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Immune System Effects on the Endocrine System

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ABSTRACT

The immune system is a host defence system that combines multiple mechanisms to protect an organism from several pathogens and the development of disease. The endocrine and immune system crosstalk and multiple immune processes are involved in endocrine diseases. Defects of immune tolerance associated with genetic and environmental factors result to the development of autoimmune diseases such as autoimmune thyroiditis and diabetes mellitus type 1. In addition, a mixture of immune cells and mediators is considered to be implicated in thyroid cancer development and progression. Multiple cytokines and the evolving inflammatory process are involved in the pathogenesis of insulin resistance and diabetes mellitus type 2 whereas immune mechanisms related to lymphocytes and cytokine circuits may play a role in the pathogenesis of osteoporosis. Several studies have recently been published regarding the therapeutic implications of immune system mechanisms on endocrine diseases.

INTRODUCTION

The immune system is a host defense system that integrates many biological structures and processes to protect an organism from invading pathogens. Overall, the immune response is a combination of multiple mechanisms that include innate immunity (phagocytosis by macrophages, neutrophils, monocytes and dendritic cells, or cytotoxicity by natural killer cells) and adaptive immunity (antibody-dependent complement or cell mediated cytotoxicity by T-cells that recognize heat shock proteins and cytotoxicity by CD4 or CD8 T cells) (1). Briefly, antigens taken up by antigen presenting cells (APCs) are presented to T-cells through binding with major histocompatibility complex (MHC) molecules in the APCs surface and co-stimulation by several critical molecules. Activated CD4 helper T-cells stimulate the release of cytokines such as interleukin-2 (IL-2) that induce T-cell proliferation and activation, killer cell activity in CD8 suppressor T-cells and stimulation of B-cells to differentiate to plasma cells and produce antibodies. Cytokines are small molecules that assist the immune system by triggering, maintaining and amplifying immune responses (1). In addition, immunosurveillance is a process during which immune cells recognize and eliminate cancer cells and there is a dynamic interaction between immune system and cancer cells that influences all stages of tumorigenesis. (2)

Naïve T-cells differentiate in two subsets that produce different cytokines and regulate distinct immune functions. T-helper 1 (Th1) cells produce mainly interferon-γ (IFN-γ), tumor necrosis factor α (TNF-α) and IL-12 to regulate cell mediated responses while T-helper 2 (Th2) cells secrete IL-4, IL-5 and IL-13 in order to provide help for antibody production (3). Type 1 cytokines are pro-inflammatory and have been implicated in the pathogenesis of several autoimmune diseases, whereas type 2 cytokines are anti-inflammatory. However, newly discovered T-cells subsets such as Th22 and Th17 may also play a role in autoimmune diseases (4).

The immune system is constantly confronted with various molecules and recognize them as foreign substances that need to be destroyed or as self-components that should not trigger an immune response. In order to ensure that no self-molecules cause an immune response, multiple mechanisms are involved to maintain central and peripheral B and T-cell tolerance (1). Disorders of the immune system can lead to autoimmune diseases, inflammatory diseases, or cancer.

Multiple studies have shown that the endocrine system is under the regulation of immune processes. This has been observed for autoimmune endocrine diseases such as autoimmune thyroiditis, diabetes mellitus type 1 (DM1), and Addison's disease as well as for endocrine malignancies such as papillary thyroid cancer (5-7). Defects of the processes ensuring immune cell tolerance resulting in an adaptive immune response to a self-antigen are related to the pathogenesis of autoimmune diseases whereas environmental factors are also considered to be involved (8). Furthermore, a mixture of immune cells and mediators such as chemokines and cytokines has been described to play a critical role in thyroid cancer progression and is associated with patient clinical outcome. (9)

The purpose of this chapter is to review the effect of immune process on endocrine organs and diseases and comment on possible therapeutic implications of immune mechanisms in endocrine disorders.

IMMUNE SYSTEM AND THYROID DISEASE

Autoimmune Thyroid Disease

Autoimmunity is involved in the pathogenesis of multiple diseases associated with the thyroid gland including Graves' disease (GD), Hashimoto thyroiditis (HT), and silent or postpartum thyroiditis. HT and GD have a prevalence of approximately 2% (10) and develop as a consequence of loss of tolerance to thyroid antigens due to several factors such as genetic predisposition, dietary iodine, environmental chemicals, interferon alpha (INF-α), molecular mimics, drugs, and selenium (11). There are three major thyroid auto-antigens: thyroglobulin (Tg), thyroid peroxidase (TPO) and thyrotropin (TSH) receptor. Circulating auto-antibodies to these antigens are useful markers of thyroid autoimmunity but it is generally considered that the pathogenesis of thyroid diseases is associated with T-cell immune mechanisms. Thyroid cells ingest antigens (eg. Tg) and present them to T-cells after stimulation by cytokines such as IFN-γ and under the control of co-stimulatory signals from APCs. Genetic factors play an important role in thyroid autoimmunity but it is generally considered that external antigens initiate or promote the immune process probably through cross reactivity (5).

Autoimmunity to TPO and/or Tg is related to thyroid lymphocytic infiltration and may result to hypothyroidism. In HT the humoral immune response is characterized by the presence of autoantibodies to TPO or Tg. However, the mechanism of development of these autoantibodies is still not completed elucidated. A direct attack of T-cells on the thyroid gland could lead to thyroiditis and exposure of thyroid antigens that trigger subsequently the production of autoantibodies (5, 12). Autoantibodies are themselves cytotoxic or may affect the antigen processing or presentation to T-cells. In iodine-sufficient regions the prevalence of autoantibodies to TPO or Tg is approximately 15-25%, increases with age, and is highest in females (13). Interestingly, anti-TPO and anti-Tg specific clones derived from HT thyroid tissue produce high levels of IFN-γ, a pro-inflammatory cytokine (14). Th1 cells, the predominant T-cell clones found in patients with HT, may also affect autoimmune thyroid disease through induction of thyrocyte apoptosis, which appears to be a major mechanism of thyroid tissue damage, indirectly through IL-1β production by activated macrophages (15). In addition, thyrocytes themselves can produce inflammatory cytokines such as TNF-α, TGF-β, IL-1, IL-6, and IL-8, which can also cause thyrocyte destruction.

Toll-like receptors (TLR) are a family of cell surface receptors, consisting of more than ten members, that associate with the recognition of molecules that trigger the activation of innate and adaptive immune response. A recent study showed that TLR3 is overexpressed in thyroid cells surrounded by immune system cells in patients with HT, suggesting a potential role of TLR3 in the pathogenesis of HT and immune cell infiltration (16).

In patients with Graves' disease, the predominant antibodies are directed against the thyroid-stimulating hormone (TSH) receptor (TSH-R). Thyrotrophin receptor antibodies (TRAb) exist as stimulating or blocking antibodies in the serum; however, neutral TRAb are also identified. Thyroid stimulating antibodies (TSAbs) that activate the TSH-R are the cause of Graves' disease. Rarely, TSH blocking antibodies that competitively inhibit the ligand activation of TSH receptor cause hypothyroidism and thyroid atrophy (5). However, GD, as already mentioned for HT, is also considered to be primarily related to a T-cell abnormality.

It is generally believed that thyroid autoimmunity is related to an imbalance between Th1 and Th2 response. In HT an immune response deviation towards Th1 has been observed while in GD there is a shift towards Th2 differentiation. However, recent studies have shown that newly recognized T cells subsets such as Th17 and Th22 and their cytokines (IL-17, IL-23 and IL-22) may contribute to the pathogenesis of thyroid autoimmune diseases (3).

Both in GD and HT, thyroid cells are exposed to complement attack, with subsequent release of prostaglandin E2, IL-1α, and IL-6, which promote infiltration by lymphocytes leading to cell destruction (17). In GD, inflammatory mediators, such as interleukins and TNF-α, stimulate the production of external thyroid-stimulating antibodies that bind the TSH-R. In thyroid tissue, Th1 recruited lymphocytes may be responsible for enhanced IFN-γ and TNF-α production, which in turn stimulate C-X-C motif chemokine 10 (CXCL10:the prototype of the IFN-γ-inducible Th1 chemokines) secretion from the thyroid cells, creating an amplification feedback loop, that initiates and perpetuates the autoimmune process (18).

In thyroid-associated ophthalmopathy, fibrocytes which are precursor cells of bone-marrow-derived monocyte lineage expressing the hematopoietic cell antigen CD34 ($CD34^+$ fibrocytes), also express the TSHR. TSHR-expressing fibrocytes in which the receptor is activated by its ligand generate extremely high levels of several inflammatory cytokines. Acting in concert with TSHR, the insulin-like growth factor 1 receptor (IGF-1R) expressed by orbital fibroblasts and fibrocytes may participate in TSHR-dependent cytokine production, as anti-IGF-1R blocking antibodies attenuate these pro-inflammatory TSH actions leading to GD ophthalmopathy (19)

Postpartum thyroiditis (PPT) is characterized by the development of postpartum thyroid dysfunction (PPTD), which may occur up to 12 months after delivery. Postpartum exacerbation of autoimmunity may reflect an imbalance in specific regulatory T cells, which is caused by the rapid fall in the numbers of these cells after delivery, and is associated with fluctuations in transforming growth factor-beta1 (TGF-β1) serum levels (17,20)

Usually, PPT presents as transient hyperthyroidism (median time of onset, 13 weeks post-delivery) followed by transient hypothyroidism (median time of onset, 19 weeks post-delivery). In the majority of patients later restoration of normal thyroid function is

observed (21). A plausible explanation for the development of postpartum thyroiditis is that during pregnancy there is a shift from Th1 to Th2 cytokine production followed by a "rebound" shift back to Th1 after delivery (Figure 1). The pathogenesis of the disease has an autoimmune basis as anti-TPO and anti-Tg antibodies are found in almost all patients although anti-TPO are those best correlating with the development of PPT. Postpartum thyroiditis occurs in up to 50% of women who are found to have anti-TPO antibodies at the end of the first trimester of gestation (*i.e.* before thyroid antibody titers start to decline during pregnancy). Furthermore, there is evidence that the TPO antibody titer at 16 weeks of gestation is related to the severity of the PPTD (22). In addition, activation of complement is also thought to play a role in the development of PPT (23).

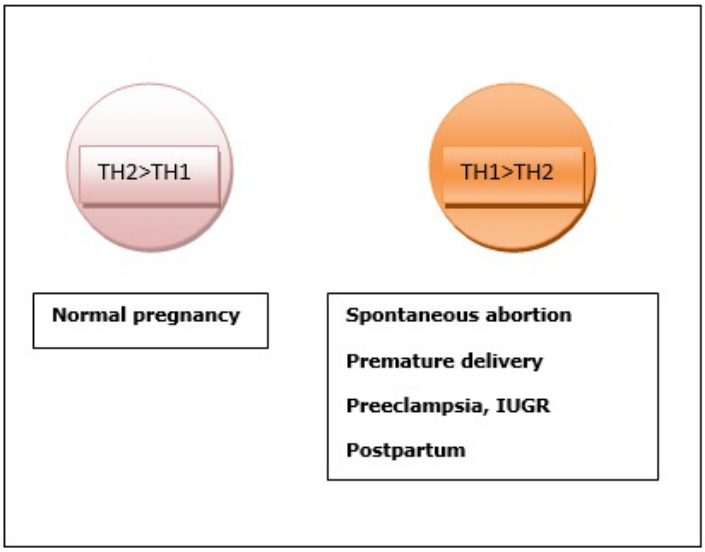

Figure 1.

Th1/Th2 Balance During Pregnancy and Postpartum. IUGR: Intrauterine growth retardation

Euthyroid Sick Syndrome

The term "Euthyroid Sick Syndrome" (ESS) has been used for more than thirty years to describe a pattern of thyroid hormone alterations during non-thyroidal illness. Conditions associated with ESS include systemic inflammation, myocardial infarction, starvation, sepsis, surgery, trauma, chronic degenerative diseases, malignancy and every other condition associated with severe illness. The characteristic laboratory abnormalities of the ESS include low triiodothyronine (T3) and/or free T3 (fT3), elevated reverse T3 (rT3), normal or low TSH, and normal or low serum thyroxine (T4) or free T4 (fT4) concentrations. These abnormalities develop as a result of cytokine action on several pathways of thyroid hormonal synthesis and/or degradation while the more severe the illness is the more extensive the hormonal alterations are. In particular, thyroid hormone changes are the result of suppression of thyrotropin-releasing hormone (TRH) and TSH release, and inhibition of hepatic type-1 5Ά deiodinase (D1) that facilitates conversion of T4 to T3 and of rT3 to diiodothyronine (24). Thus, the cause of the decreased T3 concentration in ESS is decreased T3 production, whereas the cause of the increased rT3 concentration is the result of attenuated degradation. Prolonged and severe illness is marked by a decrease in circulating total T4 along with low T3 and high rT3; furthermore, very low T4 levels carry a poor prognosis and have been associated with an increased mortality rate (24). Cytokines including IL-1α, IL-1β, IL-6, IFN-γ, TNF-α, and TGF-β2, exert an inhibitory role on sodium–iodine symporter (NIS) protein expression and NIS gene transcription, an intrinsic membrane protein that facilitates the active transport of iodine into the thyroid cell (25-27). In addition to the effects on iodide uptake, cytokines have also been shown to decrease thyrocyte growth (28), iodide organification (29, 30), thyroglobulin synthesis (31, 32), and thyroid hormone release in vitro (33).

Cytokines can also affect hepatic deiodinase type 1 D1 activity (Figure 2). The main role of D1 is to peripherally convert T4 to T3 and rT3 to diiodothyronine. In ESS, there is a decrease in D1 activity leading to decreased T3 and increased rT3 concentrations. However, the exact mechanism of decreased D1 activity in ESS still remains unclear. In vitro studies, evaluating the effects of cytokines IL-1β, IL-6, and TNF-α on D1 levels in rat thyroid FRTL-5 and liver cells, have produced controversial results. The D1 activity in rat thyroid FRTL-5 was inhibited by these cytokines (34), whereas liver D1 activity was surprisingly increased (35).

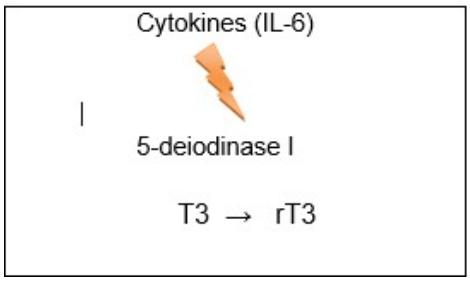

Figure 2.

IL-6 Inhibition of 5´Deiodinase-I Resulting in Decrease in T3 and Increase in rT3 Concentration

While the *in vitro* studies of cytokine effect on D1 activity are controversial, *in vivo* studies have revealed that cytokines can inhibit D1 activity either directly or indirectly. To delineate the effects of IL-6 on D1 activity, IL-6 knockout mice (36) were used in whom Listeria monocytogenes infection or turpentine injection induced a ESS state. The decrease in serum T3 concentration was attenuated in the IL-6 knockout mice compared to wild-type animals. This was associated with only a modest decrease in hepatic D1 activity (compared to wild-type animals), implying that IL-6 played a significant role in the pathogenesis of ESS in that model.

In exploring the effects of cytokines on the hypothalamic-pituitary unit, in vitro studies demonstrated that IL-1β and TNF-α can inhibit TSH release from the pituitary through stimulation of K+-mediated release of somatostatin from the hypothalamus (Figure 3) (37). IL-6 exhibited no effect on TSH secretion or somatostatin release, implying that this cytokine had no direct effect on the hypothalamic-pituitary unit of the thyroid axis (38).

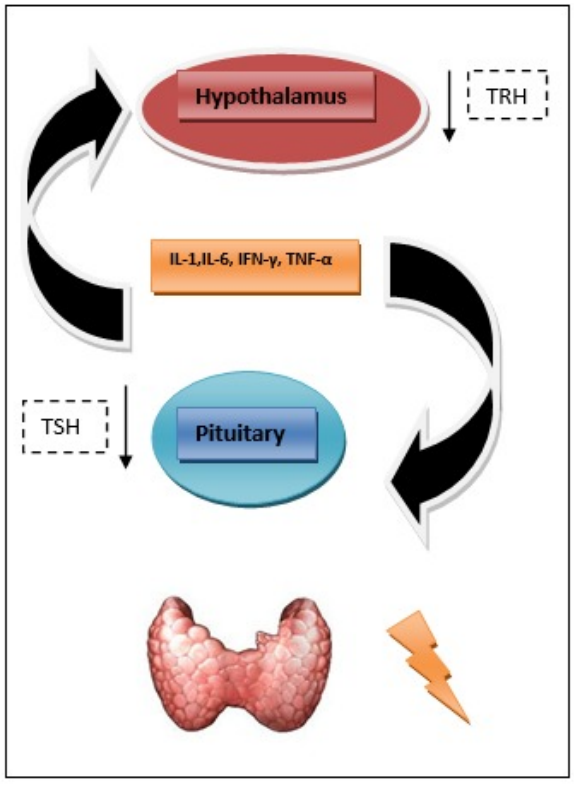

Figure 3.

Cytokine-Mediated Decrease in Thyrotropin-Releasing Hormone (TRH) and TSH Secretion

In animal studies, administration of TNF-α to rats had a similar effect (39, 40). After IL-6 was administered to rats, TSH decreased without any change in hypothalamic pro-TRH mRNA levels, or in stored β-TSH in the pituitary (41). These data, along with the lack of

any IL-6 effect on TSH release *in vitro*, suggest that the observed decrease of circulating TSH *in vivo* following IL-6 administration was the result of an indirect rather than a direct action on the TRH-TSH unit.

The central role of cytokines in the pathophysiology of ESS has been further elucidated in studies involving cytokine administration to humans. Following TNF-α administration to healthy volunteers a decrease in serum T3 and an increase in serum rT3 concentration was found (42). Unlike IL-6, serum TNF-α levels did not correlate with any of the typical thyroid parameters such as low T3, increased rT3, or decreased TSH levels, as seen in ESS (43, 44), suggesting that the changes of thyroid hormonal profile following TNF-α administration might be indirect (i.e. through TNF-α increase in circulating IL-6 levels) rather than direct. Furthermore, both IL-6 and TNF-α can regulate type 2 iodothyronine 5'-deiodinase in the anterior pituitary, affecting TSH release, thus contributing to the development of the non-thyroidal illness syndrome (45, 46).

A link between leptin and pro-inflammatory cytokines such as TNF-α leading to the development of ESS, has also been suggested following the finding that TNF-α levels were associated with increased leptin levels in patients with chronic obstructive pulmonary disease (47). Moreover, serum leptin levels were increased and significantly associated with IL-6 levels and disease activity in men with ankylosing spondylitis (48). It has been suggested that the primary action of leptin on the hypothalamic-pituitary-thyroid (HPT) axis is alteration of the set point for feedback sensitivity of hypophysiotropic TRH producing neurons in the paraventricular nucleus (PVN) of the hypothalamus to thyroid hormones (mainly T3) through lowering of the set point when leptin levels are suppressed during fasting (49). Two anatomically distinct and functionally antagonistic populations of neurons in the arcuate nucleus of the hypothalamus, α-melanocortin-stimulating hormone (α-MSH) producing neurons that co-express cocaine and amphetamine-regulated transcript, and neuropeptide Y (NPY) producing neurons that co-express agouti-related peptide (AGRP), are responsible for the actions of leptin on hypophysiotropic TRH. It is thought that the inhibitory effect of AGRP on TRH gene expression is the result of antagonizing the activating effects of α-MSH at the melanocortin 4 receptor on the surface of hypophysiotropic TRH neurons, whereas the inhibitory effect of NPY occurs by reducing cAMP levels (0). A direct action of leptin on hypophysiotropic TRH neurons has also been proposed (51). These data suggest that leptin can act via two different and independent mechanisms (cytokine dependent and directly) in seriously ill patients, affecting the thyroid function as a whole.

Amiodarone-Induced Thyroid Disease

Amiodarone, a benzofuran derivative with a similar structure to thyroid hormones, is a highly effective antiarrhythmic agent widely used in the treatment of various types of tachyarrhythmias (supraventricular and ventricular arrhythmias). Amiodarone contains two iodine atoms per molecule which is approximately 37,5% iodine by molecular weight (52). Administration of amiodarone is associated with complex changes in thyroid physiology. The iodine load results in an inhibition of thyroid hormone synthesis and metabolism, particularly 5'-monodeiodination of T4 to T3. Such alterations occur in all patients and although the majority remain clinically euthyroid, approximately 14% of amiodarone-treated patients develop thyroid dysfunction (52-54). Treatment with amiodarone may be related with an increase in lymphocyte subsets leading to an exacerbation of pre-existing autoimmunity (52, 55, 56). The relative proportion of patients developing either thyrotoxicosis or hypothyroidism depends on the iodine content of the local diet and pre-existing thyroid autoimmunity. In relatively iodine replete areas, approximately 25% of patients with amiodarone-induced thyroid dysfunction become thyrotoxic, accounting for approximately 3% of amiodarone treated individuals (544).

Amiodarone-induced hypothyroidism is attributed to an increased susceptibility to the inhibitory effect of iodide in thyroid hormone synthesis and/or to a failure to escape the Wolff-Chaikoff effect (52, 57). HT is the most common risk factor for amiodarone-induced hypothyroidism and it is considered the most likely reason for the female preponderance of this clinical entity (58). Female patients with positive Anti-TPO and Anti-Tg autoantibodies have a relative risk of 13.5 for developing amiodarone-induced hypothyroidism compared with men without thyroid autoantibodies (59). A probable explanation for this could be an exacerbation of the autoimmune response by amiodarone's iodide while excess iodide could also confer to the damage caused by an underlying autoimmune disease by inducing non-specific thyroid injury (52).

The pathogenesis of amiodarone-induced thyrotoxicosis (AIT) is complex although two distinct forms, type 1 and type 2, are recognized; Type 1 develops in patients with latent thyroid disease, predominantly nodular goiter in whom the amiodarone iodine load triggers increased synthesis of thyroid hormones. Type 2 is the result of a destructive thyroiditis in a previously normal gland, with leakage of preformed thyroid hormones despite a reduction in hormone synthesis (52-55). A cross-sectional study in patients with AIT revealed that serum IL-6 concentration was elevated in such patients without a goiter or circulating thyroidal autoantibodies (AIT-) compared to patients with AIT in the presence of a goiter or thyroidal autoantibodies (AIT+) (60). AIT- patients had a very low (<3%) 24-hour thyroidal radioiodine uptake suggesting that a subacute thyroiditis-like mechanism was responsible for the thyrotoxicosis. To determine if plasma IL-6 concentration was elevated in other destructive processes besides AIT, serum IL-6 concentration was measured in patients undergoing fine needle aspiration of the thyroid, percutaneous ethanol injections into thyroid nodules, or radioactive iodine treatment. Serum IL-6 concentration increased significantly following any of these procedures, suggesting that IL-6 could be used as a marker of any thyroid destructive process regardless of the etiology (61).

Differentiating between the two types of AIT is an essential step in their management as treatment of each type is different (54). Type 1 usually responds to thionamide therapy that blocks hormone synthesis and perchlorate that blocks active transport of iodine into the thyroid, whereas type 2 responds to high-dose of corticosteroids (54, 55, 61, 62). Nevertheless, several studies now suggest that these two types should be treated concomitantly, and thus patients with AIT receive both anti-thyroid drugs and prednisolone. In resistant to medical treatment cases and/or in patients with severe cardiac diseases who cannot interrupt amiodarone or require quick amiodarone reintroduction, total thyroidectomy may be offered after rapid correction of thyrotoxicosis following combination treatment with thionamides, $KClO_4$, corticosteroids, and a short course of iopanoic acid (63).

Thyroid Cancer

Thyroid cancer is the most common endocrine cancer and its incidence has steadily increased over the past decades (64). The association of chronic inflammation and thyroid cancer has long been recognized and a mixture of immune cells and mediators frequently observed within or surrounding the tumor is considered to play a role in tumor progression and clinical outcome (9).

Immunosurveillance is a process during which the immune system recognizes and eliminates the development of tumor cells but if this mechanism fails, acquisition of new mutations may facilitate evasion from immunological mechanisms of surveillance and result to uncontrolled tumor growth and cancer development. This process is called immunoediting. As a consequence, current research has been focused on developing immunotherapies that enhance tumor specific immune responses or counteract the immunosuppression caused by tumor cells (4).

Currently, there are a lot of studies that support the presence of multiple types of leukocytes in thyroid cancers, which is considered to be associated with positive or negative clinical outcome. The number of tumor-associated macrophages has been found to be increased in thyroid cancer and is related to de-differentiation, lymph node metastases, larger tumors and reduced survival (9, 65-69). Myeloid derived suppressor cells are associated with aggressive characteristics of differentiated thyroid cancer and related to poor prognosis (9, 70). The dendritic cells, that play a critical role in antigen presentation, are also increased in papillary thyroid cancer while neutrophils are found in more aggressive thyroid cancers (poorly differentiated or anaplastic). In addition, natural killer cells that display an important role in immunosurveillance are increased in papillary thyroid cancer and are negatively correlated with tumor stage while lymphocytic infiltration is associated with better overall survival and low recurrence rate (7, 65, 71).

Cytokines may be produced by thyroid follicular cells as well as by immune cells infiltrating thyroid tumors and are related to tumor development. IL-1 and IL-6 stimulate thyroid cell proliferation and tumor growth while TGF-β which is a suppressive cytokine is overexpressed in aggressive cancers (7). A recent study found a correlation of ionizing radiation and oxidative stress with IL-13 while IL-17 has tumorigenic and anti-tumor effects (72-74). In addition, multiple chemokines may be secreted by thyroid cancer or immune cells and affect chemiotaxis, angiogenesis, and lymphangiogenesis (7).

The mixture of immune cells and mediators observed in thyroid tumors may be related to cancer development and growth through production of proangiogenic and lymphangiogenic molecules. Research regarding targeting these pathways or blocking immunosuppressive molecules may lead to development of immunotherapy for thyroid cancer as for other cancer types (65).

IMMUNE SYSTEM AND DIABETES MELLITUS

Over recent years our understanding of the etiology of diabetes mellitus and its vascular complications has widened considerably. Diabetes mellitus type 1 (DM1) is considered an autoimmune disease while inflammation plays an important role in the pathogenesis of diabetes mellitus type 2 (DM2). In addition, an interplay between inflammatory and metabolic abnormalities leads to tissue damage in patients with diabetes and results to various chronic complications that increase morbidity and mortality.

Type 1 Diabetes Mellitus

DM1 is immune mediated in more than 95% of cases and it is considered an organ specific autoimmune disease that is characterized by lymphocytic infiltration and inflammation that leads to β cell destruction and absolute insulin deficiency. Both genetic and environmental factors are involved in the pathogenesis but the precise mechanism behind the initiation and progression of the disease remains to be elucidated (75). Two animal models, the nonobese diabetic (NOD) mouse and the bio breeding (BB) rat, have been extensively used to study the pathophysiology of DM1 (76, 77).

The susceptibility to develop DM1 is associated with multiple alleles of the MHC I and II locus. More than 90% of patients with DM1 express either HLA DR3, DQ2 or DR4, DQ8 (78). On the other hand, HLA haplotype DR2, DQ6 is protective against DM1 development. In addition, multiple environmental factors may trigger the autoimmune process leading to DM1 in patients genetically susceptible. These factors include dietary compounds (e.g., cow's milk) or viruses (e.g., Coxsackie B4, mumps, rubella) but further investigation is required to establish the exact mechanism of their action (79, 80).

Three different mechanisms have been proposed for the pathogenesis of DM1. One mechanism involves molecular mimicry-activated

T-cell proliferation. This mechanism is based on the assumption that epitopes of proteins expressed by infectious agents can be shared by unrelated molecules encoded by host genes (81). A second mechanism that triggers molecular mimicry-activated T-cell proliferation is "by stander" T-cell proliferation. This mechanism involves the stimulation of non-antigen-specific T cells by various cytokines during infection simply because they are in the area. The cytokines thought to be involved in this nonspecific stimulation are IFN-α and IFN-β (82). A third theory involving a superantigen-mediated T-cell proliferation mechanism proposes that auto-reactive T-cells can be inappropriately primed to react against self-structures through an encounter with a superantigen (83).

Most patients diagnosed with DM1 have circulating islet cell autoantibodies directed against β cell proteins. Multiple types of autoantibodies have been identified: islet cell antibodies (ICA), insulin autoantibodies (IAA), and antibodies to glutamic acid decarboxylase 65 (GAD), tyrosine phosphatase IA2 (ICA512), and zinc transporter 8 (ZnT8). These autoantibodies may be detected a long time before the onset of hyperglycemia and usually decline during the course of the disease (84, 85).

Despite the fact that the detection of autoantibodies may be useful for DM1 diagnosis and prediction, there is evidence that the cellular immune system infiltrates the islets and causes β cell destruction. Particularly, autoreactive T cells are involved in disease initiation and progression. Studies in NOD mice have shown that an initial failure of immune regulation results in an amplification of autoreactive CD4 and CD8 T cells, autoantibody producing B lymphocytes, macrophages, and dendritic cells that ultimately damage islets. Further β cell destruction may lead to self-antigen presentation and subsequent amplification of the immune response (75, 86, 87).

While CD4 T helper cells are required for the development of the autoimmune process in the pancreatic islets, CD8 T cytotoxic are probably the responsible cells for β cell destruction. In addition, studies in NOD mice suggest that the Th1 subset plays a crucial role in DM1 pathogenesis. It has been observed that IL-21, a cytokine produced by CD8 T cells, is required for the development of DM1 while TNF-α may also be involved in the disease (88, 89). However, further studies are needed to specify the role of other cytokines such as IFN-γ, IL-12, IL-17 and IL-23. On the contrary, it has been observed that IL-4, a cytokine produced by Th2 cells, protected NOD mice from developing insulinitis or diabetes (75, 83, 88-91). In addition, IL-6 plays an important role in the pathogenesis of vitiligo-associated DM1 and is likely to gain favor as a therapeutic target in these patients (92). IL-6 may also contribute to DM1 and increased albumin-to-creatinine ratio as well as to poor glycemic control and hyperlipidaemia (93).

Understanding both the pathophysiology and the regulatory mechanisms involved in DM1 may be a useful tool in an attempt to develop antigen-specific, β-cell directed, immunomodulatory or cellular treatment modalities (94).

Type 2 Diabetes Mellitus

DM2 is one of the most common metabolic disorders that accounts for 90% of cases of diabetes worldwide (95, 96). DM2 is a heterogeneous disorder that is associated with insulin resistance (IR) in the presence of an impairment in insulin secretion. The increasing prevalence of DM2 has been largely attributed to unhealthy lifestyle and development of obesity and overweight around the world. Obesity is strongly related to DM2 mainly through inducing IR which is the impaired ability of insulin to effectively induce glucose uptake by cells. DM2 is also associated with hypercholesterolemia, atherosclerosis, hypertension, kidney disease, and coronary artery disease.

The concept that a smoldering inflammatory process is important in the pathogenesis of DM2 (92) has recently attracted much attention and is supported by evidence of inflammation in islets, adipose tissue, liver, and muscle that can provoke IR and β-cell dysfunction(97-99). Adipose tissue is characterized by infiltration by macrophages and other immune cells that produce cytokines and chemokines and contribute to the development of local and systemic chronic low-grade inflammation. This inflammatory milieu is considered to be the link between obesity, IR and diabetes mellitus (100-101).

Initially nonspecific indicators of inflammation such as white cell count and fibrinogen were found to be predictive of diabetes (102-103). Subsequently, elevated plasminogen activator inhibitor-1 (PAI-1), CRP, and fibrinogen levels were shown to be independent predictors (104). These observations are supported by a number of prospective studies, in which tissue plasminogen activator (tPA), another marker of reduced fibrinolysis (1055), and von Willebrand factor (vWf), a marker of endothelial injury, were also shown to be predictive (106). There have been many studies demonstrating an association between CRP and/or IL-6 and incident DM2 that was independent of adiposity or IR (104, 107). In addition, the early markers of inflammation, monocyte chemotactic protein-1 (MCP-1), IL-8, and interferon-γ-inducible protein-10, were also found to predict the development of DM2 with MCP-1 being independent of traditional risk factors (108).

The visceral adipose tissue appears to be a major source of circulating IL-6 in humans. The secretion of IL-6 by immune cells such as macrophages is triggered by other cytokines such as TNF-α and IL-1 and reduced by IL-4 and Il-10. Plasma IL-6 concentration correlates well with body mass index (BMI=kg/m^2) (109, 110), and has been found to be elevated in obese people with IR (111,112). In addition, Il-6 levels may predict the development of DM2 (113).

TNF-α has also received considerable attention with regard to IR and may be a key mediator of its pathogenesis. TNF-α has been shown

to be significantly increased in obese individuals with IR (114), and is thought to play a major role in the pathogenesis of obesity-linked DM2 (115). TNF-α is associated with increased release of free fatty acids by adipose tissue and leads to impaired insulin secretion and signalling (116, 117).

At the molecular level, chronic exposure of adipocytes to low doses of TNF-α led to a dramatic decrease in the insulin-stimulated auto-phosphorylation of the insulin receptor and the phosphorylation of insulin receptor substrate 1 (IRS-1) (118). Furthermore, IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in the presence of TNF-α has been demonstrated. Treatment of cultured murine adipocytes with TNF-α has been shown to induce serine phosphorylation of IRS-1 and convert IRS-1 into an inhibitor of the IR tyrosine kinase activity in vitro (119). It was concluded that TNF-α plays an inhibitory role on the insulin-stimulated tyrosine kinase phosphorylation cascade. The question of whether TNF-α induces IR directly or indirectly through inhibitors of tyrosine kinase or counter-regulatory hormones on muscle, fat, and liver in vivo needs further investigation. TNF-α has also been shown to down-regulate glucose transporter GLUT4 mRNA levels in adipocyte and myocyte cultures as well (120-122).

TNF-α may also play a role in the hyperlipidemia observed in DM2 as it has been shown to have profound effects on whole body lipid metabolism (123-125). Circulating triglycerides and very low density lipoproteins in rats and humans are increased after administration of TNF-α (123, 124). Moreover, an animal study has provided evidence of increased TNF-α levels in animals receiving a high-fat diet (126). In addition to TNF-α, IL-1 and IFN-γ also stimulate fatty acid synthesis whereas IL-6 influences fat metabolism as well. Several studies have suggested that certain polymorphisms in the promoter region of the IL-6 gene can affect lipid levels through changes in IL-6 gene transcription and ultimately IL-6 production (127). IL-6 has been proposed to cause an increase in circulating lipid levels probably through a decrease in peripheral lipoprotein lipase activity (128).

Oxidative stress, as a result of increased cytokine levels in DM2, is also thought to play an important role in activating inflammatory genes (129, 130). It is possible that oxidative stress markers do not adequately reflect the impact of increased reactive oxygen species (ROS) on β-cells or insulin signaling. Inflammatory, pro-coagulant or endothelial dysfunction markers are more specific because they may be more proximate to the pathophysiology of hyperglycemia (129, 130). Recently, Hasnain et al showed that islet-endogenous and exogenous IL-22, by regulating oxidative stress pathways, suppresses oxidative and endoplasmic reticulum (ER) stress caused by cytokines or glucolipotoxicity in mouse and human β cells. In obese mice, antibody neutralization of IL-23 or IL-24 partially reduced β cell ER stress and improved glucose tolerance, whereas IL-22 administration modulated oxidative stress regulatory genes in islets, suppressed ER stress and inflammation, promoted secretion of high-quality efficacious insulin and fully restored glucose homeostasis followed by reinstitution of insulin sensitivity (131).

In addition, recent studies have shown that the chemokine system is associated with obesity and IR. MCP-1 that acts on monocytes, macrophages, T cells and NK cells has been found to be increased in obese compared to lean patients and is related to non-alcoholic fatty liver disease and other lipid overload states (132-136). Furthermore, a recent clinical report showed significant benefit in glycemic and lipid profile along with a decrease of MCP-1 levels after a 4-month program of lifestyle improvement (137).

These findings support the investigation of new therapeutic approaches that target inflammation to ameliorate diabetes and its complications. Multiple studies investigate the effect of salicylates, TNF-α inhibitors and IL-1β antagonists on insulin sensitivity, glucose and lipid control, and cardiovascular disease (,138). A recent trial showed improvement of glycemia and secretory function of β cells after treatment with anakinra, a competitive antagonist of the IL-1β receptor IL-1Ra (139). Monoclonal antibodies against IL-1β may reduce inflammatory proteins CRP, IL-6 and fibrinogen in patients with DM2 and high cardiovascular risk (140). In addition, a recent study investigating tocolizumab, a monoclonal antibody against IL-6 receptor showed a significant inhibition of migration of smooth muscle cells under hyperglycemic conditions suggesting it could be a useful therapeutic candidate for atherosclerosis in diabetic patients (141).

OSTEOPOROSIS AND THE IMMUNE SYSTEM

Osteoporosis is a condition of low bone mass and microarchitectural disruption which is associated with an increased risk of fracture in response to low velocity force. It is more frequent in postmenopausal women and in older men or women due to age-related bone loss while it is classified in primary and secondary osteoporosis according to the presence of precipitating factors. Recently, there is growing evidence regarding the effect of immune system on bone metabolism leading to the emergence of the new field of osteo-immunology (142). States of immune dysfunction such as immunodeficiency, inflammatory diseases or immune response to infections may lead to osteoporosis and increased risk fracture. These states are associated with an increased bone resorption from osteoclasts compared to bone formation from osteoblasts resulting to net bone loss (143, 144).

Osteoclasts originate from the same myeloid precursor that derive macrophage and dendritic cells and are specialized in bone degradation (145). Osteoblasts are the main bone forming cells and are derived from mesenchymal stem cells. Osteoclast formation and differentiation is regulated by macrophage colony stimulating factor (M-CSF) and the receptor activator of nuclear factor-kB (RANK) ligand (RANKL) produced by osteoblasts. RANKL is also expressed by fibroblasts and immune cells, including antigen-stimulated T

cells and dendritic cells (142, 146). In addition, osteoprotegerin (OPG) which is produced by osteoblasts, B lymphocytes and dendritic cells binds to RANKL preventing its association with RANK and inhibits osteoclast formation and differentiation (147, 148).

Activated T cells increase the production of TNF-α and RANKL and stimulate osteoclastogenesis during inflammation (142, 149-151). Multiple cytokines may promote osteoclastogenesis mainly by regulating the RANK/RANKL/OPG axis. TNF-α, IL-1, IL-6, IL-7, IL-11, Il-17 and IL-23 promote osteoclast differentiation while IFN-α, IFN-γ, IL-3, IL-4, IL-10, IL-27 and IL-33 are considered anti-osteoclastogenic cytokines that protect bone integrity (148). Th17 cells are considered an osteoclastogenic subset of T cells as they enhance osteoclastogenesis by secreting IL-1, IL-6, Il-17, RANKL, TNF-α and IFN-γ. It has been observed that Th17 cells are increased in patients with osteoporosis and could be used as a potential marker (151, 152). Activation of Th2 leads to enhanced production of PTH and promotes the anabolic activity of osteoblasts in several inflammatory states. Furthermore, Th2 lymphocytes are associated with a low RANKL/OPG ratio and inhibition of bone loss (152). In addition, B cells produce RANKL and OPG and may influence bone formation and absorption while it has been observed that in HIV infected patients there is an altered B cell RANKL/OPG ratio that is inversely correlated with BMD (153).

Interleukin 6 (IL-6) plays a major role in osteoclast development and function. IL-6 is produced by both stromal and osteoblastic cells in response to stimulation by systemic hormones such as parathyroid hormone (PTH), PTH-related peptide (PTH-rP), thyroid hormones and 1,25-dihydroxyvitamin D3 while TGF-β and other cytokines such as IL-1 and TNF-α increase IL-6 production (154). IL-6 has been shown to stimulate osteoclast formation and bone resorption in fetal mouse bone in vitro and along with IL-1 also stimulates bone resorption in vivo (155, 156). Furthermore, IL-6 has been shown to play a role in the abnormal bone resorption observed in patients with multiple myeloma (157), Paget's disease (158), rheumatoid arthritis (159), and Langerhans cell histiocytosis (160). Effects of increased osteoclast-induced bone resorption are not solely attributed to IL-6, but to all IL-6 family cytokines such as leukemia-inhibitory factor (LIF). It appears that LIF acts on osteoclasts indirectly via stimulating IL-6 release by osteoblasts, resulting in an increase in bone resorption (161).

TNF-α has also been shown to induce bone resorption and plays an important role in inflammatory bone diseases (160, 162). TNF-α promotes RANK expression in osteoclast precursors and the formation of multinucleated osteoclasts in the presence of M-CSF. Furthermore, TNF-α may indirectly induce osteoclastogenesis by increasing RANKL and M-CSF expression in osteoblasts, stromal cells and T lymphocytes while it has been observed that RANKL can also enhance TNF-α mediated osteoclastogenesis (148). IL-1β increases RANKL expression and stimulates osteoclast formation and bone resorption while promotes also TNF-α induced osteoclastogenesis (163-164). The Th17 cytokine IL-17 is associated with RANKL increase as well as with stimulation of the osteoclastogenic cytokines TNF-α, IL-1, IL-6 and IL-8 and promotes bone resorption.

Estrogen deficiency is associated with an increased rate of bone resorption relative to bone formation resulting to net bone loss (143). Estrogen loss is associated with an expansion of T and B lymphocytes that could be related with the enhanced bone resorption (165-166). Furthermore, studies have shown that there is an increased production of RANKL by T and B lymphocytes in postmenopausal compared to premenopausal women (167). It has been observed that TNF-α levels are significantly increased in ovariectomized women and mice and a model of enhanced bone resorption due to TNF-α mediated RANKL increase has been proposed (143, 168-169). It has also been shown that after ovariectomy IL-17 levels are increased while studies in ovariectomized mice have revealed that anti-IL-17 antibodies or IL-17 gene deletion may reduce bone loss (170-172). In addition, B lymphocytes may partially contribute to trabecular bone loss (173).

Regarding thyrotoxicosis-induced osteoporosis, it appears that IL-6 and IL-8 play a major role. as they have been found to be increased in patients with thyrotoxicosis due to GD or toxic multinodular goiter (172-175). Siddiqi A et al. have shown that patients with thyroid carcinoma on TSH suppressive therapy had significantly raised circulating levels of IL-6 and IL-8 compared to controls (175). In both groups, plasma levels of IL-6 and IL-8 correlated with serum T3 and free T4 concentrations. Both IL-6 and IL-8 have also been shown to be released by human bone marrow stromal cell cultures containing osteoblast progenitor cells in response to T3 (174). TNF-α elevations due to low TSH signaling in human hyperthyroidism contribute also to the bone loss that has traditionally been attributed solely to high thyroid hormone levels (176). Hyperthyroid mice lacking TSHR had greater bone loss and resorption than hyperthyroid wild-type mice, thereby demonstrating that the absence of TSH signaling contributes to bone loss (177).

Bone resorption in primary hyperparathyroidism (PHP) also appears to be related to immune system effects. Circulating levels of IL-6 and TNF-α have been found to be significantly elevated in patients with PHP and return to normal after successful treatment. In addition, it has been observed a significant correlation of these cytokines with biochemical markers of resorption suggesting they may play a role in the pathogenesis of osteoporosis in PHP (178). The hypothesis that IL-6 mediates the catabolic effects of parathyroid hormone (PTH) on the skeleton has been further strengthened by the finding that neutralizing IL-6 *in vivo* attenuates PTH-induced bone resorption in mice while the resorptive response to PTH was also reduced in IL-6 knockout mice (179). Furthermore, it has been observed that transplantation of parathyroid from humans with hyperparathyroidism to mice lacking T cells was not associated with bone loss suggesting a possible role of T lymphocytes in PTH related osteoporosis (180). A recent study has shown a direct action of PTH on T lymphocytes as deletion of PTH receptor from T cells failed to induce bone loss (181). It has been proposed that PTH action

on T cells results to secretion of TNF-α and in combination with RANKL increase and OPG suppression guides their differentiation to Th17 subsets with subsequent IL-17 secretion and further RANKL amplification (182).

EFFECTS OF THE IMMUNE SYSTEM ON THE STRESS SYSTEM

The Hypothalamo-Pituitary-Adrenal (HPA) Axis

Acute stress increases the expression of cytokines and other inflammatory-related factors in the central nervous system (CNS), plasma, and endocrine glands. Activation of inflammatory signaling pathways within the HPA axis may play a key role in prevention of the self-damaging effects of the immune system. Data on this topic have been provided by a series of experiments that characterize stress effects on members of the IL-1β super-family and other inflammatory-related genes in key structures comprising the HPA axis.(183).

The HPA-axis is activated in states of inflammation or infection. This activation is mediated by the inflammatory cytokines, TNF-α, IL-1, and IL-6, which are secreted in tandem in response to various infectious and non-infectious stimuli. The inflammatory cytokines are produced by a variety of cells, including monocytes, macrophages, astrocytes, endothelial cells, and fibroblasts and lead to an increase of corticotropin releasing hormone (CRH), adrenocorticotroph hormone (ACTH) and finally glucocorticoids (38, 184). The underlying mechanisms are not very well understood but Toll like receptor 4 found in immune and endocrine pituitary cells is considered to be related to the induction of local cytokine production (185).

The pro-inflammatory cytokine interleukin-1, especially its β form, is probably the most important molecule capable of modulating cerebral functions during systemic and localized inflammation. Systemic IL-1β injection activates the neurons involved in the control of autonomic functions, and neutralizing antibodies or IL-1 receptor antagonists are capable of preventing numerous responses during inflammatory stimuli (186). Other cytokines implicated in neuroendocrine and febrile responses include TNF-α and IL-6. Similar to IL-1β, intravenous IL-6 stimulates the hypothalamic-pituitary unit leading to the secretion of cortisol by the adrenal glands, and subsequent termination of the inflammatory cascade (187). Although all three inflammatory cytokines (IL-1, IL-6 and TNF-α) have the capacity to activate the HPA-axis, it appears that IL-6 is the critical component of this cascade. Studies in rats have demonstrated that immunoneutralization of IL-6 abolishes the effects (as potent activators) of the other two cytokines on the HPA-axis (188). TNF-α and IL-1 stimulate the production of IL-6 and IL-6 in turn stimulates the HPA-axis. While acute stimulation with IL-6 stimulates the HPA-axis through activation of the hypothalamic CRH neurons, chronic exposure to IL-6 can stimulate directly the corticotroph cells of the pituitary and the adrenal cells (Figure 4).

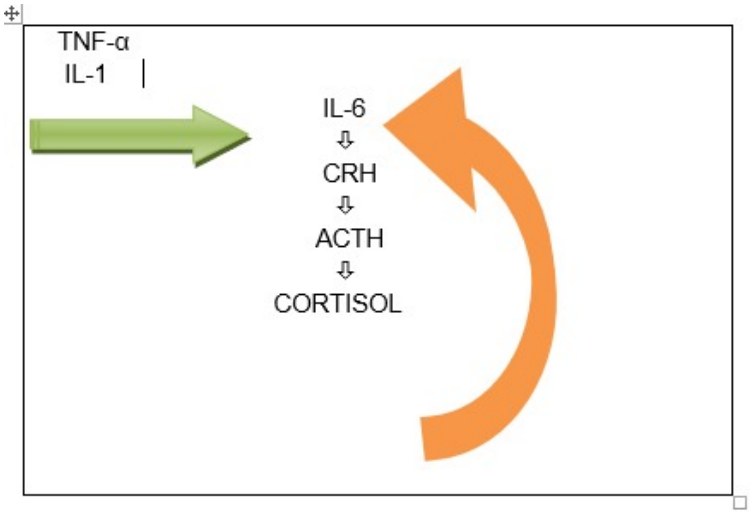

Figure 4.

TNF-α and IL-1 Stimulate the Production of IL-6 and IL-6 in Turn Stimulates the HPA-Axis

Glucocorticoids appear to inhibit IL-6 secretion at the transcriptional level through interaction of the ligand-activated glucocorticoid receptor with nuclear factor-Kappa B. This demonstrates that glucocorticoids and IL-6 participate in a feedback loop, in which IL-6 stimulates glucocorticoid release and glucocorticoids subsequently through negative feedback inhibit IL-6 release. This explains the inverse relationship with diurnal variation between circulating IL-6 and glucocorticoid levels (189-190). Furthermore, acute hypocortisolism has been shown to result in a four to five-fold elevation of circulating IL-6 and TNF-α levels. In a study involving

patients with Cushing's disease studied before and after transsphenoidal adenectomy, cytokines were measured during the hypercortisolemic, hypocortisolemic, and eucortisolemic (while patients were on glucocorticoid replacement) states (191). When patients were hypocortisolemic, plasma IL-6 concentration increased, while they experienced symptoms of glucocorticoid deficiency, which are part of the "steroid withdrawal syndrome". This syndrome consists of pyrexia, headache, anorexia, nausea, fatigue, malaise, arthralgias, myalgias, and somnolence of variable degree. Interestingly, IL-6 levels did not increase in patients who did not become hypocortisolemic after surgery (and did not develop symptoms consistent with the withdrawal syndrome), indicating that hypocortisolism was necessary for the rise in IL-6. Glucocorticoid replacement was followed by a dramatic decrease of IL-6 levels concomitantly with relief of the observed symptoms (191).

Furthermore, increased cortisol turnover is a feature of obese individuals and is exaggerated in upper body (visceral) obesity (192). Some studies indicate that IL-6 directly stimulates adrenal cortisol release in addition to stimulating hypothalamic CRH and pituitary ACTH release (193-195). Adipose tissue IL-6 may, therefore, act as a feed-forward regulator of the hypothalamic-pituitary axis function. Cortisol suppression of adipose IL-6 production may serve as a feedback inhibitor of this regulatory loop. Adrenal cortisol production could be influenced by IL-6 originating from peri-renal adipose tissue that surrounds the adrenal glands.

Similar to IL-6, leukemia-inhibitory factor (LIF) can also stimulate the hypothalamic pituitary axis. LIF is a multifunctional cytokine of the IL-6 cytokine family, sharing the common gp130 receptor subunit together with IL-6, interleukin-11, oncostatin-M, ciliary neurotrophic factor and cardiotrophin-1. Both LIF and its receptor have been found to be expressed in the pituitary gland during development (196). Furthermore, LIF binding sites (LIFR) have been found in one third of ACTH-positive cells and approximately 20% of growth hormone (GH)-positive cells of the pituitary. In several tissues, LIF, LIFR, and gp130 mRNA expression is stimulated by various inflammatory stimuli, whereas LIF gene expression is negatively regulated by glucocorticoids. It has been observed that LIF stimulates ACTH secretion in vitro and in vivo.

Adrenal Medulla

The chromaffin cells of the adrenal medulla are considered to play a role in stress response by secreting catecholamines and various biologically active peptides. Recent studies have shown that cytokines such as TNF-α, IL-1 and IFN-γ act directly to chromaffin cells (197-200). It has also been demonstrated that cytokines regulate the secretion of various peptides that are co-secreted with catecholamines such as vasoactive intestinal peptide (VIP), galanin and secretogranin II, enkephalin and neuropeptide Y (198, 201-204).

A recent study evaluated the regulation of adrenal chromaffin cells by IL-6. It has been observed that IL-6 directly modulates the secretion of catecholamines and neuropeptides by chromaffin cells and therefore influences the adrenal stress response. It has been hypothesized that medullary peptides may serve as paracrine modulators of glucocorticoid production (205). It has also recently been demonstrated that IL-6 increases intracellular Ca^{2+} concentration and induces catecholamine secretion in rat carotid body glomus cells, a finding which eventually confirms a relationship between IL-6 and catecholamine secretion (206).

REFERENCES

1. Understanding the immune system: How it works. National Institute of Allergy and Infectious Diseases, 2003.
2. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. Immunity. 2004;21(2):137–48. [PubMed: 15308095]
3. McLachlan SM, Rapoport B. The molecular biology of thyroid peroxidase: cloning, expression and role as autoantigen in autoimmune thyroid disease. Endocr Rev. 1992;13(2):192–206. [PubMed: 1618162]
4. Li Q, Wang B, Mu K, Zhang JA. The pathogenesis of thyroid autoimmune diseases: New T lymphocytes - Cytokines circuits beyond the Th1-Th2 paradigm. J Cell Physiol. 2018. Epub ahead of print. [PubMed: 30246383]
5. McLachlan SM, Rapoport B. Breaking tolerance to thyroid antigens: changing concepts in thyroid autoimmunity. Endocr Rev. 2014;35(1):59–105. [PMC free article: PMC3895862] [PubMed: 24091783]
6. Szablewski L. Role of immune system in type 1 diabetes mellitus pathogenesis. Int Immunopharmacol. 2014;22(1):182–91. [PubMed: 24993340]
7. Galdiero MR, Varricchi G, Marone G. The immune network in thyroid cancer. Oncoimmunology. 2016;5(6):e1168556. [PMC free article: PMC4938375] [PubMed: 27471646]
8. McLachlan SM, Rapoport B. Breaking tolerance to thyroid antigens: changing concepts in thyroid autoimmunity. Endocr Rev. 2014;35(1):59–105. [PMC free article: PMC3895862] [PubMed: 24091783]
9. Cunha LL, Marcello MA, Ward LS. The role of the inflammatory microenvironment in thyroid carcinogenesis. Endocr Relat Cancer. 2014;21(3):R85–R103. [PubMed: 24302667]
10. Hollowell JG, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87(2):489–99. [PubMed: 11836274]
11. Merrill SJ, Minucci SB. Thyroid Autoimmunity: An Interplay of Factors. Vitam Horm. 2018;106:129–145. [PubMed: 29407432]
12. Bliddal S, Nielsen CH, Feldt-Rasmussen U. Recent advances in understanding autoimmune thyroid disease: the tallest tree in the

forest of polyautoimmunity. F1000Res. 2017;6:1776. [PMC free article: PMC5621109] [PubMed: 29043075]
13. Pedersen IB, et al. Thyroid peroxidase and thyroglobulin autoantibodies in a large survey of populations with mild and moderate iodine deficiency. Clin Endocrinol (Oxf). 2003;58(1):36–42. [PubMed: 12519410]
14. Fisfalen M.E., et al. Thyrotropin-receptor and thyroid peroxidase-specific T cell clones and their cytokine profile in autoimmune thyroid disease. J Clin Endocrinol Metab. 1997;82(11):3655–63. [PubMed: 9360522]
15. Meeusen E.N., Premier R.R., Brandon M.R. Tissue-specific migration of lymphocytes: a key role for Th1 and Th2 cells? Immunol Today. 1996;17(9):421–4. [PubMed: 8854560]
16. Harii N, et al. Thyrocytes express a functional toll-like receptor 3: overexpression can be induced by viral infection and reversed by phenylmethimazole and is associated with Hashimoto's autoimmune thyroiditis. Mol Endocrinol. 2005;19(5):1231–50. [PubMed: 15661832]
17. Weetman A.P., Bennett G.L., Wong W.L. Thyroid follicular cells produce interleukin-8. J Clin Endocrinol Metab. 1992;75(1):328–30. [PubMed: 1619027]
18. Antonelli A., et al. Autoimmune thyroid disorders. Autoimmun Rev. 2015;14(2):174–80. [PubMed: 25461470]
19. Smith T.J. TSH-receptor-expressing fibrocytes and thyroid-associated ophthalmopathy. Nat Rev Endocrinol. 2015;11(3):171–181. [PMC free article: PMC4687015] [PubMed: 25560705]
20. Olivieri A., et al. Postpartum thyroiditis is associated with fluctuations in transforming growth factor-beta1 serum levels. J Clin Endocrinol Metab. 2003;88(3):1280–4. [PubMed: 12629119]
21. Lazarus J.H. The continuing saga of postpartum thyroiditis. J Clin Endocrinol Metab. 2011;96(3):614–6. [PubMed: 21378224]
22. Premawardhana L.D., et al. Postpartum thyroiditis and long-term thyroid status: prognostic influence of thyroid peroxidase antibodies and ultrasound echogenicity. J Clin Endocrinol Metab. 2000;85(1):71–5. [PubMed: 10634366]
23. Parkes A.B., et al. The role of complement in the pathogenesis of postpartum thyroiditis. J Clin Endocrinol Metab. 1994;79(2):395–400. [PubMed: 8045954]
24. Papanicolaou D.A. Euthyroid Sick Syndrome and the role of cytokines. Rev Endocr Metab Disord. 2000;1(1-2):43–8. [PubMed: 11704991]
25. Ajjan R.A., Watson P.F., Weetman A.P. Cytokines and thyroid function. Adv Neuroimmunol. 1996;6(4):359–86. [PubMed: 9183517]
26. Dohan O., De la Vieja A., Carrasco N. Molecular study of the sodium-iodide symporter (NIS): a new field in thyroidology. Trends Endocrinol Metab. 2000;11(3):99–105. [PubMed: 10707050]
27. Chung J.K. Sodium iodide symporter: its role in nuclear medicine. J Nucl Med. 2002;43(9):1188–200. [PubMed: 12215558]
28. Simons P.J., Delemarre F.G., Drexhage H.A. Antigen-presenting dendritic cells as regulators of the growth of thyrocytes: a role of interleukin-1beta and interleukin-6. Endocrinology. 1998;139(7):3148–56. [PubMed: 9645688]
29. Asakawa H., et al. Interferon-gamma reduces the thyroid peroxidase content of cultured human thyrocytes and inhibits its increase induced by thyrotropin. J Clin Endocrinol Metab. 1992;74(6):1331–5. [PubMed: 1592878]
30. Ashizawa K., et al. Interferon-gamma inhibits thyrotropin-induced thyroidal peroxidase gene expression in cultured human thyrocytes. J Clin Endocrinol Metab. 1989;69(2):475–7. [PubMed: 2546966]
31. Poth M., Tseng Y.C., Wartofsky L. Inhibition of TSH activation of human cultured thyroid cells by tumor necrosis factor: an explanation for decreased thyroid function in systemic illness? Thyroid. 1991;1(3):235–40. [PubMed: 1668616]
32. Yamashita S., et al. Interleukin-1 inhibits thyrotrophin-induced human thyroglobulin gene expression. J Endocrinol. 1989;122(1):177–83. [PubMed: 2788696]
33. Yamazaki K., et al. Interleukin-6 (IL-6) inhibits thyroid function in the presence of soluble IL-6 receptor in cultured human thyroid follicles. Endocrinology. 1996;137(11):4857–63. [PubMed: 8895357]
34. Hashimoto H., et al. Effects of tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-6 on type I iodothyronine 5'-deiodination in rat thyroid cell line, FRTL-5. J Interferon Cytokine Res. 1995;15(4):367–75. [PubMed: 7627812]
35. Davies P.H., Sheppard M.C., Franklyn J.A. Inflammatory cytokines and type I 5'-deiodinase expression in phi1 rat liver cells. Mol Cell Endocrinol. 1997;129(2):191–8. [PubMed: 9202402]
36. Boelen A., et al. Induced illness in interleukin-6 (IL-6) knock-out mice: a causal role of IL-6 in the development of the low 3,5,3'-triiodothyronine syndrome. Endocrinology. 1996;137(12):5250–4. [PubMed: 8940342]
37. Wassen F.W., et al. Effects of interleukin-1 beta on thyrotropin secretion and thyroid hormone uptake in cultured rat anterior pituitary cells. Endocrinology. 1996;137(5):1591–8. [PubMed: 8612490]
38. Lyson K., McCann S.M. The effect of interleukin-6 on pituitary hormone release in vivo and in vitro. Neuroendocrinology. 1991;54(3):262–6. [PubMed: 1658674]
39. Ozawa M., et al. Effects of tumor necrosis factor-alpha/cachectin on thyroid hormone metabolism in mice. Endocrinology. 1988;123(3):1461–7. [PubMed: 3402392]
40. Pang X.P., et al. The mechanism of action of tumour necrosis factor-alpha and interleukin 1 on FRTL-5 rat thyroid cells. Acta Endocrinol (Copenh). 1990;123(2):203–10. [PubMed: 2171291]
41. van Haasteren G.A., et al. Different effects of continuous infusion of interleukin-1 and interleukin-6 on the hypothalamic-

hypophysial-thyroid axis. Endocrinology. 1994;135(4):1336–45. [PubMed: 7925094]
42. van der Poll T., et al. Tumor necrosis factor: a putative mediator of the sick euthyroid syndrome in man. J Clin Endocrinol Metab. 1990;71(6):1567–72. [PubMed: 2229314]
43. Chopra I.J., Sakane S., Teco G.N. A study of the serum concentration of tumor necrosis factor-alpha in thyroidal and nonthyroidal illnesses. J Clin Endocrinol Metab. 1991;72(5):1113–6. [PubMed: 2022711]
44. Girvent M., et al. Euthyroid sick syndrome, associated endocrine abnormalities, and outcome in elderly patients undergoing emergency operation. Surgery. 1998;123(5):560–7. [PubMed: 9591009]
45. Davis P.J. Cytokines and growth factors and thyroid hormone. Curr Opin Endocrinol Diabetes Obes. 2008;15(5):428. [PubMed: 18769214]
46. Baur A., et al. Effects of proinflammatory cytokines on anterior pituitary 5'-deiodinase type I and type II. J Endocrinol. 2000;167(3):505–15. [PubMed: 11115778]
47. Calikoglu M., et al. Leptin and TNF-alpha levels in patients with chronic obstructive pulmonary disease and their relationship to nutritional parameters. Respiration. 2004;71(1):45–50. [PubMed: 14872110]
48. Park M.C., et al. Serum leptin levels correlate with interleukin-6 levels and disease activity in patients with ankylosing spondylitis. Scand J Rheumatol. 2007;36(2):101–6. [PubMed: 17476615]
49. Lechan R.M., Fekete C. Feedback regulation of thyrotropin-releasing hormone (TRH): mechanisms for the non-thyroidal illness syndrome. J Endocrinol Invest. 2004;27(6) Suppl:105–19. [PubMed: 15481810]
50. Lechan R.M., Fekete C. Role of melanocortin signaling in the regulation of the hypothalamic-pituitary-thyroid (HPT) axis. Peptides. 2006;27(2):310–25. [PubMed: 16310285]
51. Harris M., et al. Transcriptional regulation of the thyrotropin-releasing hormone gene by leptin and melanocortin signaling. J Clin Invest. 2001;107(1):111–20. [PMC free article: PMC198547] [PubMed: 11134186]
52. Harjai K.J., Licata A.A. Effects of amiodarone on thyroid function. Ann Intern Med. 1997;126(1):63–73. [PubMed: 8992925]
53. Loh K.C. Amiodarone-induced thyroid disorders: a clinical review. Postgrad Med J. 2000;76(893):133–40. [PMC free article: PMC1741517] [PubMed: 10684321]
54. Newman C.M., et al. Amiodarone and the thyroid: a practical guide to the management of thyroid dysfunction induced by amiodarone therapy. Heart. 1998;79(2):121–7. [PMC free article: PMC1728611] [PubMed: 9538302]
55. Martino E., et al. The effects of amiodarone on the thyroid. Endocr Rev. 2001;22(2):240–54. [PubMed: 11294826]
56. Amico JA, et al. Clinical and chemical assessment of thyroid function during therapy with amiodarone. Arch Intern Med. 1984;144(3):487–90. [PubMed: 6703817]
57. Trohman RG, et al. Amiodarone and the thyroid physiology, pathophysiology, diagnosis and management. Trends Cardiovasc Med. 2018. Epub ahead of print. [PubMed: 30309693]
58. Narayana SK, Woods DR, Boos CJ. Management of amiodarone-related thyroid problems. Ther Adv Endocrinol Metab. 2011;2(3):115–26. [PMC free article: PMC3474631] [PubMed: 23148177]
59. Trip MD, Wiersinga W, Plomp TA. Incidence, predictability, and pathogenesis of amiodarone-induced thyrotoxicosis and hypothyroidism. Am J Med. 1991;91(5):507–11. [PubMed: 1951413]
60. Bartalena L., et al. Serum interleukin-6 in amiodarone-induced thyrotoxicosis. J Clin Endocrinol Metab. 1994;78(2):423–7. [PubMed: 8106631]
61. Bartalena L., et al. Treatment of amiodarone-induced thyrotoxicosis, a difficult challenge: results of a prospective study. J Clin Endocrinol Metab. 1996;81(8):2930–3. [PubMed: 8768854]
62. Mosher M.C. Amiodarone-induced hypothyroidism and other adverse effects. Dimens Crit Care Nurs. 2011;30(2):87–93. [PubMed: 21307683]
63. Piga M., et al. Amiodarone-induced thyrotoxicosis. A review. Minerva Endocrinol. 2008;33(3):213–28. [PubMed: 18846027]
64. Kent WD, et al. Increased incidence of differentiated thyroid carcinoma and detection of subclinical disease. CMAJ. 2007;177(11):1357–61. [PMC free article: PMC2072986] [PubMed: 18025426]
65. Mould RC, et al. Immune responses in the thyroid cancer microenvironment: making immunotherapy a possible mission. Endocr Relat Cancer. 2017;24(12):T311–T329. [PubMed: 28912377]
66. Fang W, et al. Tumor-associated macrophages promote the metastatic potential of thyroid papillary cancer by releasing CXCL8. Carcinogenesis. 2014;35(8):1780–7. [PubMed: 24608042]
67. Ryder M, et al. Increased density of tumor-associated macrophages is associated with decreased survival in advanced thyroid cancer. Endocr Relat Cancer. 2008;15(4):1069–74. [PMC free article: PMC2648614] [PubMed: 18719091]
68. Kim S, et al. The Expression of Tumor-Associated Macrophages in Papillary Thyroid Carcinoma. Endocrinol Metab (Seoul). 2013;28(3):192–198. [PMC free article: PMC3811699] [PubMed: 24396678]
69. Jung KY, et al. Cancers with Higher Density of Tumor-Associated Macrophages Were Associated with Poor Survival Rates. J Pathol Transl Med. 2015;49(4):318–24. [PMC free article: PMC4508569] [PubMed: 26081823]
70. Angell TE, et al. BRAF V600E in papillary thyroid carcinoma is associated with increased programmed death ligand 1 expression and suppressive immune cell infiltration. Thyroid. 2014;24(9):1385–93. [PMC free article: PMC4148060] [PubMed: 24955518]

71. Kuo CY, et al. Characteristics of lymphocyte-infiltrating papillary thyroid cancer. J Cancer Res Pract. 2017;4:95–99.
72. Ameziane-El-Hassani R, et al. NADPH oxidase DUOX1 promotes long-term persistence of oxidative stress after an exposure to irradiation. Proc Natl Acad Sci U S A. 2015;112(16):5051–6. [PMC free article: PMC4413347] [PubMed: 25848056]
73. Akdis M, et al. Interleukins, from 1 to 37, and interferon-γ: receptors, functions, and roles in diseases. J Allergy Clin Immunol. 2011;127(3):701–21. [PubMed: 21377040]
74. Jiang G, et al. The prevalence and distribution of Th17 and Tc17 cells in patients with thyroid tumor. Immunol Lett. 2014;162 1 Pt A:68–73. [PubMed: 25068436]
75. Bluestone JA, Herold K, Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. Nature. 2010;464(7293):1293–300. [PMC free article: PMC4959889] [PubMed: 20432533]
76. Anderson MS, Bluestone JA. The NOD mouse: a model of immune dysregulation. Annu Rev Immunol. 2005;23:447–85. [PubMed: 15771578]
77. Makino S, et al. Breeding of a non-obese, diabetic strain of mice. Exp Anim. 1980;29:1–13. [PubMed: 6995140]
78. Erlich H, et al. HLA DR-DQ haplotypes and genotypes and type 1 diabetes risk: analysis of the type 1 diabetes genetics consortium families. Diabetes. 2008;57(4):1084–92. [PMC free article: PMC4103420] [PubMed: 18252895]
79. Nerup J, Lernmark Å. Autoimmunity in insulin-dependent diabetes mellitus. Am J Med. 1981;70:135–41. [PubMed: 7006386]
80. Klemetti P. T-cell mediated immunity in the pathogenesis of insulin-dependent diabetes mellitus. (Academic Dissertation) Helsinki: Hospital for Children and Adolescent, University of Helsinki and National Public Health Institute, 1999.
81. Atkinson M.A., et al. Cellular immunity to a determinant common to glutamate decarboxylase and coxsackie virus in insulin-dependent diabetes. J Clin Invest. 1994;94(5):2125–9. [PMC free article: PMC294659] [PubMed: 7962558]
82. Tough D.F., Borrow P., Sprent J. Induction of bystander T cell proliferation by viruses and type I interferon in vivo. Science. 1996;272(5270):1947–50. [PubMed: 8658169]
83. Katz J.D., Benoist C., Mathis D. T helper cell subsets in insulin-dependent diabetes. Science. 1995;268(5214):1185–8. [PubMed: 7761837]
84. Bottazzo GF, Florin-Christensen A, Doniach D. Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. Lancet. 1974;2(7892):1279–83. [PubMed: 4139522]
85. Ziegler AG, Nepom GT. Prediction and pathogenesis in type 1 diabetes. Immunity. 2010;32(4):468–78. [PMC free article: PMC2861716] [PubMed: 20412757]
86. Burton AR, et al. On the pathogenicity of autoantigen-specific T-cell receptors. Diabetes. 2008;57(5):1321–30. [PubMed: 18299317]
87. Serreze DV, et al. B lymphocytes are critical antigen-presenting cells for the initiation of T cell-mediated autoimmune diabetes in nonobese diabetic mice. J Immunol. 1998;161(8):3912–8. [PubMed: 9780157]
88. Sutherland APR, et al. Interleukin-21 is required for the development of type 1 diabetes in NODmice. Diabetes. 2009;58:1144–55. [PMC free article: PMC2671036] [PubMed: 19208913]
89. Lechleitner M., et al. Relationship of tumor necrosis factor-alpha plasma levels to metabolic control in type 1 diabetes. Diabetes Care. 1999;22(10):1749. [PubMed: 10526750]
90. Zhang J., et al. IFN-gamma induced by IL-12 administration prevents diabetes by inhibiting pathogenic IL-17 production in NOD mice. J Autoimmun. 2012;38(1):20–8. [PubMed: 22186068]
91. Arif S., et al. Peripheral and islet interleukin-17 pathway activation characterizes human autoimmune diabetes and promotes cytokine-mediated beta-cell death. Diabetes. 2011;60(8):2112–9. [PMC free article: PMC3142078] [PubMed: 21659501]
92. Farhan J., et al. Interleukin-6: a possible inflammatory link between vitiligo and type 1 diabetes. Br J Biomed Sci. 2014;71(4):151–7. [PubMed: 25562992]
93. Ururahy M.A., et al. Association of polymorphisms in IL6 gene promoter region with type 1 diabetes and increased albumin-to-creatinine ratio. Diabetes Metab Res Rev. 2014 [PubMed: 25384728]
94. Jacobsen LM, et al. Immune Mechanisms and Pathways Targeted in Type 1 Diabetes. Curr Diab Rep. 2018;18(10):90. [PubMed: 30168021]
95. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature. 2001;414(6865):782–7. [PubMed: 11742409]
96. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010;87(1):4–14. [PubMed: 19896746]
97. Varma V., et al. Muscle inflammatory response and insulin resistance: synergistic interaction between macrophages and fatty acids leads to impaired insulin action. Am J Physiol Endocrinol Metab. 2009;296(6):E1300–10. [PMC free article: PMC2692398] [PubMed: 19336660]
98. Ehses J.A., et al. Macrophages, cytokines and beta-cell death in Type 2 diabetes. Biochem Soc Trans. 2008;36(Pt 3):340–2. [PubMed: 18481953]
99. Shoelson S.E., Lee J., Goldfine A.B. Inflammation and insulin resistance. J Clin Invest. 2006;116(7):1793–801. [PMC free article: PMC1483173] [PubMed: 16823477]

100. Sell H, Habich C, Eckel J. Adaptive immunity in obesity and insulin resistance. Nat Rev Endocrinol. 2012;8(12):709–16. [PubMed: 22847239]
101. Nikolajczyk BS, et al. State of the union between metabolism and the immune system in type 2 diabetes. Genes Immun. 2011;12(4):239–50. [PubMed: 21390053]
102. Duncan B.B., et al. Factor VIII and other hemostasis variables are related to incident diabetes in adults. The Atherosclerosis Risk in Communities (ARIC) Study. Diabetes Care. 1999;22(5):767–72. [PubMed: 10332679]
103. Schmidt M.I., et al. Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities study): a cohort study. Lancet. 1999;353(9165):1649–52. [PubMed: 10335783]
104. Festa A., et al. Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the insulin resistance atherosclerosis study. Diabetes. 2002;51(4):1131–7. [PubMed: 11916936]
105. Eliasson M.C., et al. High levels of tissue plasminogen activator (tPA) antigen precede the development of type 2 diabetes in a longitudinal population study. The Northern Sweden MONICA study. Cardiovasc Diabetol. 2003;2:19. [PMC free article: PMC328088] [PubMed: 14690546]
106. Meigs J.B., et al. Hemostatic markers of endothelial dysfunction and risk of incident type 2 diabetes: the Framingham Offspring Study. Diabetes. 2006;55(2):530–7. [PubMed: 16443791]
107. Lee C.C., et al. Association of C-reactive protein with type 2 diabetes: prospective analysis and meta-analysis. Diabetologia. 2009;52(6):1040–7. [PubMed: 19326095]
108. Herder C., et al. Chemokines as risk factors for type 2 diabetes: results from the MONICA/KORA Augsburg study, 1984-2002. Diabetologia. 2006;49(5):921–9. [PubMed: 16532324]
109. Vgontzas A.N., et al. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab. 2000;85(3):1151–8. [PubMed: 10720054]
110. Vgontzas A.N., et al. Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. J Clin Endocrinol Metab. 1997;82(5):1313–6. [PubMed: 9141509]
111. Vozarova B, et al. Circulating interleukin-6 in relation to adiposity, insulin action, and insulin secretion. Obes Res. 2001;9(7):414–7. [PubMed: 11445664]
112. Kern P.A., et al. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am J Physiol Endocrinol Metab. 2001;280(5):E745–51. [PubMed: 11287357]
113. Pradhan AD, et al. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA. 2001;286(3):327–34. [PubMed: 11466099]
114. Hotamisligil G.S., et al. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest. 1995;95(5):2409–15. [PMC free article: PMC295872] [PubMed: 7738205]
115. Kirwan J.P., et al. TNF-alpha is a predictor of insulin resistance in human pregnancy. Diabetes. 2002;51(7):2207–13. [PubMed: 12086951]
116. Ruan H, et al. Profiling gene transcription in vivo reveals adipose tissue as an immediate target of tumor necrosis factor-alpha: implications for insulin resistance. Diabetes. 2002;51(11):3176–88. [PubMed: 12401708]
117. Hotamisligil GS. The role of TNFalpha and TNF receptors in obesity and insulin resistance. J Intern Med. 1999;245(6):621–5. [PubMed: 10395191]
118. Vilcek J., Lee T.H. Tumor necrosis factor. New insights into the molecular mechanisms of its multiple actions. J Biol Chem. 1991;266(12):7313–6. [PubMed: 1850405]
119. Hotamisligil G.S., et al. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. Science. 1996;271(5249):665–8. [PubMed: 8571133]
120. Hotamisligil G.S., Shargill N.S., Spiegelman B.M. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science. 1993;259(5091):87–91. [PubMed: 7678183]
121. Cornelius P., et al. Monokine regulation of glucose transporter mRNA in L6 myotubes. Biochem Biophys Res Commun. 1989;165(1):429–36. [PubMed: 2556143]
122. Stephens J.M., Pekala P.H. Transcriptional repression of the GLUT4 and C/EBP genes in 3T3-L1 adipocytes by tumor necrosis factor-alpha. J Biol Chem. 1991;266(32):21839–45. [PubMed: 1939208]
123. Feingold K.R., Grunfeld C. Role of cytokines in inducing hyperlipidemia. Diabetes. 1992;41 Suppl 2:97–101. [PubMed: 1526345]
124. Grunfeld C., Feingold K.R. The metabolic effects of tumor necrosis factor and other cytokines. Biotherapy. 1991;3(2):143–58. [PubMed: 2054255]
125. Spiegelman B.M., Hotamisligil G.S. Through thick and thin: wasting, obesity, and TNF alpha. Cell. 1993;73(4):625–7. [PubMed: 8500160]
126. Margoni A., et al. Serum leptin, adiponectin and tumor necrosis factor-alpha in hyperlipidemic rats with/without concomitant diabetes mellitus. Mol Med. 2011;17(1-2):36–40. [PMC free article: PMC3022981] [PubMed: 20838752]
127. Fernandez-Real J.M., et al. Interleukin-6 gene polymorphism and lipid abnormalities in healthy subjects. J Clin Endocrinol

Metab. 2000;85(3):1334–9. [PubMed: 10720087]
128. Greenberg A.S., et al. Interleukin 6 reduces lipoprotein lipase activity in adipose tissue of mice in vivo and in 3T3-L1 adipocytes: a possible role for interleukin 6 in cancer cachexia. Cancer Res. 1992;52(15):4113–6. [PubMed: 1638523]
129. Meigs J.B., et al. Association of oxidative stress, insulin resistance, and diabetes risk phenotypes: the Framingham Offspring Study. Diabetes Care. 2007;30(10):2529–35. [PubMed: 17586736]
130. Rosen P., et al. The role of oxidative stress in the onset and progression of diabetes and its complications: a summary of a Congress Series sponsored by UNESCO-MCBN, the American Diabetes Association and the German Diabetes Society. Diabetes Metab Res Rev. 2001;17(3):189–212. [PubMed: 11424232]
131. Hasnain S.Z., et al. Glycemic control in diabetes is restored by therapeutic manipulation of cytokines that regulate beta cell stress. Nat Med. 2014;20(12):1417–26. [PubMed: 25362253]
132. Huma ZE, et al. Key determinants of selective binding and activation by the monocyte chemoattractant proteins at the chemokine receptor CCR2. Sci Signal. 2017;10(480) [PubMed: 28536301]
133. Catalán V, et al. Proinflammatory cytokines in obesity: impact of type 2 diabetes mellitus and gastric bypass. Obes Surg. 2007;17(11):1464–74. [PubMed: 18219773]
134. Townsend SA, Newsome PN. Review article: new treatments in non-alcoholic fatty liver disease. Aliment Pharmacol Ther. 2017;46(5):494–507. [PubMed: 28677333]
135. Chistiakov D. A., et al. Potential of anti-inflammatory agents for treatment of atherosclerosis. Experimental and Molecular Pathology. 2018;104(2):114–124. [PubMed: 29378168]
136. França CN, et al. Monocyte subtypes and the CCR2 chemokine receptor in cardiovascular disease. Clin Sci (Lond). 2017;131(12):1215–1224. [PubMed: 28566450]
137. Gokulakrishnan K, et al. Effect of lifestyle improvement program on the biomarkers of adiposity, inflammation and gut hormones in overweight/obese Asian Indians with prediabetes. Acta Diabetol. 2017;54(9):843–852. [PubMed: 28620678]
138. Goldfine AB, Shoelson SE. Therapeutic approaches targeting inflammation for diabetes and associated cardiovascular risk. J Clin Invest. 2017;127(1):83–93. [PMC free article: PMC5199685] [PubMed: 28045401]
139. Larsen CM, et al. Interleukin-1-receptor antagonist in type 2 diabetes mellitus. N Engl J Med. 2007;356(15):1517–1526. [PubMed: 17429083]
140. Ridker PM, et al. Effects of interleukin-1β inhibition with canakinumab on hemoglobin A1c, lipids, C-reactive protein, interleukin-6, and fibrinogen: a phase IIb randomized, placebo-controlled trial. Circulation. 2012;126(23):2739–2748. [PubMed: 23129601]
141. Wu TC, et al. Tocilizumab, a Humanized Monoclonal Antibody Against the Interleukin-6 Receptor, Inhibits High Glucose-Induced Vascular Smooth Muscle Cell Migration Through Mitogen-Activated Protein Kinase Signaling Pathways. J Interferon Cytokine Res. 2018. Epub ahead of print. [PubMed: 30383519]
142. Pietschmann P, et al. Immunology of Osteoporosis: A Mini-Review. Gerontology. 2016;62(2):128–37. [PMC free article: PMC4821368] [PubMed: 26088283]
143. Weitzmann MN, Pacifici R. Estrogen deficiency and bone loss: an inflammatory tale. J Clin Invest. 2006;116(5):1186–94. [PMC free article: PMC1451218] [PubMed: 16670759]
144. Weitzmann MN, Ofotokun I. Physiological and pathophysiological bone turnover -role of the immune system. Nat. Rev. Endocrinol. 2016;12:518–532. [PMC free article: PMC5857945] [PubMed: 27312863]
145. Xiao Y., et al. Identification of the common origins of osteoclasts, macrophages, and dendritic cells in human hematopoiesis. Stem Cell Rep. 2015;4(6):984–994. [PMC free article: PMC4471835] [PubMed: 26004632]
146. Walsh MC, Choi Y. Biology of the RANKL-RANK-OPG system in immunity, bone, and beyond. Front Immunol. 2014;5:511. [PMC free article: PMC4202272] [PubMed: 25368616]
147. Soysa NS, et al. Osteoclast formation and differentiation: an overview. J Med Dent Sci. 2012;59:65–74. [PubMed: 23897045]
148. Amarasekara Dulshara Sachini, et al. Regulation of Osteoclast Differentiation by Cytokine Networks. Immune Netw. 2018;18(1):e8. [PMC free article: PMC5833125] [PubMed: 29503739]
149. Rauner M, Sipos W, Pietschmann P. Osteoimmunology. Int Arch Allergy Immunol. 2007;143:31–48. [PubMed: 17191007]
150. Cenci S, et al. Estrogen deficiency induces bone loss by enhancing T-cell production of TNF-alpha. J Clin Invest. 2001;06:1229–37. [PMC free article: PMC381439] [PubMed: 11086024]
151. Srivastava RK, Dar HY. Front Immunol. 2018;9:657. and Mishra PK3. Immunoporosis: Immunology of Osteoporosis-Role of T Cells. [PMC free article: PMC5895643] [PubMed: 29675022]
152. Pacifici R. T cells: critical bone regulators in health and disease. Bone. 2010;47:461–71. [PMC free article: PMC2926258] [PubMed: 20452473]
153. Titanji K, et al. Dysregulated B cell expression of RANKL and OPG correlates with loss of bone mineral density in HIV infection. PLoS Pathog. 2014;10:e1004497. [PMC free article: PMC4231117] [PubMed: 25393853]
154. Manolagas S.C., et al. Estrogen, cytokines, and the control of osteoclast formation and bone resorption in vitro and in vivo. Osteoporos Int. 1993;3 Suppl 1:114–6. [PubMed: 8461536]

155. Ishimi Y., et al. IL-6 is produced by osteoblasts and induces bone resorption. J Immunol. 1990;145(10):3297–303. [PubMed: 2121824]
156. Lowik C.W., et al. Parathyroid hormone (PTH) and PTH-like protein (PLP) stimulate interleukin-6 production by osteogenic cells: a possible role of interleukin-6 in osteoclastogenesis. Biochem Biophys Res Commun. 1989;162(3):1546–52. [PubMed: 2548501]
157. Klein B., et al. Murine anti-interleukin-6 monoclonal antibody therapy for a patient with plasma cell leukemia. Blood. 1991;78(5):1198–204. [PubMed: 1715218]
158. Roodman G.D., et al. Interleukin 6. A potential autocrine/paracrine factor in Paget's disease of bone. J Clin Invest. 1992;89(1):46–52. [PMC free article: PMC442817] [PubMed: 1729280]
159. Kotake S., et al. Interleukin-6 and soluble interleukin-6 receptors in the synovial fluids from rheumatoid arthritis patients are responsible for osteoclast-like cell formation. J Bone Miner Res. 1996;11(1):88–95. [PubMed: 8770701]
160. Anastasilakis AD, et al. Bone metabolism in Langerhans cell histiocytosis. Endocr Connect. 2018;7(7):R246–R253. [PMC free article: PMC6063875] [PubMed: 29967185]
161. Martin T.J., et al. Leukaemia inhibitory factor and bone cell function. Ciba Found Symp. 1992;167:141–50. [PubMed: 1425010]
162. Walsh MC, et al. Osteoimmunology: interplay between the immune system and bone metabolism. Annu Rev Immunol. 2006;24:33–63. [PubMed: 16551243]
163. Ruscitti P, et al. The role of IL-1β in the bone loss during rheumatic diseases. Mediators Inflamm. 2015;2015:782382. [PMC free article: PMC4410538] [PubMed: 25954061]
164. Wei S, et al. IL-1 mediates TNF-induced osteoclastogenesis. J Clin Invest. 2005;115:282–290. [PMC free article: PMC544608] [PubMed: 15668736]
165. Cenci S, et al. Estrogen deficiency induces bone loss by increasing T cell proliferation and lifespan through IFN-gamma-induced class II transactivator. Proc Natl Acad Sci U. S. A. 2003;100:10405–10410. [PMC free article: PMC193574] [PubMed: 12923292]
166. Miyaura C, et al. Increased B-lymphopoiesis by interleukin 7 induces bone loss in mice with intact ovarian function: similarity to estrogen deficiency. Proc Natl Acad Sci U. S. A. 1997;94:9360–9365. [PMC free article: PMC23193] [PubMed: 9256487]
167. Eghbali-Fatourechi G, et al. Role of RANK ligand in mediating increased bone resorption in early postmenopausal women. J. Clin. Invest. 2003;111:1221–1230. [PMC free article: PMC152939] [PubMed: 12697741]
168. Cenci S, et al. Estrogen deficiency induces bone loss by enhancing T-cell production of TNF-alpha. J. Clin. Invest. 2000;106:1229–1237. [PMC free article: PMC381439] [PubMed: 11086024]
169. Pacifici R, et al. Effect of surgical menopause and estrogen replacement on cytokine release from human blood mononuclear cells. Proc Natl Acad Sci U. S. A. 1991;88:5134–5138. [PMC free article: PMC51826] [PubMed: 2052592]
170. Tyagi AM, et al. Enhanced immunoprotective effects by anti-IL-17 antibody translates to improved skeletal parameters under estrogen deficiency compared with anti-RANKL and anti-TNF-alpha antibodies. J Bone Miner Res. 2014;29:1981–1992. [PubMed: 24677326]
171. Tyagi AM, et al. Estrogen deficiency induces the differentiation of IL-17 secreting Th17 cells: a new candidate in the pathogenesis of osteoporosis. PLoS One. 2012;7:e44552. [PMC free article: PMC3438183] [PubMed: 22970248]
172. DeSelm CJ, et al. IL-17 mediates estrogen-deficient osteoporosis in an Act1-dependent manner. J. Cell. Biochem. 2012;113:2895–2902. [PMC free article: PMC3640304] [PubMed: 22511335]
173. Onal M, et al. Receptor activator of nuclear factor kappaB ligand (RANKL) protein expression by B lymphocytes contributes to ovariectomy-induced bone loss. J. Biol. Chem. 2012;287:29851–29860. [PMC free article: PMC3436192] [PubMed: 22782898]
174. Siddiqi A., et al. Tri-iodothyronine regulates the production of interleukin-6 and interleukin-8 in human bone marrow stromal and osteoblast-like cells. J Endocrinol. 1998;157(3):453–61. [PubMed: 9691978]
175. Siddiqi A., et al. Serum cytokines in thyrotoxicosis. J Clin Endocrinol Metab. 1999;84(2):435–9. [PubMed: 10022397]
176. Sun L., et al. Genetic confirmation for a central role for TNFalpha in the direct action of thyroid stimulating hormone on the skeleton. Proc Natl Acad Sci U S A. 2013;110(24):9891–6. [PMC free article: PMC3683712] [PubMed: 23716650]
177. Baliram R., et al. Hyperthyroid-associated osteoporosis is exacerbated by the loss of TSH signaling. J Clin Invest. 2012;122(10):3737–41. [PMC free article: PMC3461920] [PubMed: 22996689]
178. Grey A., et al. Circulating levels of interleukin-6 and tumor necrosis factor-alpha are elevated in primary hyperparathyroidism and correlate with markers of bone resorption--a clinical research center study. J Clin Endocrinol Metab. 1996;81(10):3450–4. [PubMed: 8855783]
179. Grey A., et al. A role for interleukin-6 in parathyroid hormone-induced bone resorption in vivo. Endocrinology. 1999;140(10):4683–90. [PubMed: 10499526]
180. Hory BG, et al. Absence of response to human parathyroid hormone in athymic mice grafted with human parathyroid adenoma, hyperplasia or parathyroid cells maintained in culture. J Endocrinol. Invest. 2000;23:273–279. [PubMed: 10882144]
181. Bedi B, et al. Silencing of parathyroid hormone (PTH) receptor 1 in T cells blunts the bone anabolic activity of PTH. Proc Natl Acad Sci U. S. A. 2012;109:E725–733. [PMC free article: PMC3311391] [PubMed: 22393015]

182. Weitzmann MN. Bone and the Immune System. Toxicol Pathol. 2017;45(7):911–924. [PMC free article: PMC5749254] [PubMed: 29046115]
183. Hueston C.M., Deak T. The inflamed axis: the interaction between stress, hormones, and the expression of inflammatory-related genes within key structures comprising the hypothalamic-pituitary-adrenal axis. Physiol Behav. 2014;124:77–91. [PubMed: 24184413]
184. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med. 1995;332:1351–1362. [PubMed: 7715646]
185. Renner U, et al. Intrahypophyseal Immune-Endocrine Interactions: Endocrine Integration of the Inflammatory Inputs. Front Horm Res. 2017;48:37–47. [PubMed: 28245450]
186. Laflamme N., Lacroix S., Rivest S. An essential role of interleukin-1beta in mediating NF-kappaB activity and COX-2 transcription in cells of the blood-brain barrier in response to a systemic and localized inflammation but not during endotoxemia. J Neurosci. 1999;19(24):10923–30. [PubMed: 10594073]
187. Nadeau S., Rivest S. Regulation of the gene encoding tumor necrosis factor alpha (TNF-alpha) in the rat brain and pituitary in response in different models of systemic immune challenge. J Neuropathol Exp Neurol. 1999;58(1):61–77. [PubMed: 10068315]
188. Perlstein R.S., et al. Synergistic roles of interleukin-6, interleukin-1, and tumor necrosis factor in the adrenocorticotropin response to bacterial lipopolysaccharide in vivo. Endocrinology. 1993;132(3):946–52. [PubMed: 8382602]
189. Sothern R.B., et al. Circadian characteristics of interleukin-6 in blood and urine of clinically healthy men. In Vivo. 1995;9(4):331–9. [PubMed: 8555432]
190. Silverman MN, Sternberg EM. Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. Ann N Y Acad Sci. 2012;1261:55–63. [PMC free article: PMC3572859] [PubMed: 22823394]
191. Papanicolaou D.A., et al. Acute glucocorticoid deficiency is associated with plasma elevations of interleukin-6: does the latter participate in the symptomatology of the steroid withdrawal syndrome and adrenal insufficiency? J Clin Endocrinol Metab. 1996;81(6):2303–6. [PubMed: 8964868]
192. Marin P., et al. Cortisol secretion in relation to body fat distribution in obese premenopausal women. Metabolism. 1992;41(8):882–6. [PubMed: 1640867]
193. Imura H., Fukata J., Mori T. Cytokines and endocrine function: an interaction between the immune and neuroendocrine systems. Clin Endocrinol (Oxf). 1991;35(2):107–15. [PubMed: 1934523]
194. Path G., et al. Interleukin-6 and the interleukin-6 receptor in the human adrenal gland: expression and effects on steroidogenesis. J Clin Endocrinol Metab. 1997;82(7):2343–9. [PubMed: 9215317]
195. Weber M.M., et al. Interleukin-3 and interleukin-6 stimulate cortisol secretion from adult human adrenocortical cells. Endocrinology. 1997;138(5):2207–10. [PubMed: 9112422]
196. Auernhammer C.J., Melmed S. Leukemia-inhibitory factor-neuroimmune modulator of endocrine function. Endocr Rev. 2000;21(3):313–45. [PubMed: 10857556]
197. Bunn SJ, Ait-Ali D, Eiden LE. Immune-Neuroendocrine Integration at the Adrenal Gland: Cytokine Control of the Adrenomedullary Transcriptome. J Mol Neurosci. 2012;48(2):413–9. [PMC free article: PMC3488108] [PubMed: 22421803]
198. Ait-Ali D, et al. Tumor necrosis factor (TNF)-alpha persistently activates nuclear factor-kappaB signaling through the type 2 TNF receptor in chromaffin cells: implications for long-term regulation of neuropeptide gene expression in inflammation. Endocrinology. 2008;149:2840–2852. [PMC free article: PMC2408812] [PubMed: 18292192]
199. Douglas SA, Bunn SJ. Interferon-alpha signalling in bovine adrenal chromaffin cells: involvement of signal-transducer and activator of transcription 1 and 2, extracellular signal-regulated protein kinases 1/2 and serine 31 phosphorylation of tyrosine hydroxylase. J Neuroendocrinol. 2009;21:200–207. [PubMed: 19207826]
200. Rosmaninho-Salgado J, et al. Regulation of catecholamine release and tyrosine hydroxylase in human adrenal chromaffin cells by interleukin-1beta: role of neuropeptide Y and nitric oxide. J Neurochem. 2009;109:911–922. [PubMed: 19309436]
201. Ait-Ali D, et al. The proinflammatory cytokines tumor necrosis factor-alpha and interleukin-1 stimulate neuropeptide gene transcription and secretion in adrenochromaffin cells via activation of extracellularly regulated kinase 1/2 and p38 protein kinases, and activator protein-1 transcription factors. Mol Endocrinol. 2004;18:1721–1739. [PubMed: 15087472]
202. Eskay RL, Eiden LE. Interleukin-1 alpha and tumor necrosis factor-alpha differentially regulate enkephalin, vasoactive intestinal polypeptide, neurotensin, and substance P biosynthesis in chromaffin cells. Endocrinology. 1992;130:2252–2258. [PubMed: 1372239]
203. Turquier V, et al. Proinflammatory cytokines TNF-alpha and IL-1alpha stimulate neuropeptide gene expression in adrenochromaffin cells. Ann N Y Acad Sci. 2002;971:45–48. [PubMed: 12438087]
204. Rosmaninho-Salgado J, et al. Regulation of catecholamine release and tyrosine hydroxylase in human adrenal chromaffin cells by interleukin-1beta: role of neuropeptide Y and nitric oxide. J Neurochem. 2009;109:911–922. [PubMed: 19309436]
205. Jenkins DE, et al. Interleukin-6-mediated signaling in adrenal medullary chromaffin cells. J Neurochem. 2016;139(6):1138–1150. [PMC free article: PMC5177545] [PubMed: 27770433]

206. Fan J., et al. Interleukin-6 increases intracellular Ca2+ concentration and induces catecholamine secretion in rat carotid body glomus cells. J Neurosci Res. 2009;87(12):2757–62. [PubMed: 19396873]

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