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The effect of diabetes on thyroid gland and the subsequent effect on the oral cavity

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

صدق الله العلي العظيم

Dedication

(And their last supplication is Praise be to God Lord of the worlds)

Praise be to **God** for the joy of accomplishment, and praise be to God at the beginning and at the end.

To my **father,** who illuminated my path, and my role model in every step I took.

To my tender **mother**, my role model who never left me and my day is not complete without her.

To my beloved **friends**, who supports me with their love, compassion, encouragement, understanding, and standing by my side.

To my **brothers** and sisters who always stood with me, supported me during my scientific career, and trusted me.

To all my dear doctors who taught me, guided me and directed me.

I dedicate this humble work to you all, and the fruit of my effort and God is the Grantor of success.

Acknowledgment

I would like to express my deep appreciation and indebtedness particularly to my supervisor

Dr.Ibtisam Kareem

for her invaluable guidance and experience. Her ideas and comments greatly influenced my work and contributed to its quality and for her support, kind efforts, time, advice and scientific opinions and I'm proud to be one of his students.

All family and friends and others who in one way or another shared their support , thank you GOD bless all.

Certification

I certify that the preparation of this project entitled:

The effect of diabetes on thyroid gland and the subsequent effect on the oral cavity

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Abstract

Thyroid diseases and diabetes mellitus are the two most common endocrine disorders encountered in clinical practice. Diabetes and thyroid disorders have been shown to mutually influence each other and associations between both conditions have long been reported ,the thyroid gland disorder are common and the ". The oral cavity is adversely affected by either an excess or deficiency of these hormones. Before treating a patient who has thyroid disorder, the endocrinologist needs to be familiar with the oral manifestations of thyroid dysfunctions, Thus, communication of dentist with endocrinologist must be bidirectional, to maintain patient's oral and thyroid health ,same about diabetes affected individuals may be more prone to infections and have more severe periodontal diseases. A broad spectrum of oral symptoms has been reported, DM can give rise to immunological and salivary dysfunction that will increase the risk of common oral diseases such as caries and periodontitis.

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abbreviations	Meaning	No.
Dm	Diabetes mellitus	1
IDDM	insulin-dependent diabetes mellitus	1
NIDDM	non-insulin-dependent diabetes mellitus	1
T3	Triiodothyronine	2
T4	Thyroxine	2
TSH	Thyroid Stimulating Hormone	4
GLUT-4	glucose transporter type 4	5
HIF-1a	Hypoxia Inducible Factor 1 Subunit Alpha	5
TRH	Thyrotrophin-releasing hormone	5
SMG	sub mandibular gland	7
NHE-1	Na^+/H^+ exchanger	8
ROS	reactive oxygen species	11
PKC	protein kinase C	11
ET-1	cytokine endothelin-1	11
VEGF	vascular endothelial growth factor	11

Chapter One

Introduction

Diabetes mellitus (DM), or simply diabetes, is commonest endocrine disorder that affects more than 100 million people worldwide (6% population), a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin (Type 1 DM), or because cells do not respond to the insulin that is produced (Type 2 DM). This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger) (1).

Conventionally, diabetes has been divided into three types namely:

Type 1 DM or insulin-dependent diabetes mellitus (IDDM) in which body fails to produce insulin, and presently requires the person to inject insulin or wear an insulin pump. This is also termed as "juvenile diabetes"(2).

Type 2 DM or non-insulin-dependent diabetes mellitus (NIDDM), results from insulin resistance, a condition in which cells fail to use insulin properly, with or without an absolute insulin deficiency. This type was previously referred to as or "adult-onset diabetes"(3).

The third main type is gestational diabetes which occurs when women without a previous history of diabetes develop a high blood glucose level during her pregnancy. It may precede development of type 2 DM (4).

Currently available pharmacotherapy for the treatment of diabetes mellitus includes insulin and oral hypoglycemic agents. Such drugs acts by either increasing the secretion of insulin from pancreas or reducing plasma glucose concentrations by increasing glucose uptake and decreasing gluconeogenesis.

Long standing type 1 DM patients are susceptible to microvascular complications; and macrovascular disease (coronary artery, heart and peripheral vascular diseases) (5).

Type 2 DM caries a high risk of large vessel atherosclerosis commonly associated with hypertension, hyperlipidemia and obesity (6).

Most patients with type 2 diabetes die from cardiovascular complications and end stage renal disease.

The thyroid gland is a highly vascularized organ located anteriorly in the neck between the C5 and T1 vertebrae, deep in the platysma, sternothyroid, and sternohyoid muscles. The thyroid weighs 15–20 g and weighs more in men than in women. It is an H-shaped, soft and reddish parenchymal organ, consisting of two lobes (left and right) and one isthmus that binds them together(7).

Thyroid hormones are key regulators of metabolism and development and are known to have pleiotropic effects in many different organs. The thyroid gland synthesizes and releases triiodothyronine (T3) and thyroxine (T4), which represent the only iodine-containing hormones in vertebrates. T4 is the main product of thyroid secretion and local deiodination in peripheral tissues produces T3, the biologically active thyroid hormon(8).

Both hypo- and hyperthyroidism and their treatments have been linked with increased risk from cardiovascular disease and the adverse effects of thyrotoxicosis in terms of osteoporosis risk are well established.

Thyroid disease and type 1 but also type 2 diabetes mellitus (DM) are strongly associated, and this has important clinical implications for insulin sensitivity and treatment requirements. The pathophysiological basis of this association has only recently been better elucidated (9).

It rests on a complex interaction of common signaling pathways and, in the case of type 1 diabetes and autoimmune thy- roid disease, on a linked genetic susceptibility. The pathophysiological mechanisms underlying this linked regulation are increasingly being unraveled (10).

In fact, if you have type 1 diabetes, type 2 diabetes, insulin resistance, or metabolic syndrome, your risk of developing thyroid disease is increased.

On the flip side, thyroid disease increases your risk of developing metabolic syndrome or type 2 diabetes. The association is even stronger if you are overweight or obese. Abnormal thyroid function can alter how your body responds to insulin. An underactive thyroid may even contribute to low blood sugar levels **(11)**

(Figure 1-1)

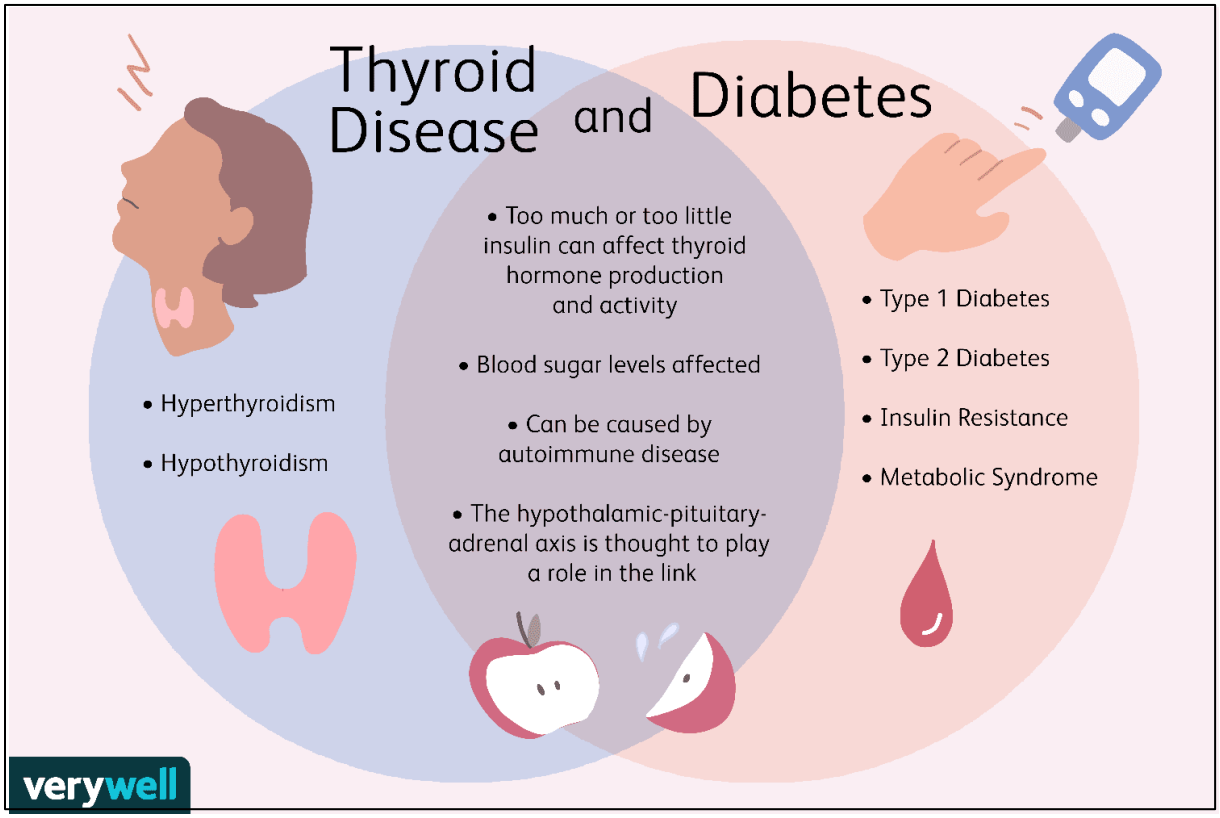

Figure 1-1 | The connection between Diabetes and Thyroid diseases

Chapter Two

1- Effect of diabetes mellitus on thyroid gland

Diabetes and thyroid disorders have been shown to mutually influence each other and associations between both conditions have long been reported (12). Thyroid disorders remain the most frequent autoimmune disorders associated with type 1 diabetes. Physiological and biochemical interrelationship between insulin and the influence of both insulin and iodothyronines on the metabolism of carbohydrate, proteins and lipid are recorded (13). Thyroid disease is a pathological state that adversely affects diabetic control and is commonly found in most forms of DM which is associated with advanced age in type 2 diabetes and autoimmune diseases in type 1diabetes.

DM appears to influence thyroid function in two sites;
firstly, at the level of hypothalamic control of TSH release
secondly at the conversion of T4 to T3 in the peripheral tissue.

Marked hyperglycemia causes reversible reduction of the activity and hepatic concentration of T4-5-deiodinase, low serum concentration of T3, elevated levels of reverse T3 and low, normal, or high level of T4 **(Figure 2-1)** (14).
Higher levels of circulating insulin associated with insulin resistance have shown a proliferative effect on thyroid tissue resulting in larger thyroid size with increased formation of nodules (15, 16). A higher prevalence of type 1 diabetes is observed in patients with Grave's orbitopathy than in the normal population. Furthermore, the vasculopathy changes associated with diabetes renders the optic nerve more susceptible to the pressure exerted by the enlarged extraocular muscles. Consequently, a higher incidence of dysthyroid optic neuropathy is observed in diabetic subjects with Graves ophthalmopathy compared to nondiabetic (17).

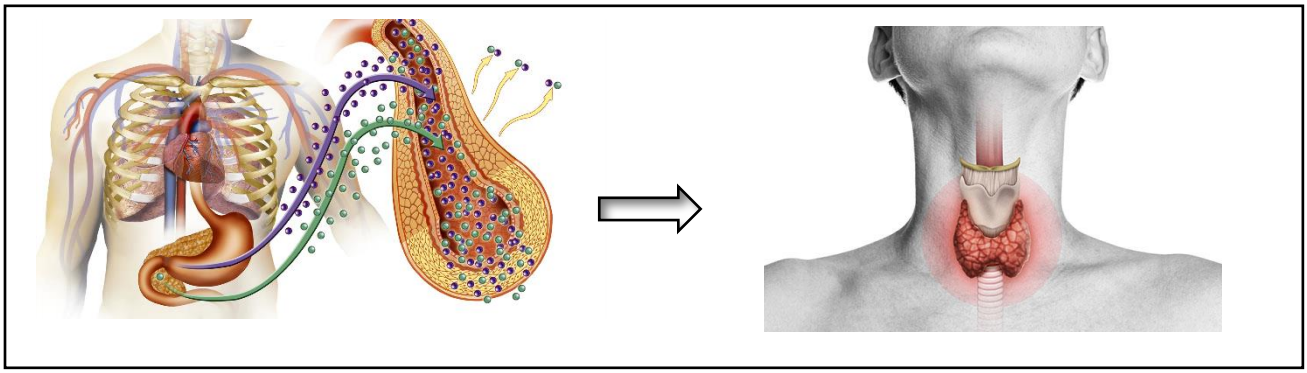

Figure 2-1 | Relation between diabetes mellitus, thyroid hormones.

1-2 Pathological mechanisms common to thyroid disorders and diabetes

Thyroid hormones exert profound effects in the regulation of glucose homeostasis. These effects include modifications of circulating insulin levels and counter-regulatory hormones, intestinal absorption, hepatic production and peripheral tissues (fat and muscle) uptake of glucose. It has long been known that thyroid hormones act differentially in liver, skeletal muscle and adipose tissue – the main targets of insulin action (18-19). While thyroid hormones oppose the action of insulin and stimulate hepatic gluconeogenesis and glycogenolysis, they up-regulate the expression of genes such as GLUT-4 and phosphoglycerate kinase, involved in glucose transport and glycolysis respectively, thus acting synergistically with insulinin facilitating glucose disposal and utilisation in peripheral tissues (20-21). The recent identification of another gene regulated by thyroid hormones in cultured human fibroblasts, the transcription factor HIF-1a, responsible for elevated expression of glycolytic enzymes and glucose transporters, is an example that the field of thyroid diabetes is still open to new discoveries (22).

1-3 Effects of Diabetes Mellitus on Thyroid Hormones

Thyroid hormone acting a role in regulatory metabolism of glucose and pancreatic role, but diabetes mellitus changed thyroid function. Such as, “TSH to thyrotropin-releasing hormone response” it is reduced in diabetes, that lead to accompanying reduced T3 level and hypothyroidism (23).

Altered thyroid hormones have been described in patients with diabetes especially those with poor glycemic control. In diabetic patients, the nocturnal TSH peak is blunted or abolished, and the TSH response to TRH is impaired. Reduced T3 levels have been observed in uncontrolled diabetic patients. This “low T3 state” could be explained by an impairment in peripheral conversion of T4 to T3 that normalizes with improvement in glycemic control (23).

1-3-1 Alterations of thyroid hormones in diabetes mellitus

The prevalence of hyperthyroidism in subjects suffering DM is greater than in non-diabetic subjects (24), and a nationwide Danish study has determined that patients suffering hyperthyroidism have greater risk to develop DM (25). Among adult patients with T2DM, ~4.4% have overt hyperthyroidism and 2%–4% have subclinical hyperthyroidism (26). Interestingly, improved diabetic control in T2DM patients normalizes TSH levels in patients with subclinical hyperthyroidism, suggesting that treatments improving T2DM might contribute to normalize thyroid

function However, a recent report has indicated that non-diabetic patients diagnosed with hyperthyroidism have increased risk to develop T2DM later in life, suggesting that thyroid dysfunction might precede diabetogenic processes (27).

Longitudinal studies have also investigated the association of alterations in thyroid function and the prevalence of DM and metabolic syndrome in older adults (28).

At baseline, individuals in the metabolic syndrome group exhibited significantly higher TSH values than individuals not included in the metabolic syndrome group. The authors indicated that increased circulating levels of TSH were associated with greater prevalence of metabolic syndrome, even in participants within the normal range. Another longitudinal study also associated higher prevalence of metabolic syndrome and obesity with individuals exhibiting higher circulating levels of TSH (28).

1-3-2 The Mechanism of Impaired T3 Production from T4 in diabetes

Once your thyroid releases thyroxine (T4) into your bloodstream, certain cells in your body transform it into triiodothyronine (T3) through a process called de-iodination. This is because cells that have receptors that receive the effect of thyroid hormone are better able to use T3 than T4. Therefore, T4 is generally considered to be the inactive form of thyroid hormone, and T3 is considered the active form of it. And this transformation done in brain and pituitary through D2 or in peripheral tissues through D1(29), are shown in **(Figure 2-2)**

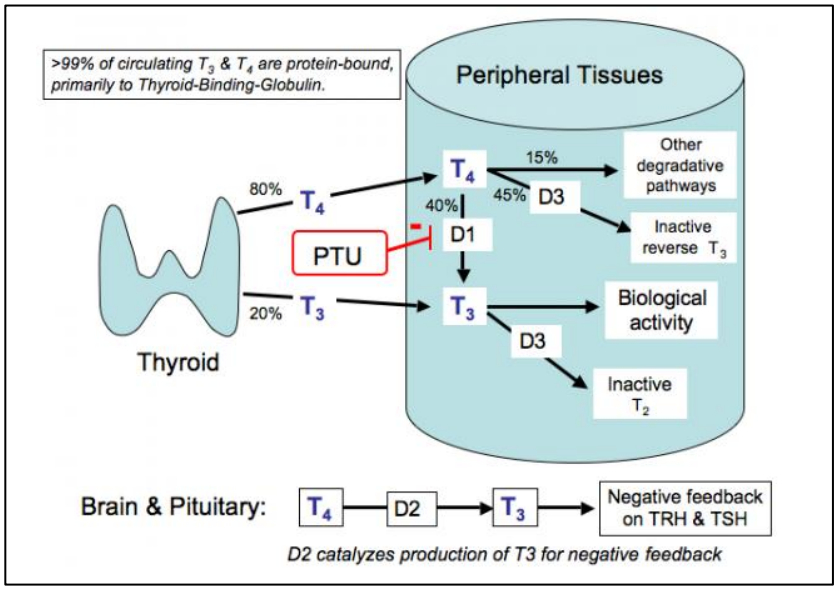

Figure 2-2 | Metabolism of thyroid hormone in peripheral tissues & CNS

Uncontrolled diabetes in man is associated with low serum T3 values and impaired production of T3 from T4. Because the thiol-dependent enzyme T4-5'-deiodinase catalyzes T4-deiodination to T3, the present study was conducted to determine

Serum 3,5,3'-triiodothyronine (T3) levels are low in uncontrolled diabetic man (30). This effect appears to be due to a reduced production of T3 from T4. Reversal of the hyperglycemia with insulin therapy corrects the serum T3 values. The impairment of glucose utilization consequent to the diabetic state may be responsible for the impairment of T4-metabolism and the low serum T3 concentrations. (31,32).

2- Effect of diabetes mellitus on Oral Cavity

Diabetes mellitus (DM) is a metabolic disease which affects many organs. Often in the oral cavity undergo changes that are associated with diabetes. Many dental practitioners are often not aware of the attendant oral manifestations in diabetic patients, which results in prescription of a non-accurate treatment.

Untreated oral infections can adversely affect metabolic control. Patients may present with oral conditions that suggest undiagnosed diabetes: progressing severe periodontitis, enlarged gums which bleed easily, multiple periodontal abscesses. Diabetic patients with poor oral hygiene, a history of smoking, rare visits to dentists, high carbohydrate intake are more likely to present caries and periodontitis and to respond poorly to dental treatment. If the doctor suspects undiagnosed diabetes, the patient should be examined to reveal the history of polydipsia, polyuria, polyphagia, unexplained weight loss, and family history of diabetes.(33)

2-1 Effects of Diabetes Mellitus on Salivary Glands

The gross morphological effects of diabetes on the salivary glands have been well documented. Insulin treatment reversed the effects of diabetes, and thus diabetes and insulin are generally considered to have parallel effects on salivary gland growth . The notable exception was the sublingual gland, which was relatively unaffected (34,35).however, that the effects of diabetes on sub mandibular gland (SMG) growth were not due to insulin insufficiency alone. Moreover, diabetes resulted in a decrease in the weights of several endocrine glands, including the thyroid, the adrenal and the pituitary, suggesting that the effects of diabetes on salivary glands might be mediated indirectly through a decrease in the circulating levels of hormones other than insulin. (36)

insulin and insulin insufficiency have both **direct** and **indirect** effects on the structure and function of the salivary glands. Insulin appears to play a **direct** role in the regulation of gene expression in the acinar cells, whereas its role in modulate gene expression in the granular ducts of the SMG is likely to be an **indirect** one, mediated via the effects of diabetes on pituitary-dependent hormones. Diabetes may also influence salivary gland function through altered autonomic nerve function perse. (37)

Dry mouth, hyposalivation, or xerostomia is a significant problem in diabetic patients, however, there has been no way to relieve these symptoms. In diabetes condition, the salivary flow rate, amylase activity, and Na^+/H^+ exchanger (NHE-1) expressions were markedly decreased (38) **(Figure 2-3)**

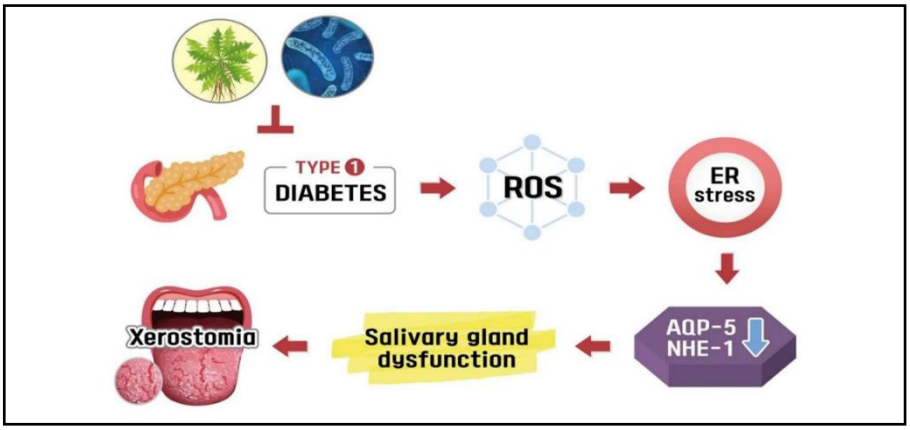

Figure 2-3 | pathogenesis of xerostomia in diabetes patient

2-2 Effects of Diabetes Mellitus on Teeth

Diabetes is well known for causing hyperglycemia, impaired immunity, hyperlipidemia, insulin resistance, and hypertension (39). In a later stage, these conditions can trigger more downstream effects, these downstream mechanisms are precursors of numerous oral complications (40). For example, T1DM affects osteoblast, osteocytes, osteoclast, and odontoblast functions, causing significant bone cell resorption and hypomineralization in mineralized structures like teeth (41).

Additionally, DM has been found to affect the levels of inorganic trace minerals like Sr, Mg, Zn, P, and F in the hydroxyapatite of dentin and enamel. Reduced concentrations of these trace minerals in the teeth of diabetic patients may negatively affect many tooth mechanical properties (42).

Inorganic trace elements have various effects on hard tissue:

(i) fluoride stimulates bone formation by increasing osteoblast function and is the most effective cariostatic agent in dentistry (43)

(ii) A reduction in Mg has been associated with decreased osteoblastic activity, bone fragility, and bone loss (44)

(iii) Zn in the oral cavity alters the organic component in demineralization and remineralization of the dentin due to its astringent properties. It also plays a role in the prevention of dentin demineralization and hence is being tested as an additive to toothpaste (45). Zn deficiency is associated with reduced bone density and antibacterial properties, increasing the instances of caries (46)

(iv) Sr improves bone formation, bone resistance, and bone mass, leading to improved overall bone quality (47,48).

Levels of Mg in diabetic patients have been found to be low as compared to non-diabetic patients (49). Studies also indicate a lower level of Zn observed in diabetic patients. Sr is believed to add protection from acidic demineralization to hydroxyapatite, and has been found in lower levels in T2DM patients (50).

(Figure 2-4)

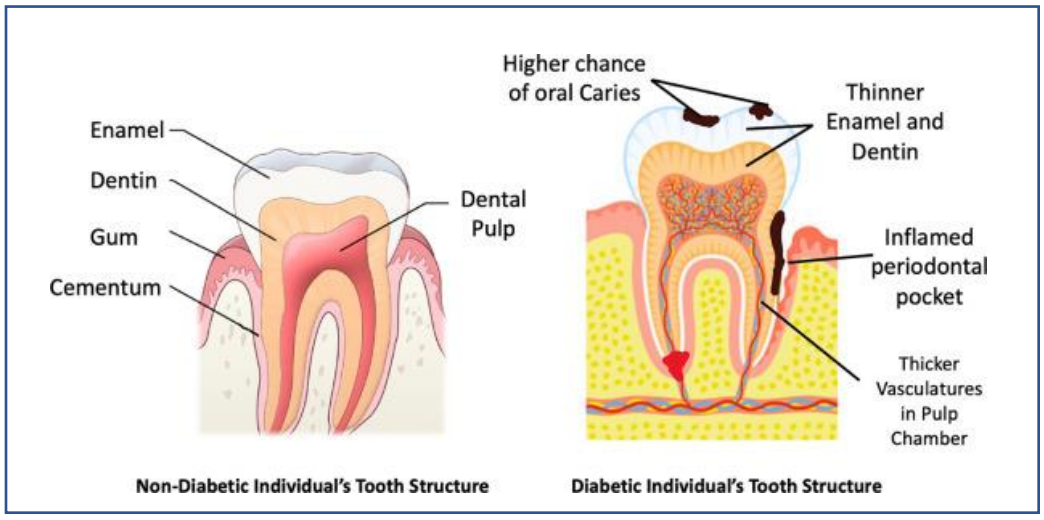

Figure 2-4 | Comparison view between non-diabetic and diabetic tooth structure.

2-2-1 Effects of Diabetes Mellitus on Enamel

Enamel consists of many hydroxyapatite crystals that form a strong mesh layer that is relatively fracture-resistant (51). Due to its strong integrity, enamel is very thick with hydroxyapatite crystals forming a rod shape pattern that is hard for bacteria to penetrate(52). Type I diabetes affects the enamel's mineralization process by reducing calcium and fluoride content, making type I diabetic patients more prevalent in getting oral caries. In further discussion, diabetic individuals have an irregular arrangement of hydroxyapatite crystals (53).

Oxidative stress induced by hyperglycemia can cause changes in ion transport, such as magnesium and calcium. T1DM patient have higher magnesium and lower calcium concentration, which is not ideal for hard tooth tissues (enamel and dentin) mineralization. This mechanism of hyperglycemia in DM changes the tooth tissue formation and increases the susceptibility of oral caries development (53).

When induing diabetes in rodents, they observed a reduction in calcium and phosphorous in the enamel structure using energy dispersive X-ray. These histological findings show how DM affects the enamel and why it is essential to prevent enamel destruction (54). Enamel hypoplasia was observed in diabetic mice due to insufficient calcium concentration by the effect of hyperglycemia ion transport (55).

In further discovery, when applying enamel matrix derivatives on damaged enamel tissue, the results showed successful enamel regeneration to repair the damage caused by diabetes mellitus (56).

2-2-2 Effects of Diabetes Mellitus on Dentin

Dentin is a thick, soft connective tissue layer composed of minerals and organic matrixes covered by enamel at the crown and cementum at the root. Dentin functions as the structural support for the tooth from the interior portion. Dentin is primarily formed by odontoblast derived from embryonic connective ectomesenchyme cells that originate at the neural crest (57). These precursors of odontoblasts migrate to the oral lamina and bind with epithelial cells to initiate dental pulp formation (58). As the terminal division of odontoblast reaches, odontoblasts will align on the pulp surface and remain in place for mineralization (59).

Due to insulin resistance in DM individuals, osteoblast activity is affected by hyperglycemia. The production of excess glucose increases the reactive oxygen

species (ROS) activity, which then actively removes calcium concentration in the serum and causes an insufficient amount of calcium to be used for mineralization of dentin tubules . Both enamel and dentin formation were found to be affected by Type I diabetes mellitus (T1DM) (60).

Using microtomography and micro-CT image analysis to evaluate the incisors and molar tissue thickness, diabetic patient showed significantly thinner tissue layers decrease thickness at buccal, mesial, and lingual side (60).

2-2-3 Effects of Diabetes Mellitus on Cementum

Cementum surrounds the dentin of the tooth's root structure in the periodontium. The cementum is composed of a thin layer of mesenchymal tissue that protects the interior structure of the root. When a bacterial or fungal infection occurs below the gum, the cementum is the primary infection site that slowly progresses and damages the dentin layer. Interestingly, the thickness of cementum has become thicker in patients with periodontal disease with type II diabetes compared to healthy individuals, which was adversely expected (61).

Hyperglycemia increases the blood glucose level and activates protein kinase C (PKC) activity, increasing the production of proteolytic enzymes and increasing collagenase action to break down collagen fibrils to form cementum structure (62).

Simultaneously, when PKC activation occurs, there is an increased secretion of pro-inflammatory cytokine NF-κB, vasoconstriction promoting cytokine endothelin-1 (ET-1), and vascular endothelial growth factor (VEGF) that increase the permeability of bacteria, fungi and microbe into abnormally function vasculature at the inflamed gingival pocket where cementum resides.

The central part of the root and the midpoint of the coronal half of the root were thinner in thickness. Therefore, significantly larger changes of cementum thickness can differ from the apical region to the coronal region in diabetic individuals (62).

2-2-4 Effects of Diabetes Mellitus on Pulp

The dental pulp is a mass of connective tissue that houses vasculatures in the root chamber of the tooth (63). The pulp chamber is surrounded by the dentin and has an interrelated complex layer called endodontium. Since the dental pulp is not directly connected to the collateral circulation, periodontitis effects induced by diabetes mellitus can pass into dental pulp via the periapical pathway (64).

Downstream effects of DM can cause damage and destruction in the pulp chamber as it induces periodontitis and metabolic alterations. Diabetes patients have a significantly higher prevalence of 79.2% of Candida culture collected in the pulp chamber (65). Candida species in the pulp induced periodontitis due to pro-inflammatory condition caused by increased expression of NF-κB ligand (RANKL) at the periodontium.

From hyperglycemia, the pulp and gingival pocket of T1DM individuals show a high accumulation of AGEs, which inhibits cell proliferation of collagens and then impairs wound healing at the inflammatory site. In the early stage, hyperglycemia caused by diabetes increases the concentration of kallikrein and nitrites in the dental pulp. Then, kallikrein generates cytokines, such as IL-1 and TNF, that upregulates the production of neutrophils and macrophages to promote inflammation in dental pulp and periodontium (66).

This increased production of cytokines in the endothelial cell also increases the permeability of dental pulp. In the later stage of dental pulp alteration, necrosis was observed in the pulp chamber and led to permanent damage. In addition, mentioned that the effects of hyperglycemia might delay or even exacerbate the pulpal healing process from the damage (67). **(Figure 2-5)**

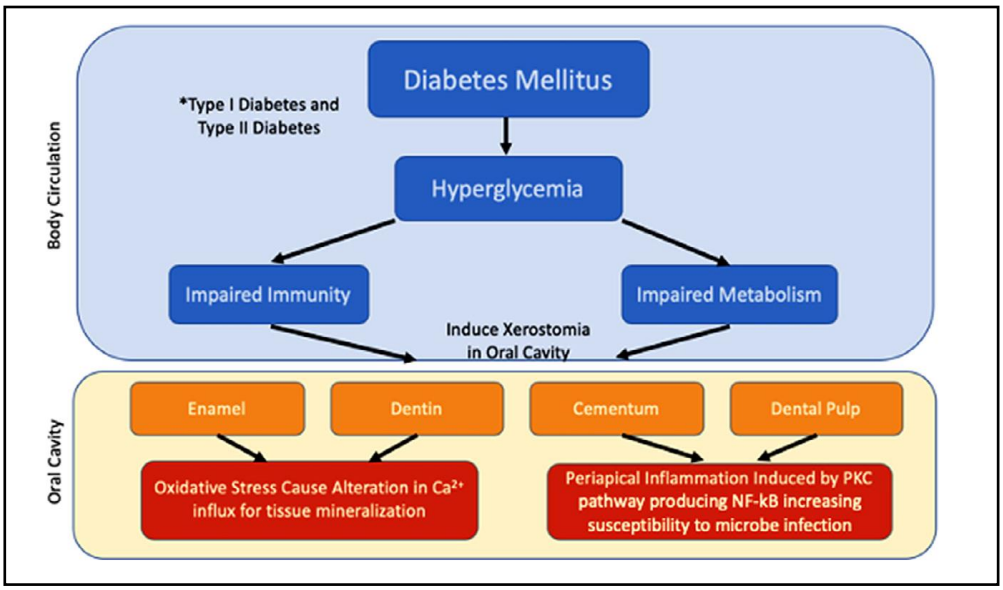

Figure 2-5 | Flow chart of effects starts with diabetes mellitus; xerostomia introduce by impaired metabolism of glucose; mineral loss from ion transport will induce alteration in tooth tissue's thickness and strength; hyperglycemia activates PKC pathway can induce NF-κB production, which promotes inflammatory response at lower periodontal pocket and become prone to infection.

2-3 Effects of Diabetes Mellitus on Periodontium

The susceptibility of periodontitis also increased approximately by three-fold in patients with uncontrolled diabetes (68).

There also existed a high correlation co-efficient of periodontal disease among diabetic individuals when compared to non-diabetic subjects, hence periodontitis is considered as the sixth complication of diabetes. However, type 1 diabetes also exaggerates the likelihood of periodontitis. (69)

2-3-1 Effects of Diabetes Mellitus on PDL and Bone

Type 1 diabetes mellitus and type 2 diabetes mellitus have a significant impact on bone. Type 1 diabetes mellitus patients have a 6-7-fold higher fracture risk, and type 2 diabetes mellitus patients have a 1.5-fold higher risk of fracture. Bone mineral density is reduced in type 1 diabetes mellitus while type 2 diabetes mellitus reduces bone strength without decreasing bone mineral density, probably caused by diminished bone quality (70).

These include a reduction in osteoclast numbers, improved angiogenesis, and greater expansion of mesenchymal stem cells. In a type 2 diabetes mellitus patient diabetes enhanced the intensity and duration of the inflammatory response in the gingiva and periodontal ligament with prolonged osteoclast to genesis (71). Similarly, type 1 diabetes mellitus in patient caused increased periodontal inflammation, osteoclast formation, and alveolar bone loss (72).

Diabetes reduces the numbers of bone-lining cells, osteoblasts, and periodontal ligament fibroblasts, and increases apoptosis of these cells. Advanced glycation end-products may contribute to the reduced osteoblast precursor pool seen in diabetics. Mesenchymal stem cell and periodontal ligament cell apoptosis is increased, and differentiation of mesenchymal stem cells to osteoblasts is reduced by advanced glycation end-products (73).

2-3-2 Link between Diabetes, Periodontal disease and inflammation

Both type 1 diabetes mellitus and type 2 diabetes mellitus lead to an increase in inflammatory cytokine expression in human periodontal tissues. For example, increases in interleukin-1beta and prostaglandin E2 are found in gingival crevicular fluid of both type 1 diabetes mellitus and type 2 diabetes mellitus subjects (74). Various studies have reported increased expression of tumor necrosis factor, interleukin-1beta, interleukin-17, interleukin-23, and interleukin-6 in the gingiva of diabetic humans. The increased expression of inflammatory cytokines leads to increased vascular permeability and recruitment of inflammatory cells (75). **(Figure 2-6)**

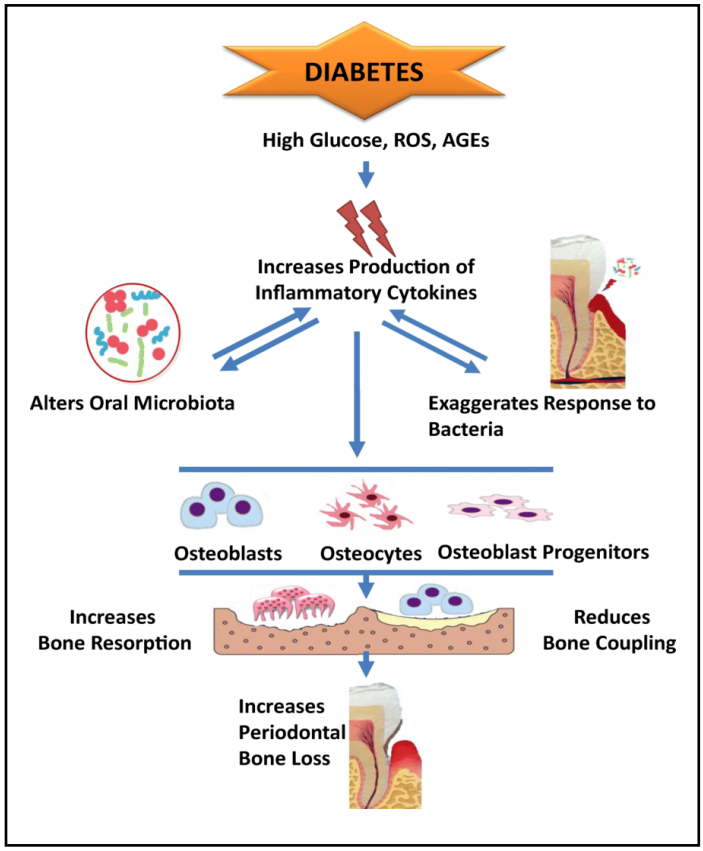

Figure 2-6 | Diabetes is associated with an increased risk and severity of periodontitis.

2-4 Effects of Diabetes Mellitus on Oral Mucosa

A series of alterations in the oral mucosa in diabetic patients have been reported, including gingivitis, periodontitis, oral mucosal diseases that favor infections such as candidiasis, salivary gland dysfunction, altered taste, glossodynia, and stomatopyrosis (76).

A high prevalence of oral mucosal lesions among patients with diabetes mellitus., preliminary study with diabetic patients reported a prevalence of 80%. This finding, which is close to that found in the present study, highlights the importance of dentists monitoring the oral health of patients with diabetes mellites this study, the most common lesions in the oral mucosa were ulcerative lesions. We found a prevalence of 24.6% of both types of ulcers (traumatic and aphtous). A case-control study similar to the present study, reported a prevalence of 22% for ulcerative lesions in the oral cavity among patients with diabetes type 2. The literature shows that alterations in oral mucosa related to diabetes cause symptoms such as glossodynia, stomatopyrosis, and changes in taste. Thus, the occurrence of oral ulcers causes pain, dis-comfort and burning, which damages the oral health of patients, and, in some cases, may prevent them from undertaking professional activities (77).

The second most frequent type of lesion was actinic cheilitis, along with the cases of melanin pigmentation. This is an important finding because of the malignant potential of actinic cheilitis, mostly found in the elderly population. Furthermore, other lesions (angular cheilitis, fissured tongue, and hairy tongue) found in the study facilitate the emergence of opportunistic infections such as candidiasis (78).

The sociodemographic characteristics of the population such as age, gender, education, and skin color were not statistically associated with the presence of oral lesions among diabetics.

The presence of oral mucosal lesions such as lichen planus and recurrent aphthous ulceration has frequently been diagnosed in diabetic patients, although the actual prevalence is rarely addressed in clinical studies. Some studies have shown a prevalence of 80% of oral mucosal lesions in patients with diabetes mellitus (79).

(Figure 2-7)

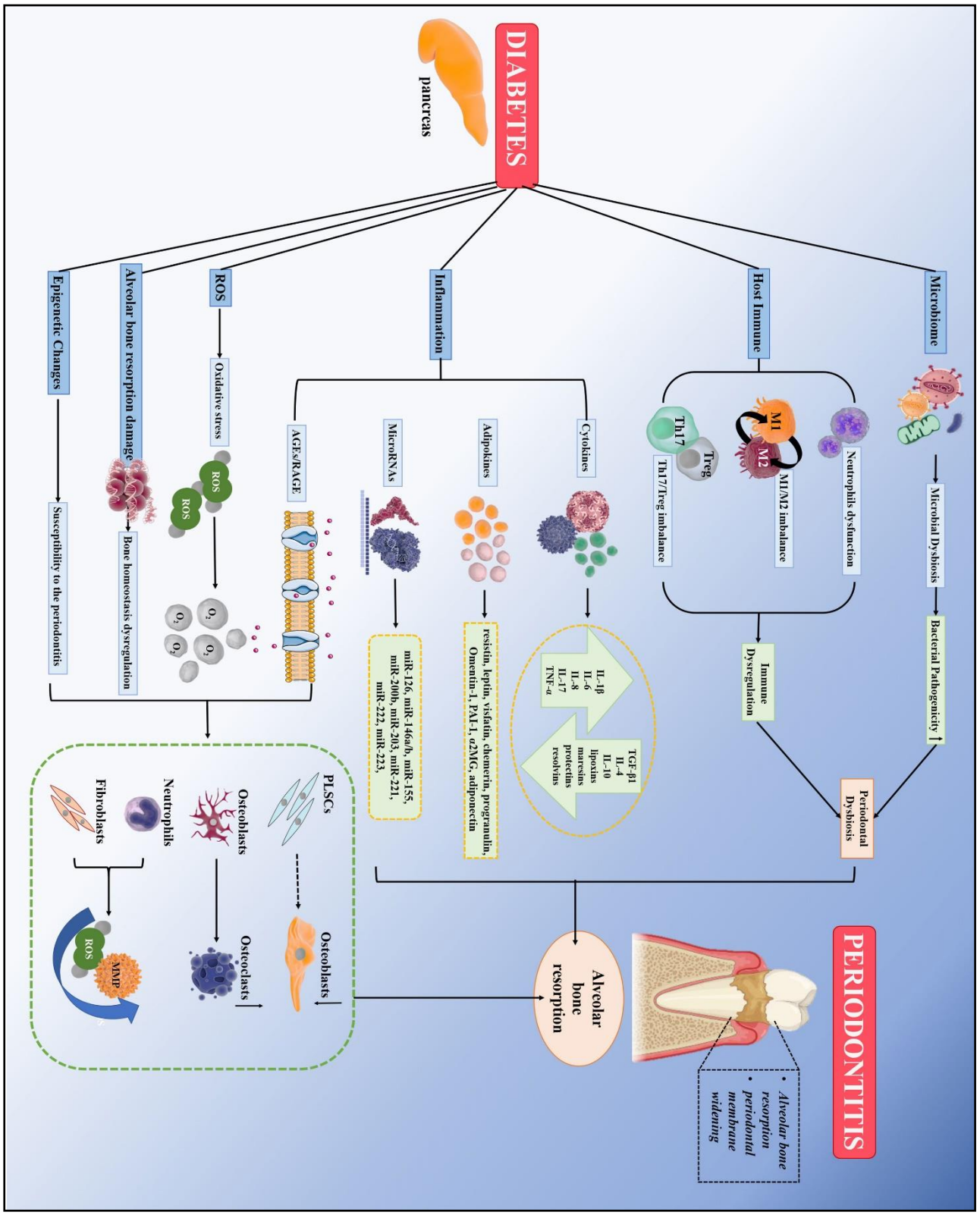

Figure 2-7 | Diabetes mellitus can promote susceptibility to severe periodontitis

3- The effect of thyroid gland on oral cavity

Abnormality in thyroid functioning is the second most prevalent endocrine system abnormality, and it can affect any system in the body including the oral cavity. Nevertheless, the excess or shortage of these hormones has a negative impact on the oral cavity (80).

The oral physician as well as the endocrinologist must be conversant with the oral symptoms of thyroid gland dysfunctions so as to provide appropriate treatment. Before considering dental treatment, a patient suffering from thyroid dysfunction that may or may not be on medication for the same should be adequately evaluated, so as to manage the risk accurately. A surprising fact that cannot be ignored is that even if the thyroid disorders are very common the dental manifestations of the same are less discussed about.

Thus, the purpose of this review is to describe clinical features of thyroid disorders with a detailed emphasis on the oral manifestations and dental considerations in thyroid disorders (81).

3-1 Hypothyroidism

Hypothyroidism is defined as failure of the thyroid gland to produce sufficient thyroid hormone to meet the metabolic demands of the body.

Untreated hypothyroidism can contribute to hypertension, dyslipidemia, infertility, cognitive impairment, and neuromuscular dysfunction.

Hypothyroidism may occur as a result of primary gland failure or insufficient thyroid gland stimulation by the hypothalamus or pituitary gland. Primary gland failure can result from congenital abnormalities, autoimmune destruction (Hashimoto disease), iodine deficiency, and infiltrative diseases (82).

3-1-1 Oral manifestations of hypothyroidism

Childhood hypothyroidism known as cretinisim is characterized by thick lips, large protruding tongue (macroglossia), malocclusion and delayed eruption of teeth.

Thickening of the lips and macroglossia is due to increased accumulation of subcutaneous mucopolysaccharides i.e., glycosaminoglycans due to decrease in the degradation of these substances. The long-term effects of severe hypothyroidism on craniofacial growth and dental development have also included impaction of the mandibular second molars. This seems to be caused by

a dissociation of ramus growth and failure of normal resorption of the internal aspect of the ramus, resulting in insufficient space for proper eruption of these teeth (83).

The common oral findings in hypothyroidism include the characteristic macroglossia, dysgeusia, delayed eruption, poor periodontal health, altered tooth morphology and delayed wound healing. Before treating a patient, who has a history of thyroid disease, the dentist should obtain the correct diagnosis and etiology for the thyroid disorder, as well as past medical complications and medical therapy (84).

3-2 Hyperthyroidism

Hyperthyroidism is a condition caused by unregulated production of thyroid hormones. Thyrotoxicosis is a serious sequela of hyperthyroidism that corresponds to an overt tissue exposure to excess circulating thyroid hormones. It is characterized by tremor, emotional instability, intolerance to heat, sinus tachycardia, marked chronotropic and ionotropic effects, increased cardiac output (increased susceptibility to congestive heart failure), systolic heart murmur, hypertension, increased appetite and weight loss. It can be caused by thyroid hyperfunction, metabolic imbalance or extra glandular hormone production (85).

3-2-1 Oral manifestations of hyperthyroidism

The oral manifestations of thyrotoxicosis, includes increased susceptibility to caries, periodontal disease, enlargement of extra glandular thyroid tissue (mainly in the lateral posterior tongue), maxillary or mandibular osteoporosis, accelerated dental eruption and burning mouth syndrome (86).

Burning mouth syndrome, a condition that causes a burning pain in the mouth, and Sjogren's syndrome, a condition that causes dry mouth, are more common in people with thyroid disease.

In Graves' disease, on extra-oral examination the thyroid may be enlarged or noticeably palpable. The enlarged gland may be more visually noticeable when the patient is in a supine position in the dental chair. But in more severely enlarged thyroids, the bulge in the neck is noticeable even when the patient is sitting upright or standin (87).

Hypothyroidism	Hyperthyroidism
• Salivary gland enlargement • Compromised periodontal health - delayed bone resorption • Macroglossia • Glossitis • Dysgeusia • Delayed dental eruption • Enamel hypoplasia in both dentitions, (being less intense in the permanent dentition) • Anterior open bite • Micrognathia • Thick lips • Mouth breathing	• Increased susceptibility to caries • Increased susceptibility to periodontal disease • Enlargement of extraglandular thyroid tissue • Burning mouth syndrome • Accelerated dental eruption • Maxillary and mandibular osteoporosis • Development of connective tissue diseases like Sjogren's syndrome or Systemic lupus erythematosus

Recommendation

After a full and thorough overview of this research, still a lot of aspects that remains unfolded, as a dentist we sure will be concerned about oral associated aspect, like the effect of other endocrine disease on the oral cavity (teeth, saliva, periodontium, soft tissue... etc.) their effect, management of the associated effect and also the impact of the such diseases on the general health،one of the most important endocrine gland is **parathyroid gland**, due to the role of parathyroid hormone that stimulates the Release of calcium by bones into the bloodstream, Absorption of calcium from food by the intestines. Conservation of calcium by the kidneys, and by which is clearly connected to the health and immunity of oral cavity against disease, so as a research team we recommend the study of the impact of the parathyroid gland disorders in oral health.

If you are a person living with diabetes, it is recommended that you:

- Follow your doctor's advice about diet and medication to keep your blood glucose levels as close to the target levels as possible.
- Clean your teeth and gums twice a day with toothpaste that contains fluoride.
- Use dental floss or interdental cleaners once a day to clean between your teeth.
- Visit your dentist every 6 to 12 months so that they can check your mouth, teeth and gums for any signs of oral conditions, professionally clean your teeth and give advice about caring for your teeth and gums at home. Talk to your dentist about your blood glucose levels and what medications you are taking.
- Avoid having a dry mouth – drink plenty of water and chew sugar-free gum to stimulate saliva flow.
- Don't smoke

Conclusion

After a full research and a thorough study of this subject and the aspects of it, a scientific discussion about how the oral condition is affected by the general health is should be highlighted in diabetes the oral cavity is one of the first sites to be shows a sign xerostomia , unpleasant odor (keto acidosis) , bone loss delayed healing , soft tissue and hard tissue susceptibility to be injured these conditions are all to be observed in diabetic patients. Meanwhile the excess or shortage of thyroid hormones has a negative impact on the oral cavity, The common oral findings include , poor periodontal health, altered tooth morphology and delayed wound healing, increased susceptibility to caries, hard tissue disorders , dental eruption disturbance, and soft tissue diseases. Usually, there is a genetic or hormonal link with the effect of one of them on the latter, which doubles their impact on oral health and general health. We know how general health is very important to the dentist, as he judges the patient by his ability to carry out oral care tasks, so these diseases are important to the dentist based on their effect. Oral health directly or indirectly.

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