The Effects of Thyroid Hormone Abnormalities on Periodontal Disease Status

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Abstract

Thyroid hormones play an important role in the regulation of physiologic processes. Thyroid disease can lead to imbalance in the homeostasis of the body and affect the healing capacity of tissues. However, limited data are available regarding the relationship between thyroid hormone imbalance (thyroid disease) and periodontal health. This review is carried out to summarize the relationship between thyroid disease and periodontal status. PUBMED and MEDLINE searches of both human and animal studies were performed to investigate the relationship between thyroid disease, periodontal status, and dental implants. Results suggest that thyroid diseases may affect the status of periodontal diseases, especially in hypothyroid conditions. The duration from disease onset to treatment of thyroid disorders may be critical, since uncontrolled thyroid disease may result in destruction of the periodontium. Further controlled studies are needed to explore the relationship between thyroid hormone imbalance and periodontal status. Periodontal therapies, including dental implant placement, appear to be safe with no increase in treatment failure, so long as the status of the thyroid gland is controlled.

Key words: Thyroid disease, periodontitis, dental implants.

Thyroid gland

The thyroid gland is a butterfly-shaped organ located in the neck inferior to the thyroid cartilage. It produces three hormones, principally thyroxine (T4), and to a lesser extent triiodothyronine (T3) and calcitonin (Little, 2006). Major control of the synthesis and secretion of thyroid hormones is via the hypothalamic-pituitary axis. Thyrotropin-releasing hormone (TRH) is secreted by the hypothalamus and acts on the thyrotrophs of the anterior pituitary to cause secretion of thyroid-stimulating hormone (TSH). TSH then acts on the thyroid gland to stimulate the synthesis and secretion of thyroid hormones. Thyroid function, like many hormonal somatic regulators, is controlled by feedback mechanisms (*Figure 1*), in which the thyroid hormones act as direct inhibitors of TRH, thus regulating their own production.

Thyroid hormones are essential for maintenance of systemic health. Several studies have suggested that an imbalance in the thyroid hormones, either hypothyroidism or hyperthyroidism, may affect the healing process and alter the healing rate of soft tissues and the bone (Burch and Lebovitz, 1982a, 1982b; Burch and Van Wyk, 1987; Herndon *et al.*, 1979; Hwang and Wang, 2007; Kivirikko *et al.*, 1967; Lennox and Johnston, 1973; Lewinson *et al.*, 1989; Mosekilde *et al.*, 1990; Urabe *et al.*, 1999).

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Hypothyroidism

Hypothyroidism is a systemic condition in which the thyroid gland is underactive and production of thyroid hormones is diminished, resulting in metabolic slowdown. Hypothyroidism affects bone healing, where reduction in recruitment, maturation, and activity of bone cells leads to reduction of bone resorption and formation (Mosekilde *et al.,* 1990). The National Health and Nutrition Examination Survey (NHANES 1999-2002) demonstrated that the prevalence of hypothyroidism (defined as TSH levels > 4.5 mIU/L) is 3.7% of the US general population (Aoki *et al.*, 2007).

The diagnosis of primary hypothyroidism depends on the patient's symptoms, medical history, risk factors, family history, physical examination, and circulatory levels of T4 and T3. Primary hypothyroidism can also

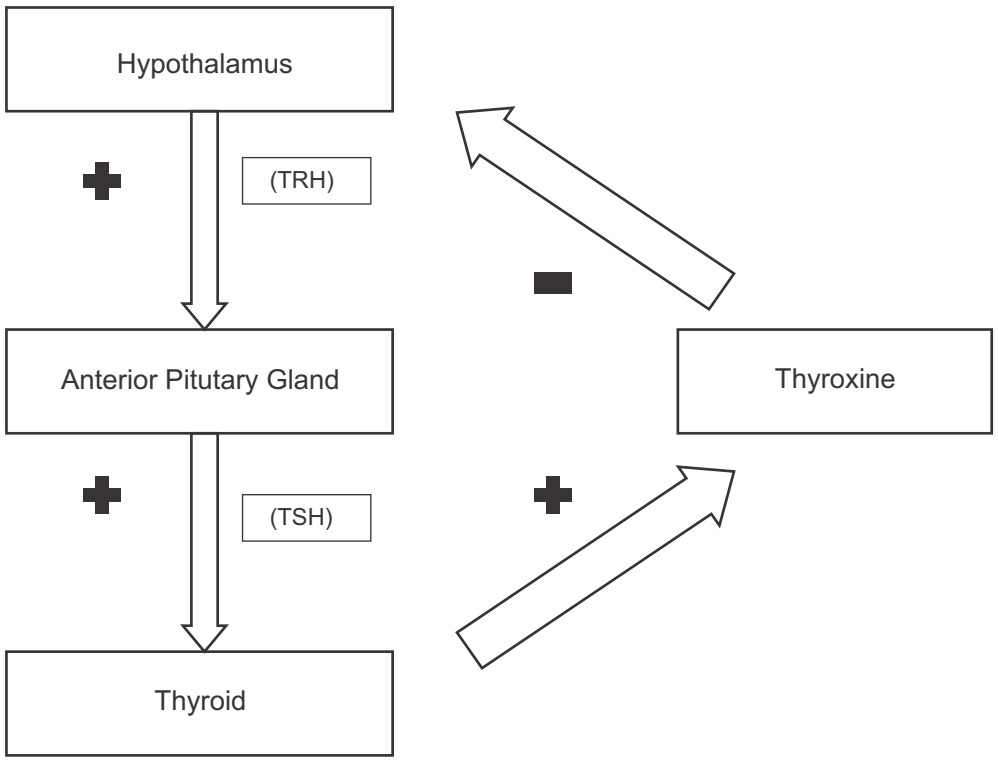

Figure 1. Regulation of thyroid hormone secretion: TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone

be diagnosed through assessment of thyroid-stimulating hormone (TSH), where patients demonstrate elevated levels of TSH with normal levels of T3 and T4. Treatment of hypothyroidism involves daily use of synthetic hormones such as levothyroxine (Levothroid, Levoxyl, Synthroid, and Unithroid) to replace the missing endogenous hormone.

Hyperthyroidism

Hyperthyroidism is a condition in which thyroid hormone production is increased, leading to an excess of circulating T3 and T4; this excess may be due to many diseases and conditions. Elevation of thyroid hormone levels will significantly accelerate the body's metabolism, leading to a variety of different manifestations including sweating, sudden weight loss, rapid or irregular heartbeat, and nervousness or irritability. It occurs more frequently in females. The incidence of the disease in the United States has been reported to be 0.5% in the general population (Aoki *et al.*, 2007).

Hyperthyroidism can mimic other health problems, which sometimes makes its diagnosis difficult. It can be diagnosed using medical history, physical examination, and blood tests. Blood tests for hyperthyroidism can be conducted with a radioactive iodine uptake test or thyroid scan test (Little, 2006). Hyperthyroidism treatment may involve radioactive iodine, anti-thyroid medications (propylthiouracil, carbimazole, and methimazole), and thyroidectomy.

Thyroiditis

Thyroiditis is inflammation of the thyroid gland that includes a group of disorders such as Hashimoto thyroiditis, subacute thyroiditis (de Quervain thyroiditis), silent thyroiditis, postpartum thyroiditis, drug-induced thyroiditis, radiation-induced thyroiditis, and acute infectious thyroiditis. Hashimoto thyroiditis (HT) is the most common cause of primary hypothyroidism in the United States. It is an autoimmune disease caused by anti-thyroid antibodies. HT progresses slowly over a long period of time, leading to diminished production of thyroid hormones. There are no specific signs and symptoms for HT. However, its presentation is similar to hypothyroidism, due to the diminished production of thyroid hormones. It can be diagnosed by measuring the TSH level and testing for the presence of thyroid antibody in the blood. Treatment of HT generally will consist of thyroid hormone replacement.

Thyroid hormones and bone metabolism

Thyroid hormones act on virtually every organ system in the human body (*Figure 2*). Thyroid hormones act synergistically with growth hormone and somatomedins to promote bone formation. They also increase basal metabolic rate, heat production, and oxygen consumption, and they alter the cardiovascular and respiratory systems to increase blood flow and oxygen delivery to the tissues.

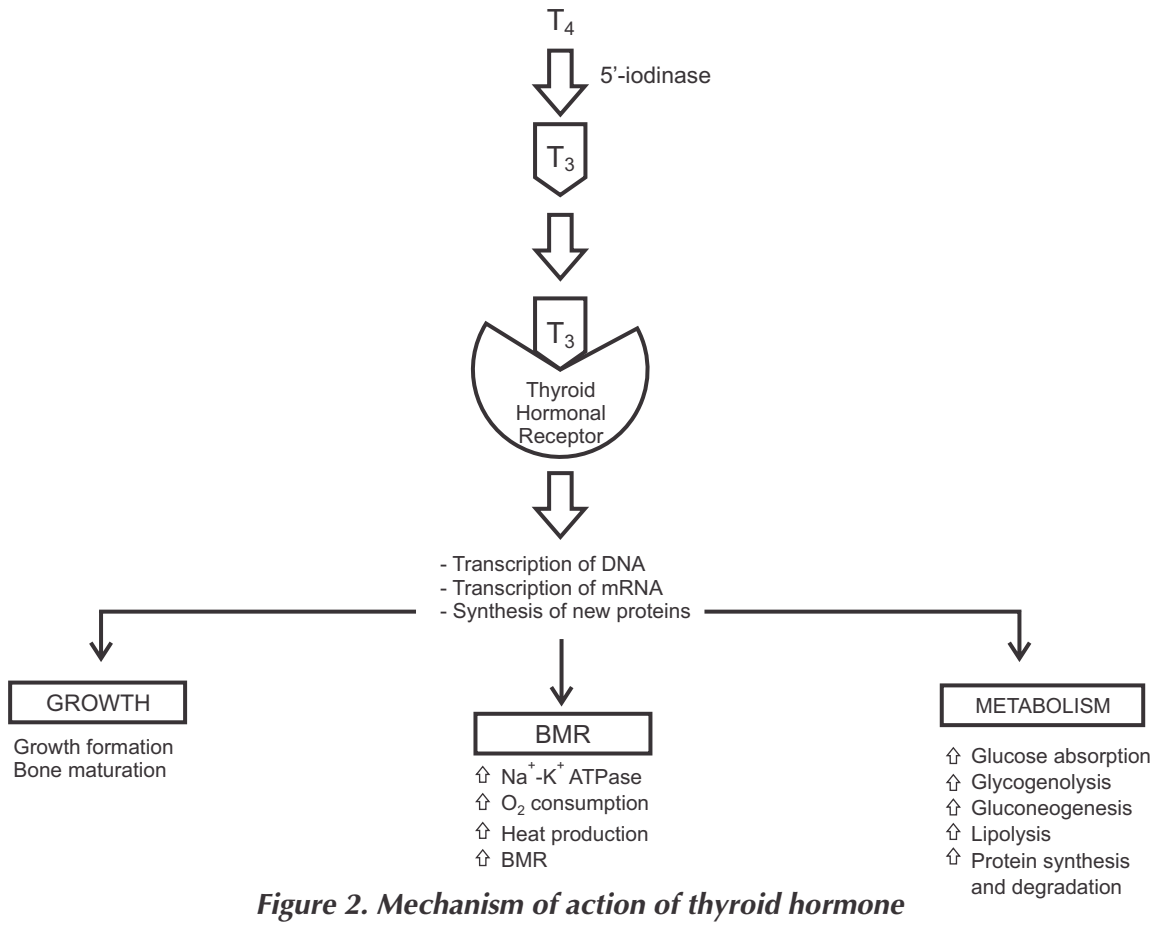

Figure 2. Mechanism of action of thyroid hormone

Thyroxine (T4) is synthesized in the thyroid gland. It is converted to triiodothyronine (T3) in the gland and the tissues by deiodinating enzymes. The thyroid hormone receptor is a nuclear receptor that acts as a transcription factor and is activated by binding to thyroid hormones. Thyroid-stimulating hormones, synthesized by thyrotrope cells in the anterior pituitary gland, stimulate and regulate secretion of the thyroid hormones from the thyroid gland. Thyroid hormones stimulate production of type II and type X collagens and alkaline phosphatase. T3 functions to regulate chondrocyte proliferation, promote terminal differentiation, and induce mineralization and angiogenesis.

Thyroid hormones influence bone remodeling by direct stimulation of osteoblasts and osteoclasts. In hyperthyroidism, the resorptive and formative phases are accelerated and shortened in length, leading to normal resorption depth and reduced wall thickness of the osteon, the bone structural unit, at the end of each cycle. In hypothyroidism, the resorption depth is reduced and the completed wall thickness of the osteon is increased (Mosekilde *et al.*, 1990).

Thyroid gland dysfunction may affect mineral metabolism and absorption, leading to imbalance in the distribution of body minerals. For example, hyperthyroidism patients, even with increased dietary calcium intake, demonstrate reduced absorption and increased fecal and dermal calcium loss, which will lead to negative calcium balance (Mosekilde *et al.*, 1990).

Effect of hypothyroidism on periodontal status

Sharma *et al.* (2007) described a prominent hyperostosis in the anterior maxillary region of a patient with Pendred syndrome, a genetic disorder leading to congenital bilateral hearing loss and goiter with occasional hypothyroidism. They speculated that the hyperostosis was related to hypothyroidism, because the condition is typically associated with lower trabecular resorption and increased thickness of cortical bone. They suggested that the oral presentation was due to the patient's hypothyroidism.

Soni *et al.* (2005) reported a case of a 42-year-old male with a 5-year history of recurrent gingival bleeding who was diagnosed with acquired von Willebrand disease and associated hypothyroidism. The hypothyroidism was treated with levothyroxine, which initially corrected the bleeding problem. However, the bleeding reoccurred after the patient failed to comply with levothyroxine supplementation. The authors suggested that hypothyroidism should be included in the differential diagnosis of patients who present with repeated bleeding, laboratory evidence of acquired von Willebrand disease, and no personal or family history of coagulopathy.

Feitosa *et al.* (2008) studied the impact of thyroid hormone imbalance on alveolar bone loss using a rat

model of ligature-induced periodontitis. Hypothyroidism was induced by blocking thyroid hormone synthesis via administration of an anti-thyroid drug (Propilracil). Hyperthyroidism was induced by ingestion of sodium L-thyroxine and sodium triiodothyronine. The rats were randomly assigned to three groups (healthy, hypothyroidism, and hyperthyroidism). Hormonal treatment continued for four months and was confirmed with assessment of total serum levels of T3 and T4. Ligatures were placed and the animals sacrificed 30 days later, followed by histometric analysis. They demonstrated a statistically significant increase in alveolar bone loss in the hypothyroid rats, relative to the controls. The authors suggested that the progression in periodontal disease in rats might be not related to the effect of the hormone imbalance on the alveolar bone quality. They further speculated that the progression of periodontal disease in a hypothyroid state is more related to the negative effect of hypothyroidism on the immune system, leading to a less proficient immunogenic response to the infection induced by the experimental periodontitis.

Moskvina *et al.* (2001) evaluated the effect of rinsing with lithium chloride and taking potassium orotate in 70 female patients (32 with hypothyroidism and 38 with hyperthyroidism) with different degrees of chronic generalized periodontitis. The authors concluded that using those medicaments enhanced the effect of periodontal treatment in patients with hypothyroidism or hyperthyroidism. The authors did not discuss the possible mechanism.

Molloy *et al.* (2004) reported a case-controlled retrospective chart review of 2006 patients. The inclusion criteria for patients were ≥ 50 years of age, ≥ 6 remaining teeth, and having a fully completed medical questionnaire, as well as a full set of periapical radiographs. Age, sex, diabetic and smoking status were adjusted. Fisher's exact test and logistic regression were used to examine any association between the systemic medical conditions and the percentage of bone loss. They found a statistically significant relationship between alveolar bone loss and thyroid disorders. Patients with thyroid problems exhibited mild alveolar bone loss (up to 25%) from crestal bone to cemento-enamel junction. The questionnaire utilized in the study did not differentiate between hypothyroidism and hyperthyroidism.

Scardina and Messina (2008) compared the microvascularity of the interdental papilla in healthy individuals and Hashimoto thyroiditis patients. A total of 30 patients were assigned to the two groups. Patients with potential compromised microcirculation due to medical conditions such as diabetes were excluded from the healthy patient group. Gingival capillaroscopy was performed using computerized video microscopic techniques. They demonstrated microvasculature alterations consisting of an increase in capillary density and reduction in the capillary diameter in Hashimoto thyroiditis patients. The authors stated in the discussion that the alteration of microvascularity might act as a risk factor for periodontitis.

Hypothyroidism can coexist with other systemic diseases such as diabetes, which may have synergistic effects on the periodontal status. Diabetic patients have a higher prevalence of hypothyroidism compared with the normal population, as it slows the body's metabolic processes and affects insulin production (Aoki *et al.*, 2007; Crespi *et al.*, 2009; Guarnieri *et al.,* 2005; Irinakis, 2006; Torres-Lagares *et al.*, 2010).

Effect of hyperthyroidism on the periodontal status

Binderman *et al.* (1968) performed an animal study using guinea pigs. The authors increased thyroid hormone intake through diet. The dietary increase of thyroid hormones resulted in "marked changes in tooth structure, periodontal membrane and alveolar structure." However, they did not document their experimental design in detail and the "marked changes" were not described.

Vázquez-Landaverde *et al.* (2002) studied the protective effect of administering low dose thyroid hormones on root surface resorption during orthodontic treatment in Sprague-Dawley rats. Thyroid hormones were provided orally or intraperitoneally. The study was designed to assess whether the route of administration would affect the ability of the hormones to prevent root resorption. Orthodontic appliances were inserted and activated in rats and the animals sacrificed 10 days after the initiation of hormonal treatment. The results indicated that the animals receiving thyroid hormones, either intraperitoneally or orally, had significantly less root resorption lesions than the controls. They concluded that administering low doses of thyroid hormones may have a protective effect on the root surface during orthodontic treatment.

One should be aware that, in some animal studies, thyroid disease may be induced by medication and uncontrolled; while in human studies the thyroid condition typically is controlled. Consequently, those differences should be considered when interpreting the literature. Such differences in disease induction might explain some of the variation observed when comparing human and animal studies.

Although the cited studies in this review indicated that thyroid disorders may play a role in periodontal diseases, further studies such as longitudinal randomized or interventional studies are required to fully elucidate the relationship between thyroid disorders and periodontitis.

Thyroid diseases and dental implants

A limited number of clinical reports explored the effect of thyroid gland dysfunction on the success rate of dental implants. Attard and Zarb (2002) enlisted 27

controlled hypothyroidism patients and 29 healthy subjects. One hundred sixty-three implants were placed in both groups (82 in the hypothyroidism group and 81 in the control group). Three implants failed in the thyroid group and two implants failed in the control group, yielding a success rate of 97% from the 163 implants. Statistical analysis showed that hypothyroid patients had more soft tissue complications when compared to the controls. The authors concluded that medically controlled hypothyroidism does not appear to be contradicted for dental implant therapy.

In a prospective study, Alsaadi *et al.* (2008b) evaluated 720 implants placed in 283 consecutive patients. Medical history was recorded via questionnaire and medical record review. Smoking habits, systemic diseases, medication record, and local and systemic bone factors were recorded. Implant failure criteria for this study included any detectable peri-implant radiolucency, implant mobility, and subjective signs of pain or infection around the implant. The authors reported a 100% success rate for implants placed in patients with thyroid diseases (21 in hypothyroid patients and four in hyperthyroid patients), relative to a global success rate of 98.1%. There was no statistically significant difference between the success rates for patient groups with or without thyroid conditions.

In a different retrospective study, the same author (2008a) assessed the effect of systemic factors on dental implant failure. They reviewed the records of 700 randomly chosen patients who received dental implants. The implants were evaluated two years after receiving the abutment. The same implant failure criteria as described in previous studies were used, with reported implant failure rates of 6.31% and 13.64%, out of a total of 123 implants placed in 25 hypothyroidism (104 implants) and 6 hyperthyroidism patients (19 implants), respectively. The authors did not find any statistically significant relationship between the implant failure and thyroid dysfunction. It should be noted that the author excluded the implants that failed before the abutment insertion.

Feitosa *et al.* (2008), in an animal study using a rat-tibia model, reported results that conflicted with Alsaadi *et al.* (2008a; 2008b) from the two above-mentioned publications. In this study, machined screw-shape implants were placed in the tibia of medication-induced hypothyroid or hyperthyroid rats. The authors noticed significantly less bone-implant contact in hypothyroid rats than in hyperthyroid rats ($p < 0.05$). The bone surrounding the implants was significantly decreased in rats with hypothyroidism. The authors concluded that a thyroid hormone imbalance might affect healing of the cortical bone, with less effect on cancellous bone. However, it should be noted that the rat tibia model might not be entirely reflective of the human oral environment.

Shcherbakov *et al.* (2008) evaluated 223 patients who received dental implants. They evaluated the total amount of T4, free T4, total level of T3, and free T3 in serum and saliva. The authors observed a notable difference in salivary thyroid hormone levels relative to serum. Although the thyroid hormone level was much lower in saliva than that in serum, the authors elected to use the salivary thyroid hormone level rather than serum level for their definition of thyroid deficiency. The authors concluded that thyroid insufficiency was observed in 25% of patients with dental peri-implantitis, whereas thyroid gland dysfunction was absent in cases of peri-implant mucositis.

Dental management of thyroid patients

Dentists should be able to recognize local or systemic symptoms and manifestations that might indicate undiagnosed thyroid disease. Elective dental treatment should be postponed and the patient be referred to his/her physician for evaluation. Common oral findings in hypothyroidism include macroglossia, dysgeusia, delayed eruption, poor periodontal health and delayed wound healing (Young, 1989). A common manifestation in young patients with hyperthyroidism is Graves' disease, while middle-aged men and women present most commonly with toxic nodular goiter.

Before treating patients with thyroid disease, dentists should obtain appropriate diagnoses and consider the etiology, past medical complications, medical treatment and compliance with that treatment. While treating patients with hyperthyroidism, dentists should be familiar with the oral manifestations of thyrotoxicosis, such as increased caries susceptibility, periodontal disease, enlargement of extraglandular thyroid tissue, maxillary or mandibular osteoporosis, accelerated dental eruption and burning mouth syndrome (Greenspan and Greenspan, 1999).

Using epinephrine in hypothyroidism patients has been shown to be safe and without significant interactions in controlled patients with minimal cardiovascular involvement (Johnson *et al.*, 1995). On the other hand, for patients with hyperthyroidism who exhibit signs or symptoms of thyroid storm (crisis), epinephrine usage is contraindicated and should be avoided.

Conclusion

In children, the role of the hypothalamic–pituitary–thyroid axis in bone has been well documented, with delayed bone maturation in hypothyroidism and advanced bone age in hyperthyroidism. In adults, the integrity of the mature bone is maintained by bone remodeling, a process controlled by thyroid hormones and TSH with interactions with their receptors bone cells (Murphy and Williams, 2004). Abnormalities in the adult bone remodeling sequence have been documented primarily in animal studies, since earlier recognition of thyroid diseases and effective treatment

have resulted in controlled thyroid function in the majority of adults.

Thyroid diseases may affect the periodontal status, especially in hypothyroid conditions. The duration from disease onset to treatment of thyroid disorders might be critical, since uncontrolled thyroid diseases may result in abnormalities in alveolar bone remodeling. Further controlled studies are needed to explore the relationship between thyroid diseases and periodontal status and to determine if an imbalance of thyroid hormone might be a factor in periodontal bone loss. Periodontal therapies, including dental implant placement, appear to be safe with no increased risk in treatment failure as long as the status of the thyroid is controlled.

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