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Review

Diabetes mellitus and potential oral complications – A review

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Abstract

It is a fact that diabetes affects 9.3% of the world's population and the number of afflicted individuals is anticipated to increase by 11% by 2045. Diabetes mellitus (DM) is a category of metabolic disease characterized by hyperglycemia caused by abnormalities in insulin production, insulin action, or both. It is also attributed to a number of micro and macrovascular problems, the etiology of which is complicated and involves metabolic and hemodynamic abnormalities such as hyperglycemia, dyslipidemia, insulin resistance, and immunological dysfunction. Since the oral cavity is likewise extensively vascularized and innervated, diabetic oral sequelae are to be expected. Despite the fact that there is significant data supporting the link between diabetes and dental health, there is a lack of oral health knowledge among health professionals and even diabetic patients. In this review, we will assess potential oral complications, elaborate on the pathogenic mechanisms and some literature studies that might explain the associations between DM and potential oral manifestations.

Keywords: diabetes mellitus, oral manifestations, oral hygiene, inflammation.

Introduction

Diabetes mellitus (DM) is a widespread ailment with associated oral manifestations that impair dental care services. There has been some skepticism regarding the capability of these oral presentations to have a substantial impact on diabetes metabolic control. Practitioners attempting to enhance these patients' metabolic control should acknowledge the significance of limiting oral complications from arising. This demands a comprehensive approach incorporating effective collaboration between physicians and oral health specialists that will positively impact glycemic control throughout the whole patient population while also reducing the influence of these potentially disabling co-morbid conditions on personal and societal burdens [1].

Type 1 diabetes (cell destruction, often leading to total insulin shortage, immune-mediated diabetes) affects only 5–10% of the population. The etiology is described as lysis of pancreatic cells by the immune system using cellular pathways which were previously referred to as insulin-dependent diabetes or juvenile-onset diabetes. Insulin autoantibodies, GAD (GAD65), autoantibodies phosphatase IA-2α and IA2β along with islet cell autoantibodies are all markers of immunological destruction of β cells. When fasting hyperglycemia is first discovered one or more of these autoantibodies are present in 85–90% of people. Furthermore, the illness has significant HLA connections with DRB genes influencing the DQA and DQB gene linkage. All such HLA/DR/DQ alleles have the potential to be either predisposing or protecting.

Type 2 diabetes (which can vary from an insulin secretory deficiency that causes insulin

resistance to relative insulin insufficiency) is a type of diabetes that affects 90–95% of diabetics. It was formerly known as adult-onset diabetes or non-insulin-dependent diabetes. Insulin resistance is frequently accompanied by relative (rather than absolute) insulin deficiency. These people do not require insulin therapy to survive, at least not to begin with nor on a regular basis. This kind of diabetes is most likely caused by a variety of factors. Even though the precise etiologies are unknown, autoimmune cell destruction does not occur, and the majority of patients are overweight, which causes a significant degree of insulin resistance. Ketoacidosis seldom happens spontaneously in this form of diabetes; when it does occur, it is generally associated with the stress of another condition like an infection. Since hyperglycemia develops slowly and isn't often severe enough for the patient to notice any of the traditional symptoms of diabetes in the preliminary phase, type-2 diabetes sometimes goes undiagnosed for years [2]. Diabetic hyperglycemia has been revealed to be a substantial risk factor for a series of complications. Retinopathy, neuropathy, nephropathy, macrovascular consequences (coronary artery disease, stroke, and peripheral vascular disease), and delayed wound healing are the five typical complications of DM. Periodontal disease has lately been identified as the DM's 'Sixth' consequence.

Diabetic oral complications can cause debilitating effects to the patient. These complications might include but are not limited to gingivitis, periodontitis, salivary gland dysfunctions, xerostomia, taste impairment, dental caries, and mucosal conditions like candidiasis, lichen planus, burning mouth syndrome, and other neurosensory disorders [1]. The motivation behind this review article is to feature different pathologies concerning DM and their potential impact on the oral cavity.

Epidemiological data

According to the WHO Global Diabetes Report, 2019 the number of diabetes increased from 108 million in 1980 to 422 million in 2014. Diabetic premature mortality boosted by 5% between 2000 and 2016. Diabetes was directly responsible for an estimated 1.5 million fatalities in 2019 [3].

According to the International Diabetes Federation (IDF) Diabetes Atlas ninth edition 2019, about 463 million (20–79 years) people with diabetes; by 2045 this figure is expected to grow to 700 million. Diabetes affects 1 out of every 5 adults over the age of 65.1 in every 2 (232 million) diabetes were undetected. Type-1 diabetes affects about 1.1 million children and adolescents, and diabetes impacts over 20 million live births (1 in every 6 live births) during pregnancy. Three hundred and seventy-four million people are at a higher risk of developing type-2 diabetes [4].

Potential oral complications

Dental caries

The association between DM and dental caries is complicated. Adults and children with type-2 diabetes, which is often associated with obesity and high calorie and carbohydrate food intake, might be expected to have a larger exposure to cariogenic foods. Similarly, diabetes with neuropathy has been associated with diminished salivary flow [5] and reduced salivary flow is reported to result in dental caries. In 2007, a study by Hinata et al. found that although type-2 diabetes is a significant risk factor for root surface caries, it is not really a risk factor for coronal caries [6]. However, a Belgian investigation on type-1 and type-2 diabetic individuals done by Buysschaert Martin et al. in 2018 revealed that the prevalence of caries on average was comparable in both groups, despite the fact that more type-2 diabetes patients than type-1 diabetes patients had >5 caries [7].

Pulpal and periapical pathologies

The dental pulp in type-2 diabetes mellitus patients have impaired immune response, dental pulp necrosis/increased risk of infection and limited collateral circulation. In terms of molecular pathophysiology hyperglycemia inhibits osteoblast development, stimulates bone resorption, and reduces bone repair capability [8]. According to a cross-sectional study

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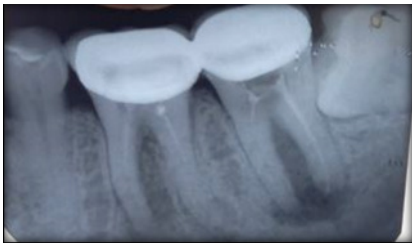
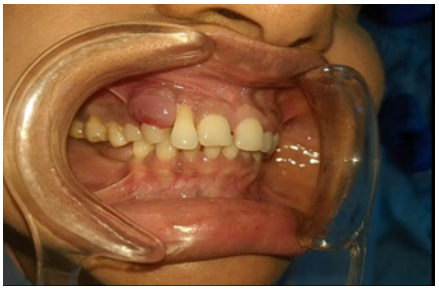
conducted on 8,67,526 patients by Wafaa Saleh in 2020, the subjects without periodontal diseases, diabetic patients were almost 3 times likely to have periapical lesions compared with non-diabetic subjects [9].



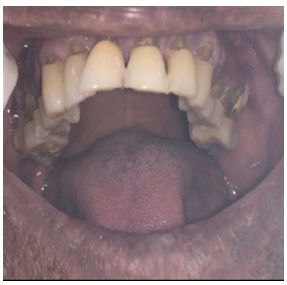
Gingivitis

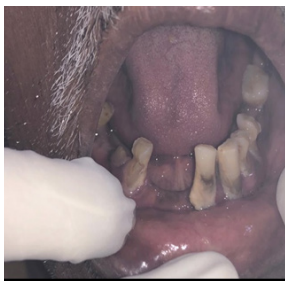
Diabetes is linked with gingival alterations such as enlarged gingiva, inflammatory or erythematous gingival hyperplasia, sessile or pedunculated gingival polyps and polypoid gingival proliferation [10]. An exfoliative cytological study performed in the oral mucosa by Sandra Alberti et al. in 2003, showed a nuclear area was markedly higher in the diabetic group and the cytoplasmic nucleus mean was 37.4% lower in the type-2 diabetic group while the epithelial cells of the diabetic group exhibited figures of binucleation and occasional karryohexis in all layers [11].



Periodontitis

Insulin resistance was caused by inflammation due to a shift in the subgingival microbiome [12, 13]. Diabetes patients are more susceptible to infections as a result of the cumulative consequences of polymorphonuclear (PMN) leucocyte deficits such as faulty phagocytosis, decrease adherence, and reduced chemotaxis [14]. Destructive alterations in the periodontium are caused by altered collagen metabolism which results in reduced collagen production, decreased alveolar bone height, osteoporosis, and degradation of tissue integrity [15]. Besides that, accumulated glycated end products (AGEs) in periodontal regeneration ability, exacerbate the already existing damage [13]. Federico Romano et al. understood cross-sectional interventional research in 2021. Periodontal health was examined in 104 type-2 diabetes patients (64 men and 43 women) using periodontal inflamed surface area index (PISA) and CDC/AAP periodontitis criteria. A 1% rise in HbA1c was associated with a PISA increase of 89.6 mm^2. The probability of having HbA1c > 7% shot up by 2% as PISA increased by 10 mm^2, showing a persistent bidirectional relationship between periodontitis and poorly maintained glycemic control [16].





Dry mouth (xerostomia)

Diabetes is accompanied by polyuria – a loss of fluids due to insufficient insulin supply which induces secondary dry mouth due to lack of water for salivation. A study by Robinson Sabino Silva et al. showed that in diabetic rats, the salivary flow tends to reduce when SGLT1 expression begins to rise in the luminal membrane present within the ductal cells of the salivary gland, which may be connected to sympathetic activity. In the salivary glands, SGTL1 behaves as a water transporter that might explain diabetic hyposalivation promoting ductal water reabsorption [17].

Salivary gland dysfunction

The protein component of saliva also known as the salivary peptidome fluctuates in

quality and quantity owing to a variety of factors such as individual physiology, health status, and time of the day [18]. Obesity in type-2 diabetes causes considerable alterations in the morphometric evaluation of the submandibular glands, such as widening of the size of adenomas and granules, increment in the density of microfolds, and protrusions throughout the luminal membranes, decrement in glandular mass and a lessen in mitochondrial size. Despite the fact that the gland's function appears to remain unchanged, the morphological modifications reflect functional changes pertaining to the primary sensory activity [19]. In animal models of obesity-induced by monosodium glutamate (MSG), a massive increase in the content of substances reactive to thiobarbituric acid was observed, as there was a dramatic drop in the activity of superoxide dismutase and catalase, implying an imbalance in the antioxidant and prooxidant system and the emergence of oxidative stress on the salivary gland which causes destruction [20].

Parotid hypertrophy

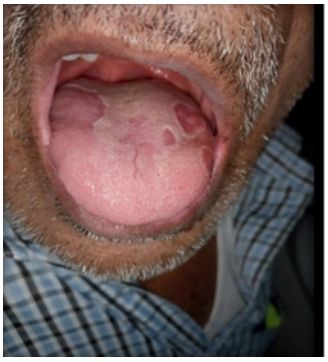
Non-inflammatory non-neoplastic adenomere hypertrophy and a spike in the proportion of ducts following induction of hyperphagia by damage to the ventromedial nucleus of the hypothalamus and storage of adipocytes in the parenchyma might result in parotid hypertrophy in diabetes patients [21]. Samuel B. et al. found 48 individuals (24%) with asymptomatic parotid gland enlargement in a study of 200 patients with overt or latent diabetes. The majority of the patients were unaware of the growth. All individuals with enlarged asymptomatic parotid glands should be tested for DM [22].

Altered taste sensations

A variety of factors influence the taste threshold, including age, drugs, ethnic background, smoking, tobacco use, alcohol, local and systemic illnesses. DM is one of the causes that modify the physiological taste threshold. The pathophysiology of taste variation in diabetes may be linked to a slower turnover rate of receptors [23]. A relationship between taste impairment and diabetes type-1 neuropathies has also been documented, however, it is controversial [24]. The most frequent type of diabetic neuropathy that can produce impaired taste sensation is distal symmetric sensorimotor polyneuropathy [25].

Burning mouth syndrome (BMS)

BMS can be primarily owing to idiopathic causes or secondary due to known precipitating conditions, one of which is DM [26]. BMS has been associated with poor glycemic control, neuropathy, angiopathy, and metabolic changes in the oral mucosa in diabetic individuals. Symptoms improve when metabolic management is appropriate [27]. Although numerous views have been proposed in the pathophysiology of BMS, it is widely acknowledged that the oral burning sensation is caused by a mix of events including chordatympani destruction and tiny fiber neuropathy [28].



Increased incidence of infections

The pathophysiology in diabetic patients can be associated with numerous abnormalities in host defense. There is a possible association of diabetes with the prevalence of infections like pneumonia, influenza, cystitis, bacteremia, candida vulvovaginitis, pyelonephritis, mucormycosis, malignant otitis externa, Fournier's gangrene, chronic bronchitis, and pulmonary tuberculosis. Diabetes and the incidence of chronic sinusitis have debatable correlations with *Staphylococcus aureus* colonization [29].

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Delayed wound healing

A high AGEs concentration has been implicated to impaired wound healing in a myriad of contexts including structural and functional changes to proteins useful in wound repair, including oxidative stress, a boosted inflammatory response via possible exaggerated apoptosis of wound repair cells and transcription factor activation [30]. Cytological investigation in a diabetic mouse performed by Seiichi Yamano et al. in 2013 revealed that epithelial tissue migration causing wound healing was delayed following tooth extraction compared to controls. Transformation growth factor (TGF)-1, TGF-2, TGF-3, TGFRII, and TGFRIII gene expression was substantially downregulated during wound healing 4–7 days following tooth extraction according to quantitative real-time polymerase chain reaction (QT-PCR) [31].

Impaired tooth eruption

Although the impact of hyperglycemia on periodontal disease has been well established in the medical and dental literature, there appears to be little and out-of-date evidence on the impact of diabetes on tooth eruption. Alder et al. observed in 1973 that children with diabetes who were less than 11.5-years-old had enhanced dental growth, but older diabetic children experienced a setback in dental development. These very same findings were ascribed to the disease's local and systemic impacts as well as "Pre-diabetic" condition regulating tooth eruption [32]. These findings were consistent with the findings of White and colleagues who observed a "biphasic" effect of diabetes on tooth maturation. In a recent study, children with diabetes had faster tooth eruption compared with healthy children during the late mixed dentition stage according to Shantanu Lal et al. in 2008 [33].

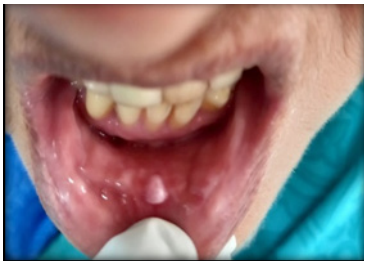
Neurosensory disorders

Diabetes, obesity, insulin resistance, altered insulin sensitivity, and abundant or inadequate insulin secretion are all found to be associated with over 20 syndromes among the extending and expanding range of degenerative diseases of the nervous system. They include Down's syndrome, Parkinson's disease, Prader-Willi syndrome, Werner syndrome, Wolfram syndrome, Alzheimer's disease, Ataxia telangectasia, Huntington's disease, several disorders of mitochondria affecting oxidative phosphorylation, vitamin B11 efficiency/hereditary thiamine-sensitive megaloblastic anemia syndrome along with their linkages to malignancies, aging, and the inheritance framework (including triplet repeat theories), functional biochemistry, and specific gene loci [34].

Benign mucosal disturbances

Irritation fibromas

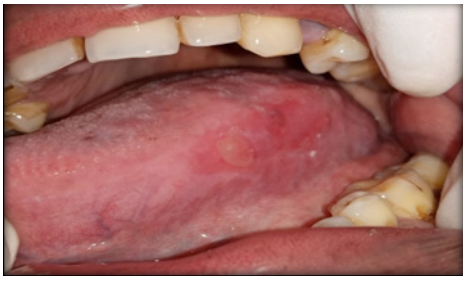
These lesions were assumed to be the result of an increased rate of tooth loss and a greater proportion of individuals with type-1 diabetes who wore dentures. The only character traits of type-1 diabetic patients that were attributed to irritant fibroma were smoking, consuming more alcohol, and having overt neuropathy. In a study done by James Guggenheimer et al. 3 out of 10 patients with type-1 diabetes had irritation fibromas [35].



Traumatic ulcers

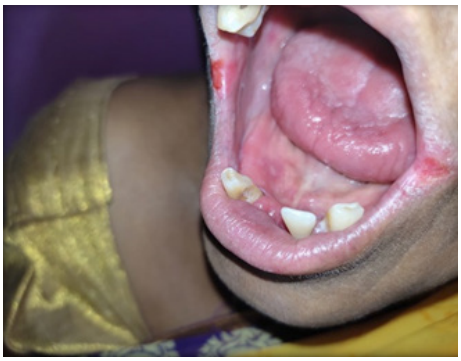
The higher frequency of traumatic ulcers in type-1 diabetes participants did not appear to be correlated to any type of the factors studied by Devlin H. et al. As a result, this might be linked to other variables such as the delayed healing period for those with type-1 diabetes mellitus. A longer duration of the ulcers may represent

a symptom of delayed wound repair or a slower healing rate rather than a true incidence [36]. A study done by James Guggenheimer, et al. found that 14 subjects (3.5%) of type-1 diabetes had more prevalence of traumatic ulcers than controls with 3 (1.1%) [35].



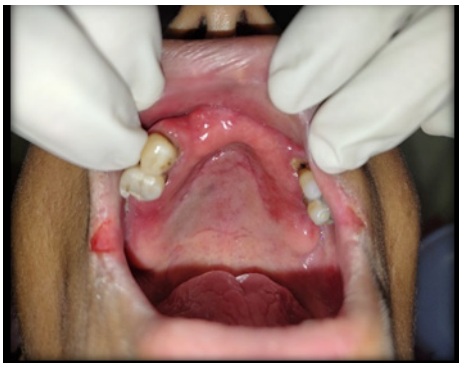
Angular chelitis

The labial commissures are significantly impacted by angular chelitis, which is a persistent inflammatory condition. Clinically, it appears as fissured erythematous lesions mostly around mouth angles. It is frequently bilateral and symptomatic. Saliva accumulation and a persistent wet environment may result from wrinkles along the labial commissures and nasolabial folds and facial skin folds, predisposing to angular chelitis. This is prevalent among denture wearers with reduced vertical occlusal dimensions [37]. A study was done by Alliny desouza Bastos et al. in 2011 on DM and oral mucosal alterations revealed a prevalence of 15% in type-2 diabetic subjects when it was only 9% in controls [38].



Denture stomatitis

Denture stomatitis is a widespread inflammatory lesion of oral mucosa that emerges on the mucosa in interface with a denture's fitting surface. Typically, edema and erythema localized to the denture-supporting area are the most common manifestations. Lesions are generally asymptomatic however, patients may experience burning sensations and soreness of the mouth. While moist lesions are associated with candida infection, other etiologic determinants that are implicated with candida infection include inadequate oral and denture hygiene, ill-fitting dentures, and nocturnal denture usage [39]. A case-control study on denture stomatitis in type-1 and type-2 diabetes conducted by Bharati Doni et al. in 2019, revealed a greater prevalence of denture stomatitis in type-2 diabetes (74.5%) and type-1 diabetes (69.4%) than the controls (31%) suggesting that excellent oral hygiene is crucial for improving oral health care in diabetic patients as DM can increase candida colonization indentures and mouth, leading to denture stomatitis [40].



Geographic tongue/benign migratory glossitis

It is a well-known inflammatory disease that generally affects the dorsal surface of the tongue mucosa. The lesions can be solitary or numerous, intermittent or continuous, and show up as non-ulcerated patches in the clinical picture devoid of keratin making them look redder than the neighboring keratinized mucosa. The prevalence of type-1 diabetes was shown to be four times higher in George P's research of 87 type-1 diabetic patients and 105 age and gender-matched non-diabetic control participants of geographic tongue as well as an uncharacteristic increase in the prevalence of the HLA B15 gene, which may be inherently associated with type-1 diabetes [41].

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Median rhomboid glossitis

A rhomboidal or erythematous elliptical patch that is symmetrical on the posterior dorsal surface of the tongue, approximately anterior to the circumvallate papillae, characterizes the lesion [42]. The filiform papillae are atrophied in this region. Fungal hyphae are observed histologically infiltrating the parakeratotic superficial layers of the epithelium with rete pegs that are hyperplastic. In most cases, fungiform and filiform papillae are missing [43]. In 2011, Ghabanchi J et al. conducted case-control research on 463 people, including 202 diabetic patients and 261 controls and found that 13 (6.43%) of diabetic patients and 4 (1.53%) of controls had Median Rhomboid Glossitis [44].

Fissured tongue

Fissured tongue with extensive plication and a longitudinally spreading double fissure across the tongue's dorsum [45]. A genetically driven developmental variant, a consequence of aging, or changes in the oral environment are considered to constitute the etiology of this condition. In a research done in 2000 by James Guggenheimer et al. more on type-1 diabetes associated with dry mouth and no noticeable decrease in salivary flow rates, 22 (5.4%) patients with fissured tongues were found compared to controls 1 (0.4%) [35].

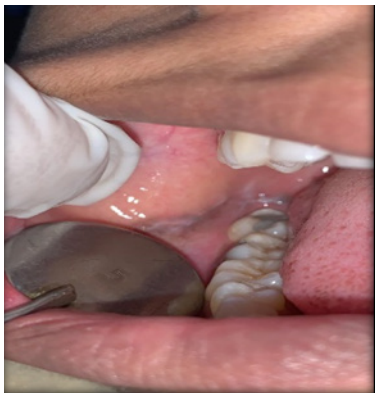
Fungal infections

Oral candidiasis

Candida species, with a mortality rates ranging from 40% to 80% in immunocompromised hosts [46, 47]. In diabetic patients, the major pathophysiologic and nutritionally relevant sugars, other simple carbon sources, such as glucose and fructose, are important in the growth of candida species. Man et al. looked at the growth rate of *Candida albicans* (*C. albicans*) in the presence of various amounts of glucose and fructose and its probable relationship to diabetes patients' hyperglycemic state. The researchers found that glucose content is closely associated with *C. albicans* development, which might explain the frequent yeast infections seen in uncontrolled diabetes individuals. Interestingly, fructose inhibited *C. albicans* growth. This implies that meals high in fructose may help to prevent candidiasis from developing. This is a concerning discovery in oral candida species biofilms, particularly for patients who wear dentures [48].

Oral lichen planus (OLP)

Grinspan et al. revealed the affiliation between oral lichen planus and DM for the first time in 1966, and it has been extensively investigated since then. Two facts may shed insight on the pathophysiology of OLP. (a) In diabetes, the poor endocrine function may lead to an immunological imbalance that might eventually lead to OLP lesions [49]. (b) A few anti-diabetic drugs might induce an allergic reaction, leading in an oral lichenoid lesion in individuals with diabetes [50]. Mazaffari et al. revealed a statistically significant difference in the incidences of OLP in diabetic patients compared to controls in a meta-analysis study published in 2016 (1.37% patients with DM and 0.75% in the control population) [51].



Rhinocerebral zygomycosis (mucormycosis)

Mucormycosis is a life-threatening invasive fungal infection that affects diabetics with or without other underlying conditions

including the need for solid organ donation and hemophilia. Mucormycosis is most commonly seen in the rhino-orbital-cerebral region, although the lack of symptoms may contribute to a delay in diagnosis. Thus, every instance of non-bacteriological sinusitis in diabetic individuals, even if there is no ketoacidosis, should raise the possibility of mucormycosis. The pathogenesis of mucormycosis is described as (a) Diabetic patients have altered innate immunity, as evidenced by well-documented PMN dysfunction and decreased adaptive immunity. (b) The hyphae of these organisms take on tissue invasive forms, with a predilection for blood vessels, leading to tissue necrosis and thrombosis. (c) Phagocytosis is impaired. (d) Alterations in the metabolism of Fe^{3+} delivered by protein transferrin (TF), H^{+} efflux reduce TF-iron binding ability in circumstances of low pH, such as ketoacidosis, and free iron is liberated in blood. A mucorales spore membrane reductase enzyme converts available iron to the ferrous ion Fe^{2+}, allowing free iron to enter spores via the high-affinity permease FTR1, resulting in a ferric form that accelerates mucorale spore growth. Platelets, in addition to innate immunity, have a time-dependent function in destroying mucorales hyphae and limiting fungal growth through their ability to inhibit germination and hyphal development [52]. As the coronavirus disease 2019 (COVID-19) pandemic progresses, additional COVID-19 consequences emerged. A case report describes a 41-year-old man with type-1 diabetes who was diagnosed with mucormycosis and survived after three surgical debridements [53].

Aspergillosis

Aspergillosis refers to a variety of clinical symptoms produced by a fungus of the aspergillus species. Aspergillus is a common fungus that can cause a variety of clinical manifestations of differing severity. Although aspergillus-conidia inhalation is widespread the illness is unusual in healthy people. Colonization invasive infections and allergy forms are the clinical manifestations. The invasive type is the most dangerous, especially in immune-compromised patients with pulmonary or extrapulmonary localization. Cases of invasive paranasal sinusitis or allergic broncho-pulmonary aspergillosis are not rare in these patients. Oral aspergillosis is uncommon and mostly affects individuals that are at high risk or have a compromised immune system [54]. In a diabetic patient, an aspergillus species infection of the jaw bone was documented following tooth extraction [55]. It's still unclear if COVID-19 individuals who are critically sick are vulnerable to fungal infections. Invasive pulmonary aspergillosis (IPA) occurred 2 weeks after symptoms began in a 69-year-old COVID-19 afflicted man with chronic obstructive pulmonary disease (COPD), grade-2 obstructive sleep apnoea (OSA), and type-2 diabetes with end-organ failure but no other known risk factors. In spite of intensive care unit (ICU) treatment and the administration of vorniconazole, the patient died of multiorgan failure three days after commencing antifungal therapy [56].

Conclusion

DM is an endemic, incessant non-transmittable illness. The oral indications and complexities of this illness have recently been viewed as a substantial discomfort. Although some studies show that microvascular pathways play a role in the etiology of oral complications, which is not the case for all the oral difficulties described and their overall higher prevalence cannot be overlooked. A dearth of good research has frequently prevented us from establishing or rejecting obvious parallels between diabetes and non-diabetes. To tackle some of these problems, avoid morbidity and mortality and decrease the inflammatory burden system, doctors and dentists must be vigilant to make an early diagnosis.

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