REVIEW ARTICLE

# Probable autoimmune causal relationship between periodontitis and Hashimotos thyroidits: A systemic review

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## Abstract

Periodontitis is a multifactorial disease with microbial dental plaque as the initiator of periodontal disease. However, the manifestation and progression of the disease is influenced by a wide variety of determinants and factors. The strongest type of causal relationship is the association of systemic and periodontal disease. Hashimotos thyroiditis has also been considered as one of the causes of periodontal disease. As a matter of fact, on an autoimmune basis, in Hashimotos disease and periodontal disease, we have made an attempt to derive the common mechanisms, with an evidence base. The need for this kind of review was due to the fact that the outcome of periodontal therapy did not give the expected results in patients with Hashimoto's thyroiditis. Hence, a possible link between Hashimotos thyroiditis and periodontitis was considered.

**Key words:** Autoimmunity, chronic periodontitis, Hashimoto's thyroiditis, periodontal medicine

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## Introduction

The cellular and molecular biology research tools in the field of pathobiology and immunology have revealed the importance of the host immune system, and have led to the understanding of the undesirable immunological responses in susceptible individuals.[1] Periodontitis is a multifactorial infectious disease caused by mixed microbiota. Apart from the microbial etiology a number of factors, namely, environmental and genetic factors, have been proposed, to modulate host microbial interactions that ultimately decide the clinical picture of periodontal disease.[2]

Indeed, animal and population-based studies now suggest that periodontal diseases may be linked with systemic diseases and conditions, including cardiovascular (CVS) diseases, diabetes, respiratory diseases, adverse pregnancy outcomes, and osteoporosis.[3]

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In 1965, Brandtzaeg and Kraus were the first to postulate the autoimmune basis in the pathogenesis of periodontal disease.[4] The involvement of autoantibodies in the pathogenesis of aggressive periodontitis has been observed, suggesting the role of autoimmunity in periodontitis.[5] Few antinuclear cytoplasmic autoantibody (ANCA)-associated diseases are known to coexist with periodontitis in humans. Such diseases include Rheumatoid arthritis (RA) and to a lesser extent, systemic lupus erythematosus (SLE).[6]

Hashimotos thyroiditis (HT), a common autoimmune disease, presents with similar factors of disease progression. The strong association of periodontitis and other systemic conditions such as CVS disorders and preterm low birth weight babies, are systematically reviewed with the evidence base.[7,8] However, more studies are required to explore the

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link between periodontitis and the autoimmune conditions and a probable common mechanism in these disease processes. This review revisits autoimmunity as a potential etiological basis for the pathogenesis of periodontal disease and also focuses on the current knowledge linking periodontal infection and Hashimotos Thyroiditis. Several hypotheses correlating to periodontal infection and Hashimotos thyroiditis are drawn with the evidence base, in this review.

## Probable Common Autoimmune Mechanisms in Periodontitis and HT

- Role of antinuclear antibodies (ANA)
- Role of apoptosis
- Role of superantigens

Hashimoto's thyroiditis – Autoimmunity as a potential etiological basis

In 1912, Hashimoto described four patients with a chronic disorder of the thyroid, which he termed 'struma lymphomatosa'. Hashimoto's thyroiditis (chronic autoimmune thyroiditis) is the most common cause of hypothyroidism in iodine-sufficient areas of the world. Thyroid failure is seen in up to 10% of the population and its prevalence increases with age.[9] It is characterized clinically by gradual thyroid failure, goiter formation, or both, due to autoimmune-mediated destruction of the thyroid gland involving apoptosis of the thyroid epithelial cells.[10] Nearly all patients have high serum concentrations of antibodies against one or more thyroid antigens, diffuse lymphocytic infiltration of the thyroid, which includes predominantly thyroid-specific B and T cells, and follicular destruction.[11] The cause of Hashimoto's thyroiditis is thought to be a combination of genetic susceptibility and environmental factors.[12,13]

Hashimoto's thyroiditis is one of the most common human autoimmune diseases responsible for considerable morbidity.[14] Autoimmune failure of the thyroid requires several genetic and environmental abnormalities and is a multistep process to converge before the full-blown disease develops. At the onset of disease, major histocompatibility complex (MHC) class II-positive antigen-presenting cells (APC), particularly dendritic cells, and different subclasses of macrophages, accumulate in the thyroid.[15,16] APC present thyroid-specific autoantigens to the T cells, leading to activation and clonal expansion of the latter. Thus, the initial stage of the disease is followed by a clonal expansion phase and maturation of the autoreactive T and B lymphocytes in the draining lymph nodes. Taking up the relevant autoantigens, the APC travel from the thyroid to the draining lymph nodes. A central phase occurs in the draining lymph nodes, wherein interactions between APC, autoreactive (AR) T cells (that survive as result of dysregulation or breakage of immune tolerance), and B cells result in inducing the production of thyroid autoantibodies. In the next step, antigen-producing B lymphocytes, cytotoxic T cells, and macrophages infiltrate and accumulate in the thyroid, through expansion of the lymphocyte clones and propagation of lymphoid tissue within the thyroid gland. This process is preferentially mediated by the T-helper type 1 ($T_{H1}$) cells, which secrete regulatory cytokines (interleukin-12, interferon-gamma γ and tumor necrosis factor-alpha. In a final stage, the generated autoreactive T cells, B cells, and antibodies cause massive depletion of the thyrocytes via antibody-dependent, cytokine-mediated, and apoptotic mechanisms of cytotoxity that leads to Hashimoto's disease.[16]

## Role of Environmental Factors in Autoimune Thyroiditis

Long-term iodine exposure leads to increased iodination of thyroglobulin, which increases its antigenicity and initiates the autoimmune process in genetically susceptible individuals.[17] Iodine is a necessary component of normal thyroid hormonogenesis. High iodine intake, selenium deficiency, pollutants such as tobacco smoke, infectious diseases such as chronic hepatitis C, and certain drugs are implicated in the development of autoimmune thyroiditis, primarily in the genetically predisposed.[18] It has been demonstrated that a highly iodinated thyroglobulin molecule is a better immunogen than a low iodine content.[18,19] Therefore, highly iodinated residues may facilitate antigen uptake and processing by APC. Similarly, high doses of iodine have shown to directly affect macrophages, dendritic cells, and B and T lymphocytes, resulting in the stimulation of macrophage myeloperoxidase activity, acceleration of the maturation of dendritic cells, increasing the number of circulating T cells, and stimulating B cell immunoglobulin production.[20] Excessive amounts of iodide ions are rapidly oxidized by Thyroid peroxidase (TPO), thereby generating excessive amounts of reactive intermediates such as hypoiodous acid and oxygen radicals. These oxidative species damage the thyrocyte cell membrane by oxidation of the membrane lipids and proteins, causing thyrocyte necrosis.[21]

Selenium deficiency decreases the activity of the selenoproteins, including glutathione peroxidases, which can lead to raised concentrations of hydrogen peroxide and thus promote inflammation and disease. Environmental pollutants such as smoke, polychlorinated biphenyls, solvents, and metals have been implicated in the autoimmune process and inflammation.[22]

## Antinuclear Autoantibodies

### Role of ANA in autoimmunity

Davis *et al.*, documented anti-neutrophil cytoplasmic antibodies (ANCAs) for subjects with acute necrotizing

glomerulonephritis.[23] ANCAs represent a heterogeneous group of antibodies, also known as antinuclear factors (ANF).[24] These factors target antigens that are primarily present in the azurophil granules of polymorphonuclear leukocytes (PMNs). The role of ANCA is determined in several other known autoimmune diseases, such as, inflammatory conditions, infectious diseases, and neoplasms.[24] Few include systemic vasculitis, Wegener's granulomatosis, Churg Strauss syndrome, classic polyarteritis nodosa, microscopic polyarteritis, rheumatoid arthritis, systemic lupus erythematosus, acute / chronic infection, HIV infection, and chronic periodontitis. Indirect immunofluorescence was advocated during the 1970s, to demonstrate granulocyte-specific antinuclear factors in sinovial fluids and the sera of RA patients.[25]

The tendency for all the chronic inflammation to undergo dysfunction could be related to the immune-specific genes, such as, alleles of human leukocyte antigens and the other genes that determine the level of the host immune response. In recent times, microbial superantigens (SAgs) and mechanisms related to disturbed apoptosis or removal of apoptotic cells have been proposed for the induction of ANCA.[26]

### Antinuclear antibody testing

The ANA test was designed by Dr. George Friou, in 1957. The ANA test is performed using a blood sample. The antibodies in the serum of the blood are exposed to cells, in the laboratory. It is then determined whether or not antibodies are present that react to various parts of the nucleus of the cells. Fluorescence techniques are frequently used to actually detect the antibodies in the cells, thus ANA testing is sometimes referred to as the fluorescent antinuclear antibody test (FANA).[27] The ANA test is a sensitive screening test used to detect autoimmune diseases.

### Role of ANA in autoimmune Hashimotos thyroiditis

Antinuclear antibodies have been detected in other non-connective tissue disorder (CTD) autoimmune diseases, such as, autoimmune thyroiditis (also termed 'chronic lymphocytic thyroiditis' or 'Hashimoto's thyroiditis'). The frequency of ANA positivity in children with autoimmune thyroiditis has been reported to be in the range of 30 to 70%.[28]

In patients with autoimmune thyroiditis, the thyroid dysfunction might be induced by cytokine-mediated apoptosis of thyroid epithelial cells and the infiltrating T lymphocytes may not directly be involved in the thyrocyte cell death. However, fragmented DNA, a characteristic feature of apoptosis, was frequently found in the thyroid follicular cells in Hashimoto's thyroiditis.

Possible theories for the high association of ANA with autoimmune thyroiditis are, enhanced apoptosis of thyroid follicular cells, exposing nuclear antigens to elicit development of ANA, and B-cell hyperactivity with production of multiple autoantibodies.[29]

The ANCA Type for Hashimotos Thyroiditis has positive thyroid antibodies, ATG (Anti-thyroglobulin), ATPO (Anti-thyroid peroxidase), and ATPO, indicating the ANCA-mediated autoimmune thyroiditis (or Hashimoto's thyroiditis)[29] [Figure 1].

## Evidence of the Autoimmune Basis of Periodontal Disease

The presence of auto-antibodies or antibodies against self-antigens has been investigated for their association with periodontal disease.[30] Elevated levels of antibody to collagen have been reported in the sera and are produced by the gingival tissues of the subjects with periodontal disease.[31] Cells were observed, in the diseased gingival tissues, to produce an antibody to the collagen, only against the types of collagen present in those tissues.[31] Antibody specificity for collagen types I, III, IV, V, and VI were found, but not against type II collagen. Type II collagen was not commonly found in gingival tissues, suggesting that destruction of the collagen in the disease process may have caused the auto-antibody responses. The autoimmune condition, rheumatoid arthritis, was shown to be associated with an increased incidence of periodontal disease.[32] However, in a study of periodontal disease in elderly individuals, no increase in rheumatoid factor or incidence of anti-nuclear antibodies was found

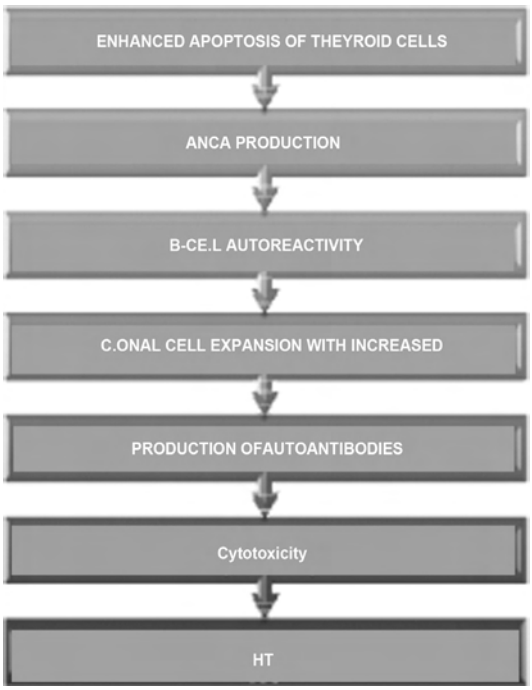


**Figure 1**: ANCA leading to HT

to be associated with the disease.[32] However, in another study, the antinuclear antibody levels were higher in the periodontal disease subjects than in the controls, but no data were presented. Humoral immune response to Porphyromonas gingivalis in older adults with periodontal disease has also been reported.[33]

### Role of ANA in periodontal pathogenesis

Studies are currently underway to study the potential pathogenic role of ANCA in periodontal tissue destruction. ANCA was first described by Parsons et al.,[34] in a condition of localized hyperplastic 'strawberry' gingival lesion, which was later diagnosed to be Wegener's granulomatosis. A similar case was also recently reported by Manchanda *et al*.[35] The first controlled study to explore the possible link between ANCA and periodontal disease was conducted by Novo and Viera,[36] and a statistically significant number of ANCA-positive patients were reported in the periodontitis group than healthy controls. Although the mechanisms that trigger the development of ANCA are not completely understood, several hypotheses have been postulated, including immunospecific genes, such as alleles of human leukocyte antigens and other genes that determine the level of the host immune response.[37] In recent times, microbial superantigens (SAgs) and mechanisms related to disturbed apoptosis or removal of apoptotic cells have been proposed for the induction of ANCA.[38]

The two mechanisms that trigger ANCA are

1. Hyperprimed neutrophils produce myeloperoxidase (MPO) and proteinase-3 (PR-3), which triggers ANCA
2. The exposure of the host to periodontal pathogens, along with a genetic susceptibility, could trigger ANCA by TNF-alpha
3. The other known pathway is the ability of periodontal pathogens to possess a 'superantigen' property, where they can directly activate the autoreactive B-lymphocytes in a T-cell–independent and mediated pathway, which can also result in the production of ANCA.

Furthermore, these invoke an antigen antibody–dependent immune response, which results in the activation of neutrophils. The activated neutrophils release reactive oxygen radicals, enzymes, and various proinflammatory cytokines, all of which are known to mediate periodontal destruction.[39] ANCA-activated neutrophils are also known to delay apoptosis, which can prolong the activity of neutrophils and thereby increase tissue destruction.

### Role of apoptosis in autoimmunity

Autoimmune apoptosis of neutrophils is essential for controlling the duration of early inflammatory response and thus limiting local tissue damage, which can result from the prolonged activation of neutrophils. Utz and Anderson.[40] suggested that defects in apoptosis or in the process of removal of apoptotic cells could lead to exposure of these cellular fragments to the immune system and activate a humoral immune response. Further opsonization of these apoptotic neutrophils by ANCA might accelerate inflammation and augment the autoimmune response.[41]

## Altered Apoptosis in Hashimotos Thyroiditis

Aberration in the regulatory mechanism of apoptosis is considered to be contributory to ANCA-associated autoimmune diseases, such as RA.[42] Furthermore, various proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and granulocyte monocyte colony stimulating factor (GM-CSF) are known to have a role in delaying neutrophil apoptosis, by altering the levels of Bcl-2 proteins.[43,44] Such prolonged survival of neutrophils is associated with a sustained inflammatory response.

Certain responses against specific antigens are primary determinants in thyroid. The normal thyroid gland has been shown to act as an immune-privileged site, having carefully regulated mechanisms of cell death and self-protection against attack by infiltrating activated T-cells induced by apoptosis. [45,46] Cell apoptosis occurs in the normal thyroid at a low level, to maintain normal thyroid volume and function. Deregulation of apoptosis, which is weakly determined by genetic susceptibility, can lead to destructive processes. Initiation of an out-of-control apoptotic mechanism in the thyroid cells may be caused by various non-genetic injuries that affect the expression of the apoptosis inhibitor molecule Bcl-2 or membrane ligand FasL.[47] Thyrocytes from HT thyroid glands are able to hyperproduce Fas and FasL on their surfaces, thus inducing fratricide apoptosis.[48] IL-1β, abundantly produced in HT glands, induces Fas expression in normal thyrocytes; the cross-linking of Fas resulting in massive thyrocyte apoptosis. This can play a role in the progression of Hashimoto's thyroiditis.[49] Immune-mediated apoptosis of thyrocytes is directed by CD8+ cells. Receptors on the target cell are triggered by lymphocyte ligands and / or released soluble factors.[50]

The predominance of $T_{H1}$ or $T_{H2}$ cytokines might regulate thyrocyte survival through the induction of pro-apoptotic and anti-apoptotic proteins. $T_{H1}$-mediated mechanisms lead to thyrocyte depletion in Hashimoto's thyroiditis, through the involvement of death receptors and cytokine-regulated apoptotic pathways.[51,52]

### Role of apoptosis in periodontitis

Apoptosis is induced in the periodontal tissue by host and microbial factors, which supports the hypothesis that apoptotic mechanisms could be implicated in the inflammatory process associated with gingival tissue

destruction observed in adult periodontitis patients.[40] Recent studies have a reported association between hyperreactive neutrophils in the periodontal disease and an increased release of oxygen radicals in the periodontal damaged tissue. Neutrophil activity would produce a delay in the death of the cell by apoptosis, increasing the damage to the periodontal tissue. Gamonal *et al*. demonstrated aberrant, that is, accelerated or delayed neutrophil apoptosis, with a shift in balance between the mammalian Bcl-2 family of apoptosis-associated proteins, a reduction in the cellular (neutrophil) expression of proapoptotic protein Bax, and an elevated anti-apoptotic protein Bcl-253. In addition, they suggested that the presence of elevated levels of GM-CSF and TNF-α in gingival crevicular fluid (GCF) from periodontitis sites relative to that of the healthy sites could also be attributed as the causative factor for the delay in neutrophil apoptosis.[54] Utz and Anderson[40] suggested that defects in apoptosis or in the process of removal of apoptotic cells could lead to exposure of these cellular fragments to the immune system, thus activating a humoral immune response.

### Role of superantigens in autoimmunity

Superantigens are microbial or viral toxins that comprise of a class of disease-associated, immunostimulatory molecules and act as variant β (Vβ)-restricted extremely potent polyclonal T cell mitogens. Superantigens are unique, in that, they induce tremendous activation and expansion of specific subsets of T cells in an antigen-independent manner; thereby causing immune dysfunction. They bind the major histocompatibility complex (MHC) class-II molecules without any prior processing and stimulate a large number of T cells (up to 20% of all T cells) on the basis of the epitope specified by this receptor.[55,56] These properties are attributable to their unique ability to cross-link MHC class II and the T cell receptor (TCR), forming a trimolecular complex. The superantigens can be Endogenous[57-59] (produced by mouse mammary tumor virus and Epstein-Barr virus), Exogenous[57,58] (exotoxins secreted by microorganisms), and B-cell superantigens[60], which stimulate predominantly B cells.

### Role of superantigens in periodontitis

Immunological research studies in periodontics have been directed toward determining superantigenic periodontal pathogens. Immunomodulation by periodontopathic bacteria has been implicated in the pathogenesis of inflammatory periodontal diseases. Zadeh HH[38] has provided evidence to support the hypothesis that a large proportion of T cells in periodontitis sites have been stimulated and expanded by superantigens, presumably produced by periodontitis-associated bacteria, by demonstrating the elevated levels of proportion of one or a few V beta families. In another study Mathur *et al*.,[61] has studied the ability of *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis*, and *Prevotella intermedia*, to determine the SAg activity *in vitro* and has reported that only *P. intermedia* has the capacity to increase the expression of T-cell Vab2, Vb5, and Vb6, thereby providing evidence of the possible involvement of SAg in human periodontal diseases. Of late, a study by Leung and Torres[62] demonstrated that the *P. intermedia* strain, which is a clinical isolate, induced the strongest expansion of CD4 + T-cell subsets that express Vb8, Vb12, and Vb17 TCRs. Furthermore, to confirm the role of A. actinomycetemcomitans–derived SAg, Zadeh *et al*.,[63] reported that the response to this bacterial stimulus was a large-scale T-cell activation in a Vb-specific manner, demonstrating the superantigenic property by A. actinomycetemcomitans.[63] Thus, these studies specify a possibility of the role of superantigen in periodontitis.

## Evidence for a Link Between Periodontitis and Hashimotos Thyroiditis

The two possible hypothetical models that can be drawn for the causal relationship of periodontitis and Hashimotos thyroiditis with evidence base include [Figure 2].

### Autoimmune model

ANCA, cell apoptosis, superantigens activating autoreactive

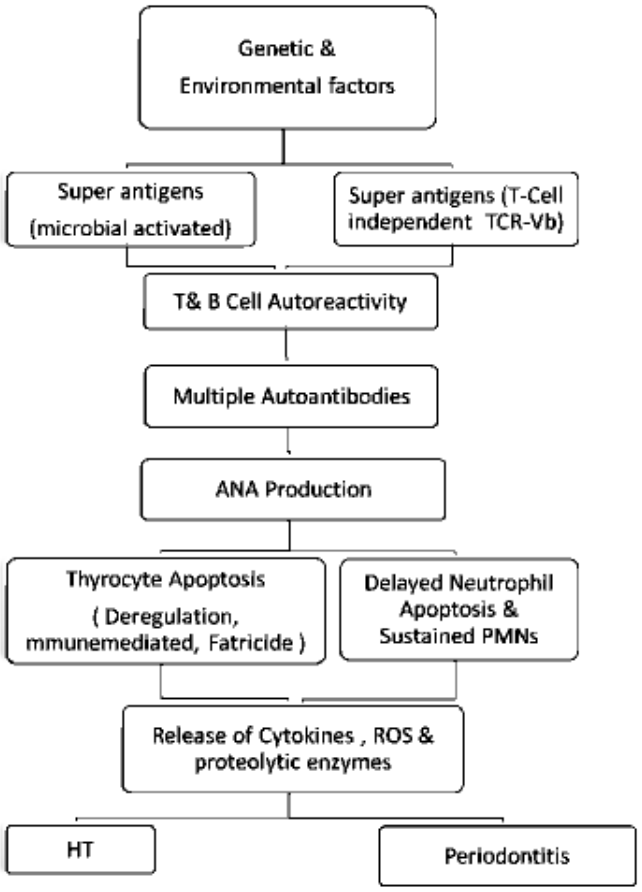


**Figure 2**: Common mechanisms in HT and periodontitis

T-cells and B-cells with clonal expansion, followed by proinflammatory cytokines–mediated destruction further modified by genetic and environmental factors.[64]

## Endothelial dysfunction model

leading to reduced caliber and a greater number and tortuosity of gingival capillary loops in the interdental region, observed in HT cases.[65] The altered gingival microcirculation compromises the first line of defense, with increased PGE and cytokines leading to periodontitis.

As the association of periodontitis and HT is from infancy, the possible role of autoimmunity in these two chronic conditions needs to be evaluated. Novo *et al.*,[36] found that ANCA was detectable in 10% of RA patients with periodontitis and 6.6% of RA patients without periodontitis. Studies in association with RA, SLE, and periodontitis have a similar natural history, etiology, pathogenesis, immune potential and progression patterns of the disease Some ANCA-associated diseases are known to coexist during periodontitis in humans. Such diseases include RA and SLE and to a lesser extent HT, which again holds good with these factors. Other common factors for these diseases include proinflammatory cytokine profiles such as IL-1, TNF-α, and prostaglandin E2, and a role for ROS.

To date, significant progress has been made in identifying and characterizing those components that frequently associate autoimmunity in periodontitis and other chronic conditions. Although HT is not a contributory factor because of its complexity, efforts to detect the possibility of risk factors are a key role in the identification of periodontal disease, with association of autoimmunity and HT. Endothelial dysfunction model [Figure 3].

Scardina and Messina[65] suggested a possible association of HT and periodontitis, in relation to the poor tissue response to periodontal therapy. Reduced caliber and a greater number and tortuosity of gingival capillary loops in the interdental region are observed in HT cases [Figure 3]. The clinical consequences of altered gingival microcirculation can be a compromise of the first line of defense. For the defense cells to perform their function, some receptors must be expressed in correspondence with the endothelial wall.

Thus, the first step of the non-specific defense involves a greater vulnerability in the subject. Such morphological data appear extremely relevant, as they would certainly be altered during particular pathologies, such as, HT. The endothelial dysfunction in these patients, presenting with low-grade chronic inflammation, impairs nitric oxide availability by a Cox-2 dependent pathway, leading to increased production of oxidative stress.[65] Oral findings include macroglossia65dysgeusia, delayed root resumption,[66] decreased salivary gland secretion,[67] poor periodontal health, delayed wound healing, and osteoarthritis of the temporomandibular joint (TMJ).[68] Recent studies have pointed to potentially periodontal risk indicators, however, no information is available on the impact of changes in the thyroid hormone levels on the progression of periodontitis and on the quality of the alveolar bone. D. S. Feitosa *et al*., thus, aimed to evaluate histologically, in rats, the influence of thyroid hormones on the rate of periodontal bone loss, resulting from ligature placement, and on the quality of the tooth-supporting alveolar bone. They concluded that decreased serum levels of

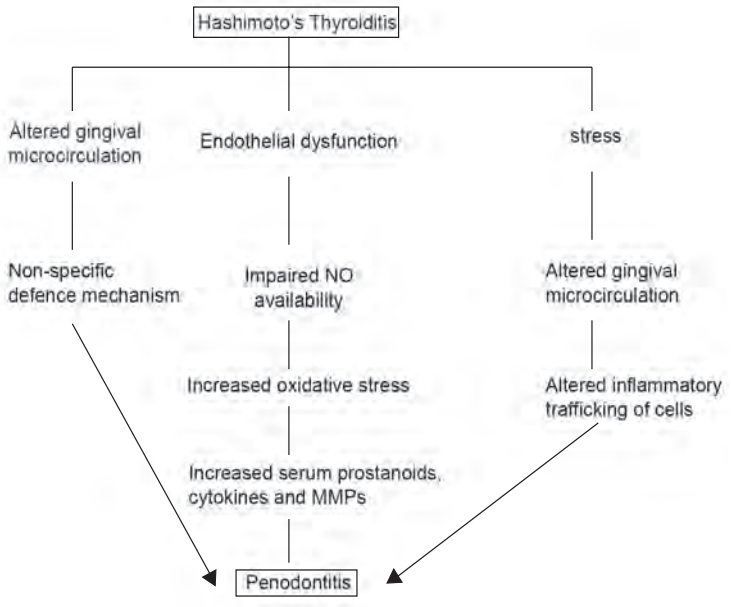


**Figure 3**: A schematic presentation of HT and Periodontitis is shown

thyroid hormones may enhance periodontitis-related bone loss, as a function of an increased number of resorbing cells, whereas, the tooth-supporting alveolar bone seems to be less sensitive to alterations in hormone levels.[69]

Stress or mood alteration are the characteristic features of HT. Evidence suggesting stress and periodontal disease is already stated.[70] Therefore a correlation of stress altering the blood flow and trafficking of inflammatory cells can induce a set of reactions that have effects on virtually all body systems. However association of HT, Stress, and Periodontitis need to be evaluated.

## Diagnostic Algorithm for HT and Periodontitis

1. ANCA test
2. Stress analysis
3. Superantigens
4. Gene test (HLA-antigens / MHC molecules)

## Future Perspectives

The relationship of HT and periodontitis holds worthy for refractory periodontal disease with low plaque scores, uncontrolled periodontal disease, generalized aggressive periodontitis, and those with associated chronic conditions like RA and SLE. Anti-nuclear antibodies are found to be associated with HT and periodontitis. Hence, a future in periodontal medicine should be based upon the autoimmune nature of these chronic conditions in relation to periodontitis. Moreover, females are more susceptible to autoimmune disease than males. This is attributed to the high immune reactivity, due to sex hormones. Therefore, female patients diagnosed with recurrent and / or refractory periodontitis may possibly be associated with undiagnosed HT. Apart from that children are more susceptible to HT. Therefore, children presenting with periodontitis associated with systemic diseases can be referred to the physician for possible involvement of HT.

Thus, the clinical implication of understanding the possible link between HT and periodontitis can be realized from the fact that a stable and healthy periodontium can be achieved only when HT has been controlled / treated. Therefore, a periodontist needs to modify the therapeutic procedures depending on the underlying systemic condition, however, this review supports the hypothesis of an association between periodontitis and HT. Furthermore, research is needed on the possible impact of periodontitis on the HT condition.

## Conclusions

More studies are required to explore the link between these conditions and a probable common mechanism in these disease processes. The causal relationship presents periodontal disease in a rather weak association, as one of the confounding factors. There exists a lack of control of the confounding factors, residual confounders, and over-control of cofounders. Categorization of the diseases, potential evidence to establish the etiologies, and possibly to diagnose and monitor disease activities is the goal of research conducts. As yet, this study is in its infancy. Future work, in the form of cohort studies and controlled studies are required. This area should concentrate on the functional mechanisms of the action of these autoantibodies, the critical immunogenic potential of ANAs, and on superantigens that play an important role in assessing periodontal disease with HT. Identification of the relationship of the autoantibody responses with the other immune and inflammatory mechanisms active during periodontal diseases is the key factor for diagnosis. Although at a very preliminary stage, the available data suggest that the autoantibody to specific periodontal pathogens and immune cells can modulate various aspects of periodontal disease.

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