.

Causes:

1. Decreased vertical dimension.

2. Nutritional deficiency (iron, vitamin B12, folic acid).

3. Diabetes.

4. Co-existent denture stomatitis.

5. Dry skin.

Clinically: it appears as a deep crack, sometimes covered with a white membrane; develop at the corners of the mouth (commissures).

Diagnosis by: history, clinical examine, blood investigation, smear and culture.

***Median Rhomboid Glossitis:-** clinically characterized by an erythematous lesion in the center of the posterior part of the dorsum of the tongue (immediately anterior to the circumvallate papillae). The lesion has an oval configuration, a symptomatic and management is restricted to a reduction of predisposing factors, the erythema resulting from atrophy of the filiform papillae and the surface may be lobulated. The lesion shows a mixed bacterial/fungal microflora. Smokers and denture-wearers have an increased risk of developing median rhomboid glossitis. The lesion does not entail any increased risk for malignant transformation.

***Oral Candidiasis Associated with HIV**

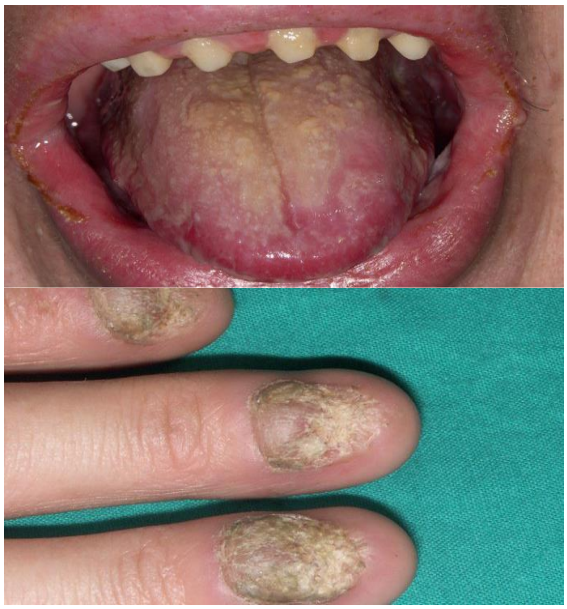
More than 90% of acquired immune deficiency syndrome (AIDS) patients have had oral candidiasis during the course of their HIV infection, and the infection is considered a portent of AIDS development.

The most common types of oral candidiasis in conjunction with HIV are:

Pseudomembranous candidiasis, Erythematous candidiasis, Angular cheilitis and chronic plaque-like candidiasis

Chronic mucocutaneous candidiasis (CMC)

- Involves a heterogeneous group of disorders, which in addition to oral candidiasis, also affect the skin, typically the nail and other mucosal linings, such as the genital mucosa.
- The face and scalp may be involved.
- Approximately 90% of the patients with CMC also present with oral candidiasis.
- The oral manifestations may involve the tongue, and lesions are seen in conjunction with fissures.
- CMC can occur as part of endocrine disorders, including hyperparathyroidism and Addison's disease.
- Recent studies revealed that an impairment of interleukin-17 (IL-17) immunity underlies the development of CMC
- T-helper 17 cells produce IL-17 and play an important role in host mucosal immunity to Candida



Chronic candidiasis of dorsum of tongue and fingernails of a patient with chronic mucocutaneous candidiasis

Diagnosis and treatment:

To increase the sensitivity, a second scrape can be transferred to a transport medium followed by cultivation on **Sabouraud agar**. To discriminate between different candidal species, an additional examination can be performed on Pagano-Levin agar. The result is expressed as colony forming units per cubic millimeter (CFU/mm2). **Salivary culture techniques** are primarily used in parallel with other diagnostic methods to obtain an adequate quantification of candidal organisms. Patients who display clinical signs of oral candidiasis usually have more than 500 CFU/mL.

In chronic plaque-type and nodular candidiasis, cultivation techniques have to be supplemented by a histo-pathological examination. This examination is primarily performed to identify the presence of **epithelial dysplasia and to identify invading candidal organisms by PAS staining.**

Treatment for fungal infections, which usually include antifungal regimens, will not always be successful unless the clinician addresses predisposing factors that may cause recurrence. Local factors are often easy to identify but sometimes not possible to reduce or eradicate.

- In smokers, cessation of the habit may result in disappearance of the infection even without antifungal treatment

- Antifungal drugs belong to the groups of **polyenes or azoles Polyenes such as nystatin and amphotericin B are usually the first choices** in treatment of primary oral candidiasis and are both well tolerated.

- Elimination or reduction of predisposing factors should always be the first goal for treatment

- This involves improved denture hygiene, not to use the denture while sleeping.

- The denture hygiene is important to remove nutrients, including desquamated epithelial cells, which may serve as a source of nitrogen essential for the growth of the yeasts

- Denture cleaning also disturbs the maturity of a microbial environment established under the denture.

- **Porosities** in the denture can harbor microorganisms, which may not be removed by physical cleaning; **the denture should be stored in antimicrobial solutions during the night.** Different solutions including alkaline peroxides, alkaline hypochlorites acids, disinfectants, and enzymes, have been suggested. Chlorhexidine may also be used but can discolor the denture and also counteracts the effect of nystatin.

- Type III denture stomatitis may be treated with surgical excision in an attempt to eradicate microorganisms present in the deeper fissures of the granular tissue. If this is not sufficient, continuous treatment with topical antifungal drugs should be considered.

- Topical treatment with **azoles s**uch **as miconazole** is the treatment of choice for angular cheilitis often infected by both S. aureus and candidal strains. (Biostatic effect on S. aureus in and fungistatic effect)

- If angular cheilitis comprises an erythema surrounding the fissure; **a mild steroid ointment** may be required to suppress the inflammation.

- To prevent recurrences, patients have to apply a moisturizing cream, which may prevent new fissure formation.

Systemic azoles may be used for deeply seated primary candidiasis, such as **chronic hyperplastic candidiasis, denture stomatitis, and median rhomboid glossitis with a granular appearance,**

There are several disadvantages with the use of azoles.

- They are known to interact with warfarin, leading to an increased bleeding propensity.

- Topical applications as the azoles are fully or partly resorbed from the GIT.

- Development of resistance is particularly compelling for fluconazole in individuals with HIV disease. In such cases, ketoconazole and itraconazole have been recommended as alternatives.

- The azoles are also used in the treatment of secondary oral candidiasis associated with systemic predisposing factors and for systemic candidiasis.

• Oral Hairy leukoplakia (HL):

One of etiological factors of Leukoplakia is viruses; it is associated with HIV infection. The lesion is not pathognomonic for HIV since other immune deficiencies, such as immunosuppressive drugs and cancer chemotherapy, are also associated with HL. The HL is strongly associated with Epstein-Barr virus (EBV) and with low levels of CD4+ T lymphocytes. The Antiviral medication, which prevents EBV replication, is curative

Clinically:

The typical clinical appearance is vertical white folds along the borders of the tongue. The lesions may also be displayed as white and somewhat elevated plaque, which cannot be scraped off. It also presents on (dorsum of tongue and in the buccal mucosa). It is asymptomatic,although symptoms may be present when the lesion is superinfected with candidal strains.

The diagnosis of HL is based on clinical characteristics and histopathological examination and detection of EBV can be performed to confirm the clinical diagnosis.

Management

- It can be treated successfully with antiviral medication, but this is not often indicated as this disorder is not associated with adverse symptoms.

- the disorder may show spontaneous regression.

Oral Potentially Malignant Disorders Oral Leukoplakia

Oral Leukoplakia is defined as a white plaque of questionable risk for malignant transformation having excluded other known white lesions or disorders that carry no increased risk for cancer. Global review points at a prevalence oral Leukoplakia of 1.5 to 2.6%

- Most oral leukoplakias are seen in patients beyond the age of 50 and infrequently encountered below the age of 30.

- Leukoplakias are more common in men but a slight majority for women has been found in some studies. It can be further divided into: **Homogeneous type** characterized as a white, often well-demarcated plaque with an identical reaction pattern throughout the entire lesion. **Non-homogeneous type** combined appearance of white and red areas; the nonhomogeneous oral leukoplakia has also been called erythroleukoplakia and speckled leukoplakia.

Oral erythroplakia:

Erythroplakia is a fiery red patch that cannot be characterized clinically or pathologically as any other definable disease. Oral erythroplakia is not as common as oral leukoplakia, and the prevalence has been estimated to be in the range of 0.02 – 0.1%.

The gender distribution is reported to be equal Erythroplakia is defined as a red lesion of the oral mucosa that excludes other known pathologies. Erythroplakia is usually asymptomatic, although some patients may experience a burning sensation with food intake. A special form of erythroplakia has been reported that is related to reverse smoking of chutta, predominantly practiced in India. Both those diagnoses thus require exclusion of other similar-looking lesions of known causes or mechanisms before being applied.

Oral leukoplakia may be found at all sites of the oral cavity, smokers have a higher percentage of leukoplakia at the border of the tongue compared with non-smokers. The relative importance of one versus the other is that leukoplakia is very common and can sometimes transform into cancer, whereas erythroplakia is rather uncommon but frequently represents a precursor to cancer. The floor of the mouth and the lateral borders of the tongue have been considered high-risk sites for malignant transformation. However, the distinction between high- and low-risk sites has been questioned leaving the size of the lesion and the homogenous/non-homogenous pattern being for the prognosis.

In oral leukoplakia, where the white component is dominated by papillary projections, similar to oral papilloma, are referred to as **verrucous or verruciform leukoplakias.** The oral leukoplakia with a more aggressive proliferation pattern and high recurrence rate are designated **as proliferative verrucous leukoplakia (PVL)**

PVL is usually

Seen in older women and the lower gingiva is a predilection site.

The malignant potential is very high and verrucous carcinoma or squamous cell carcinoma may be present at the primary examination.

similar to what is seen in oral papillomas, the PVL has been suspected to have a viral etiology

Diagnosis

The diagnostic procedure of oral leukoplakia and erythroplakia is identical.

The provisional diagnosis is based on the clinical observation of a white or red patch that is not explained by a definable cause, such as trauma.

If trauma is suspected, the cause, such as a sharp tooth or restoration, should be eliminated.

If healing does not occur in two weeks, a tissue biopsy is essential to rule out malignancy

Homogeneous leukoplakia is associated with a decreased risk for malignant transformation than nonhomogeneous and erythroplakia and lesions not exceeding 200 mm2 appear to have a better prognosis than larger lesions.

No consensus has been reached regarding management and follow-up of oral leukoplakia & erythroplakia and the surgery will remain the treatment of choice for oral leukoplakia and erythroplakia.

A general recommendation is to reexamine the premalignant site irrespective of surgical excision every three months for the first year.

If the lesion does not relapse or change in reaction pattern, the follow-up intervals may be extended to once every six months.

New biopsies should be taken if new clinical features emerge.

Following five years of no relapse, self-examination may be a reasonable approach.

Oral Submucous Fibrosis: Is a chronic disease affecting the oral mucosa, as well as the pharynx and the upper two-thirds of the esophagus. Areca nuts in the etiology behind oral submucous fibrosis. Areca nut–derived products are commonly used by several hundred million individuals in different parts of ASIA.

There is dose dependence between areca quid chewing habit and the development of this oral mucosal disorder.

During the development of fibrosis, a decrease in water-retaining proteoglycans will occur in favor of increased collagen type I production.

Genetic predisposition of importance for the etiology

Polymorphism of the gene, which is coding for tumor necrosis factor α (TNF-α), has been reported to promote the development of the disorder.

Fibroblasts are stimulated by TNF-α, thereby participating in the development of fibrosis

The oral complications are most commonly observed: on the lips, buccal mucosa, retromolar area, and soft palatal mucosa.

Clinical Findings

The First Signs are erythematous lesions, sometimes in conjunction with petechiae, pigmentations,and vesicles followed by a paler mucosa, (white marbling)

The most prominent clinical characteristics include fibrotic bands located beneath an atrophic epithelium.

Increased fibrosis eventually interferes with speech, tongue mobility, and a decreased ability to open the mouth.

The atrophic epithelium may cause inability to eat hot and spicy food.

Diagnosis:

The diagnosis of oral submucous fibrosis is based on the clinical characteristics and on the patient's report of a habit of betel chewing. An international consensus has been reached where at least one of the following characteristics should be present:

•• Palpable fibrous bands

•• Mucosal texture feels tough and leathery

•• Blanching of mucosa together with histopathological features consistent with oral submucous fibrosis (atrophic epithelium with loss of rete ridges and juxta-epithelial hyalinization of lamina propria)

Management: Products derived from areca nuts are carcinogenic, regardless of concomitant use of tobacco products.Thus, treatment of oral submucous fibrosis should be focused on cessation of the chewing habits. If this is successfully implemented, early lesions have a good prognosis as they may regress.

Several treatment strategies have been tried, such as:

- topical and systemic steroids,
- Supplement of vitamins and nutrients,
- Repeated dilatation with physical devices,
- and surgery.

Immunopathological Diseases: Assist. Prof. Dr. Rehab Faisal

Lichen Planus: It is a family of lesions

with different etiologies

With a common clinical and histologic appearance

neither clinical nor histopathologic features enable discrimination between different lichenoid reactions but may be used to distinguish them from other pathologic conditions of the oral mucosa.

This group includes the following disorders:

•• Oral lichen planus

••Lichenoid contact reactions

••Lichenoid drug eruptions

••Oral Lichenoid reactions of graft-versus-host disease (GVHD)

These lesions represent a delayed hypersensitivity reaction to constituents derived from dental materials or flavoring agents in foods and other ingested substances.

The etiology of OLP is not known, but in the recent studies evident the immune system has a primary role in the development of this disease. This is supported by the histopathologic characteristics of a subepithelial band–formed infiltrate dominated by T lymphocytes and macrophages and the degeneration of basal cells known as liquefaction degeneration. The OLP is a chronic inflammatory disease of skin and mucous membrane; it mainly affects patients of middle age or over especially women, it is common and if untreated can persist for many years.The condition usually occurs in people older than 40 years, the mean age of onset being 53 years.It is very rarely encountered in children, and does not seem to have a hereditary predisposition.

Other factors, such as stress, may also be of importance to establish this inflammatory process. It is not unusual that patients report that they have

been exposed to negative social events months before the onset of the disease. Altogether, this makes the etiology behind OLP a multifactorial process

Clinically:

OLP may contain both red and white elements and provide together with the different textures, types of OLP

Reticulum

Papules

Plaque-like

Bullous

Erythematous (atrophic)

Ulcerative

The distribution of lesion is mostly the buccal mucosa particularly posteriorly; the next most common site is the tongue, lip, palate and gingiva. The lesions are very often symmetrical, but in some cases are more prominent on one side than another.

OLP confined to the gingiva may be entirely erythematous, with no reticular or papular elements present, and this type of lesion has to be confirmed by a biopsy.

Hyperkeratotic white striations Wickham's striae, which are a hallmark of the condition.Typically, the reticular, papular, and plaque-like, are asymptomatic, although the patient may experience a feeling of roughness.

-Reticular: - is characterized by fine white lines or striae that may form a network but can also show annular (circular) patterns. The striae often display a peripheral erythematous zone, which reflects the subepithelial inflammation, most frequently this form is observed bilaterally in the buccal mucosa and rarely on the mucosal side of the lips.

-Papular type:- It is clinically characterized by small white dots, sometimes the papular elements merge with striae as part of the natural course.

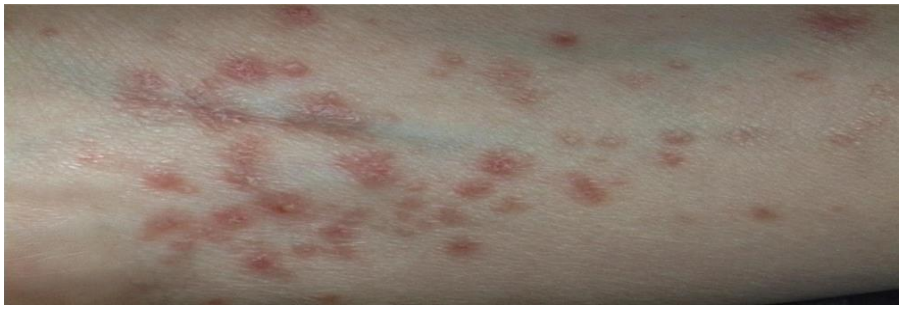
-Plaque-type:- shows a homogeneous well-demarcated white plaque often, but not always, surrounded by striae. Plaque-type lesions may clinically be very similar to homogeneous oral leukoplakia.

-Erythematous (atrophic) OLP:- is characterized by a homogeneous red area. It is present in the buccal mucosa or in the palate and striae are frequently seen in the periphery. Some patients may display erythematous OLP affecting attached gingiva.

-Ulcerative type:- Clinically, the fibrin-coated ulcers are surrounded by an erythematous zone frequently displaying radiating white striae. As for the erythematous form of OLP, the affected patient complains of a smarting sensation in conjunction with food intake.

Cutaneous lesions may be seen in approximately15% of patients with OLP. The classic appearance of skin lesions consists of pruritic erythematous flat topped.The predilection sites are the trunk and flexor surfaces of arms and legs

 Symptoms including burning and pain, following intense scratching of the lesions, trauma may aggravate the disease, which is referred to as a Koebner phenomenon (appearance of new skin lesions on previously unaffected skin secondary to trauma). This phenomenon may also be of relevance for OLP, which is continuously exposed to physical trauma during mastication and brushing.



Cutaneous lichen planus on the flexor side of the fore arm.

Diagnosis: - A biopsy for histopathology examination.

In patients with gingival erythematous lesions, it may be difficult to find striae or papules. A biopsy is usually required for an accurate diagnosis of this type of OLP.It is important that the biopsy is taken as far as possible from the gingival pocket to avoid inflammatory changes due to periodontal disease

-**Treatment:**

-Topical corticosteroids. Are preferably used as a mouth rinse or a gel.These formulas are often easier for the patient to administer than a paste. **A reasonable approach may be to apply the drug two to four times a day for one to two months**, followed by tapering during the following eight weeks until a maintenance dose of two to three times a week is reached.

-Kenalog in ora-base ointment (1% Triamicnolone in oral past) is given by 2-4 times daily.

-In severe cases, the treatment become with systemic corticosteroid. A dose of 0.5–1 mg/kg prednisolone daily for seven days has been suggested, followed by a reduction of 5 mg each subsequent day. Maintenance dose with topical steroids may be commenced during tapering of systemic steroids.

How can differentiate clinically between LP and OLP?

•In LP the demarcation is usually very distinct, while in OLP the white components have a more diffuse transition to the normal oral mucosa.

• The lack of a peripheral erythematous zone in LP.

Oral lichenoid drug eruptions:

-Have the same clinical and histopathologic characteristics as OLP

The patient's disease history may give some indication as to which drug is involved, Drugs or their metabolites act as haptens trigger a lichenoid reaction, like Penicillin, gold, and sulfonamides. The other drugs like antihypertensive agents (methyldopa), thiazide (diuretic) & anti-malaria.

Clinically: Lichenoid drug eruptions appear similar to lichen planus and may be severely pruritic.

Management: Discontinuance or change the drug and symptomatic treatment with topical steroids are often sufficient, **Withdrawal** of the drug are the most reliable ways to diagnose lichenoid drug eruptions. It may also take **several weeks** before an OLDE disappears following withdrawal.

Lichenoid reaction of graft-versus-host disease (GVHD):

The oral lesion of GVHD has the same clinical appearance of OLP but the lesion is usually more generalized, also skin involvement (pruritic maculopapular primarily affecting the palms and soles), however the oral cavity may be the primary or even the only site of chronic GVHD. The lichenoid reactions are frequently seen simultaneously with other characteristics, such as xerostomia and the presence of localized skin involvement and liver dysfunction.

The development of secondary malignancies has been recognized as a potentially serious complication of GVHD.Patients with a history of oral GVHD should therefore be examined for oral malignancies as part of the medical follow-up

Management: The same treatment strategy as for OLP may be used for chronic oral GVHD, that is, topical steroid preparations، such as fluocinonide and clobetasol gel.

Oral mucosal lesions that do not belong to the group of lichenoid reactions may sometimes comprise a differential diagnostic problem

.Discoid lupus erythematosus (DLE) shows white radiating striae sometimes resembling those of OLP. The striae present in DLE are typically more prominent, with a more marked hyperkeratinization, and the striae may abruptly terminate against a sharp demarcation. Histopathologic criteria for lupus erythematosus (LE) have been reported to discriminate against OLP.

Plaque-like OLP is discriminated from homogeneous oral leukoplakia as the latter is not featured with papular or reticular elements.

Erythematous OLP of the gingiva exhibits a similar clinical presentation as mucous membrane pemphigoid. In pemphigoid lesions, the epithelium is easily detached from the connective tissue by a probe or a gentle searing force (Nikolsky's phenomenon). A biopsy for routine histology and direct immunofluorescence are required for an accurate differential diagnosis.

Ulcerating conditions such as erythema multiforme and adverse reactions to non-steroidal anti-inflammatory drugs (NSAIDs) may be difficult to distinguish from ulcerative OLP.The former lesions, however, do not typically appear with reticular or papular elements in the periphery of the ulcerations.

Lupus Erythematosus: (SLE, DLE)

There are two types which are chronic discoid L.E. (localized type) and systemic L.E. (disseminated type). Etiology not known but genetic factors appears to be important. Autoimmune disease involves immune complexes. Environmental factors as sun exposure, drugs, chemical substances, and hormones which all have been reported to aggravate the disease. Females are affected much more frequently than males.

Clinically:

The oral lesions observed in SLE and DLE are similar in their characteristics. The typical clinical lesion comprises white striae with a radiating orientation, and these may sharply terminate toward the center of the lesions, which has a more erythematous appearance. The most affected sites are the gingiva, buccal mucosa, tongue, and palate.

DLE is restricted to the skin and usually occur on the face. These lesions may form butterfly-like rashes over the cheeks and nose known as malar rash. While the SLE characterized by skin rash (maculopapular), lymphadenopathy, kidney, liver, lung & nervous system are also frequently involved.

Diagnosis: SLE diagnosis with 4 or more of 11 criteria present at any time.

-Malar rash.

-Discoid lesion.

-Photosensitivity.

-Presence of oral ulcers.

-Non erosive arthritis of two joints or more.

-Serositis.

-Renal disorder.

-Neurological disorder.

-Hematological disorder (leukopenia, lymphopenia, thrompocytopenia and hemolytic anemia)

-Immunologic disorder (anti-DNA, anti-SM, or antiphospholipid antibodies).

-Direct immunohistochemistry is conducted to reveal granular deposition of IgM, IgG, IgA, and C3 (lupus band test) anti-nRNA (antinuclear ribonucleo-protein)

Laboratory Findings:

-Antinuclear antibodies are frequently found in patients with SLE and can be used to indicate a systemic involvement, but patients with other rheumatologic diseases, such as Sjögren's syndrome and rheumatoid arthritis, may be positive.

-Moderate to high titers of anti-DNA and anti-Smith antibodies are almost pathognomonic of SLE.

-Antibodies associated with Sjögren's syndrome, SLE [anti-SS-A(RO) and anti-SS-B(La).

Management:

-Topical steroids to relief of oral symptoms such as clobetasol propionate gel 0.05%, betamethasone dipropionate 0.05%

-Immunosuppressive drugs used to treat LE.

▼Allergic Reactions:

Oral Lichenoid Contact Reactions (LCR):

Due to a delayed hypersensitivity reaction to constituents derived from dental materials.

The majority of patients are patch test positive to mercury (Hg), which lends support to LCR being an allergic reaction.

Although Hg is usually considered the primary etiologic factor; other amalgam constituents may also initiate LCR.Other filling materials such as gold, composites, and glass ionomers may also generate reactions.

Clinically:

LCRs display the same reaction patterns as seen in OLP. The most clinical difference between OLP and LCR is the extension of the lesions. LCRs are confined to sites that are in contact with dental materials, such as the buccal mucosa and the border of the tongue, non-symptomatic, but when erythematous or ulcerative the patient may has discomfort from spicy and warm food constituents. Lichenoid reactions in contact with composites have been observed on the mucosal side of both the upper and lower lips.

Management: Replacement of dental materials in direct contact with LCR will result in cure or considerable improvement in at least 90% of the cases, the majority of this type of LCR resolve following treatment with chlorhexidine.

Most lesions should be expected to heal within one to two months.

Reactions to Dentifrice and Chlorhexidine:

Delayed hypersensitivity reactions to toothpastes and mouthwashes have been reported, but such reactions are rare.

The compounds responsible for the allergic reactions may include cinnamon or preservatives flavor additives such as carvone and these flavoring constituents may also be used in chewing gum and produce similar forms of gingivostomatitis.

The clinical manifestations include **fiery red edematous gingiva,** which may include both ulcerations and white lesions.

Similar lesions may involve other sites, such as the labial, buccal, and tongue mucosae.

The clinical manifestations are characteristic and form the basis of the diagnosis, which is supported **by healing of the lesions after withdrawal of the allergen-containing agent**

Dentifrice may also cause a disturbed desquamation, which clinically can be observed as **thin veils of scaling keratin.**

▼Toxic Reactions:

Reactions to smokeless tobacco: Smokeless tobacco can be divided into three different groups: chewing tobacco, moist snuff, and dry snuff. The mildest form, of the lesion wrinkles at the site of application whereas high consumers may display a white and leathery lesion with ulcerations. Hyperkeratinization, acanthosis, and epithelial vacuolizations together with different degrees of subepithelial inflammation

Gingival retractions are the most common adverse reaction with a smokeless tobacco habit. These retractions **are irreversible**, whereas the mucosal lesion usually **regresses within a couple of months.** The etiology is probably more related to **the high temperature** rather that the chemical composition of the smoke, **although there is a synergistic effect of the two**

Clinically: There is a difference between lesions caused by smokeless tobacco and oral leukoplakia with respect to the presence of epithelial dysplasia, which is more frequently found in the latter, The carcinogenic potential tobacco is related to smokeless tobacco products which contain nitrosamines, polycyclic hydrocarbons, aldehydes heavy metals which all have a potential to cause harm.

The most common effects of smoking are presented clinically as dark brown pigmentations of the oral mucosa **(smoker's melanosis)** while the white leathered lesions of the palate, usually referred to as **(nicotine stomatitis or smoker's palate)**, as part of this lesion, red dots can be observed representing orifices of accessory salivary glands, which can be enlarged .Persistence of the lesion after cessation of smoking confirms a sublingual leucoplakia, which must be biopsied due to the high risk of malignant transformation.

- ▼Reactions to trauma:

Mechanical: like 1-Morsicatio (Mucosal Nibbling)

Parafunctional behavior (habitual chewing) is done unconsciously and is therefore difficult to bring to an end.

Morsicatio is most frequently seen in the buccal and lip mucosa and never encountered in areas that are not possible to traumatize by habitual chewing.

Typically, morsicatio does not entail ulcerations but encompasses an asymptomatic shredded area. In cases of more extensive destruction of oral tissues by habitual chewing, a **psychiatric disorder** should be suspected; it is three times more common among women.

Management

Is limited to assurance, and the patient should be informed about the Para- functional behavior. The condition **does not involve malignant potential**

2. - linea alba due to chronic chewing & sucking of the cheek produce a thin band on buccal mucosa bilaterally at the level of the occlusal plane.

3. - Frictional hyperkeratosis clinically characterized by a white lesion without any red elements and observed in areas of the oral mucosa subjected to increased friction caused by food intake (edentulous alveolar ridge or any part of oral mucosa exposed to trauma) which stimulates the epithelium to respond with an increased production of keratin and it is non-symptomatic but can cause anxiety to the patient (supposed as a malignant or premalignant lesion).

Smoking and alcohol consumption have been reported as predisposing factors.

Diagnosis: Based on clinical features, frictional hyperkeratosis does not carry any symptoms. If the diagnosis is doubtful, biopsy is mandatory to exclude premalignant. The ultimate way to differentiate between frictional keratosis and Leukoplakia is to reduce or eliminate predisposing factors and await remedy

Management

- No surgical intervention is indicated.
- No malignant nature of the lesions
- attempts to reduce predisposing factors are sufficient

Chemical: like

-Aspirin burn: in the buccal sulcus adjacent to painful tooth lead to white sloughy epithelium.

-Uremic stomatitis: extensive pseudomembranous white lesion in patients with renal failure due to increase blood urea nitrogen level (above 50 mg/dl)

Thermal: Smokers of cigarettes, cigars and pipes.

▼Other Red and White lesions: include the

Benign Migratory Glossitis (Geographic Tongue), Leukoedema, White Sponge Nevus, Hairy Tongue

Benign migratory glossitis (geographic tongue):

•Is an annular lesion affecting the dorsum and margin of the tongue.The typical clinical presentation comprises a white, yellow, or gray slightly peripheral zone

•ONE of the most prevalent oral mucosal lesions،

•Heredity has been reported, suggesting the involvement of genetic factors in the etiology.

•The gender distribution equal.

The peripheral zone disappears after some time, and healing of the depapillated and erythematous area starts.

The lesion may commence at different starting points, the peripheral zones fuse, and the typical clinical features of a geographic tongue emerge.

Depending on the activity of the lesion, the clinical appearance may vary from single to multiple lesions occupying the entire dorsum of the tongue.Disappearance of the peripheral zone may indicate that the mucosa is recovering

The disorder is usually **non-symptomatic**, but some patients are experiencing **sensation**

A Para functional habit, revealed by indentations at the lateral border of the tongue, may be a contributing factor to the symptoms. Patients often reports that their lesions are aggravating during periods of stress. Geographic tongue and fissured tongue may be observed simultaneously. Most likely, fissured tongue should be interpreted as an end stage of geographic tongue in some patients.

Mamagment:

No special treatment is required, although many approaches have been tried. If symptoms are reported, topical anesthetics may be used to obtain temporary relief.

 Other suggested treatment strategies include antihistamines, anxiolytic drugs, or steroids, but none of these has been systematically evaluated.

Geographic tongue may regress, but it is not possible to predict when and to which patient this may happen.

 The prevalence of the disease seems to decrease with age

Leukoedema:

Leukoedema is defined as edematous mucosa with a whiteish, often apparently translucent appearance. The etiology of leukoedema is not clear

Leukoedema is a white and veil-like alteration of the oral mucosa that is merely considered a normal variant.

The condition is often bilaterally in the buccal mucosa and sometimes at the borders of the tongue.

Leukoedema is less clinically evident after stretching the mucosa but reappears after this manipulation is discontinued. The condition is asymptomatic and has no malignant potential.

The clinical features of leukoedema are quite different from oral keratosis, such as leukoplakia, as the demarcation is diffuse and gentle stretching results in a temporary disappearance

Treatment

There is no demand for treatment as the condition is non-symptomatic and has no complications, including premalignant features

White sponge nevus:

it is an autosomal dominant disorder and it is a totally benign condition

Clinically: It is a white lesion with an elevated and irregular surface. The most affected sites are the buccal mucosa, but the lesion may also be in other areas of the oral cavity covered by keratinized epithelium.

Management: no treatment

Hairy tongue:

The etiology of hairy tongue is unknown in most cases.

Number of predisposing factors that have been related to this disorder:

-Neglected oral hygiene،

-a shift in the microflora،

-antibiotics and immunosuppressive drugs،

-Oral candidiasis.

-Excessive alcohol consumption.

-Therapeutic radiation.

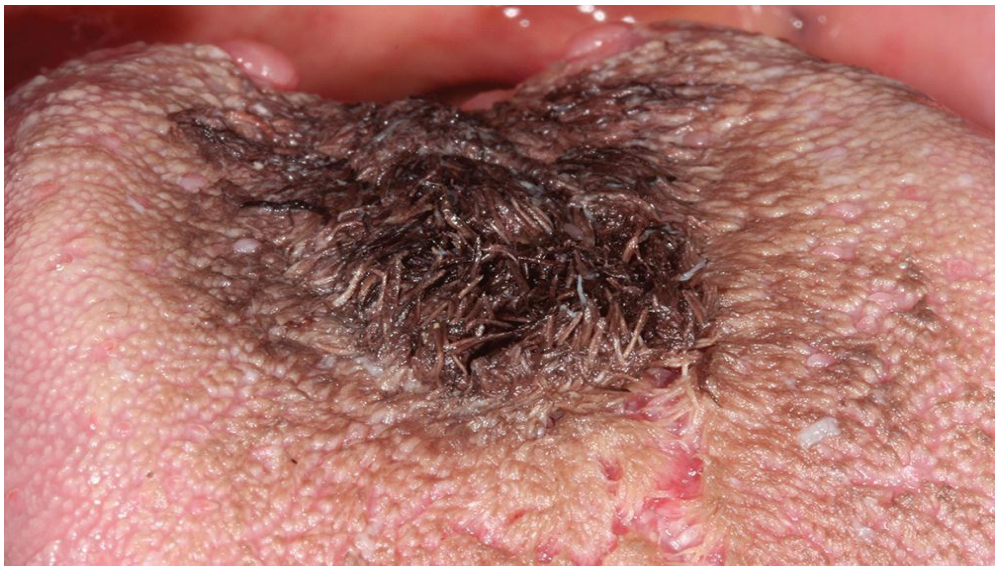
-Smoking habits.

Clinically:

Hairy tongue is characterized by an impaired desquamation of the filiform papilla, which leads to the hairy-like clinical appearance.The elongated papillae have to reach lengths in excess of 3 mm.The lesion is commonly found in the posterior one-third of the tongue but may involve the entire dorsum. Hairy tongue may adopt colors from white to black depending on food constituents and the composition of the oral micro-flora.

Diagnosis: The diagnosis is based on the clinical appearance.

Management: The treatment of hairy tongue is reduction or elimination of predisposing factors and removal of the elongated filiform papillae. The patients should be instructed on how to use devices developed to scrape the tongue.



Hairy tongue

Oral cancer and early detection

Diagnostic Aids

Diagnostic Aids for Early detection

- Early detection of potentially malignant and malignant lesions is a continuing goal.

- Patient history, thorough head and neck and intraoral examinations, is a prerequisite.

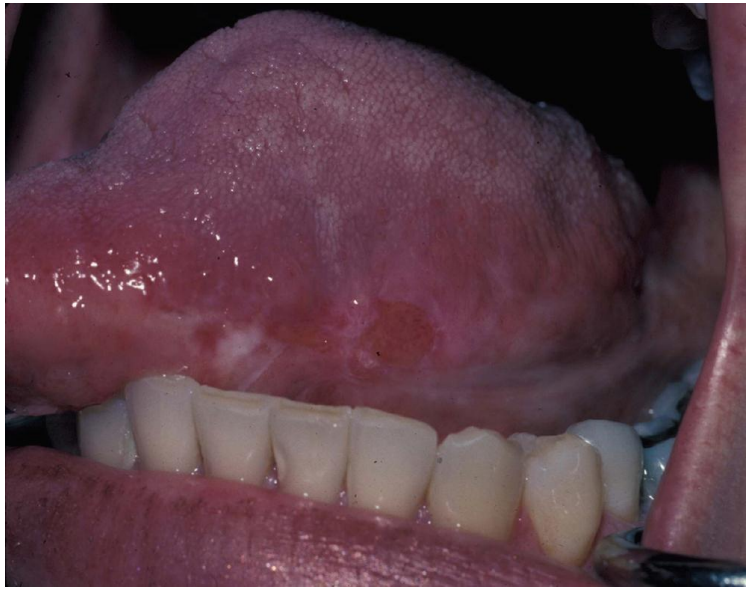
- The definitive test for diagnosis remains tissue biopsy.

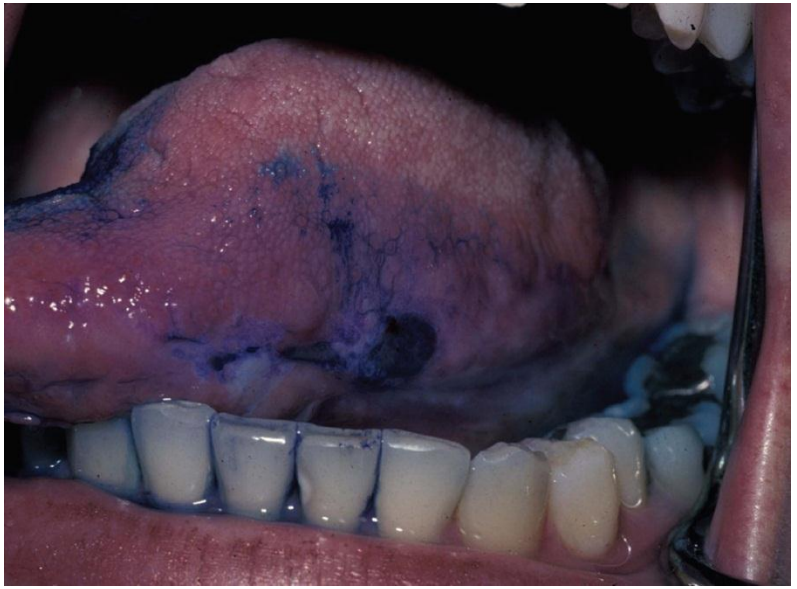
- Several aids to the oral examination have been suggested in the past, including:
  light technologies,
- vital tissue staining using toluidine blue (TB),
- and computer-assisted cytology of oral brush biopsy specimens.
- Additional markers based on blood or saliva samples are also under investigation.

Toluidine Blue

- Vital staining with TB may be used as an adjunctive aid in assessing potentially malignant oral mucosal lesions.

- TB is a metachromatic dye, which has an affinity to bind with DNA.
- TB staining has been correlated with LOH profiles in tissue biopsies.
- TB can be applied directly to suspicious lesions or used as an oral rinse.
- The assessment of dye uptake depends on clinical judgment and experience
- Positive retention of TB (particularly in areas of leukoplakia, erythroplakia, and uptake in a peripheral pattern of an ulcer) may indicate the need for biopsy or assist in identifying the site of biopsy.





- **False-positive** dye retention may occur in inflammatory and ulcerative lesions, but **false-negative** retention is uncommon.

- A return appointment in 14 days, providing time for inflammatory lesions to improve, may lead to a decrease in false-positive results.

- TB has been suggested as a **diagnostic tool** in potentially malignant oral lesions at risk of progressing to squamous cell cancer, where it may provide guidance for the selection for the biopsy site and accelerates the decision to biopsy.

- In postradiotherapy follow-up, the retention of TB may assist in distinguishing Non-healing ulcers and persistent or recurrent disease.

Visualization Adjunctive Tools

- **Chemiluminescent devices** generate **light based on chemical reactions**. The suspected area of mucosa appears **brighter**.

- Other products **generate fluorescent light using a LED source**, sometimes combined with **optical filtration of a viewfinder**, to enhance natural tissue fluorescence.
- When using the **fluorescence light**, the suspected area shows **loss of fluorescence, which appears dark.**

- **Oral cavity fluorescence**, using **blue light excitation**, is thought to represent the tissue structure, metabolic activity, presence of hemoglobin, vessel dilatation, and possibly inflammation.

- Localized modification in these factors may change the reflective features of the tissue.

- These products are promoted to assist the practitioner in discovering mucosal abnormalities, specifically oral potentially malignant disorders and evaluate margins of resection site.

- There is no consensus regarding the sensitivity and specificity of these devices, and their ability to detect early disease. Nonetheless, fluorescence has been shown to provide evidence on lesion margins in patients with known malignant lesions.
- There is an increasing interest in the use of confocal microscopy and optical coherent tomography systems to provide tissue diagnosis in real time, noninvasively, and in situ.

- Such diagnostic approach is available in dermatology and anticipated to be developed for oral mucosal application in the future.

- Other imaging modalities are being studied due to the need for improved detection and to assist in diagnosis and treatment.

Cytology

- Cytology of the oral mucosa is used to assess cellular morphology. The introduction of a brush designed to sample the entire thickness of the oral epithelium renewed interest in cytology for oral disease.

Originally, the cytobrush was combined with a computer- assisted analysis of the cytologic sample, assessing the cell morphology and keratinization.

- The final diagnosis was made by a pathologist based on the standard histomorphologic criteria.

- Further developments in cytology include molecular evaluation of exfoliated cells for molecular markers of dysplasia or carcinoma to improve the diagnostic and prognostic value.

Molecular Analysis

- Molecular markers obtained from tissue specimens have been suggested to assist with detection and evaluation of cancerous lesions including c-erbB2, Ki67/Mcm2, Cyclin D1, p53, COX-1 and 2, telomerase, loss of 3p or 9p, 8p, 4q, 11q, 13q, 17p.
- Studies have also shown that biomarkers of OSCC are present in saliva

Imaging

- Routine radiology, computed tomography (CT), nuclear scintiscanning, magnetic resonance imaging, and ultrasonography can provide evidence of bone involvement or can indicate the extent of some soft tissue lesions.

- The selection of the appropriate imaging modality is dependent on the type and location of the suspected tumor.

- Positron emission therapy using the radiolabeled glucose analog 18fluorodeoxyglucose offers a functional imaging approach for the entire body.
- Positron emission tomography (PET) is a type of nuclear medicine procedure that measures metabolic activity of the cells of body tissues.

- PET is actually a combination of nuclear medicine and biochemical analysis.

- Used mostly in patients with brain or heart conditions and cancer,
- PET helps to visualize the biochemical changes taking place in the body, such as the metabolism.

- PET differs from other nuclear medicine examinations in that PET detects **metabolism** within body tissues, whereas other types of nuclear medicine examinations detect the amount of a **radioactive substance** collected in body tissue in a certain location to examine the tissue's function.
- PET is most often used by oncologists, neurologists, neurosurgeons, cardiologists
- PET may also be used in conjunction with other diagnostic tests, such as computed tomography (CT) or magnetic resonance imaging (MRI) to provide more definitive information about malignant (cancerous) tumors and other lesions.

Acquisition of a Tissue Specimen

- In addition to standard surgical biopsy techniques, tissue can be acquired for histopathology by using fine-needle aspiration (FNA) or core needle biopsy (CNB).

- Open biopsy of enlarged lymph nodes is not recommended; in such cases, FNA biopsy should be considered.

- FNA/CNB also may aid in the evaluation of suspicious masses in other areas of the head and neck, including masses that involve salivary glands, tongue, and palate, or when there is contraindication for conventional biopsy (e.g., thrombocytopenia).
- Ultrasound may assist in guiding FNA/CNB.

Treatment

- The principal objective of treatment is to cure the patient of cancer.
- The choice of treatment depends on cell type and degree of differentiation, the site and size of the primary lesion, lymph node status, the presence of local bone involvement, the ability to achieve adequate surgical margins, and the presence or absence of metastases.
- Treatment decisions are also impacted by appraisal of the ability to preserve oropharyngeal function, including speech, swallowing, and esthetics, as well as the medical and mental status of the patient.

❑Surgery

Surgery is indicated for
(1) early or localized oral cancer,
(2)tumors involving bone, and when the side effects of surgery are expected to be less significant than those associated with radiation,
(3) tumors that lack sensitivity to radiation, and
(4) recurrent tumor in areas that have previously received radiotherapy.

Surgery also may be used in palliative cases to reduce the bulk of the tumor and to promote drainage from a blocked cavity (e.g., antrum).

- Surgical excision of dysplastic and malignant lesions can be accomplished with laser therapy.
- Such therapy for these lesions is generally well tolerated and usually decreases the period of hospitalization and may have similar outcomes as traditional surgical interventions.

- However, laser therapy has the disadvantage of limiting the assessment of the margins for histopathologic confirmation.

- New surgical approaches and new approaches to reconstruction, such as vascularized flaps, microvascular reconstruction, and neurologic anastomoses of free grafts.
- Reconstruction with the use of osseointegrated implants offers the ability to provide stable prostheses and enhanced esthetic and functional results.
- The ability to place implants in irradiated bone has increased options for rehabilitation

Radiation Therapy

- Radiation therapy may be administered with intent to cure, as a single modality, as part of a combined radiation surgery and/or chemotherapy management, or for palliation.
- Radiotherapy with intent to cure causes early and late toxicities.
- In palliative care, radiation may provide symptomatic relief from pain, bleeding, ulceration, and oropharyngeal obstruction.
- Hyperfractionation of radiation (usually twice daily dosing) is one of the strategies to increase intensity of treatment to increase tumoricidal effects, which results in more severe acute effects.

- High-dose re-irradiation is offered in some centers as save treatment and may be considered in case of recurrent or second primary head and neck cancer, particularly when salvage surgery is not feasible.

- Radiation kills cells by interaction with water molecules in the cells, producing charged molecules that interact with biochemical processes in the cells and by causing direct damage to DNA
- The affected cells may die or remain incapable of division.
- Due to a greater potential for cell repair in normal tissue than in malignant cells and a greater susceptibility to radiation due to the higher growth fraction of cancer cells, a differential effect is achieved.
- To achieve therapeutic effects, radiation therapy is delivered in daily fractions for a planned number of days.

The biologic effect of radiation depends on the dose per fraction, the number of fractions per day, the total treatment time, the total dose of radiation, and the radiation used (electron, neutron, proton).

Methods for representing the factors of dose, fraction size, and time of radiation with a single calculation using the time-dose fraction (TDF) and the nominal standard dose (NSD) calculations have been described.

- Radiation therapy has the advantage of treating the disease in situ and avoiding the need for the removal of tissue and may be the treatment of

choice for many T1 and T2 tumors, particularly in the base of the tongue and oropharynx.

- Radiation may be administered to a localized lesion by using implant techniques (brachytherapy) or to a region of the head and neck by using external beam radiation.

Cancer Treatment Planning

The radiation treatment plan is determined by the tumor site and size, relation to vital structures, the volume to be radiated, radiation technology available, the number of treatment fractions, the total number of days of treatment, and the tolerance of the patient.

Chemotherapy Cytotoxic Chemotherapy

- Chemotherapy may be used as induction therapy prior to local therapies, concurrent chemoradiotherapy (CCRT), and adjuvant chemotherapy after local treatment.
- The common chemotherapy protocols are listed in Table (8-6).
- The objective of induction chemotherapy is to promote initial tumor reduction and to provide early treatment of micrometastases due to the recognition that local control.

The principal agents that have been studied alone or in combination in head and neck cancer are taxol and derivatives, platinum derivatives (cisplatin and carboplatin), 5-fluorouracil, and hydroxyurea, although hydroxyurea is rarely used in current protocols.

Photodynamic Therapy

- Photodynamic therapy applies light over a tissue that initially absorbed exogenous sensitizer.

- The sensitizing agent may be delivered systemically or topically and then after it selectively accumulates in target tissue.

- The subsequent light delivery to the target tissue results in cellular destruction.

- Due to the focused cellular destruction, the complications and disfigurement associated with this treatment are relatively small.

- Although photodynamic therapy in oral cancer has some encouraging preliminary results, it is not accepted routine treatment.

Gene Therapy

- Gene therapy is being studied with the objective of reversing dysplasia in oral epithelial lesions.

- The modalities evaluated include suicide gene therapy, immunotherapy, oncolytic virus therapy, inhibition of tumor angiogenesis, gene deletion therapy, and antisense RNA.

- Considering the high rate of mutation in p53 in oral cancer, gene therapy focused on p53 gene, mostly with adenoviral vectors, shows promise.

- Additional target genes and vectors are currently being studied.

- None of these approaches have reached conventional clinic care settings

Immunotherapy

- Immunotherapy offers the potential for additional approaches to management, alone or in combination with other therapies.

- Clinical practice guidelines for management of malignant melanoma and other cancers are forthcoming.

- **Keytruda** May be used with the chemotherapy medicines fluorouracil and a platinum as first treatment when head and neck cancer has spread or returned and cannot be removed by surgery.

- Based on an analysis of a gene expression profile in matched tumor and normal fibroblast cell lines, a number of proteins have been detected that might be potential targets for immunotherapy in individuals with head and neck cancer.

- Cell lines studies and animal models support the introduction of immunotherapy for treatment of head and neck cancer.

Benign Lesions of the Oral Cavity

Assist. Prof. Dr. Rehab Fasial

Structural variations of the oral cavity are sometimes mistakenly identified as tumors, but they are usually easily recognized as being within the range of normal findings .

- Examples of such structural variants are tori; localized nodular connective tissue thickening of the attached gingiva; enlarged papillae associated with the opening of Stensen's duct; Fordyce spots; and sublingual varicosities in older individuals.

1. BENIGN SOFT TISSUE LESIONS:
Inflammatory/Reactive Hyperplasia of Soft Tissue

The term inflammatory hyperplasia is used to describe a large range of commonly occurring nodular growths of the oral mucosa that histologically represent inflamed fibrous and granulation tissue.

The major etiologic factor for these lesions is generally assumed to be chronic trauma from:

-Ill-fitting dentures ،

-Calculus ،

-Overhanging dental restorations ،

-Acute or chronic tissue injury from biting, or fractured teeth

-Some of these lesions (e.g., pregnancy epulis), the levels of circulating hormones play a role.

Clinical appearance is swollen, distended, ulcerated, red to purple in color due to dilated blood vessels, and they exhibit acute and chronic inflammatory exudates and localized abscesses . Erosion of the underlying cortical bone rarely occurs with peripheral inflammatory hyperplasias; if noted, there should be a strong suspicion that an aggressive process or even malignancy is involved .

An excisional biopsy is indicated except when the procedure would produce marked deformity

Fibromas:

It is occur as either pedunculated or sessile (broad based) growths on any surface of the oral mucous membrane .They are also called traumatic or irritation fibromas and the majority remain small, lesions that are >1 cm in diameter are rare . The giant cell fibroma exhibits a somewhat nodular surface and is histologically distinguished from other fibromas by the presence of stellate-shaped and multinucleated cells in the

Connective tissue .The etiology of the giant cell fibroma is not known.

- Multiple fibromas may indicate Cowden syndrome (multiple hamartoma and neoplasia syndrome) or tuberous sclerosis. Cowden syndrome is inherited as an autosomal dominant trait.

Clinically: Oral and perioral findings include multiple papules on the lips and gingivae; papillomatosis (benign fibromatosis) of the buccal, palatal, faucial, and oropharyngeal mucosa and the tongue is also pebbly or fissured.

Fibrous Inflammatory Hyperplasia:

-epulis fissuratum is a reactive inflammatory lesion associated with the periphery of ill-fitting dentures that histologically resembles the fibroma .

The growth is often split by the edge of the denture, resulting in a fissure, one part of the lesion lying under the denture and the other part lying between the lip or cheek and the outer denture surface.

Many such hyperplastic growths will become less edematous and inflamed following the removal of the associated chronic irritant, but they rarely resolve entirely. In the preparation of the mouth to receive dentures, these lesions are excised to prevent further irritation and to ensure a soft tissue seal for the denture periphery.

-Pulp polyps or chronic hyperplastic pulpitis represents an analogous condition. They occur when the pulpal connective tissue proliferates through a large pulpal exposure and fills the cavity in the tooth with a mushroom-shaped polyp that is connected by a stalk to the pulp chamber .Masticatory pressure may lead to keratinization of the epithelium covering these lesions .

Pulp polyps contain few sensory nerve fibers and are remarkably insensitive. The crowns of teeth affected by pulp polyps are usually so badly destroyed by caries that endodontic treatment is not feasible.

Inflammatory papillary hyperplasia is a common lesion with a characteristic clinical appearance that develops on the central hard palate in response to chronic denture irritation in approximately 3%–4% of denture wearers. Old and ill-fitting complete maxillary dentures appear to be the strongest stimuli, but the lesion is also seen under partial maxillary dentures .

The exact pathogenesis is unclear, but this palatal lesion is usually associated with denture stomatitis due to chronic candidal infection. When the candidal infection is eliminated, either by removing the denture or by topical administration of an antifungal agent, the papillary surface becomes less erythematous than the rest of the palate and consists of tightly packed nodular projections.

Mild cases may be treated successfully by topical or systemic antifungals alone; otherwise, papillary hyperplasia is surgically excised or removed by electro cautery, cryosurgery, or laser surgery.

The fibrous inflammatory hyperplasia has no malignant potential, and recurrence following excision is almost always a result of the failure to eliminate the source of chronic irritation.

* *All fibrous inflammatory hyperplasia of the oral cavity should be treated by: Local excision, with microscopic examination of the excised tissue*

Pyogenic Granuloma, Pregnancy Epulis, and Peripheral Ossifying or Cementifying Fibroma

Pyogenic granuloma is a hemorrhagic nodule that occurs most frequently on the gingiva (although it can occur on any surface) and that has a strong tendency to recur after simple excision if the associated irritant is not removed.

- It may be difficult on occasion to identify the causative chronic irritation for these lesions, but their proximity to the gingival margin suggests that calculus food material, and overhanging dental restoration margins are important irritants that should be eliminated when the lesion is excised.

Identical lesions with the same histologic structure occur in association with the florid gingivitis and periodontitis that may complicate pregnancy and are referred to as pregnancy epulis or pregnancy tumor . The prevalence of pregnancy epulis increases toward the end of pregnancy (when levels of circulating estrogens are highest), and they tend to shrink after delivery (when there is a precipitous drop in circulating estrogens) .This suggests that hormones play a role in the etiology of the lesion.

Both pyogenic granulomas and pregnancy epulis may mature and become less vascular and more collagenous, gradually converting to fibrous epulis . Small isolated pregnancy tumors occurring in a mouth that is otherwise in excellent gingival health may sometimes be observed for resolution following delivery, but the size of the lesion or the presence of a generalized pregnancy gingivitis or periodontitis supports the need for treatment during pregnancy.

The peripheral ossifying or cementifying fibroma is found exclusively on the gingiva; it does not arise in other oral mucosal locations.

Clinically: it varies from pale pink to cherry red and is typically located in the interdental papilla region. This reactive proliferation is named because of the histologic evidence of calcifications that are seen in the context of a hypercellular fibroblastic stroma.

Peripheral ossifying or cementifying fibromas occur in teenagers and young adults and are more common in women. The existence of these lesions indicates the need for a periodontal consultation, and treatment should include the elimination of subgingival irritants and gingival pockets throughout the mouth, as well as excision of the gingival growth.

Peripheral Giant Cell Granuloma

Giant cell granuloma occurs either as a peripheral exophytic lesion found exclusively on the gingiva or as a centrally located lesion within the jaw, skull, or facial bones (the central giant cell granuloma is described in the section that includes bone lesions).

Peripheral giant cell granulomas are five times as common as the central lesions. Both peripheral and central lesions are histologically similar and are considered to be examples of benign inflammatory hyperplasia in which cells with fibroblastic, osteoblastic, and osteoclastic potential predominate.

Gingival enlargement or overgrowth:

It is usually caused by local inflammatory conditions such as poor oral hygiene, food impaction, or mouth breathing. Systemic conditions such as hormonal changes, drug therapy, or tumor infiltrates may also cause or contribute to the severity of gingival enlargement.

Histologically :

-Hypertrophy (an increase in cell size)

-Hyperplasia (an actual increase in cell number)

-edema, vascular engorgement, the presence of an inflammatory cell infiltrate, or an increase in dense fibrous connective tissue

Drug-Induced Gingival Enlargement:

It is most commonly associated with the administration of anticonvulsants (principally phenytoin), cyclosporine, and calcium channel blocking agents. The extent of inflammation, fibrosis, and cellularity depends on the duration, dose, and identity of the drug; on the quality of oral hygiene.

Nifedipine and diltiazem are responsible for most cases of calcium channel blocker–induced gingival enlargement, with a prevalence of approximately 5%–20%.

2. Benign Soft Tissue Tumors

Oral mucosal benign tumors comprise lesions that form from fibrous tissue, adipose tissue, nerve, and muscle . Benign proliferations of blood vessels and lymphatic vessels resemble neoplasms but do not have unlimited growth potential and therefore are more appropriately considered hamartomatous proliferations.

Epithelial Tumors:

There are several benign oral epithelial virus–induced growths, principally those caused by the human papillomavirus (HPV), of the benign oral epithelial HPV–induced growths; viral papilloma (also called squamous papilloma) is relatively common.

It usually occurs in the third to fifth decades, most commonly as an isolated small growth (<1 cm diameter) on the palate, ranging in color from pink to white, rugose (ridged or wrinkled), exophytic, and pedunculated. The common wart, verruca vulgaris, is generally found on the skin (sometimes in association with similar skin lesions, often on the fingers) and is caused by the cutaneous HPV subtypes 2 and 57.

When involving the oral cavity, these warts are similar in appearance to viral papillomas and tend to involve the lips, gingivae, and hard palate. Oral papillomas and warts are clinically similar, and local excision is desirable. Care should be exercised when removing HPV-related oral lesions with electrocautery or laser as there exist the possibility of aerosolizing HPV particles. Although these lesions are probably infectious, a history of direct contact with another infected person is unusual, except in the case of multiple and often recurrent oral warts associated with sexual contact or maternal transmission. HPV 6 and 11 are detected in these lesions.

Keratoacanthoma: is a localized lesion that is typically found on sun-exposed skin, including the upper lip. The rapid growth of a keratoacanthoma may be often mistakenly diagnosed as squamous or basal cell carcinoma .

These lesions appear fixed to the surrounding tissue (similar to some carcinomas), often grow rapidly, and are usually capped by thick keratin. Occasionally, the lesion matures, exfoliates, and heals spontaneously, but more frequently, block excision is required, and the diagnosis is established from microscopic evaluation. The lesion's usual location on the upper lip (where squamous cell carcinoma of actinic etiology is rare, compared with the lower lip) should remind the clinician to consider keratoacanthoma in the differential diagnosis.

Intraoral keratoacanthoma are rare .

Treatment: is conservative excision, although some believe that it is not clearly separable from squamous cell carcinoma and advocate wide excision to prevent recurrence.

Vascular Anomalies:

Hemangiomas are true neoplasms and appear a few weeks after birth and grow rapidly .They are characterized by endothelial cell hyperplasia and fatty, or scar tissue apparent in approximately 40%–50% of patients.

Capillary of caverneous hemangiomas involving any organ system are now classified as infantile hemangiomas; the former is superficial and the latter is deeper.They have been described in almost all head and neck locations in a variety of presentations:

-Superficial and deep ،

-Small and large ،

Most commonly as solitary lesion but also as multiple lesions .Small lesions may be clinically indistinguishable from pyogenic granulomas and superficial venous varicosities. Vascular malformations are structural aberrations in components of the vascular apparatus .

They may be classified depending on the vessel type involved or flow types: arterial and arteriovenous (high flow), capillary, or venous (low flow). Arterial and arteriovenous malformations may first develop following hormonal changes (such as puberty), infections, or trauma, and, clinically, they may be firm, pulsatile, and warm. Venous malformations can sometimes appear first in early adulthood.

Lymphangioma:

It considered being a lymphatic malformation similar to other vascular malformations . It is characterized by an abnormal proliferation of lymphatic vessels. The most common extra oral and intraoral sites are the neck (predominantly in the posterior triangle) and tongue, respectively. The vast majority (80%–90%) of lymphangioma arise within the first 2 years of life .

Clinically: lymphangiomas are a slow-growing and painless soft tissue masses. They may undergo a rapid increase in size secondary to inflammation from an infection or hemorrhage from trauma.

Large lymphangiomas may become life threatening if they compromise the airway or vital blood vessels and those spreading into and distending the neck are macrocystic.

Differential diagnoses of lymphatic malformations of the tongue include infantile hemangioma or other vascular malformations, congenital hypothyroidism,mongolism,

amyloidosis, neurofibromatosis and primary muscular hypertrophy of the tongue, all of which may cause macroglossia.

Treatment: The treatment of lymphatic malformations is depending on their type, anatomic site, and extent of infiltration into surrounding structures.

-Surgical excision is the most common and sclerotherapy (with chemotherapeutic agents).

Neurogenic Lesions:

Traumatic Neuroma

A traumatic neuroma is not a true tumor but a proliferation of nerve tissue that is caused by injury to a peripheral nerve .Nerve tissue is encased in a sheath composed of Schwann cells and their fibers. When a nerve and its sheath are damaged, the proximal end of the damaged nerve proliferates into a mass of nerve and Schwann cells mixed with dense fibrous scar tissue.

In the oral cavity, injury to a nerve may occur from injection of local anesthesia, surgery, or other sources of trauma and it is often painful .The discomfort may range from pain on palpation to severe and constant pain .

Traumatic neuromas in the oral cavity may occur in any location where a nerve is damaged; the mental foramen area is the most common location .The definitive diagnosis is made on the basis of a biopsy and microscopic examination.

Treatment: by surgical excision .

Recurrence rates for neuromas are rare.

Neurofibromatosis:

Multiple neurofibromas occur in a genetically inherited disorder known as neurofibromatosis one (NF1)

This disease is transmitted as an autosomal dominant trait, and the NF1 gene has been identified .Oral neurofibromas are a common feature of the disease. The presence of numerous neurofibromas or a plexiform-type neurofibroma is pathognomonic of NF1. Patients with NF1 are at increased risk of the development of malignant tumors, especially malignant peripheral nerve sheath tumor, leukemia, and rhabdomyosarcoma.

Lipoma:

The lipoma is a benign tumor of mature fat cells .When occurring in the superficial soft tissue, the lipoma appears as a yellowish mass with a thin surface of epithelium .Because of this thin epithelium, a delicate pattern of blood vessels is usually observed on the surface .

Deeper lesions may not demonstrate this finding and therefore are not as easily identified clinically.The majority of oral lipomas are found on the buccal mucosa and tongue and occur in individuals over 40 years of age, without any sex predilection. There are several microscopic variants of the lipoma. The classic description is of a well-delineated tumor composed of lobules of mature fat cells that are uniform in size and shape.

A lipoma that infiltrates among skeletal muscle bundles is called an intramuscular lipoma. It has been reported in the oral soft tissues but is rare.The lipoma is treated by conservative surgical excision and generally does not recur whereas the Intramuscular lipoma has a somewhat higher recurrence rate because they are more difficult to remove completely.

Tumors of Muscle:

Tumors of muscle are extremely uncommon in the oral cavity .The rhabdomyoma, a benign tumor of striated muscle, has been reported to occur on the tongue .The vascular leiomyoma, a benign tumor of smooth muscle cell and vascular endothelium, occasionally occurs in the oral cavity .

Treatment: by local surgical excision, and recurrence is rare.

Thank you

Salivary Gland Tumors:

Benign Tumors: - Pleomorphic Adenoma

-Monomorphic Adenoma

-Papillary Cystadenoma Lymphomatosum

-Oncocytoma

-Others

Malignant Tumors: Include the following ……..

- Mucoepidermoid Carcinoma.

- Adenoid cystic carcinoma.

- Acinic cell carcinoma.

- Adenocarcinoma.

- Lymphoma.

The majority of salivary gland tumors (about80%) arise in the parotidglands, the submandibular glands (10 to 15% of tumors), and the remaining tumors develop in the sublingual or minor salivary glands.

-Any tumors arising from salivary duct epithelium are adenocarcinomas. For minor salivary glands, pleomorphic adenoma is the most common benign tumor.

-The mucoepidermoid carcinoma is the most common malignant tumor and the risk of malignancy for all salivary tumors increases as the size of the tumor decreases.

PLEOMORPHIC ADENOMA:

Is the most common tumor of the salivary glands (about 60% of all salivary gland tumors.(. It is often called a mixed tumor because it consists of both epithelial and mesenchymal elements. Pleomorphic adenomas may occur at any age, but the highest incidence is in the fourth to sixth decades of life. It also affects the children .

Clinical Presentation.:

-slow growing painless, firm, and mobile masses.

-usually occur in the posterior inferior aspect of the superficial lob, while in the submandibular gland present as well-defined palpable masses.

-It is difficult to distinguish these tumors from malignant neoplasms and indurated lymph nodes. Pleomorphic adenomas can vary in size, depending on the gland in which they are located .

-In the parotid gland, the tumors are usually several centimeters in diameter but can reach much larger sizes if left untreated. Intraoral, mostly occur on the palate, followed by the upper lip and buccal mucosa.

Treatment:

-Surgical removal with adequate margins is the principal treatment. Because of its microscopic projections, this tumor requires a wide resection to avoid recurrence .

-A superficial parotidectomy is sufficient for the majority of this lesion.

MONOMORPHIC ADENOMA:

A monomorphic adenoma is a tumor that is composed predominantly of one cell type, as opposed to a mixed tumor (pleomorphic adenoma), in which different elements are present .

Management is the same as pleomorphic adenoma.

Papillary cystadenoma lymphomatosum:

-It is known as Warthin's tumor, is the second most common benign tumor of the parotid gland .

-It represents ≈6 to 10% of all parotid tumors and is most commonly located in the inferior pole of the gland, posterior to the angle of the mandible.

Clinical features: well-defined, slow-growing mass in the tail of the parotid gland. It is usually painless unless it becomes superinfected.

-Surgical removal, recurrences is rare

Malignant Tumors-:

MUCOEPIDERMOID CARCINOMA:

-It is the most common malignant tumor of the salivary glands mainly in the parotid gland and the second tumor in the submandibular gland, after adenoid cystic. The palate is the second most common site .Men and women are affected equally by this tumor, and the highest incidence occurs in the third to fifth decades of life.

-Mucoepidermoid carcinoma consists of both epidermal and mucous cells .

-The tumor is classified as of either a high grade or a low grade, depending on the ratio of epidermal cells to mucous cells. The low-grade tumor has a higher ratio and is a less aggressive lesion whereas the high-grade form is considered to be a more malignant tumor and has a poor prognosis.

Clinical Presentation:

-The clinical course of this lesion depends on its grade. The high-grade mucoepidermoid carcinomas often demonstrate rapid growth and a higher likelihood for metastasis،

-Pain and ulceration of overlying tissue are associated with this tumor .

-If the facial nerve is involved, the patient may exhibit a facial palsy.

Treatment :

-A low-grade mucoepidermoid carcinoma can be treated with a superficial parotidectomy if it involves only the superficial lobe .

-High grade lesions should be treated by wide excision but the tumor may recur .

-Neck dissections may be necessary for lymph node removal and staging in high-grade lesions.

-Postoperative radiation therapy has been shown to be a useful adjunct in treating the high-grade tumor.

ACINIC CELL CARCINOMA:

Acinic cell carcinoma represents about 1% of all salivary gland tumors. This tumor occurs with a higher frequency in women.

Clinical presentation:

- These lesions often present as slow growing masses .

- Pain may be associated with the lesion but is not indicative of the prognosis .

- The superficial lobe and the inferior pole of the parotid gland are common sites of occurrence .

- Bilateral involvement of the parotid gland has been reported in approximately 3% of cases.

Treatment:

-Acinic cell carcinomas initially undergo a relatively benign course,the treatment consists of superficial parotidectomy, with facial nerve preservation if possible .

-When these tumors are found in the submandibular gland, total gland removal is the treatment of choice .

ADENOID CYSTIC CARCINOMA:

Adenoid cystic carcinomas make up about 6% of all salivary gland tumors and are the most common malignant tumors of the submandibular and minor salivary glands. The tumor affects men and women equally and usually occurs in the fifth decade of life.

Clinical presentation:

Adenoid cystic carcinoma usually presents as a firm unilobular mass in the gland. The tumor is painful, and parotid tumors may cause facial nerve paralysis in a small number of patients. Unfortunately, the tumor's slow growth may delay diagnosis for several years.

Treatment:

Because of the ability of this lesion to spread along the nerve sheaths, radical surgical excision of the lesion is the appropriate treatment.

Radical surgery refers to the removal of blood supply, lymph nodes and sometimes adjacent structures of a diseased organ or tumor during surgery.

CARCINOMA EX PLEOMORPHIC ADENOMA:

Carcinoma ex pleomorphic adenoma is a malignant tumor that arises within a pre-existing pleomorphic adenoma. The malignant cells in this tumor are epithelial in origin and this tumor represents 2 to 5% of all salivary gland tumors.

Clinical presentation:

These tumors are slow growing and present for 15 to 20 years before they suddenly increase in size and become clinically apparent. It occurs more often in pleomorphic adenomas that have been left untreated for long periods of time (It is for this reason that early removal of pleomorphic adenomas is recommended).

Treatment:

-This is a malignant salivary gland tumor that has an aggressive course and that carries a very poor prognosis. Surgical removal with postoperative radiation therapy is the recommended treatment.

- Early removal of benign parotid gland tumors is recommended to avoid the development of this lesion.

Lymphoma :

A salivary gland is the first clinical manifestation of the disease. Primary lymphoma of the salivary glands probably arises from lymph tissue within the glands It is a rare. The major forms of lymphoma are non-Hodgkin's lymphoma (NHL) and Hodgkin's disease .

Clinical feature:

A rapidly growing tumor with extensive local growth, invasion of surrounding tissues, cervical node metastasis but high rates of distant metastasis

Treatment :

Early and aggressive surgery with close follow up is required.

THANK YOU

Assist.Prof.Dr.
Wedad Farhan

Autoimmune diseases

They represent a diverse family of conditions characterized by an immune-mediated response against self. Over 100 distinct autoimmune diseases have been described, showing a wide spectrum of manifestations from organ-specific autoimmunity (such as primary biliary cirrhosis) to organ-specific with systemic manifestations (such as Sjögren syndrome) to multiorgan systemic disease (such as SLE).

Common pathogenetic mechanism in all these disorders is the breakdown of immune tolerance. A combination of genetic susceptibility and environmental triggering is thought to underlie the pathogenesis of all autoimmune disorders, while some disorders lead to organspecific damage, others exhibit widespread systemic autoimmunity.

The orofacial area, and in particular the oral mucosa and the salivary glands, is affected by multiple autoimmune diseases, either directly as a manifestation of their clinical phenotype, or indirectly due to possible comorbidities or adverse effects of the medications used for treatment.

Sjögren Syndrome

Is an autoimmune disorder in which immunocytes damage the salivary, lacrimal, and other exocrine glands and is thus termed an autoimmune exocrinopathy. Dry mouth and dry eyes are seen with lymphoid infiltrates in these and other exocrine glands and serum autoantibodies. Sjögren syndrome has two major clinical forms:

- Primary Sjögren syndrome (SS-1), in which dry eyes and dry mouth are seen in the absence of a connective tissue disease,

- Secondary Sjögren syndrome (SS-2), which is more common, in which eyes and dry mouth are seen together with other autoimmune diseases, usually of connective tissue—most usually rheumatoid arthritis, SLE, polymyositis, scleroderma, or mixed connective tissue disease.

Sjögren syndrome shows a wide spectrum of clinical manifestations and new diagnostic criteria tend not to distinguish between the two clinical forms.

Systemic Lupus Erythematosus

SLE is considered a prototypic autoimmune disease characterized by a wide spectrum of clinical manifestations and an often unpredictable relapsing–remitting course. Patients can present with variable clinical features ranging from mild joint and skin disease to multiorgan life-threatening renal, hematologic, and CNS involvement.

The etiology and pathogenesis of SLE remain largely unknown; however, it is recognized that genetic predisposition combined with environmental and possibly hormonal factors ultimately predisposes to disease. Immune dysregulation is thought to result from the breakdown in tolerance to self-antigens, leading to excessive inflammation, autoantibody production, and destruction of end organs.

Immunologic anomalies, particularly production of antinuclear antibodies (ANA) such as those against double-stranded (ds) DNA, are a hallmark of lupus.

Diagnosis and management of lupus are particularly complex. Oral manifestations are a prominent feature that can aid in the diagnosis and should be taken into consideration during management of SLE. There is unequal gender distribution (females are affected 1.2–15 times more than males) and among different ethnic groups.

Genetic Susceptibility and Pathogenesis

SLE is considered a chronic inflammatory autoimmune disorder that is characterized by insufficient immune tolerance to nuclear antigens and pathologic production of nonspecific autoantibodies, eventually resulting in tissue damage. The role of genetic susceptibility in SLE is evident from the high heritability (43.9%) and the relative risk (5.87%) in first degree relatives of patients with SLE.

Environmental factors triggering disease in susceptible individuals are poorly understood, yet viral and other microbiome triggering has been extensively hypothesized. Additionally, hormonal deregulations and other environmental triggers,

such as ultraviolet radiation, tobacco consumption, and physiologic factors, have been investigated.

Clinical Features

SLE may be difficult to diagnose, especially in the early stages, when nonspecific signs and symptoms (constitutional symptoms), such as fatigue, headache, arthralgias, lymph node enlargement, fever, and significant weight loss occur, causing diagnostic dilemmas with other autoimmune connective tissue diseases as well as neoplastic processes or infections.

SLE may be characterized by the involvement of various specific organs.

1.Renal disease, The term lupus nephritis, which has been used to describe kidney involvement in lupus patients.

2.The musculoskeletal system is also commonly affected

3.Arthritis and arthralgias are a dominant feature of SLE.

4.Cardiovascular manifestations are also common in SLE and typically include vasculitis and pericardial effusions

5.Involvement of the central or peripheral nervous system in SLE may be associated with poor prognosis.

Anxiety, mood disorders, psychosis, seizures, headaches, and myelin defects are examples of CNS manifestations in SLE, while various types of peripheral neuropathies have also been described.

6.Pulmonary involvement, gastrointestinal disease, genitourinary disorders, ocular manifestations.

7. Mucocutaneous Manifestations

Most lupus patients will develop cutaneous and mucosal lesions during their disease. The most common lesion is a facial eruption that characterizes acute cutaneous lupus erythema (also known as the “butterfly rash”), presenting as erythema in a malar distribution over the cheeks and nose (but sparing the nasolabial folds) that appears

after sun exposure. Photosensitivity is also a common theme for skin lesions associated with SLE.

Oral Manifestations

The oral cavity is commonly affected during both systemic and cutaneous involvement in SLE. Typically, oral lesions in SLE occur in approximately 5–40% of patients, include nonspecific ulcerations and erythematous or discoid lesions, and predominantly affect the palatal mucosa, buccal mucosa, and gingiva.

Due to their significant prevalence, oral ulcerations are included among the classification criteria of SLE. The vermillion border of the lower lip can be characteristically involved (lupus cheilitis). The temporomandibular oint (TMJ) can also be affected.

The oral manifestations of the cutaneous forms of lupus erythematosus (CLE) closely mimic those of oral lichen planus. The most common sites of involvement are the lips (vermillion border and labial mucosa) and the buccal mucosa. Interestingly, a correlation between specific oral lesions (such as discoid plaques, cobblestone, or macules) and disease activity in CLE was recently reported.

On rare occasions, squamous cell carcinoma may arise in discoid lesions affecting the lips or even intraoral sites. So it is considered an oral, potentially malignant disorder based on the World Health Organization (WHO) classification.

Laboratory Findings

Main manifestations include anemia (mainly related to chronic disease, iron deficiency, or hemolysis).

- Leukopenia (lymphopenia and/or neutropenia),
- And thrombocytopenia (autoimmune or related to hypersplenism or hemolysis) and their extent correlates with disease activity.
- Erythrocyte sedimentation rate (ESR) is usually elevated along with normal C-reactive protein (CRP), which is a characteristic feature of SLE.

- ANAs are positive in more than 95% of SLE patients and, despite their lack of specificity (being detected in several other autoimmune diseases and in healthy subjects), can be used as a reliable screening test

- Other markers, despite being disease specific, are only detected in a subset of patients; for example, anti-double-stranded DNA (anti-dsDNA) and anti-Smith antigen (anti-Sm) antibodies are positive in approximately 50–70% and 30–40% of SLE patients, respectively.

- Decrease in complement markers (hypocomplementemia), especially CH50, C3, and C4.

Management

Treating SLE is challenging and depends on the extent of manifestations, the type of target organ(s), and the severity of disease as well as possible morbidities. Corticosteroids remain the main choice during management of SLE, due to their effectiveness in limiting disease and flares. However, because of common complications after their long-term use (such as diabetes, infections, osteoporosis, hypertension, and avascular necrosis of bone), other immunosuppressants have been proposed. Alternative options include cyclophosphamide, mycophenolate mofetil, and azathioprine, which should also be used with caution due to their toxic effects Biologic agents affecting the B-cell component of the immune system, including belimumab, rituximab, ofatumumab, and atacicept, are recently used drugs that present efficacy in limiting disease activity.

For the management of oral complications of lupus erythematosus, Topical or intralesional administration of corticosteroids seems to be the first treatment option.

Systemic Sclerosis (Scleroderma)

The word “scleroderma,” meaning hard skin; characterizing a diverse group of disorders that exhibit excessive cutaneous fibrosis. Major disease subsets include localized scleroderma (LSc), which is limited to skin involvement, and systemic sclerosis (SSc), a heterogenous disease, which affects a wide range of organs in addition to the skin, leading to significant morbidity. SSc is subclassified into multiple subsets of disease:

1 . Limited cutaneous SSc; refers to skin lesions in distal areas.

2. Diffuse cutaneous SSc involves the proximal limbs or trunk, with a short history of Raynaud's phenomenon and frequent renal or cardiac involvement as well as lung fibrosis.

3. Sine scleroderma is an entity that exhibits clinical and serologic evidence of SSc without skin sclerosis.

4. SSc overlap syndrome refers to one of the aforementioned subsets in addition to manifestations from other autoimmune diseases. Both LSc and SSc are considered rare entities; women are more commonly involved than men and a racial predisposition for Caucasian populations has been reported

Pathogenesis

Immune activation, vascular damage, and excessive synthesis of extracellular matrix. Interplay between early immunologic events and vascular changes, which result in the generation of a population of activated fibroblasts which is the effector cell in the disease.

Clinical Features

Cutaneous Manifestations

- Skin thickening is the hallmark of cutaneous involvement in SSc.
- Skin involvement may be of acute onset in diffuse SSc or more slowly growing in limited SSc.
- The extremities and especially the fingers may be affected, causing a "puffy" appearance; progressively, the thin overlying skin becomes prone to ulceration and, in advanced stages, deformities may occur.
- In rare occasions, calcifications of the skin may occur with the clinical presentation of multiple subcutaneous nodules.
- Additionally, hypo- or hyperpigmented areas as well as telangiectasias may be observed.

Raynaud's phenomenon is the most common initial sign, developing simultaneously or prior to cutaneous involvement.

Musculoskeletal involvement takes the form of generalized arthralgias and morning stiffness resembling RA.

Myopathy is also common and is accompanied by elevated serum muscle enzymes.

During late stages, fibrosis of the gastrointestinal tract may result in malabsorption

Pulmonary complications including interstitial lung disease and pulmonary hypertension

Inflammatory processes may involve the heart, causing arrhythmias, hypertension, pericardial effusions,

Renal involvement is common and, before the initiation of angiotensin-converting enzyme inhibitors, was the most common cause of death in SSc patients

Renal crisis is most commonly encountered in patients with early onset of diffuse scleroderma

Oral Manifestations

The orofacial area may be involved in a similar pattern to other anatomic areas of SSc patients.

The lips become rigid, which, in addition to the generalized skin sclerosis, results in a mask-like appearance of the face.

Mouth opening is significantly decreased (microstomia) and the tongue becomes hard, leading to difficulties in speech and swallowing.

Telangiectasias are also frequently present.

Mandibular movement may be limited secondary to muscular fibrosis.

Myofascial pain, especially involving the masseter and posterior belly of the digastric muscle, feeling of locked jaw, and arthralgia are common symptoms in SSc patients.

Mandibular resorption, either at the angle of the mandible, condyles, coronoid processes, or digastric region.

In the oral cavity of SSc patients, periodontal disease, xerostomia, and susceptibility to local infections.

Xerostomia, related to fibrosis of the salivary glands, secondary Sjögren syndrome, or medications, may predispose to dental and periodontal disease as well as candidiasis.

Laboratory Findings

The following routine laboratory tests are recommended in patients with suspected SSc:

●● CBC and differential, which may reveal anemia due to malabsorption of iron or gastrointestinal blood loss.

●● Serum creatinine level, which may indicate renal dysfunction.

●● Creatine kinase (CK), which may be elevated in patients with myopathy or myositis.

●● Urinalysis.

The following serologic tests may support the diagnosis if positive:

●● Antinuclear antibody (ANA).

●● Anti-topoisomerase I (anti-Scl-70) antibody.

●● Anticentromere antibody (ACA).

●● Anti-RNA polymerase III antibody

Diagnosis is made upon exclusion of similar entities that could justify the clinical manifestations, including generalized morphea (painless, discolored patches on skin).Skin sclerosis of the fingers of both hands extending proximal to the metacarpophalangeal joints is by itself sufficient for classification as SSc, while other clinical or serologic features are helpful classification criteria.

Management

The selected treatment is also based on the stage of disease and possible morbidities. Treatment of SSc aims at limiting the inflammatory process that characterizes its clinical phenotype as well as managing the distinct clinical manifestations involving separate organs. Patients with limited mouth opening should undergo several stretching exercises that have been reported to be effective. A poorer prognosis (black race or male gender). Early treatment is considered essential to reduce mortality, since the progression of disease during the first three years is fast.

Rheumatoid Arthritis

RA is a chronic inflammatory autoimmune disease that is characterized by symmetric involvement of joints in a progressively destructive manner, which can cause significant disability if not properly treated. RA is considered among the most common autoimmune diseases, presenting a reported incidence of 0.5–1%. It involves patients in their middle age with a female predominance.

Pathogenesis (Genetics and Environment)

A combination of host genetic and environmental factors is thought to underlie disease triggering. RA immune cell infiltration of the synovial membranes of joints with T cells, B cells, monocytes, and neutrophils leads to inflammation of synovial membranes, "pannus" (Pannus is an abnormal layer of fibrovascular tissue or granulation tissue formation) and subsequent bone and cartilage erosion.

Inflammatory mediators such as tumor necrosis factor (TNF) and IL-6 are clearly involved in disease activity. One interesting aspect of the disease is that autoantibodies often develop 1–10 years prior to disease onset. Specifically, antibodies to citrullinated proteins (ACPA) develop 5–10 years before disease onset.

A genetic predisposition has clearly been defined in RA, most significantly associated with HLA class II antigens. In addition to genetic susceptibility, epigenetic modifications may be observed including modified DNA methylations. Environmental triggers including smoking, alcohol consumption, socioeconomic level, and infectious agents, such as periodontal pathogens, have been associated with the development of RA.

Clinical Presentation

- The inflammatory process primarily involves the wrists and metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal articulations.
- Accompanying morning stiffness lasting from 30 minutes to several hours is also common
- The fingers are affected in a fusiform pattern, mainly around the joints, in contrast to psoriatic arthritis where the whole digit is swollen
- If RA is insufficiently treated, extraskeletal manifestations may develop. The occurrence of firm masses called rheumatoid nodules, especially in subcutaneous areas in proximity to bony prominences, is the most frequent finding. Severe complications is the necrotizing vasculitis of the small and medium-sized arteries, interstitial lung disease, or cardiovascular disease, with the latter being the most common cause of mortality among RA patients.

Intra- and Extra-oral Manifestations

The TMJ is involved in almost every patient with RA according to the Helkimo index. Clinical signs or symptoms of TMJ involvement, such as pain, crepitation, reduced mouth opening, and impaired movement, have been described in RA patients. In advanced stages, progressive condylar destruction may cause malocclusion and anterior open bite, joint ankylosis, and facial asymmetry. RA may show several other manifestations in the orofacial area; secondary Sjögren syndrome, dental and periodontal disease, oral side effects of systemic medications used to treat RA have been reported.

Diagnosis

Diagnosis is primarily made by evaluation of the clinical and immunologic findings.

Laboratory Findings

- The main laboratory findings in patients with RA include acute-phase reactants and autoantibodies.

- CRP and ESR are the most significant markers used to detect inflammatory responses, with the former being more specific in measuring disease activity due to its association with inflammatory cytokines expressed in RA.

- The main autoantibodies used for diagnosis of RA are cyclic citrullinated peptides (anti-CCP) and rheumatoid factor.

- Both are specific markers, even though they are occasionally expressed in other diseases.

Management

Due to significant progress in understanding of the disease, irreversible joint damage can be prevented today in 90% of patients. Initial-phase treatment for RA typically involves methotrexate (used as monotherapy or in combination with corticosteroids), which is considered an efficient treatment for RA and is associated with few and easily controllable adverse effects.

Symptomatology may also be improved by non-steroidal anti-inflammatory drugs (NSAIDs), which however do not inhibit disease development and should be used as supplementary therapy before a definite diagnosis of RA is established. Subsequent treatment typically involves disease-modifying anti rheumatic drugs such as TNF inhibitors, IL-6 inhibitors, and small-molecule inhibitors.

Mixed Connective Tissue Disease

- Highlights the overlapping character between autoimmune inflammatory disorders.

- Presenting clinical manifestations in the spectrum of SLE, Sjögren syndrome, as well as inflammatory myopathies.

- Females seem to be more frequently involved compared to males and the disease could show an early onset.

Pathogenesis

The cornerstone in the pathogenesis is the presence of the anti-ribonucleoprotein (RNP) antibodies. A genetic predisposition and especially the presence of distinct subsets of HLAs may play a key role.

Clinical Features

- Clinical manifestations identical to various connective tissue diseases are present, including Raynaud's phenomenon and "puffy" or swollen hands, myositis, arthritis, interstitial lung disease, pulmonary hypertension, cutaneous lesions and alopecia, esophageal dysmotility, neurologic symptoms, as well as renal disease.

- Orofacial involvements of MCTD have rarely been reported

Diagnosis

Diagnosis is typically difficult, additionally; alterations in diagnostic criteria of other autoimmune diseases render the classification of certain patients problematic.

Management

- Management mainly includes immunosuppressants, especially corticosteroids, as well as steroid-sparing medications, such as methotrexate, cyclosporine, and azathioprine.

- Specific manifestations including Raynaud's phenomenon should be treated accordingly with calcium-channel blockers.

General Considerations for Dental Management of Patients With Immunemediated Diseases

1. Susceptibility to Infections

- In the presence of ongoing odontogenic infections, microbial translocation from the oral cavity has been considered a risk factor for distal infections, particularly during invasive dental procedures.

- Odontogenic infections have been associated most commonly with infectious endocarditis, but also with infections in the CNS and less commonly with distal skeletal infections.

- Septicemia from oral infections has also been reported in immunocompromised patients in multiple cases with the organism Leptotricia buccalis.

- Patients with primary immunodeficiencies may be at an increased risk for oral infections.

- To date, there are no specific guidelines for dental management and/or for use of antibiotic prophylaxis in patients with primary immunodeficiencies.

- Common recommendations include aggressive prevention to avoid and treat early oral and dental infections in such patients, close monitoring, and coordination of treatment with the medical team.

- Due to the severity of immunodeficiency in such patients, often dental treatment will be advised to be performed within the hospital setting.

- Patients with autoimmune diseases are also often considered immunocompromised, either because of the disease itself or secondary to the use of immunosuppressive medications.

- Leukopenia is also a possible manifestation of autoimmune diseases or the medications used to treat them and is associated with susceptibility to infections

- A recent study including patients with different levels of neutropenia concluded that extractions are safe and with few associated complications.

- There is also no consensus regarding the use of antibiotics in patients under corticosteroid treatment. As a result, the main consideration is the potential modification of the dose of corticosteroids to prevent an adrenal crisis.

- Herpes zoster or HPV infection is considered common in patients with SLE and could manifest in the oral cavity.

- Oral candidiasis may also be frequently encountered in autoimmune disease patients as a side effect of corticosteroid or other immunosuppressive treatment or a consequence of reduced salivary flow, and should be managed accordingly.

SLE and other autoimmune disorders lead to valvular disease, requiring prosthesis and increasing the risk for bacterial endocarditis following surgical procedures.

Such patients will require antibiotic prophylaxis prior to surgical procedures, based on the most recent guidelines about patients with valvular disease from the American Heart Association and the American College of Cardiology.

Patients with prosthetic joints do not require antibiotic prophylaxis prior to dental procedures to avoid infection of the prosthetic joints.

2. Risk of Bleeding

Coagulation is commonly impaired in autoimmune diseases for multiple reasons, including:

Thrombocytopenia associated with the disease (e.g., in SLE),

Use of certain myelotoxic drugs

Treatment with anticoagulants or antiplatelet regimens (in patients with risk for thrombosis).

Such patients may be at increased risk of bleeding subsequent to surgical interventions.

Recent studies suggest that extractions in patients with thrombocytopenia are usually safe and complications are easily managed with local measures.

However, patients exhibiting a platelet count under 50,000/μL require platelet transfusion, so cases with severe thrombocytopenia should be managed in a hospital environment.

In patients with anticoagulant therapy, INR (PT test/PT normal)should be measured and if its value is between 2.0 and 3.5, minor interventions are allowed, while for more invasive procedures, replacement of the regimen with low molecular weight heparin should be considered.

Discontinuation of antiplatelet therapy should be considered prior to intervention.

Communication between the patient's dental and medical practitioners is necessary, especially for complex cases.

3. Adrenal Suppression

- Corticosteroids are included among the most common medications used to treat autoimmune connective tissue diseases due to their significant efficacy in limiting disease activity.

- However, their side effects, including adrenal suppression, should be taken into consideration during dental treatment.

- Due to absence of specific guidelines, every case should be individualized, and treatment planned with the caring physician.

4. Cardiovascular Disease

- The dental practitioner must always assess the general condition of these patients before starting any minor or invasive procedure and establish a communication with the patient's physician.

- Antianxiety techniques and pain control play a key role in the prevention of medical emergencies

5. Liver and/or Kidney Disease

- Renal involvement is common in patients with autoimmune diseases (lupus nephritis)

- Renal and liver function should be monitored in these patients, as the doses of common medications prescribed by the dentist may be modified.

- Dental procedures should be performed under appropriate conditions in patients under hemodialysis (treatment should be performed the day after dialysis).

6. Hyposalivation and Xerostomia

- Salivary gland involvement results in hyposalivation and the subjective feeling of xerostomia.

- The salivary glands are a common site of involvement by several autoimmune diseases as a part of their phenotypic characteristics, or an adverse effect of certain medications.

7. Dental and Periodontal Disease

Periodontal disease is more prevalent in patients with various autoimmune diseases. Appropriate periodontal treatment with frequent follow-up visits should be performed in these patients.

Oral Mucosal Involvement as an Adverse Effect of Immunosuppressive Therapy

- Specific reactions to certain medications may affect the oral cavity with heterogeneous clinical manifestations.

- Anemia, neutropenia, and thrombocytopenia induced by certain myelotoxic drugs (or by certain diseases, including SLE) may cause corresponding oral mucosal lesions in the oral cavity.

- Systemic drug administration (methotrexate) may also cause occasional adverse mucosal reactions, which may vary from mucosal ulcers or erythema to lichenoid lesions

- Other oral lesions related to medications for rheumatic diseases include pigmentation (e.g., related to hydroxychloroquine) or diffuse gingival enlargement (e.g., due to cyclosporine). The clinician should be aware and suspicious of these conditions, especially if their occurrence shows a chronological relationship with the administration of the offending drug.

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Pigmented Lesions of the Oral Mucosa

Endogenous Pigmentation

❒❒ **Focal Melanocytic Pigmentation** 1. Freckle/Ephelis 2. Oral/Labial Melanotic Macule 3. Oral Melanoacanthoma 4. Melanocytic Nevus 5. Malignant Melanoma ❒❒ **Multifocal/Diffuse Pigmentation** 1. Physiologic Pigmentation 2. Drug-Induced Melanosis 3. Smoker's Melanosis
4.Postinflammatory (Inflammatory) Hyperpigmentation 5. Melasma (Chloasma)

❒❒ **Melanosis Associated with Systemic or Genetic Disease**

1.Hypoadrenocorticism (Adrenal Insufficiency or Addison's Disease) 2. Cushing's Syndrome/Cushing's Disease 3. Hyperthyroidism (Graves' Disease) 4. Primary Biliary Cirrhosis 5. Vitamin B12 (Cobalamin) Deficiency 6. Peutz–Jeghers Syndrome 7. Café au Lait Pigmentation 8. HIV/AIDS-Associated Melanosis.

❒❒ **Idiopathic Pigmentation**

Laugier–Hunziker Pigmentation

❒❒ **Depigmentation**

Vitiligo

❒❒ **Hemoglobin and Iron-Associated Pigmentation**

1. Ecchymosis 2. Purpura/Petechiae 3. Hemochromatosis

Exogenous Pigmentation

1.Amalgam Tattoo
2.Graphite Tattoos
3.Ornamental Tattoos
4.Medicinal Metal-Induced Pigmentation
5.Heavy Metal Pigmentation
6.Drug-Induced Pigmentation
7.Hairy Tongue

Healthy oral soft tissues present a typical pink to red hue with slight topographical variations of color. This chromatic range is due to the interaction of a number of tissues that compose the mucosal lining:

The presence or absence of keratin on the surface epithelium

 The quantity, superficial or deep location of blood vessels in the subjacent stroma,
 The existence of lobules of adipocytes,
The absence of melanin pigmentation in the basal cell layer of the epithelium.
Although oral and perioral pigmentation may be physiologic in nature, particularly in individuals with dark skin complexion, in the course of disease, the oral mucosa and perioral tissues can assume a variety of discolorations, including brown, blue, gray, and black.
Such color changes are often attributed to the deposition, production, or increased accumulation of various endogenous or exogenous pigmented substances.

However, although an area may appear pigmented, the discoloration may not be related to actual pigment but rather to the deposition or accumulation of organic or inorganic substances, including various metals and drug metabolites. Hemoglobin, hemosiderin, and melanin represent the most common endogenous sources of mucosal color change. Sub mucosal collection of hemoglobin or hemosiderin, produced by extravasation and/or lysis of red blood cells, may impart a red, blue, or brown transient appearance to the oral mucosa.

Melanin, which is synthesized by **melanocytes** and nevus cells, may appear brown, blue, or black, depending on the amount of melanin and its spatial location within the tissue (superficial / deep).
Exogenous pigmentations are usually associated with traumatic or iatrogenic events that result in the deposition of foreign material directly into the mucosal tissues.
In some cases, the substances may be ingested, absorbed, and distributed hematogenously into connective tissues, particularly in areas subject to chronic inflammation, such as the gingiva. In other instances, these ingested substances can actually stimulate melanin production, thus precipitating the color change.
Chromogenic bacteria can also produce oral pigmentation, usually resulting in discoloration of the dorsal tongue.
Certain foods, drinks, and confectionaries can also result in exogenous pigmentation. However, in most cases, the discoloration can be easily reversed.

The manifestation of oral pigmentation is quite variable, Ranging from a solitary macule to large patches and broad, diffuse tumefactions. The specific hue, duration, location, number, distribution, size, and shape of the pigmented lesion(s) may also be of **diagnostic importance**. Moreover, to obtain an **accurate**

diagnosis, thorough social, family, medical, and dental histories are required, and **various diagnostic procedures** (colonoscopy) and laboratory tests, including **biopsy**, may be necessary. Thus, an understanding of the various disorders and substances that can contribute to oral and perioral pigmentation is essential for the appropriate evaluation, diagnosis, and management of the patient. Lesions that are associated with mucosal discoloration but are vascular in origin, including developmental, hamartomatous, and neoplastic lesions (hemangioma, lymphangioma, angiosarcoma, Kaposi's sarcoma), it should be noted that these entities are frequently considered in the differential diagnosis of both macular and mass-forming pigmented lesions.

Endogenous Pigmentation

Melanin is found universally in nature. Melanin is the pigment derivative of tyrosine and is synthesized by melanocytes, which typically reside in the basal cell layer of the epithelium. Investigations into normal melanocyte homeostasis have yielded the discovery that keratinocytes actually control melanocytic growth. Yet the mechanisms by which melanocytes are stimulated to undergo cell division remain poorly understood. Their presence in the skin is thought to protect against the damaging effects of actinic irradiation. They also act as scavengers in protecting against various cytotoxic intermediates. The role of melanocytes in oral epithelium is not clear. **Melanin** is synthesized within specialized structures known as melanosomes. Melanin is actually composed of eumelanin, which is a brown-black pigment, and pheomelanin, which has a red-yellow color.

The term melanosis is frequently used to describe diffuse hyperpigmentation.

Overproduction of melanin may be caused by a variety of mechanisms, the most common of which is related to increased sun exposure. However, intraorally, hyperpigmentation is more commonly a consequence of physiologic or idiopathic sources, neoplasia, medication or oral contraceptive use, high serum concentrations of pituitary adrenocorticotropic hormone (ACTH), post inflammatory changes, and genetic or autoimmune disease. Therefore, the presence or absence of systemic signs and symptoms, including cutaneous hyperpigmentation, is of great importance to elucidate the cause of oral pigmentation. **Overproduction of melanin** However, if the etiology of the pigmentation cannot be clinically ascertained, a tissue biopsy is warranted for definitive diagnosis. This is critical because malignant melanoma may present with a **misleadingly** benign clinical appearance. In addition to biopsy and histologic study, various laboratory and

clinical tests, including **diascopy, radiography, and blood tests, may be necessary for definitive diagnosis of oral pigmentation.**
Dermascopy, also known as epiluminescence microscopy, is another increasingly employed clinical test that can be useful in the diagnosis of melanocytic lesions.

Although, current instrumentation is designed primarily for the study of cutaneous pigmentation, several studies have described the use of dermascopy in the evaluation of labial and anterior lingual pigmentation. Briefly, this noninvasive technique is performed through the use of a handheld surface microscope using incident light and oil immersion. Amore advanced method makes use of binocular stereo microscopes with or without the assistance of digital technology and imaging software. This diagnostic technique has been shown to be effective in discriminating melanocytic from non-melanocytic lesions and benign versus malignant melanocytic processes.

Focal Melanocytic Pigmentation Freckle/Ephelis
The cutaneous freckle, or ephelis, is a commonly occurring, asymptomatic, small (1–3 mm), well-circumscribed, tan- or brown-colored macule that is often seen on the sun-exposed regions of the facial and perioral skin. Ephelides are most commonly observed in light-skinned individuals and are quite prevalent in red- or light blond–haired individuals. Freckles are thought to be developmental in origin polymorphisms in the MC1R gene are strongly associated with the development of childhood freckles.

Ephelides are usually more abundant in number and darker in intensity during childhood and adolescence. Freckles tend to become darker during periods of prolonged sun exposure (spring, summer) and less intense during the autumn and winter months. Yet the increase in pigmentation is solely related to an increase in melanin production without a concomitant increase in the number of melanocytes. With increasing age, the number of ephelides and color intensity tends to diminish. In general, no therapeutic intervention is required.

Oral/Labial Melanotic Macule Etiology and Pathogenesis
The melanotic macule is a unique, benign, pigmented lesion that has no known dermal counterpart.
• Melanotic macules are the most common oral lesions of melanocytic origin.
•They made up over 85% of all solitary melanocytic lesions diagnosed in a single oral pathology laboratory.

•Although the etiology remains elusive, trauma has been postulated to play a role.
•Sun exposure is not a precipitating factor.

Clinical Features

- Melanotic macules develop more frequently in females, usually in the lower lip (labial melanotic macule) and gingiva. However, any mucosal site may be affected. Although, the lesion may develop at any age, it generally tends to present in adulthood.
- Congenital melanotic macules have also been described occurring primarily in the tongue.
- Overall, melanotic macules tend to be small (<1 cm), well circumscribed, oval or irregular in outline, and often uniformly pigmented
- Once the lesion reaches a certain size, it does not tend to enlarge further.
- Unlike an ephelis, a melanotic macule does not become darker with continued sun exposure.
- Overall, the oral melanotic macule is a relatively innocent lesion, does not represent a melanocytic proliferation, and does not recur following surgical removal.

Microscopically, melanotic macules are characterized by the presence of abundant melanin pigment in the basal cell layer without an associated increase in the number of melanocytes. The pigmentation is often accentuated at the tips of the rete pegs, and melanin incontinence into the subjacent lamina propria is commonly encountered. **Differential Diagnosis** The differential diagnosis may include: melanocytic nevus, malignant melanoma, amalgam tattoo, and focal ecchymosis. If such pigmented lesions are present after a two-week period, ecchymosis can usually be ruled out, and a biopsy specimen should be obtained to secure a definitive diagnosis. Since oral mucosal malignant melanomas have no defining clinical characteristics, a biopsy of any persistent solitary pigmented lesion is always warranted.

Oral Melanoacanthoma Etiology and Pathogenesis

- It is another unusual, benign, melanocytic lesion that is unique to the mucosal tissues.
- Oral melanoacanthoma is an innocent melanocytic lesion that may spontaneously resolve, with or without surgical intervention.
- Although the term melanoacanthoma may imply a neoplastic process, the oral lesion is actually reactive in nature.
- Most patients report a rapid onset; and acute trauma or a history of chronic irritation usually precedes the development of the lesion.

A biopsy is always warranted to confirm the diagnosis, but once established, no further treatment is required. The biopsy procedure itself may lead to spontaneous regression of the lesion. The underlying source of the irritation should be eliminated to minimize recurrence

Clinical Features

Oral melanoacanthoma usually presents as a rapidly enlarging, ill-defined, darkly pigmented macular or plaque-like lesion, and mostly develop in black females. Although lesions may present over a wide age range, the majority occur between the third and fourth decades of life. Typically, melanoacanthoma presents as a solitary lesion; however, bilateral and multifocal lesions have been reported. It is generally asymptomatic; however, pain has been reported. Although any mucosal surface may be involved, close to 50% of melanoacanthomas arise on the buccal mucosa. The size of the lesion is variable, ranging from small and localized to large, diffuse areas of involvement, measuring several centimeters in diameter. The borders are typically irregular in appearance, and the pigmentation may or may not be uniform.

Microscopically, oral melanoacanthomas are characterized by a proliferation of benign, dendritic melanocytes throughout the full thickness of an acanthotic and spongiotic epithelium. A mild lymphocytic infiltrate with exocytosis is also characteristic. Occasional eosinophils may be observed.

Diagnosis Because oral melanoacanthoma may resemble other melanocytic lesions, such as pigmented nevus, melanotic macule, and melanoma, a biopsy is warranted to obtain a definitive diagnosis.

Melanocytic Nevus Etiology and Pathogenesis

Melanocytic nevi include a diverse group of clinically and/ or microscopically distinct lesions.

Unlike ephelides and melanotic macules, which result from an increase in melanin pigment synthesis, nevi arise as a consequence of melanocytic growth and proliferation.

In the oral cavity, the intramucosal nevus is most frequently observed, followed by the common blue nevus.

Compound nevi are less common, and the junctional nevus and combined nevus (a nevus composed of two different cell types) are infrequently identified.

Relatively little is known about the pathogenesis of the various melanocytic nevi.

In fact, there is still debate as to whether “nevus cells” are a distinct cell type derived from the neural crest or if they are simply a unique or immature form of melanocyte.

 Nonetheless, the lesional nevus cells are cytologically and biologically distinct from the melanocytes that colonize the basal cell layer of the epidermis and oral epithelium.
 Although native melanocytes tend to have a dendritic morphology, most nevic cells tend to be round, ovoid, or spindle shaped.
Additional differences include the tendency for nevus cells to closely approximate one another, if not aggregate in clusters, and their ability to migrate into and/or within the submucosal tissues.
The effect of sun exposure on the development of cutaneous nevi is well recognized.
 However, there are also age- and location-dependent differences in the presentation, number, and distribution of nevi.
Although most melanocytic nevi are acquired, some may present as congenital lesions (including in the oral cavity).
Moreover, there are several examples of increased nevus susceptibility in various inherited diseases, thus confirming the role of genetics.
Familial atypical multiple mole melanoma syndrome is characterized by the formation of histologically atypical nevi; epithelioid blue nevus may be associated with the Carney complex; markedly increased numbers of common nevi are characteristic in patients with
Turner's syndrome and Noonan's syndrome; and congenital nevi are typical of neurocutaneous melanosis.

Clinical Features

Cutaneous nevi are a common occurrence.

The average Caucasian adult patient may have several nevi; some individuals may have dozens. The total number of nevi tends to be higher in males than females.

In contrast, oral melanocytic nevi are rare, typically present as solitary lesions, and may be more common in female. Oral melanocytic nevi have no distinguishing clinical characteristics.

Lesions are usually asymptomatic and often present as a small (<1 cm), solitary, brown or blue, well-circumscribed nodule or macule. Up to 15% of oral nevi may not show any evidence of clinical pigmentation. Once the lesion reaches a given size, its growth tends to cease and may remain static indefinitely. Oral nevi may develop at any age; however, most are identified in patients over the age of 30.

The hard palate represents the most common site, followed by the buccal and labial mucosae and gingiva.

Pathology

 To date, transformation of an oral nevus has not been well documented in the literature.

 It is advised **that all oral nevi**, regardless of histologic type, be completely removed as they may still represent a potential precursor of malignant melanoma.

Diagnosis

 Biopsy is necessary for diagnostic confirmation of an oral melanocytic nevus since the clinical diagnosis includes a variety of other focally pigmented lesions, including malignant melanoma.

 Complete but conservative surgical excision is the treatment of choice for oral lesions.

 Recurrence has only rarely been reported.

 Laser and intense pulse light therapies have been used successfully for the treatment of cutaneous nevi.

 However, their value in the treatment of oral nevi is unknown.

Malignant Melanoma Etiology and Pathogenesis

Malignant melanoma is the least common but most deadly of all primary skin cancers.

Similar to other malignancies, extrinsic and intrinsic factors play a role in the pathogenesis of melanoma.

A history of multiple episodes of acute sun exposure, especially at a young age; immunosuppression; the presence of multiple cutaneous nevi; and a family history of melanoma are all known risk factors for the development of cutaneous melanoma.

Clinical Features

Cutaneous melanoma is most common among **white populations** that live in the Sunbelt regions of the world.

However, mortality rates are higher in blacks and Hispanics.

Epidemiologic studies suggest that the incidence is increasing in patients, especially males older than 45 years.

 In contrast, the incidence is decreasing in patients younger than 40 years.

Overall, there is a male predilection, but melanoma is one of the most commonly occurring cancers in women of child-bearing age.

 However, there is no significantly increased incidence of melanoma in pregnancy, and there is no difference in survival rates between pregnant and non pregnant women with the disease

Melanomas may develop either **de novo** or, **much less** commonly, arise from an existing melanocytic nevus.

On the facial skin, the malar region is a common site for melanoma since this area is subject to significant solar exposure.

Melanomas may present with a wide array of histologic and cytologic patterns, and clinical prognosis directly correlates with a number of different microscopic findings.

Surface ulceration, vascular or lymphatic invasion, neurotropism, high mitotic index, and absence of lymphocytes infiltrating the tumor are all associated with a poor prognosis. In addition, various clinical parameters, including tumor site, age of the patient (>60 years), gender (male), and regional or distant metastasis, also are predictive of poor prognosis. The five-year survival rate of patients with metastatic melanoma is less than 15%.

Primary mucosal melanomas comprise less than 1% of all melanomas. The majority develop in the head and neck, most in the sinonasal tract and oral cavity. The prevalence of oral melanoma appears to be higher among black-skinned and Japanese people than among other populations. The tumor presents more frequently in males than females. Unlike the cutaneous variant, which has distinct and well-recognized risk factors associated with its development, the etiology of oral melanoma remains unknown. **Oral melanoma** may develop at any age, but most present over the age of 50. Any mucosal site may be affected; however, the palate represents the single most common site of involvement. The maxillary gingiva/alveolar crest is the second most frequent site.

Oral melanomas have no distinctive clinical appearance.

They may be macular, plaquelike or mass-forming, well circumscribed or irregular, and exhibit focal or diffuse areas of brown, blue, or black pigmentation.

Up to one-third of oral melanomas may show little or no clinical evidence of pigmentation (amelanosis).

In some cases, oral melanomas may present with what appear to be multifocal areas of pigmentation.

This phenomenon is often explained by the fact that some tumors may exhibit both melanotic and amelanotic areas.

Additional signs and symptoms that may be associated with oral melanoma are nonspecific and similar to those observed with other malignancies.

Ulceration, pain, tooth mobility or spontaneous exfoliation, root resorption, bone loss, and paresthesia/anesthesia may be evident.

However, in some patients, the tumors may be completely asymptomatic.

Thus, the clinical differential diagnosis may be quite extensive and could include melanocytic nevus, oral melanotic macule, and amalgam tattoo, as well as various vascular lesions and other soft tissue neoplasms.

It is for this reason that a biopsy of any persistent solitary pigmented lesion is always warranted.

Oral mucosal malignant melanoma is associated with a very poor prognosis.

Studies have demonstrated five-year survival rates of 15%–40%.
The palate shows the worst prognosis compared to other intraoral sites.
Regional lymphatic metastases are frequently identified and contribute to the poor survival rates.
Less than 10% of patients with distant metastases survive after five years. The 10-year-survival rate is 0%..

Diagnosis One of the main clinical and microscopic challenges in diagnosing oral melanoma is determining whether the lesion is a primary neoplasm or a metastasis from a distant site.

Management

For primary oral melanomas, **ablative surgery** with wide margins remains the treatment of choice.
Adjuvant **radiation therapy** may also be necessary.
It remains unclear whether radiation therapy is beneficial for the treatment of oral mucosal melanoma.
Computed tomography and magnetic resonance imaging studies should be undertaken to explore metastases to the regional lymph nodes.
A variety of chemotherapeutic and immunotherapeutic strategies are often used if metastases are identified or for palliation.

Multifocal/Diffuse Pigmentation Physiologic Pigmentation

Physiologic pigmentation is the most common multifocal or diffuse oral mucosal pigmentation.
Dark-complexioned individuals, including blacks, Asians, and Latinos, frequently show patchy to generalized hyperpigmentation of the oral mucosal tissues.
Although in many patients, the pigment is restricted to the gingiva, melanosis of other mucosal surfaces is not uncommon.
The pigment is typically first observed during childhood and does not develop de novo in the adult.
The sudden or gradual onset of diffuse mucosal pigmentation in adulthood, even in darker-skinned patients, should alert the clinician to consider a pathological genesis.

A differential diagnosis:
may include idiopathic, drug-induced, or smoking-induced melanosis.
Hyperpigmentation associated with endocrinopathic and other systemic disease should also be considered.

A thorough history and laboratory tests are necessary to obtain a precise diagnosis.

Microscopically, physiologic pigmentation is characterized by the presence of increased amounts of melanin pigment within the basal cell layer.

The appearance of brown - black discoloration, even **intraorally**, can be esthetically displeasing to some patients.

Thus, surgical intervention may be necessary:

Gingivectomy

Laser therapy

Cryosurgery Has been reported to effectively remove oral mucosal pigmentation. However, with all these modalities, the pigmentation may eventually recur. The cause of the re-pigmentation remains unclear.

Drug-Induced Melanosis Etiology and Pathogenesis

Medications may induce a variety of different forms of mucocutaneous pigmentation, including melanosis.

Pigmentation that is caused by the soft tissue deposition of drug metabolites or complexes and pigment associated with deposition of lipofuscin or iron.

The chief drugs implicated in drug-induced melanosis are the antimalarials, including chloroquine, hydroxychloroquine, and quinacrine; used for the treatment of autoimmune disease.

Other common classes of medications that induce melanosis include the phenothiazines, such as chlorpromazine, oral contraceptives, and cytotoxic medications (cyclophosphamide and busulfan).

Clinical Features

It has been estimated that 10–20% of all cases of acquired melanocytic pigmentation may be drug induced.

Intraorally, the pigment can be diffuse yet localized to one mucosal surface, often the hard palate or it can be multifocal and involve multiple surfaces.

Some drugs may even be associated with a specific pattern of pigmentation.

The lesions are flat and without any evidence of nodularity or swelling.

Sun exposure may exacerbate cutaneous drug-induced pigmentation.

Pathology

Microscopically, there is usually evidence of basilar hyperpigmentation and melanin incontinence without a concomitant increase in the number of melanocytes.

Although, the mechanisms by which melanin synthesis is increased remain unknown;

One theory is that the drugs or drug metabolites stimulate melanogenesis.

Alternatively, some drugs, including chloroquine and chlorpromazine, have been shown to physically bind melanin.

This complexation of melanin and drugs within melanocytes may contribute to the adverse mucocutaneous effects.

Diagnosis

If the onset of the melanosis can be chronologically and accurately associated with the use of a specific medication; within several weeks or months before development of the pigmentation, then no further intervention is warranted.

In most cases, the discoloration tends to disappear within a few months after the drug is discontinued.

However, pigmentation associated with hormone therapy may tend to persist for longer periods of time, despite discontinuation of the medications.

A differential diagnosis includes other causes of diffuse mucosal pigmentation. Laboratory tests may be necessary to rule out an underlying endocrinopathy.

Smoker's Melanosis

Diffuse melanosis of the anterior vestibular maxillary and mandibular gingivae, buccal mucosa, lateral tongue, palate, and floor of the mouth is occasionally seen among cigarette smokers. Most smokers (including heavy smokers) usually fail to show such changes. However, in certain individuals, melanin synthesis may be stimulated by tobacco smoke products. Indeed, among dark-skinned individuals who normally exhibit physiologic pigmentation, smoking stimulates a further increase in oral pigmentation. The pigmented areas are brown, flat, and irregular; some are even geographic or map-like in configuration . The mechanism by which smoking induces the pigmentation remains unknown. Smokeless tobacco (snuff) does not appear to be associated with an increase in oral melanosis.

Thus, it is possible that one or more of the chemical compounds incorporated within cigarettes, rather than the actual tobacco, may be causative. Another possibility is that the heat of the smoke may stimulate the pigmentation. However, passive smoking in children may result in increased gingival pigmentation. Epidemiologic studies suggest that oral melanosis increases prominently during the first year of smoking. A reduction in smoking may lead to disappearing of the pigmentation. Histologically, basilar melanosis and melanin incontinence are observed. Unlike other smoking-related oral conditions, smoker's melanosis is not a preneoplastic condition. Alcohol has also been associated with increased oral pigmentation. In alcoholics, the posterior regions of the mouth, including the soft palate, tend to be more frequently pigmented than other areas. It has been

suggested that alcoholic melanosis may be associated with a higher risk of cancers of the upper aerodigestive tract.

Diffuse or patchy melanotic pigmentation is also associated with oral submucous fibrosis. Unlike smoker's melanosis, oral submucous fibrosis is a preneoplastic condition caused by habitual chewing of areca (betel) nut. This custom is common in some East Asian cultures. In addition to the melanosis, increased fibrosis of the oral soft tissues is characteristically present.

Postinflammatory (Inflammatory) Hyperpigmentation

- It is a well-recognized phenomenon that tends to develop more commonly in dark-complexioned individuals.
- Most cases present as either focal or diffuse pigmentation in areas that were subjected to previous injury or inflammation.
- The acne prone face is a relatively common site for this phenomenon.
- Although unusual, postinflammatory pigmentation may also develop in the oral cavity.
- In rare cases, the mucosa overlying a non melanocytic malignancy may become pigmented.
- Oral pigmentation has also been described in patients with **lichen planus**. This phenomenon has been described in various races, including Caucasians.
- In addition to the typical microscopic features associated with lichen planus, there is also evidence of basilar hyperpigmentation and melanin incontinence.
- Upon resolution of the lichenoid lesion, in most cases, the pigmentation eventually subside.
- It is unclear whether lichen planus– associated pigmentation should be appropriately characterized as postinflammatory or inflammatory pigmentation.
- In addition, spontaneous postsurgical healing pigmentation of palatal donor sites for free gingival grafts has been reported.

Melasma (Chloasma)

- Melasma is a relatively common, acquired symmetric melanosis that typically develops on sun-exposed areas of the skin and frequently on the face.
- The forehead, cheeks, upper lips, and chin are the most commonly affected areas.
- There is a distinct female predilection, and most cases arise in darker-skinned individuals.
- Unlike other forms of diffuse melanosis, melasma tends to evolve rather rapidly over a period of a few weeks.

The term melasma has been used to describe any form of generalized facial hyperpigmentation, including those related to postinflammatory changes and medication use.

This term is most appropriately used to describe the pigmentary changes associated with sun exposure and hormonal factors, including pregnancy and contraceptive hormones.

Both pregnancy and use of oral contraceptives have also been associated with oral mucosal melanosis.

Rare cases of idiopathic melasma have also been described in females and, much less commonly, males.

In most cases, it is the combination of estrogen and progesterone that induces the pigment.

Estrogen replacement therapy alone, without progesterone, does not precipitate melasma.

In idiopathic cases, significantly elevated levels of luteinizing hormone have been identified in both sexes, with associated decreases in serum estradiol (in women) and testosterone (in males).

In view of recent research studies, it appears to be that hormones may play a role in some patients' melisma but the association is weaker than previously believed. Various thyroid abnormalities, including hypothyroidism, may also play a role in the pathogenesis of pregnancy- and nonpregnancy-associated melasma.

A biopsy typically reveals basilar melanosis with no increase in the number of melanocytes. However, the melanocytes that are present may be larger than those in the adjacent normally pigmented areas.

Melasma may spontaneously resolve after parturition, cessation of the exogenous hormones, or regulation of endogenous sex hormone levels. A successful therapeutic approach for the treatment of melasma consists in the topical administration of a triple combination product (4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide) along with photoprotection (SPF 30 sunscreen).