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The Impact of Diabetes Mellitus and the Hypoglycaemic Agent Metformin on Oral Health: A Narrative Clinical Review

Azmi Darwazeh[1], Tamer Darwazeh[2]

1 Department of Oral Medicine and Surgery, Faculty of Dentistry, Jordan University of Science and Technology, Irbid, Jordan.
2 Department of Maxillofacial Surgery, Saint James's Hospital, Dublin, Ireland.

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Correspondence:
Azmi Darwazeh,
Department of Oral Medicine and Surgery, Faculty of Dentistry, Jordan University of Science and Technology, Irbid, Jordan.
Email: darwazeh@just.edu.jo

ABSTRACT

Objectives: Diabetes mellitus (DM) is a common endocrine disorder that affects more than 10% of the adult population globally, 90% of whom with type-2 DM (T2DM). DM was extrapolated to affect 20.5% of adult Jordanians by 2025, and around 50% of Jordanians attending dental clinics are at a moderate to high risk of developing T2DM in 10 years. This narrative clinical review seeks to uncover the impact of DM and the hypoglycaemic agent metformin on oral health.

Materials and Methods: The main morbidities of DM are angiopathy, nephropathy, retinopathy, and neuropathy, rendering diabetic patients at a higher risk of myocardial infarctions, chronic kidney disease, blindness, and peripheral neuro-pathological impairment, respectively. The common oral features associated with DM include gingivitis/periodontitis, dental caries, candidosis, xerostomia, sialosis, bacterial sialadenitis, burning mouth, halitosis, and dysgeusia.

Results: DM is also accused of being a risk factor for the development of oral/head and neck cancer, potentially malignant disorders and oral lichen planus.

Metformin is the first-line treatment of T2DM with versatile use. In addition to its blood glucose-lowering effect, metformin has pleiotropic effects that may influence patients' oral health and dental management. Metformin therapy has positive impacts on oral health, such as decreasing the risk of gingivitis/periodontitis, ameliorating the xerostomia, accelerating the healing of periapical pathology following endodontic treatment, increasing the success rate of the dental implant and lowering the incidence and mortality rate of oral cancer, in addition to its anti-microbial activity. On the other hand, metformin has a bitter taste, may cause taste alterations, decreases the orthodontic tooth movement rate, and can induce oral lichenoid reaction.

Conclusions: For optimum dental and medical healthcare, providers should be fully aware of the oral manifestation associated with DM and metformin therapy for proper and safer management of their patients.

Keywords: Diabetes mellitus, Metformin, Oral manifestations, Oral health.

1. Introduction

Diabetes mellitus (DM) is an endocrine/metabolic disorder characterized by relative or absolute insulin deficiency or insulin resistance, leading to hyperglycaemia. The American Diabetes Association has classified DM into four types; type-1 DM (insulin-dependent), type-2 DM (non-insulin-dependent) (T2DM), gestational DM, and specific types of diabetes due to other causes, where T2DM is the most common type constituting more than 90% of the cases (1). The main morbidities of DM are angiopathy, nephropathy, retinopathy and neuropathy, rendering diabetic patients

at higher risk of myocardial infarctions, chronic kidney disease, blindness, and peripheral neuro-pathological impairment, respectively (2).

Metformin (N-N-dimethylbiguanide hydrochloride) is the first-line treatment of T2DM, first discovered in 1922. It is either administered as monotherapy or combined with other glucose-lowering medications.(3) Metformin's anti-diabetic effect is exerted primarily by inhibition of hepatic gluconeogenesis and to a lesser extent increasing insulin sensitivity, enhancing glucose uptake in peripheral tissues, and retarding the intestinal absorption of glucose (4). In addition to the blood glucose-lowering effect, metformin is known for having multiple pleiotropic effects, some of which may influence patients' oral health and dental management. Since this old drug is gaining mounting attention in the healthcare field, dental practitioners and dental/oral healthcare workers should be aware of these effects for proper and safer management of their patients.

The DM epidemic is a global public-health concern. The overall global diabetes prevalence in the adult population in 2021 was estimated to be 10.5%, rising to 12.2% in 2045 (5). The epidemic is hitting more seriously in Middle East countries, where the prevalence of T2DM was projected in 2025 to be 20.6% in Jordan (6), 23.8% in Oman (7), and 24% in Qatar (8). This explains why metformin is the most commonly prescribed oral hypoglycemic agent worldwide, constituting 45%-50% of all prescriptions and taken by over 150 million people annually (9). In Jordan, around 49% of diabetic patients use metformin as monotherapy, and in combination with sulfonylurea in more than one-third of the patients (10).

Among patients attending dental clinics for routine dental treatment, from 4.2% to 8.7% have proved to be diabetic (11-12). A study screened dental patients who are not known to be diabetic and found that 30% had dysglycaemia (13). In Jordan, almost 50% who are not known to be diabetic attending dental clinics are at a moderate to high risk of developing T2DM in 10 years (14).

This review aims to increase the awareness of oral healthcare providers about the oral manifestations of DM and the impact of metformin therapy on oral health. This will boost the ability of dental practitioners to provide optimal patients' oral and dental healthcare and increase their ability to anticipate undiagnosed cases of DM.

2. Methods

To prepare this review, a systematic online search of the Medline, SCOPUS, Web of Science, and Google Scholar databases using a combination of the following search terms, in titles and abstracts, was conducted: diabetes mellitus, oral manifestations, metformin, periodontitis, gingivitis, dental implant, anti-microbial, adverse effects, and oral cancer. The literature was searched from March to July 2024. The search was conducted for English literature without a limited date for publication. Case reports of rare cases were excluded from this review.

3. Results

3.1 Oral Manifestations of DM

Figure 1 shows the potential oral manifestations of DM.

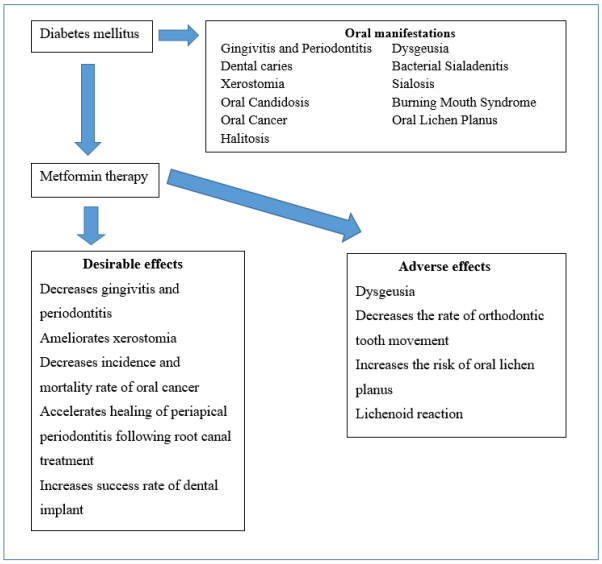

Figure 1: Oral manifestations associated with type-2 diabetes mellitus and metformin therapy

3.1.1 Gingivitis/Periodontitis

It is widely recognized that poor DM control is associated with a higher prevalence and severity of gingival and periodontal disease (15). The meta-analysis reviews clearly demonstrated that effective periodontal treatment favorably influences the metabolic control of DM2 patients and can significantly reduce glycosylated haemoglobin levels (16, 17).

DM induces alterations in subgingival microflora, qualitative and quantitative changes in gingiva vascularity, structure and metabolism of collagen and gingival crevicular fluid, impairing host defense

response and increasing the susceptibility of the patients to gingival and periodontal disease (18). Poor oral hygiene, uncontrolled DM, longer duration of diabetes, xerostomia and tobacco smoking are known to increase the prevalence and severity of periodontal disease in diabetic patients (18). In addition, DM enhances the release of inflammatory cytokines and induces osteoclastogenesis, which accelerates alveolar bone resorption, leading to deep periodontal pocketing and subsequent tooth loss (19).

There is mounting evidence of the existence of a two-way relationship between DM and periodontal disease, with diabetes increasing the risk for periodontitis, and periodontal inflammation negatively affecting glycaemic control (20). Moreover, several studies pointed to periodontitis as a possible risk factor for the development of DM (21).

3.1.2 Dental Caries

Reviewing the literature reveals conflicting data regarding the relationship between DM and dental caries. The majority of the clinical surveys show that the prevalence and risk of dental caries are higher among adult diabetics compared to non-diabetics (22, 23), especially in poorly controlled patients (24-26). However, most of these surveys were conducted on patients with Type-1 DM (22). Others reported comparable caries levels between well-controlled T2DM patients and control subjects (27). This discrepancy is possibly a reflection of differences in the quality of glycaemic control, hypo-salivation and reduced cleansing and buffering capacity of saliva, diet restrictions, and changes in the oral microbiome between patients (25-28), and level of salivary-sugar concentration (29). The composition of dental plaque is important, since there is evidence of a positive correlation between the prevalence of dental caries and the count of cariogenic bacteria *Streptococcus mutans*, *Actinomyces* spp., *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia*, and *lactobacilli* in diabetic patients (30).

3.1.3 Endodontic Treatment

Caries in diabetic patients have a higher propensity to progress into pulp necrosis, since their pulp tissue has limited dental collateral circulation and impaired immune response. This increases the risk of acquiring pulp infection, particularly with anaerobic bacteria, ending in pulpal necrosis (31). Correspondingly, a higher prevalence of periapical pathology was reported in diabetic patients (32), particularly in patients with poor glycaemic control (33). When endodontic treatment is pursued for such teeth, DM negatively affects the prognosis of endodontic treatment, and more badly in poorly controlled patients (34). Patients with diabetes have increased periodontal disease in teeth treated endodontically, which worsens the prognosis of endodontic treatment (35).

3.1.4 Xerostomia and Salivary Gland Disorders

Mouth dryness associated with a reduced salivary flow is an oral symptom reported by more than 50% of diabetic patients, particularly those with poorly controlled disease (36), and is believed to correlate positively with the magnitude of hyperglycaemia (37). The meta-analysis reviews describe remarkable wide variation in xerostomia prevalence. López-Pintor et al (2016) in their systematic review described a higher prevalence of xerostomia in diabetic patients (12.5%-53.5%) compared to non-diabetic control subjects (0%-30%) (38). Other reviews described xerostomia prevalence in diabetic patients ranging between 46.09% and 92.5% (39). The wide discrepancy in the prevalence of xerostomia among different studies may be a reflection of the diversity in glycaemic control between studied subjects.

The cause of xerostomia in diabetic patients can be multifactorial, including the associated polyuria, microvascular changes, autonomic neuropathies, and thickening in the basement membranes of salivary glands (40). Hyposalivation negatively impacts the patient's oral health by promoting gingivitis/periodontitis, oral infections, and dental caries. It also poses chewing, swallowing, and speech difficulties.

Sialosis is defined as an asymptomatic, non-inflammatory, non-neoplastic bilateral salivary gland swelling, most commonly involving the parotid glands (41). The precise aetiology of this condition is not clear, but it is reported in association with DM, among other medical conditions (27, 41).

Acute suppurative sialadenitis is an acute bacterial infection of salivary glands most commonly by *Streptococcus mutans* and *beta-hemolytic streptococci*. DM is recognized as a risk factor for this infection. The impaired salivary flow allows oral bacteria to ascend into the gland duct system and infect the gland (42).

3.1.5 Oral Candidosis

It is repeatedly reported that the qualitative and quantitative oral *Candida* species colonization is higher among diabetic patients compared to controls, regardless of the type of DM (43).

Oral candidosis is an opportunistic infection caused by *Candida* species, most commonly *Candida albicans.* DM is recognized as one of the major predisposing factors for oral candidosis, and correction of the diabetic state is an integral part of oral candidosis management (44). Pseudomembranous candidosis was found to be the most common mucosal disorder among a group of diabetics (45). Nevertheless, other clinical types of oral candidosis (acute and chronic erythematous candidosis, candidal leukoplakia, angular cheilitis, sand median rhomboid glossitis) are also common among patients with DM (44, 46). Poor glycaemic control facilitates the suitable milieu for the transformation of the candida cell from the commensal form (blastospore) to the pathogenic form (pseudohyphae).(46) *Candida*-associated denture stomatitis is a common palatal infection among denture wearers generally, but T2DM patients are much more vulnerable to this infection (47).

Several factors collectively render diabetic patients more susceptible to oral candidosis, such as xerostomia, higher salivary glucose level, impaired cellular immune system, and high affinity of *Candida* species to adhere to epithelial cells from diabetic patients (29, 48).

3.1.6 Halitosis

The prevalence of halitosis (bad breath; oral malodour) was estimated at 23% in subjects with T2DM, and 84.7% in suspected, but undiagnosed, diabetic patients (49). The relatively higher prevalence in undiagnosed diabetics may be explained partly by the neglected glycaemic control.

The causes of halitosis in diabetic patients are mainly coexisting periodontitis, xerostomia and ketoacidosis (acetone breath in uncontrolled patients) (25). Anaerobic gram-negative bacteria, the same species that have been linked to periodontal diseases, are more common in diabetic patients (15). These bacterial species are responsible for the degradation of both sulfur-containing and non-sulfur-containing amino acids into volatile, bad-smelling gases (50).

3.1.7 Taste Impairment

The sour, bitter, sweet, salt and water taste are impaired in T2DM patients compared to healthy subjects (51-54). This impairment is directly related to the hyperglycaemic state (55), regardless of the disease duration or degree of glycaemic control (52). The sweet-taste impairment may influence the patients' choice of diet, with a preference for sweety foods, which exacerbates hyperglycaemia. Different explanations were given for the decreasing taste acuity, among which is a reduction in the number and density of taste buds on the tongue, impaired salivary function, or neuropathy (30, 56).

3.1.8 Burning Mouth

Burning sensation in the mouth, particularly the tongue in diabetic patients, can be a symptom of oral candidosis, mouth dryness or peripheral neuropathy (57). Burning mouth syndrome, which is characterized by a burning sensation in a normal-appearing oral mucosa, lasting at least four to six months, is frequently reported in association with DM (58). It could be also a manifestation of iron (59) or vitamin-B12 deficiency (60) complication of metformin therapy.

3.1.9 Oral Lichen Planus (OLP)

Lichen planus is a chronic inflammatory muco-cutaneous disorder affecting the skin, scalp, mucous membranes and nails with modest malignant potential. Though it is of undetermined etiology, a T-cell-mediated immune reaction is believed to be involved (61). Several closely matched clinical surveys reported a higher prevalence of OLP among patients with DM (62-65). Inversely, DM (66) and prediabetes (67) were more prevalent among patients with OLP, which is tempting to speculate that OLP may be counted as a predictor for DM. Other investigators could not find a significant relationship between DM and OLP (68).

Grinspan's syndrome is a triad of DM, hypertension and OLP. There is doubt about whether it is a separate entity or a drug-induced lichenoid reaction emerging due to medicaments used for the management of DM and hypertension (69).

3.1.10 Oral Cancer and Potentially Malignant Disorders

According to the International Agency for Research on Cancer Handbook on Oral Cancer Prevention, oral cancer is the 13th most common cancer worldwide (70). Although the positive relationship between DM and some

types of body cancers, such as colon, rectum, pancreas and liver, is well established (71), the relationship to oral cancer is still controversial. Some studies reported an increased risk of oral cancer among diabetics (72, 73), while others refuted this observation (74).

Recent meta-analysis reviews concluded that T2DM patients are not only at a significantly higher risk of developing oral cancer, but also at a higher mortality rate when compared to otherwise healthy subjects (72, 75, 76), regardless of the tumor stage or follow-up duration (79). On the other way round, a higher prevalence of DM was noted among oral cancer patients (77).

Oral potentially malignant disorders were defined by The WHO Collaborating Centre for Oral Cancer Workshop as any oral mucosal abnormality that is associated with a statistically increased risk of developing oral cancer (78). The prevalence of the potentially malignant disorder is also higher among diabetic patients compared to controls (75, 79).

3.1.11 Miscellaneous Oro-facial Disorders

Oral screening of T2DM patients reveals a higher prevalence of general oral mucosal lesions (45-88%) compared to non-diabetic subjects (38.3-45%) (39), Some specific oral disorders are markedly prevalent among diabetic patients, including the fissured tongue (46), geographic tongue (80) and epithelial atrophy (46), while there is little evidence of higher occurrence of aphthous ulcerations (46). A fissured or lobulated tongue in diabetics may be a sequence of long-standing xerostomia (46).

Bell's palsy is a unilateral peripheral paralysis of the facial nerve that results in muscle weakness on the affected side of the face. The risk of Bell's palsy is high in patients with DM (54, 81). Bell's palsy when affecting diabetic patients tends to have more severe paralysis and a poorer prognosis compared to those in non-diabetics (82, 83).

Data analysis of cases with medication-related osteonecrosis of the jaw (MRONJ) revealed a strong association with poor control of DM, possibly attributed to hyperglycemia-associated ischemia (84). Although the exact mechanism by which DM may promote MRONJ has not yet been determined, factors related to DM pathogenesis and management may lead to poor bone quality as a sequence of microvascular ischemia, endothelial cell dysfunction, reduced bone remodeling, and increased apoptosis of osteocytes and osteoblasts (85). In an animal study on diabetic rats, metformin administration improved healing of the tooth extraction socket and reduced osteonecrosis, which suggests that metformin may exert a protective effect against MRONJ (86).

3.2 Implication of Metformin on Dentistry and Oral Health (Figure 1)

3.2.1 Gingival and Periodontal Disease (GPD)

GPD is estimated to rank sixth among the most common human diseases, where its severe form affects from 10% to 44.7% of the adult population worldwide (87). Diabetic patients are historically known for being at a high risk for GPD (21).

There is a consensus from data derived from laboratory (88), animal and clinical research (89). that metformin reduces the risk of diabetes-induced GPD. A nationwide clinical comparative study on never-users and ever-users of metformin concluded that long-term metformin therapy was associated with a significant reduction in GPD in a dose-response pattern.(89). Clinical trials on local delivery of metformin gel at concentrations of 0.5%, 1%, or 1.5% proved to significantly improve periodontal disease in patients with chronic periodontitis compared to mechanical periodontal therapy alone (90-92). Using 1% metformin combined with platelet-rich fibrin (PRF) in treating periodontitis with Grade-II furcation involvement resulted in a significant clinical and radiographic reduction of defect volume compared to using PRF alone (93, 94).

The ameliorating effect of metformin on GPD is multi-factorial. The laboratory studies proved that metformin can suppress the gingival inflammatory response (88, 95, 96), decrease oxidative stress (97), inhibit osteoclast differentiation and formation, hence retarding bone resorption (98). It also enhances proliferation, migration and osteogenic differentiation of human periodontal ligament stem cells (99, 100). Metformin could be used as a new strategy for periodontal tissue regeneration and as adjunct to conventional scaling and root planning in the management of GPD.

3.2.2 Endodontic Therapy

When intra-canal metformin medications were used, in addition to root canal debridement, to manage

experimentally-induced periapical periodontitis in rats, the experiments showed accelerated healing of periapical bone pathology (101, 102), possibly through the regulation of osteoblast and osteoclast differentiation (102).

Metformin can promote pulp tissue healing. Dental pulp stem cells cultured on metformin-containing resin exhibited increased proliferation rate, odontoblastic cell differentiation and mineral synthesis (103).

The clinical study of Sobhnamayan et al. (2023) included children undergoing regenerative endodontic procedures for non-vital immature teeth with apical periodontitis. The subjects who received metformin incorporated into a double anti-biotic paste as an intra-canal medicament exhibited accelerated resolution of the periapical periodontitis and root-regeneration process compared to non-metformin-treated subjects (104).

3.2.3 Dental Implant

It is widely known that DM jeopardizes the prognosis of dental implants (105). The accelerated peri-implant marginal bone loss and peri-implantitis correlate directly with the quality of glycaemic control (106). Nevertheless, the effect of metformin on dental implants is controversial.

The results of randomized clinical trials on animal models of dental implants exploring peri-implant health report that metformin enhances osseointegration in diabetic (107), and in non-diabetic animals (108). Metformin daily injection around implants impeded into teeth sockets in osteoporotic rats resulted in a remarkably accelerated formation of new bone, ameliorated the bone micro-architecture and enhanced osseointegration of the dental implant (109).

The tissue-culture studies that investigated the biological properties of metformin-treated mesenchymal stem cells reported increased osteogenic properties of the treated cells (109, 110). Metformin can reverse the effect of hyperglycaemia and increase bone mineralization by inhibiting osteoclastic activity *via* activating the adenosine monophosphate-activated protein kinase (AMPK) signaling pathway, which, in turn, increases the proliferative action of osteoblastic activity that causes bone regeneration *via* mesenchymal stem-cell differentiation (110).

The quality of glycaemic control is also an important prognostic factor of dental implants in DM (106). This was demonstrated in an animal study, where metformin administration improved peri-implant bone healing in type-2 diabetic rats by lowering blood glucose levels (107). The rats that have controlled blood glucose levels by metformin have bone remodeling biomarkers that were similar to those in the non-diabetic ones (107, 111). Similarly, clinical studies on implant outcomes in controlled diabetic patients showed high success rates and a low incidence of complications or adverse soft-or hard- tissue changes compared to non-diabetic subjects (112, 113), possibly due to the dual effect of controlled hyperglycaemia and anti-diabetic therapy (114).

On the contrary, despite controlled blood glucose levels, Serrao et al. (2017) did not find an osteogenic advantage of metformin, or improved peri-implant osseointegration in metformin-treated rats (111). Moreover, Bastos et al. (2017) believed that metformin negatively affects osseointegration in non-diabetic rats treated by per-oral metformin (115). The lack of standardization, fluctuation of blood glucose levels, and short duration of these studies may have led to inconsistent results (114). Therefore, more studies on the dose/treatment duration-dependent effect of metformin on the prognosis of dental implant placement are necessary. Given improving osteogenesis, whether peri-implant local drug delivery of metformin will be part of the implant placement procedures worth investigating.

3.2.4 Orthodontic Treatment

Basically, successful orthodontic tooth movement depends on the balanced remodeling of alveolar bone, in response to the applied force to the teeth. Due to the osteoclastic activity, the alveolar bone on the compression side will resorb and new bone is formed at the tension side due to the osteoblastic activity. Hence, a different rate of tooth movement is expected in patients with diseases that affect bone remodeling, such as DM. Therefore, uncontrolled diabetic patients undergoing orthodontic treatment are highly subjected to periodontal breakdown (116) due to the enhanced release of inflammatory cytokines, which induces osteoclastogenesis, accelerating bone resorption of alveolar bone and periodontal ligament (117, 118).

To the authors' knowledge, there is no clinical data from humans on the effect of metformin therapy on orthodontic treatment. The results of animal studies available conclude that metformin decreases the rate of

orthodontic tooth movement (119), and reduces periodontal damage during orthodontic force application (117).

3.2.5 Taste Alteration

An earlier publication described the metallic taste as a complication of metformin therapy (120). Metformin is highly water soluble, so it dissolves in saliva, and is known for its notorious bitter taste (121). Orally-administered metformin is absorbed from the intestine and accumulates in the salivary glands and is subsequently secreted in saliva (122). This salivary metformin may alter taste acuity and lower fatty taste perception (123).

Saluja et al. (2020) in a retrospective study described dysgeusia in about 5.8% of diabetic patients on metformin therapy (124). However, it was unclear whether this was due to the direct effect of the better taste of the medication or to other causes, such as peripheral neuropathy or changes in oral microbiota.

3.2.6 Salivary Glands and Saliva

Xerostomia in diabetic patients is believed to be closely related to hyperglycaemia (36). Unfortunately, to date, there is no effective treatment for diabetic xerostomia. A piece of promising news is coming from animal studies, where metformin has been proven to ameliorate xerostomia in drug-induced diabetic rats (125). Whether this was secondary to glycaemic control or to other causes has not yet been determined. Interestingly, metformin also ameliorated xerostomia in drug-induced Sjogren's syndrome rats, an observation that warrants investigation (126).

Fibrosis commonly complicates salivary gland injuries induced by various factors, such as inflammation, radiotherapy, ductal obstruction, trauma, aging and autoimmune disease. Metformin has been noted for its potent anti-fibrotic effects on salivary glands, thus constituting a potentially promising therapeutic option for salivary gland fibrosis (127).

3.2.7 Oral Lichenoid Drug Reaction (OLDR)

OLDR is a delayed hypersensitivity response triggered by a variety of drugs, such as anti-hypertensives, anti-malarials, non-steroidal anti-inflammatory drugs, dapsone, heavy metals and dental restorative materials commonly amalgam (128). It clinically and histologically resembles OLP, but with subtle differences which may constitute a difficulty in diagnosis. Contrary to OLP, OLDR is usually unilateral with some histopathological differences, and more importantly, its resolution is noticed with the cessation of the offending drug (129). The oral hypoglycemic agent, metformin, was linked to OLDR (69, 128, 130). It is not entirely clear whether the observed higher prevalence of OLP among T2DM patients was related to the disease itself or was a misdiagnosed lichenoid reaction induced by metformin therapy (64, 65).

3.2.8 Oral Cancer

Several clinical studies described a protective effect of metformin against oral cancer (74, 131). Moreover, it was claimed to improve oral cancer prognosis by decreasing postoperative recurrence and metastatic rate both in diabetic patients (132-134) and in non-diabetic subjects (135). However, other studies failed to detect a protective effect of metformin against head and neck cancer (136, 137).

In *in-vitro* tissue culture studies, metformin inhibited the growth of malignant salivary gland tumor cells (138). When metformin was combined with the anti-neoplastic agent Adriamycin, they inhibited the growth, invasion and migration of tongue cancer cells, and induced their apoptosis (139).

Several laboratory (140-142) and clinical studies (143) demonstrated an inhibitory effect of metformin on the malignant transformation of potentially malignant disorders with epithelial dysplasia into cancer cells, most likely by inhibiting the mammalian target of rapamycin complex-1 (mTORC1) oncogenic signaling (141-143).

The synergistic effects of metformin with chemotherapy highlight its potential as an adjunctive therapy for oro-pharyngeal cancer by reducing the likelihood of recurrence (71, 144, 145). The mechanisms underlying the possible anti-neoplastic effect of metformin have not yet been fully identified. Metformin inhibits tumor-cell proliferation, inducing G0/G1 cell cycle arrest and apoptosis (146). The cumulating data points to the ability of metformin therapy to inhibit the tumor cell electron-transport chain and ATP synthesis, to regulate AMP-activated protein kinase and the mechanistic target of rapamycin complex-1 (mTORC1) (135).

Mucositis complicating chemotherapy or radiotherapy is troublesome, and the effective

pharmacologic therapies commonly used to prevent it are still questionable. In a recent animal study, metformin significantly improved 5-Fu-induced oral mucositis (147). In humans, it reduced mucositis induced by chemotherapy in non-diabetic breast cancer patients (148).

3.2.9 Anti-microbial Effect

Metformin enhances the anti-microbial effectiveness of photodynamic therapy used in the treatment of periodontitis, leading to the reduction of periodontal infections (149).

Despite the guanidine group found in metformin demonstrating anti-fungal activity (150), the anti-fungal activity of metformin is rarely studied. In an *in vitro* study, metformin exhibited anti-fungal properties towards anti-fungal-resistant *Candida glabrata*, and potentiated the anti-fungal effect of voriconazole, fluconazole, and amphotericin (151).

Metformin may also have anti-viral properties. A large-scale epidemiological study has shown that T2DM patients on metformin therapy had significantly less risk for herpes zoster and post-herpetic neuralgia in a dose-related effect (152).

4. Discussion

Knowing that almost one in two adults with DM are unaware of their disease (153) qualifies DM to the description of a "hidden disease". However, the precise taking of the patient's medical history may bring the dentist's attention to the presence of one or more of the cardinal signs of DM; namely, polydipsia, polyphagia, polyuria, unintentional weight loss and blurred vision (1). When this is combined with the awareness of the oral clinical features associated with DM, the prudent dentist should be able to suspect the existence of DM based on the associated oral and general manifestations and can aid in the diagnosis of DM (44, 154).

Oral complications of DM are well recognized, and the bidirectional interrelationship between DM incidence and control and its oral complications has become a major aspect of modern diabetes care. For example, controlling GPD by scaling and root planning is an important adjunct to classical medical therapy for proper glycaemic control (16). Therefore, the International Diabetes Federation (IDF) published the "guideline on oral health for people with diabetes", which encourages the implementation of oral care in diabetic patient care (155). Emphasis should be more directed toward maintaining a high standard of oral hygiene in diabetics. Axiomatically, the lower salivary flow and buffering capacity,(39) increased caries (23) and periodontitis rate (15), and lower success rate of endodontic treatment (34) led to significantly higher rates of tooth loss among diabetics compared to non-diabetics (156).

Metformin, the first choice oral hypoglycemic agent, has remarkable pleiotropic effects. Metformin therapy has a favorable impact on the management outcome of GPD, oral cancer, and bone healing is not only by reversing the hyperglycaemia state. Metformin has proved to have an independent effect on the corresponding cells and tissues involved by increasing the osteogenic properties of the mesenchymal stem cells (109, 147), decreasing the gingival inflammatory response, inhibiting the growth of malignant tumor cells (138), and inhibiting the malignant transformation of epithelial dysplasia into cancer cells (143). One large-scale case-controlled study reported a lower prevalence of head and neck cancer among diabetic patients and more significantly among those who were on metformin therapy (Figueiredo et al., 2016) (131), which lent support to the metformin anti-carcinogenesis theory (74, 131).

Recently, there has been a growing interest surrounding the therapeutic potential of metformin, as adjuvant therapy, to treat *Candida septicaemia* caused by antifungal-resistant *C.glabrata* (151), oral cancer (157), chemotherapy-induced oral mucositis (147, 148), and periodontitis (92). These observed examples of favorable pleiotropic effects of metformin should open the door wide for deeper research on the feasibility and effectiveness of using metformin as a mono- or adjunct drug for treating some oral diseases, especially oral cancer.

Studies addressing the effect of metformin on orthodontic treatment and dental implants in humans are lacking. More studies are needed to affirm that the results of animal studies apply to humans.

Clinical research has concluded that metformin has a favorable effect on the dental implant success rate in dental patients. The contradictory results came from animal studies. Although it was not within the aims of this clinical review to judge the methodologies implemented, consistency can be observed. The implant success was assessed by histologic examination or

immune-histochemical analysis of the peri-implant bone cells (111, 115). These methods were criticized for not being good enough for this mission (141). In addition, different breeds of rats were used in different studies, and the implants were assessed only after 30 days of starting metformin therapy, which may not be a sufficient time to exert an effect (141). Moreover, in some studies, animals were treated with systemic metformin (115), while in others, metformin was injected around the implants (109).

5. Conclusions

Full awareness of the dental team, and other oral healthcare providers, of the oral manifestations associated with DM will enable them to suspect and detect the undiagnosed cases of DM, and to provide optimum management of the oral complications of the disease.

Understanding the impact of metformin therapy on oral health should stimulate the researchers to investigate the future use of metformin in the management of some oral disorders.

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Conflict of Interests

None of the authors of this manuscript has any potential source of conflict of interests, directly or indirectly, that may influence the author's objectivity towards this research.

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