Oral Submucous Fibrosis- A Forerunner of TMJ Changes

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Oral submucous fibrosis (OSMF) is a high risk precancerous condition and its major etiological factor is chewing areca nut. It causes a progressive inability to open the mouth due to stiffness of oral mucosa leading to temporomandibular joint changes. Temporomandibular joint is a synovial joint and oral submucous fibrosis results in reluctant movement of the jaws and its disuse occurs. Temporomandibular joint is vulnerable to changes, thus changes due to immobilization of the temporomandibular joint are expected in oral submucous fibrosis. Immobilization of the synovial joints has effects on the morphologic, biochemical and biomechanical characterization of its components, muscles and periauricular tissues. Immobilization also causes reduced water and glycosaminoglycan content thus causing impaired lubrication. Immobilization also affects the movement of synovial fluid as mentioned previously. Also reduced haemoglobin level in OSMF is likely to interfere with the bone metabolism of the condyle and mandibular fossa.

Key words: Oral submucous fibrosis, temporomandibular joint, synovial joint.

Oral submucous fibrosis is a high risk precancerous condition, first described in early 1950. This disease is predominant in India, Bangladesh, Sri Lanka, Pakistan, Taiwan, China and among other Asians with a reported prevalence ranging up to 0.4% in Indian rural population. Schwartz (1952) described 5 Indian women with a condition of oral mucosa including the palate and pillars of fauces, which he initially called as “atrophiae diopathica (tropica) mucosae oris”.

By epidemiological and in vitro experimental studies the major etiological factor for oral submucous fibrosis is chewing areca nut. Earlier in Indian culture, betel quid was the most popular and prevalent habit of areca nuts. But in 1980s, areca quid product such as pan masala and gutka were introduced as commercial preparation.

Oral submucous fibrosis has a high rate of morbidity because it causes a progressive inability to open the mouth, resulting in eating difficulties and consequent nutritional deficiencies. Oral submucous fibrosis also has significant mortality rate and it can transform into oral cancer, particularly squamous cell carcinoma at a rate of 7.6%.

Oral submucous fibrosis is a potentially malignant condition that causes stiffness of oral mucosa and expected to cause temporomandibular joint changes. Temporomandibular joint is a synovial joint. The bones involved are the mandible and the temporal bone. In a synovial joint two bones are approximated and surrounded by a capsule and thereby creates a joint cavity. This cavity is filled with synovial fluid formed by synovial membrane that lines the nonarticular surface. The cavity is divided by articular disk.
The bones of temporomandibular articulation are the glenoid fossa (on the undersurface of squamous part temporal bone) and the condyle (supported by the condylar process of the mandible). Anteriorly, the glenoid fossa is bounded by articular eminence, which is also involved in the articulation. The condyle is the articulating surface of the mandible.

Unlike most synovial joints, the articular surfaces of which are covered with hyaline cartilage, the temporomandibular articulation is covered by a layer of fibrous tissue. This histological distinction has been used to argue that temporomandibular joint is not a weight bearing joint. The glenoid fossa always is covered by a thin fibrous layer that directly overlies the bone, much as periosteum does, but this layer becomes appreciably thicker where it covers the slope of the articular eminence. Capsule of a synovial joint consists of dense collagenous membrane that seals the joint space and provides passive stability.

Oral submucous fibrosis results in reluctant movement of the jaws. As a consequence temporomandibular joint disuse occurs. Thus changes due to immobilization of the temporomandibular joint are expected in oral submucous fibrosis.

Etiopathogenesis

Fibrosis and hyalinization of subepithelial tissues is responsible for most of the clinical features encountered in OSMF. It is hypothesized that the increased collagen synthesis or reduced collagen degradation as possible mechanisms in its development.

Areca nut is considered as a main etiological factor of oral submucous fibrosis. Daily use is said to be more important than the duration of the habit. The severity and time taken to the development of oral submucous fibrosis varies according to the preparation of the areca nut consumed. Commercially freeze dried products such as pan masala, gutka and mawa have high concentrates of areca nut and causes oral submucous fibrosis more rapidly than the betel quid.

Quid is a mixture of areca nut and tobacco in raw or processed form. It is placed in the mouth or chewed and remains in contact with the mucosa. The constant contact between the mixture and oral mucosa causes absorption of alkaloids from quid into the mucosa and undergoes metabolism. Major areca nut alkaloids are Arecoline, Arecadine, Arecolidine, Guyacoline and Guacine. The coarse fibers of areca nut causes friction and produces microtrauma which paves the way for diffusion of alkaloids into the subepithelial connective tissue resulting in juxtaepithelial inflammatory cell infiltration.

Arecoline is the main agent and hydrolysis of arecoline produces arecadine which is considered to be an active metabolite in stimulation of fibroblasts and in turn resulting in collagen synthesis. Slaked lime facilitates the hydrolysis of arecoline making it available in the oral cavity. Tannin present in the areca nut inhibits the collagenase and thus reduces collagen degradation. Also the copper content is high in areca nut and soluble copper in saliva increases on chewing areca quid. The copper dependent enzyme lysyl oxidase is thus upregulated in oral submucous fibrosis and plays a role in collagen synthesis and its crosslinkage. The enzyme lysyl oxidase is found to be upregulated in oral submucous fibrosis.

The collagen production pathway and collagen degradation are regulated by TGF-beta and flavonoids present in areca nut.

Collagen production

Collagen is most abundant protein in human body and plays important role in structural element of connective tissue. TGF-beta play an important role in inducing fibrotic tissue formation and connective tissue growth factor is important in maintaining fibrosis. The TGF-beta activates procollagen genes col1a2, col3a1, col6a1, col6a3, col7a1 causing an increased expression and thus an increased collagen level in oral submucous fibrosis. Arecoline stimulates connective tissue growth factor production in fibroblasts of buccal mucosa.

Collagen degradation

The following two main events decrease the collagen degradation and they are modulated by TGF:

1. Activation of inhibitor of Matrix Metalloproteinase Gene (TIMP-tissue inhibitors of matrix metalloproteinases)

2. Activation of Plasminogen Activator Inhibitor (PAI gene)

TIMP protein is produced more by OSMF.
fibroblasts and results in increased deposition of collagen in the extracellular matrix.

Plasminogen activators and their inhibitors are said to participate in the balance of proteolytic and antiproteolytic activities that regulate extracellular matrix. Both tissue plasminogen and plasminogen activator inhibitor were increased in oral submucous fibrosis. Arecoline upregulates plasminogen activator inhibitors and tissue-plasminogen activator is also found to be increased.14

Oral submucous fibrosis is characterised by excessive and abnormal deposition of Extra Cellular Matrix(ECM) components. Certain of the actions of ECM has ability to sequester and modulate the activity of specific growth factors.15

Vulnerability of temporomandibular joint to various diseases

Temporomandibular joint is vulnerable to changes, which could be due to disuse, trauma, other diseases involving TMJ such as osteoid arthritis, rheumatoid arthritis and granulomatous diseases.

The presence of an inadequately supported occlusion can lead to clinical signs and symptoms of osteoarthritis of the TMJ. The radiographic signs of TMJ osteoarthritis such as facet formation, reduced joint space, flattening of the condyle, subcortical sclerosis was increased in patients with inadequately supported occlusion than in patients with adequately supported occlusion.16

There was also a high prevalence of temporomandibular disorders in rheumatoid arthritis patients. The severity of temporomandibular disorder variably correlated with rheumatoid arthritis severity. Clinically, a high score of hand-joint space narrowing may serve as an early indicator of rheumatoid arthritis patients at risk of severe temporomandibular disorder. This may facilitate early management and prevent the functional impairment of temporomandibular joint.17

Systemic diseases such as tuberculosis can also produce an effect on temporomandibular joint. Histopathological examination of high condylar shave showed minor degenerative changes in tuberculosis induced TMJ stiffness. The bone marrow showed unnatural foci of lymphoid infiltration, macrophages and multinucleated giant cells associated with granulomas.18

TMJ osteoarthritis is the basic disorder in craniomandibular pain and dysfunction. Degradative process of TMJ in such dysfunction disorder impairs gliding capacity of articular disc and gives rise to internal derangement.19

Temporomandibular changes that may accompany OSMF

Trismus

Trismus is one of the classical and consistent manifestation of oral submucous fibrosis. Trismus for prolonged periods may cause TMJ changes due to disuse. Impaired mouth movements and lack of functional stimuli of TMJ can lead to temporomandibular joint changes.

Effects on synovial joints due to immobilization20

Immobilization of the synovial joints has effects on the morphologic, biochemical and biomechanical characterization of its components, muscles and periauricular tissues.

Animal studies involving immobilization of knee joints of rats, dogs, rabbits and monkeys have following deleterious effects,

a. Synovium- prolonged immobilization causes proliferation of fibrofatty connective tissue into the joint space and leading to obliteration, adhesions between synovial folds.

b. Muscles- muscle atrophy and decreased proteins within muscles, reduction in blood vessels.

c. Bone- generalized osteoporosis due to invasion of proliferating mesenchymal tissues from marrow spaces.

d. Periarticular connective tissue- increased degradation and decreased production of mature collagen leading to reduced collagen mass.

Immobilization of synovial joints cause structural and functional effects. Lack of physical stimulus affects the homeostasis of the joint. The movement of the joint causes movement of the synovial fluid and transsynovial nutrient flow to cartilage and ligaments. Immobilization also causes reduced water and glycosaminoglycans content thus causing impaired lubrication.

Temporomandibular joint is also a synovial joint and its disuse also is expected to result in the above said changes such as adhesion formation, TMJ muscular atrophy, osteoporosis.

The masticatory forces exerted on the
TMJ due to areca nut chewing may result in the TMJ arthrosis. To substantiate this further studies are required.\textsuperscript{21}

**Biochemical changes-OSMF and TMJ**

An increase in the globulin fraction of protein and hence a decrease in (Albumin/Globulin)\(\frac{A}{G}\) ratio was found in OSMF patients. Due to increase in globulin fractions and other serum protein levels an increase in the total protein levels are also seen in OSMF. Ascorbic acid and iron are utilised in the collagen synthesis and hence their levels are reduced in OSMF.\textsuperscript{22}

The decreased levels of haemoglobin and protein are likely to cause decrease in synovial fluid and flow. Immobilization also affects the movement of synovial fluid as mentioned previously. Since the articular disc is depending on synovial flow, its decreased flow may have its effects on TMJ. Also reduced haemoglobin level in OSMF is likely to interfere with the bone metabolism of the condyle and mandibular fossa.

**CONCLUSION**

Oral submucous fibrosis, a potentially malignant condition mainly causes temporomandibular joint disuse (trismus). Trismus caused by OSMF leads to immobilization of the TMJ and thus affects its various morphologic, biochemical and biomechanical characteristics. The decreased levels of the laboratory parameters (haemoglobin, protein, iron) are likely to cause decrease in synovial fluid and interferes bone remodelling of condyle and mandibular fossa and thus changing the normal contours of the articular surface. The exact mechanism of such changes are yet to be completely revealed. But then the clinicians should bear in mind that such temporomandibular changes are likely to be encountered in oral submucous fibrosis patients.

**REFERENCES**

5. Antonio nanciphd, tencate’s oral histology development, structure and function, sixth edition.
8. Iarc anonymous tobacco habits other than smoking: betel quid and areca nut chewing and some related nitrosamines. \textit{larcmonogrevalcarcinog risk chem hum} \textbf{37}:141-200.
11. Trivedy c, warnakulasuriyaka et al, the upregulation of lysyl oxidase in oral submucous fibrosis and squamous cell carcinoma, \textit{j oral med pathol} 1999; \textbf{28}: 246-51.
15. Nathan c, sporn m, cytokines in context, \textit{j cell biol} 1991; \textbf{113}:981-6.
16. Ra’ed a-sadhan, the relation between tmj osteoarthritis and the inadequately supported occlusion, \textit{egyptian dental journal}, 2008; \textbf{54}: 47-54.
18. D soman and sjdavies, a suspected case of


