Inflammasome activation as a link between obesity and thyroid disorders: Implications for an integrated clinical management

Rosario Le Moli*, Veronica Vella, Dario Tumino, Tommaso Piticchio, Adriano Naselli, Antonino Belfiore and Francesco Frasca

Endocrinology Unit, Department of Clinical and Experimental Medicine, University of Catania, Garibaldi-Nesima Hospital, Catania, Italy

Obesity is strongly associated with chronic low-grade inflammation. Obese patients have an increased risk to develop thyroid autoimmunity and to become hypothyroid, suggesting a pathogenetic link between obesity, inflammation and autoimmunity. Moreover, type 2 diabetes and dyslipidemia, also characterized by low-grade inflammation, were recently associated with more aggressive forms of Graves’ ophthalmopathy. The association between obesity and autoimmune thyroid disorders may also go in the opposite direction, as treating autoimmune hyper and hypothyroidism can lead to weight gain. In addition, restoration of euthyroidism by L-T4 replacement therapy is more challenging in obese athyreotic patients, as it is difficult to maintain thyrotropin stimulation hormone (TSH) values within the normal range. Intriguingly, pro-inflammatory cytokines decrease in obese patients after bariatric surgery along with TSH levels. Moreover, the risk of thyroid cancer is increased in patients with thyroid autoimmune disorders, and is also related to the degree of obesity and inflammation. Molecular studies have shown a relationship between the low-grade inflammation of obesity and the activity of intracellular multiprotein complexes typical of immune cells (inflammasomes). We will now highlight some clinical implications of inflammasome activation in the relationship between obesity and thyroid disease.

KEYWORDS
obesity, inflammasome, thyroid autoimmunity, weight regain, thyroid cancer, L-T4 therapy
Introduction

Obesity is a public health concern with a prevalence rapidly increasing in the last ten years from 3.2% to 10.8% in adult men and from 6.4% to 14.9% in adult women (1). Adipose tissue should be considered an endocrine organ comprising various cell types such as adipocytes, preadipocytes and immune cells (2). Adipocytes are prone to secrete pro-inflammatory adipokines, such as tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), and interleukin-6 (IL-6), which recruit immune cells and amplify the inflammation process (3, 4). These mechanisms may play a major role in obesity-related disorders, including atherosclerosis, diabetes, neurodegenerative diseases and cancer (5–7). New emerging data reveal a relationship between the low-grade inflammatory state of obesity and inflammasome activation level (8, 9). Inflammasomes are intracellular multiprotein complexes typical of immune cells, such as monocytes and macrophages, which mediate the first line of defense in response to both sterile (absence of microbial and virus particles) and non-sterile (microbial and/or virus infection) injuries, leading to the processing and release of pro-inflammatory cytokines (10–16). The inflammasome oligomeric structure includes three elements: I) NOD-like receptor (NLR), that is a stress signal receptor (17–19). NLRs can contain a Pirin Domain 3 (NLRP3) or a caspase recruitment domain (NLRC4) and are present in several cells of different tissues; II) adaptor protein, that is an apoptosis associated speck-like protein containing caspase activation recruitment domain (ASC); III) pro-caspase-1 (pro-CASP1), pro-IL-β and pro-IL-18 (Figure 1).

A further mechanism that contributes to the background activation of inflammasome in obese patients is the reduced efficiency of innate immunity caused by the inhibition of autophagic processes (20, 21). This mechanism contributes to the activation of the NLRP3 inflammasome, which in turn (22) enhances chronic low-grade inflammation in adipose tissue (23, 24), thereby resulting in systemic insulin resistance and metabolic impairment (25). Here we highlight some emerging clinically relevant implications of inflammasome activation and chronic low-grade inflammation associated with obesity for patients with thyroid disorders.

Obesity, inflammasome and immune related thyroid diseases

Recent epidemiological and experimental data provided evidence of a bidirectional interaction between obesity and thyroid autoimmunity (26–28). In particular, obesity is associated with an enhanced risk of hypothyroidism and an increased risk of developing anti-thyroperoxidase antibodies (TPOAbs) (27). One prospective study of 783 obese patients referred to bariatric surgery reported a prevalence of 17.1% and 12.3% of autoimmune thyroiditis and autoimmune hypothyroidism, respectively (29). This association was confirmed by the National Health and Nutrition Examination Survey (NHANES III) which described the presence of TPOAbs in 11.3% and hypothyroidism in 4.6% of 17,353 patients (30). Autoimmune thyroid disease (AITD), including Graves’ disease (GD) and Hashimoto’s disease (HT), include thyroid disorders characterized by an
immune reaction against thyroid autoantigens that occur in individuals with a distinct genetic background after exposure to certain environmental factors (31–36). GD and HT share similar pathological features characterized by lymphocyte infiltration of the thyroid tissue and antibodies production (37). The relationship between obesity and thyroid autoimmunity is not only based on epidemiological aspects but also on common pathogenetic mechanisms. A major player of this association is insulin resistance (IR), that is present in 15.5 - 46% of the obese patients (38). IR attenuates the insulin-stimulated phosphoinositide 3-kinase (PI3K) signaling pathway, causing hyperinsulinemia and a variety of adverse effects, including increased oxidative stress due to the production of reactive oxygen radical species (ROS) which activate the inflammasome complex in different tissues (25, 39) and reduces the vasoactive/anti-inflammatory effect of nitric oxide (NO) (39, 40). A variable degree of leptin resistance (LR) is usually associated with IR and obesity and can be considered a second mechanism in the interplay between obesity and thyroid disorders. Indeed, chronic exposure of endothelial cells to increased circulating levels of leptin also leads to a decrease in NO production (41). In addition, ROS induce pro-inflammatory MCP-1 expression which further enhances leukocyte infiltration into vascular cells. Chronic activation of inflammatory response contributes to the impairment of a correct immune response to exogenous antigens and to the persistence of autoimmune processes in predisposed subjects (42–44). This concept is supported by the observation that increased NLR inflammasome activity in both obese patients and experimental animals can play a major role in macrophage recruitment and immune activation (45). The third mechanism is the increased oxidation of low-density lipoproteins (LDL) occurring in obese patients with IR. Several lines of evidence indicate that increased oxidized low-density lipoproteins (oxLDLc) and cholesterol crystals can trigger the activation of NLR inflammasome, that, in turn, leads to a tonic activation of innate immune system (45, 46) (Figure 2). Hence, insulin/leptin system dysregulation along with oxLDLc increase and inflammasome activation are associated with impaired immunological tolerance and metabolic changes favoring thyroid autoimmunity (41, 45–48). The complete NLR-mediated inflammasome activation in thyroid cells is a complex event that involves the engagement of the tool-like receptors (TLRs) and the recruitment of the myddosome complex, which triggers downstream nuclear factor - KB (NF-kB) cell signaling, resulting in the increased levels of NLR and pro-ILs (49, 50) (Figure 3).

More specifically, low-grade inflammation causes a predominance of CD4 + T helper cells over the proinflammatory Th17 subsets, increasing the IL-1β production which plays a major role in the pathogenesis of Hashimoto’s thyroiditis (HT) (40, 51, 52). It is interesting to note that both human and rat thyroid cells express functional TLRs on their surface and these receptors may directly bind both endogenous and exogenous ‘danger molecules’, thereby promptly activating the innate immune system. Several experimental evidences support the idea that the innate immune response is linked to thyroid tissue damage. Thyroid cell damage leads to the release of intracellular proteins that can be recognized by antigen-presenting cells (APC), thereby

---

**FIGURE 2**
Interaction of oxidized low density lipoprotein cholesterol (oxLDLc) with cells of innate immunity. IL - 1β = Interleukin 1β, IL-15 = interleukin 18.
activating acquired immune response, which, in turn, amplifies thyroid cell damage and ultimately causes thyroid tissue destruction (35, 53–55) (Figure 4).

Thyroid hormone are another important component of the putative bidirectional cross-talk between obesity and thyroid immunity process. All clinical conditions causing altered thyroid hormone levels may contribute to the extent of activation of inflammation and immunity response. On the other hand, alterations in thyroid hormone levels may favor obesity, atherosclerosis, and inflammation. Recent studies indicate that triiodothyronine (T3) negatively modulates NLR inflammasome and macrophage function. Conversely, low levels of thyroxine (T4) may contribute to inflammation and immune response activation in hypothyroid patients (56–59). This effect of T4 may also occur through an extra-genomic pathway by binding the cell membrane integrin receptor αvβ3, which, in turn, may modulate the immune response via the activation of signaling pathways including mitogen-activated protein kinase (MAPK), cyclooxygenase 2 (COX-2) and hypoxia factor 1 alpha (HIF-1α), all converging into inflammasome activation (60). Taken together, these studies suggest that thyroid hormone effect on immune response is indirect and can be mediated by the combination of both genomic and nongenomic actions in specific cellular/clinical contexts (61) and these mechanisms are of primary importance in obese patients who frequently display reduced T4 levels (56).

Key points

Available evidence suggests a two-way interaction between obesity and inflammation and autoimmunity. In obese, insulin-resistant patients, careful attention to thyroid hormone
homeostasis can prevent worsening of metabolic conditions and prevent thyroid dysfunction.

**Obesity, inflammasome and thyroid eyes disease**

Graves’ ophthalmopathy (GO) is an autoimmune thyroid related eye disease (TED) occurring in about 25% of patients with Graves’ disease (GD). Elevated levels of thyroid stimulating receptor antibodies (TRAbs) are considered a risk factor for severe GO. Gender, age, smoking, and duration of hyperthyroidism are additional risk factors for the severity of GO (62–64). Recently, diabetes mellitus (DM) has been related to GO severity. Moreover, the prevalence of Type 1 diabetes is higher in patients with GO than in the normal population and dysthyroid optic neuropathy (DON) occurs more frequently in patients with both GO and DM and have a worse prognosis than in those with GO alone (65). Moreover, one important study showed evidence that DM and cigarette smoking are significant predictors of severe GO. In particular, DM was a stronger determinant of GO severity (p=0.001) and significant predictor of diplopia (p= 0.03).

Additionally, in Graves’ patients with Type II diabetes (T2DM), GO preceded the onset of hyperthyroidism more frequently than in control patients (p < 0.05). GO severity was significantly associated to T2DM with a duration longer than five years (Odds Ratio = 4.9; p = 0.045) and the presence of micro and macro vascular complications (Odds Ratio = 4.8; p = 0.048). GO severity was also related to patient overweight (BMI > 26) (66). These clinical evidences suggest that GO may be related to a peculiar pathophysiologic background linked to the metabolic syndrome and obesity. Indeed, insulin-resistance and compensatory hyperinsulinemia in obese patients may exert proliferative effects on human orbital preadipocytes/fibroblasts via the phosphatidylinositol 3-kinase (PI3-K) and the mammalian target of rapamycin (mTOR) signaling pathways (67). In addition, elevated levels of insulin increase IGF-1 bioavailability, induce overexpression of the IGF-I receptors (IGF-IR) in orbital preadipocytes/fibroblasts and enhance IGF-IR/TSHR cross-talk thereby contributing to the severity of GO (68–72). Systemic low-grade chronic inflammation causes NLR inflammasome activation in fat tissues and production of neurotoxic factors such as IL-1β and TNF-α, that are determinants of GO pathogenesis (73). Moreover, low-density lipoproteins cholesterol (LDLc) and their oxidized forms are increased in obese and diabetic patients leading to reduced or incomplete autophagic processes (74) and to the activation of NLR inflammasome in macrophage cells. In GO of obese patients, activated macrophage population within the orbital microenvironment may increase the secretion of IGF-1 by fibroblasts thereby promoting adipogenesis, hyaluronan synthesis and the expansion of soft orbital tissues (50, 75). Stein et al. reported that statins are able to reduce the onset of GO in patients with GD. A recent cross-sectional study indicated that total and LDL cholesterol is associated with GO activity, suggesting that high serum cholesterol level is a risk factor for GO development (64, 76). Considering that GO is an inflammatory and autoimmune response against thyroid and orbital autoantigens, statins may protect from GO presentation and activity owing to their anti-inflammatory and hypolipemic action. Hypercholesterolemia can cause chronic inflammation per se through oxLDL by modulating inflammasome activity via TLRs and increasing the expression of dipeptidyl dipeptidase IV (DPP4) in macrophages. Raised DPP4 activity leads to an increase of CD36+ cells, which is a hallmark of the atherosclerotic inflammatory process in obese and insulin resistant patients (50). In particular, LDLc may attenuate corticosteroid transcriptional and translational activities thereby reducing their anti-inflammatory efficacy in GO (77). Taken together, these observations support the notion that chronic low-grade inflammation and inflammasome activation in dysmetabolic subjects may sustain the autoimmune process underlying TED pathogenesis and their clinical and phenotypic expression.

**Key points**

Obesity, diabetes and hypercholesterolemia contribute to GO disease. The use of statins and strict cholesterol control should be considered as part of the GO treatment plan.

**Therapy of hyperthyroidism, cytokines, and weight gain**

It is a common observation that hyperthyroidism is associated with weight loss in most cases, while approximately 10% of hyperthyroid patients experience weight increase. Therefore, restoration of euthyroidism usually results into weight regain that is sometimes excessive. The mechanism underlying this phenomenon is not entirely clear and it is commonly believed that the transition from hyper to euthyroidism can promote obesity in predisposed patients (78). On the other hand, some studies tried to identify specific risk factors for such weight increase that may include the severity of the autoimmune process in Graves’ disease (78, 79). Data regarding post-therapy body composition (lean and fat body mass) in terms of preferential accumulation and timing are still conflicting (79, 80). However, recent studies focus on the effect
of dietary programs in the prevention of weight gain compared to standard care (81). Taken together, these studies strongly suggest that weight regain after treatment of hyperthyroidism is not only caused by a decreased catabolic effect of thyrotoxicosis, but rather linked to additional, independent mechanisms (82). This hypothesis is supported by the observation of a relationship between treatment modalities for hyperthyroidism and weight regain, with a greater effect for radioiodine and surgery, compared to anti-thyroid drugs. Indeed, several studies indicate a statistically and clinically significant excess of weight gain after thyroidectomy for hyperthyroidism (83). However, this observation is mitigated by studies showing body weight gain in all thyroidectomized patients regardless of underlying thyroid disorder (83, 84). Accordingly, excessive body weight gain after thyroidectomy has been attributed to deficient replacement therapy with L-T4 and to an imbalance of thyroid hormone homeostasis due to poor tissue conversion of T4 to T3 (85). However, several studies indicate that radioiodine (RAI) therapy is also associated with significant weight gain (by 5-6 kg on average over 1 year post-treatment). This weight gain can last up to 5 years and lead to excess body weight compared to the premorbid condition similarly to what is observed in Graves’ patients after total thyroidectomy. Treatment of hyperthyroidism with anti-thyroid drugs (ATDs) is also associated with 2-4 kg weight gain which starts after the start of the initial treatment and may last one year after the end of the treatment (86, 87). This effect occurs with both treatment with ATDs alone and block-and-replace therapy regimen (ATDs plus L-T4) although studies directly comparing these two regimens are lacking (88). However, there is no clear evidence that ATD treatment leads to lasting weight gain. Conversely, several observations indicate that body weight remains unchanged after completion of ATD therapy, suggesting that the impact of these drugs on weight and energy balance differs from surgery and radioactive iodine and depends on residual thyroid function (84). These considerations were reinforced by a comparative study between different treatment modalities for hyperthyroidism. Indeed, a retrospective study including 133 patients with Graves’ disease who received ATDs, surgery or RAI indicated that treatment of hypothyroidism post-thyroidectomy or post-RAI was associated with significantly greater weight gain compared to patients who achieved euthyroidism with ATDs or hemi-thyroidectomy (78). Interestingly, this study found that these Graves’ patients experienced more weight gain compared to patients with thyroid cancer subjected to total thyroidectomy. Weight increments for both the surgical- or RAI-induced hypothyroidism groups were 10 vs 4 kg in the ATD or hemithyroidectomy-treated euthyroid groups vs only 0.6 kg in the surgically treated thyroid cancer cohort (78). Hence, these results suggested that thyroid autoimmune disease is associated with weight gain per se. The mechanisms underlying the direct effect of Graves’ disease on weight increase is still unclear. One hypothesis is that brown adipose tissue (BAT) expresses TSH receptors which are activated by anti-TSH-R stimulating antibodies of Graves’ patients. In fact, TSH may stimulate thermogenesis by binding to the TSH receptor expressed in adipocytes, a function involved in maintaining thermal status during hypothyroidism. Moreover, in vivo acute administration of recombinant human TSH at supraphysiological doses induced the release of small but significant amounts of leptin which was proportional to the adipose mass. Hence, it is reasonable to suppose that TSH stimulating activity may have per se an important effect on adipogenesis, mainly on white adipose tissue. On the other hand, this effect may be enhanced by inflammatory cytokines present in Graves’ patients (IL-1, IL-6 and TNFα) which are able to activate the hypothalamic, pituitary, adrenal axis, and cortisol secretion. In conclusion, several lines of evidence suggest that Graves’ disease is associated with excessive weight regain during therapy and may represent an important risk factor for the development of obesity. It is also possible, that the different effect of AITs on residual overweight may be due to their immunosuppressive effect (along with the use of corticosteroids).

**Key points**

Excessive weight regain may occur after treatment of hyperthyroidism, especially after radioiodine or surgery. Thyroid autoimmunity should be considered an independent mechanism that leads to inappropriate body weight increase.

**Therapy of hypothyroidism in obese patients: role of inflammasome, ubiquitination, glucurono-conjugation and activity of deiodinases**

Replacement therapy with Levothyroxine (LT4) is currently the standard treatment for hypothyroid patients. Its therapeutic goal is a TSH value within the age-related range, which is associated with an improvement in symptoms, quality of life and cardiovascular risk. However, the most appropriate treatment of hypothyroid patients is still under debate, especially in some particular conditions including old-age and obesity. In particular, daily calorie intake and nutritional status may affect leptin levels, which, in turn, may upregulate hypothalamic TRH and deiodinase 1 (D1) activity (38, 41, 89–91). Therefore, obese patients show a higher average TSH level than non-obese subjects (61). This positive correlation between BMI and TSH may reflect a compensatory pituitary-thyroid axis activation by leptin and insulin (48) to increase energy expenditure. However, it may also suggest a certain degree of thyroid hormone resistance in obese patients (92) related to the...
chronic low-grade inflammation and inflammasome activation but also to the regulation of $5'$ adenosine monophosphate-activated protein kinase (AMPK), a central target not only for the modulation of insulin sensitivity but also for the effect of thyroid hormones on appetite and energy expenditure (93). Indeed, in vivo studies performed in obese mice indicate that obesity-induced inflammasome activation up-regulates deiodinase activity by down-regulating ubiquitin-mediated protein degradation, thereby contributing to thyroid hormone (TH) resistance at pituitary level and body mass gain (94, 95). Moreover, impaired transport of TH through cell membrane by low-grade inflammation may represent an additional mechanism of thyroid hormone resistance in obese patients (96). Pituitary resistance and impaired cell membrane transport of thyroid hormones may explain the positive correlation between FT3 levels and body weight. Taken together, these studies suggest that TSH levels in obese patients (96). Pituitary resistance and impaired cell membrane transport of thyroid hormones may explain the positive correlation between FT3 levels and body weight. Taken altogether, these studies suggest that TSH levels in obese hypothyroid patients may not recapitulate the adequacy of L-T4 replacement dose (61). Indeed, some studies suggest that optimization of L-T4 replacement dose should be performed according to lean body mass (LBM), rather than whole body weight (RBW). In particular, LBM is related to body mass cells (BMC) that corresponds to lean mass of body organs (liver, kidney and heart) and correlates to D1 activity, L-T4 glucuronono-conjugation and basal metabolic rate (BMR). In contrast, fat mass, which is one of the major determinants of low-grade inflammation, may exert a confounding effect on L-T4 requirement (97, 98). Hence, further studies are needed to evaluate the role of different LT-4 dose and formulations or L-T4/L-T3 combination in the treatment of hypothyroidism in obese patients.

Key points

The most appropriate treatment of hypothyroidism in obese patients is still debated. These patients may have some degree of resistance to thyroid hormone related to chronic low-grade inflammation and activation of the inflammasome.

Bariatric surgery: impact on thyroid inflammasome, autoimmunity and thyroid function

Bariatric surgery has become a safe and efficacious treatment for patients with severe and complex obesity, who do not respond adequately to caloric restriction (99). Several studies reported a significant effect of bariatric surgery on many inflammatory markers, including thyroid autoantibodies, and a significant effect on thyroid hormone levels (100, 101). As discussed above, obesity is a condition associated with a low-grade systemic inflammation, leading to altered levels of various inflammatory markers (102, 103) and imbalanced adipokine secretion (104). For instance, adiponectin and orexin-A, two adipokines related to insulin sensitivity and calorie intake, are markedly decreased in obese patients along with a significant increase in inflammatory cytokines (105). Interestingly, there is evidence that patients with morbid obesity, subjected to bariatric surgery, display reduced levels of pro-inflammatory cytokines along with increased adiponectin levels that play an anti-inflammatory action (106). The effect of bariatric surgery in reverting the dysregulation of the inflammasome system has been extensively studied by Vicente et al. (107), who evaluated changes in inflammasome components in 22 patients with morbid-obesity before and after six months of bariatric-surgery (sleeve-gastrectomy and roux-en-Y gastric bypass). In this study, the most important changes were found in NOD-like-receptors, cell-cycle and DNA-damage regulators, while, at baseline, several components of the inflammasome were significantly related to metabolic alterations, including T2DM (CCL2/CXCR3/SIRT1), hypertension (AIM2/ASC/P2RX7) and dyslipidemia (CXCL3/NLRP7). It was interesting to note that the levels of all these markers significantly changed six-months after bariatric-surgery. Gene-expression levels of NLR4/NLRP12/CXCL3/CCL8/TLR4 were related to pre and post-operative peripheral-blood mononuclear-cells. In vitro experiments, performed to validate the mechanistic insights of these findings indicated that NLRC4/NLRP12 silencing in the hepatoma cell line HEPG2 resulted in increased cell-viability and lipid-accumulation along with a reduction in the apoptosis rate. In respect to the relationship between inflammasome activation in morbid obesity subclinical hypothyroidism (108), a report by Zhu et al. indicates that obese patients subjected to laparoscopic sleeve gastrectomy display a significant decrease in inflammation markers, such as IL-6, TNF-$\alpha$, and CRP (109) that is concomitant with a significant TSH reduction. In agreement with these results, some reports indicate a reduction/normalization in TSH levels in obese patients after weight loss induced by either bariatric surgery or a low-calorie diet (110). A recent meta-analysis confirmed that bariatric surgery is able to revert subclinical hypothyroidism in obese patients and to reduce L-T4 replacement dose. It was interesting to note that, while TSH, FT3 and T3 levels decreased significantly after bariatric surgery, FT4, T4 and rT3 levels remained unchanged (100). Although the association between bariatric surgery and thyroid function seems clear and mainly based upon thyroid autoimmunity, the mechanism of this relationship may be complex and bidirectional: some studies indicate a role for autoimmune subclinical hypothyroidism in the pathogenesis of obesity (111), while others support the hypothesis that the excess of dysfunctional
adipose tissue may be responsible for changes in serum thyroid hormone levels (90, 112). In line with this notion, Xia et al. reported a significant reduction in serum TPOAbs and thyroglobulin antibodies (TgAbs) in 101 patients with morbid obesity (BMI ≥ 32 kg/m2 or BMI ≥ 27.5 kg/m2 with one or more comorbidities) treated with bariatric surgery (101). The reduction in TPOAbs and TgAbs was from 79.3 and 177.1 IU/mL to 57.8 and 66.0 IU/mL, respectively (P < 0.05). In accordance with these results, Kyrou et al, albeit in a small population study, evaluated ultrasound thyroid morphology in obese patients treated with bariatric surgery and found a significant relationship between weight loss and an increase in thyroid echogenic pattern (113). In conclusion, these data indicate that bariatric surgery is able to attenuate inflammatory activity and may exert a beneficial effect on thyroid autoimmunity and function.

**Key points**

Bariatric surgery can attenuate the activity of the inflammasome and can exert a beneficial effect on autoimmunity and thyroid function.

**Obesity, inflammasome and thyroid cancer**

A functional relationship between chronic inflammation and cancer was first proposed by Virchow in 1863 and is supported by clinical and epidemiological evidence. As mentioned above, obesity is characterized by chronic low-grade chronic inflammation and insulin resistance. It is now widely accepted that the consequent deranged immunity, compensatory hyperinsulinemia, hyperlipidemia, and enhanced oxidative stress are risk factors for cancer development and/or progression (114–116). Several data indicate that increased inflammasome activity in adipose tissue is an important mediator of obesity-induced inflammation and insulin resistance. Inflammasome-induced cytokines are mainly produced from the hematopoietic compartment and act in autocrine and paracrine manners to form an inflammatory microenvironment (117). Recruit immune cells and interfere with insulin signaling processes thus promoting the development of diabetes (118). Obesity increases oxidative stress that in turn upregulates inflammatory cytokines (119). Indeed, chronic inflammation activates transcription of factors such as nuclear factor kappa-light-chain-enhancer of activated B (NF-kB), STAT3, and activator protein 1 (API) in pre-malignant cells. All these pathways enhance cell proliferation and survival promoting angiogenesis in conjunction with hypoxia (120). Various infiltrating cells have been identified in tumors, namely, tumor-associated lymphocytes, tumor-associated macrophages (TAM), immature dendritic cells, mast cells and myeloid-derived suppressor cells. The presence of specific inflammatory-immune cells such as macrophages and mast cells in tumor sites has been associated with a poor prognosis of thyroid cancer (121). Thyroid cancer cells and the tumoral stroma may secrete several cytokines and chemokines, thus sustaining the survival of cancer cells promoting the selection of clones that acquire additional genetic lesions becoming resistant to oncogene-induced apoptosis. Proinflammatory cytokines produced in tumor sites by inflammatory and epithelial cancer cells depend mainly on the NF-kB transcription factor and are pivotal in cancer progression (121). Consistently, several cancer histotypes are more common and more aggressive in obese patients than in the normal weight population. Several lines of evidence suggest that obesity is also associated with thyroid cancer. Various epidemiologic studies and metaanalysis have found a statistically significant association between BMI and thyroid cancer, especially in males (122). The risk of thyroid cancer appears to be positively related with the degree of obesity (123). Moreover, obesity is related to more aggressive histotypes (123). Animal models support these studies and explain the complex mechanisms between obesity and thyroid tumors demonstrating that a high-fat diet (HFD) induces thyroid cancer cell proliferation by enhancing cyclin D1 protein levels as well as the phosphorylation of RB protein, serum leptin levels and STAT3 expression (124). In addition, an inhibitor of STAT3 was able to inhibit the proliferation of HFD-induced thyroid cancer cells through the reduction of cyclins D1 and B1, CDK4, CDK6 and pRB (125). A role of inflammation and immune response in the onset of thyroid cancer and autoimmune thyroid diseases (such as Hashimoto’s thyroiditis and Graves’ disease) has already been demonstrated (126, 127). Moreover, increased TAM infiltration in poorly differentiated thyroid cancers (PTDCs) was found to be positively correlated with capsule invasion, extrathyroidal extension and poor prognosis (128). It has been also reported that the expression of BRAF V600E mutation and the RET/PTC gene rearrangement promote the activity of NF-kB, the expression of inflammatory mediators, and lymph node metastases in patients with papillary thyroid cancer (PTC) (129). Inflammation is intimately linked to the metabolic reprogramming of cancer cells. Indeed, compared with healthy tissues or benign lesions thyroid cancer is characterized by increased lactic acid production, regardless of its histotype. Moreover, PKM2, a key enzyme of glycolysis, has been found overexpressed in advanced and poorly differentiated thyroid cancer and associated with tumor aggressiveness and negative prognosis of PTC (130). In other cell models it has been shown that PKM2-dependent glycolysis promotes NLRP3 inflammasome activation (131). Indeed,
pharmacological inhibition of PKM2 attenuates the release of IL-1β, IL-18 and HMGB1 due to NLRP3 activation (131). Although a direct link between thyroid cancer and obesity-induced inflammasome activation has not been clearly demonstrated, several lines of evidence support the hypothesis that a relationship may be also present in thyroid cancer. Recent studies indicate that the inflammasomes can be activated by fatty acids and high glucose levels linking metabolic danger signals to the activation of inflammation and cancer development. These data suggest that activation of the inflammasomes may represent a crucial step in the obesity-associated thyroid cancer development.

Key point

Inflammasomes can be activated by fatty acids and high glucose levels linking metabolic danger signals to the activation of inflammation and cancer development.

A possible role of vitamin D in autoimmune thyroid diseases and obesity

Several studies have shown that the risk and the clinical evolution of autoimmune thyroid disease and other chronic inflammatory diseases are associated with low plasma levels of vitamin D (132). This is not surprising as vitamin D modulates the synthesis of IL-1, IL-6, and other cytokines, suppresses dendritic cell differentiation, and influences regulatory T cell activity. Vitamin D inhibits the activity of TLRs (Toll-like receptors) by inhibiting the identification of pathogenic or non-pathogenic molecular patterns (e.g. LDLc binding with TLR in thyroid cells) by TLRs. In addition, vitamin D via its receptor (VDR), inhibits the deubiquitination and activation of NLRP3 inflammasome (133, 134). Notably, hyperthyroidism is associated with reduced levels of vitamin D (135). Moreover, vitamin D negatively modulate lipogenesis controlling calcium influx into adipocytes (136). These data are in agreement with studies showing that vitamin D deficiency is associated with overweight, obesity and insulin resistance (137, 138). Accordingly, vitamin D supplementation may decrease the incident risk of autoimmune disease (139) and increases insulin sensitivity (140, 141).

Key points

Vitamin D attenuates the activation of the inflammasome and its immune response, modulates lipogenesis and increases insulin sensitivity. Vitamin D deficiency is related to the risk and severity of thyroid autoimmunity and obesity.

Conclusions and perspectives

Recent epidemiological and experimental data provided evidence of a bidirectional interaction between obesity and thyroid autoimmunity. In particular, obesity is associated with an enhanced risk of hypothyroidism and of developing antithyroidperoxidase antibodies. This is also true for thyroid autoimmunity related disorders like GO: low-grade inflammation and inflammasome activation in dysmetabolic subjects may enhance the autoimmune process underlying GO pathogenesis and its clinical and phenotypic expression. On the other hand, thyroid autoimmunity may favor overweight and obesity. One empirical evidence supporting this hypothesis is Graves’ disease. Indeed, a marked weight gain during GD therapy may represent an important risk factor for the development of obesity. Moreover, the lower extent of weight gain with immunosuppressive therapies unravels the possibility that thyroid autoimmunity per se is able to favor obesity, although the exact mechanisms underlying this phenomenon are not fully understood. In addition to the positive effect of obesity in thyroid autoimmunity and hypothyroidism, several lines of evidence suggest that obesity related inflammasome activation may induce a certain degree of TH resistance both in peripheral tissues and hypothalamus leading to a significant increase of TSH, thereby exerting confounding effects on L-T4 requirement in obese people. Inflammasome activation in obesity may also increase the risk of thyroid cancer and is related with a more aggressive thyroid cancer phenotype. Several in vitro data support and explain this observation. A further observation confirms the role of inflammasome related obesity in thyroid disorders: bariatric surgery is able to attenuate inflammasome activity and may exert a beneficial effect on thyroid autoimmunity and function. Taken together these results indicate that thyroid function should be always screened in obese people and that thyroid disorders should be carefully addressed in obese and dysmetabolic people. Further studies are needed to unravel the mechanisms underlying the bidirectional relationship between obesity and thyroid disorders as well as to evaluate the role of different LT-4 doses and formulations or L-T4/L-T3 combination in the treatment of hypothyroidism in obese patients.

Ethics statement

Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.
**Author contributions**

Conceptualization, RM, AB, VV, FF; methodology, RM, VV; software, RM, AN, TP; validation, AB, FF, RM, VV; investigation, RM, TP, VV, FF, AB; resources, RM, FF, AB; writing—original draft preparation, RM, FF, AB, VV; writing—review and editing, RM, FF, AB, VV; supervision, RM, FF, AB, VV; project administration, AB; funding acquisition, AB. All authors have read and agreed to the published version of the manuscript.

**Funding**

This research was supported in part by Fondazione AIRC: IG n. 23369 to AB and by Ministero della Salute, Italy, grant RF-2019-12368937 to AB.

**References**

1. Di Cesare M, Benthem J, Stevens GA, Zhou B, Danaei G, Lo Y, et al. Trends in adult body-mass index in 200 countries from 1975 to 2014: A pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet (2016) 387(10026):1577–96. doi: 10.1016/S0140-6736(16)30034-X

2. Bilher M. Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol (2019) 15(5):288–98. doi: 10.1038/s41574-019-0176-8

3. Coppack SW. Pro-inflammatory cytokines and adipose tissue. Proc Nutr Soc (2001) 60(3):349–56. doi: 10.1079/PS2001110

4. Wang C, Ha X, Li W, Xu P, Gu Y, Wang T, et al. Correlation of TLR4 and NLRP3 in adipose tissues and its implications on metabolic diseases. Int J Mol Sci (2020) 21(11):1–22. doi: 10.3390/ijms21114184

5. Wu KKL, Cheung SWM, Cheng KKY. NLRP3 in adipose tissues: a link between obesity and metabolic diseases. Trends Biochem Sci (2016) 41(12):1012–21. doi: 10.1016/j.tibs.2016.09.002

6. He Y, Hara H, Nüesch G. Mechanism and regulation of NLRP3 inflammasome activation. Trends Biochem Sci (2016) 41(12):1012–21. doi: 10.1016/j.tibs.2016.09.002

7. Mangan MSJ, Olhava EJ, Roush WR, Seidel HM, Glick GD, Latz E. Targeting the NLRP3 inflammasome in inflammatory diseases. Nat Rev Drug Discov (2018) 17(8):588–606. doi: 10.1038/nrd.2018.97

8. Schroder K, Tschopp J. The inflammasomes. Cell (2010) 140(6):821–32. doi: 10.1016/j.cell.2010.01.049

9. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipocyte macrophage polarization. J Clin Invest (2007) 117(1):175–84. doi: 10.1172/JCI29881

10. Benham V, Chakraborty D, Bullard B, Bernard JJ. A role for FGF2 in visceral adiposity-associated mammary epithelial transformation. Adipocyte (2018) 7(2):113–20. doi: 10.1080/21623945.2018.1445889

11. Chakraborty D, Benham V, Bullard B, Kearney T, Hsia HC, Gibbon D, et al. Fibroblast growth factor receptor 2 mediates a phenotypic switch in visceral adipocyte macrophage polarization. Trends Biochem Sci (2016) 41(12):1012–21. doi: 10.1016/j.tibs.2016.09.002

12. Addobba C, da Cruz HLA, Adelino JE, Melo Tavares Ramos AL, Fragoso TS, Domingues A, et al. Polymorphisms and expression of inflammasome genes are associated with the development and severity of rheumatoid arthritis in Brazilian patients. Inflammation Res (2018) 67(3):255–64. doi: 10.1007/s00011-017-1119-2

13. Leavy O. Inflammasome: NALPs: Pathogen-sensing proteins. Nat Rev Immunol (2011) 11(10):644–50. doi: 10.1038/nri3069

14. Malhotra S, Lui ADM, Urcelay E, Nurtdinov R, Bustamante MF, Fernandez O, et al. NLRP3 inflammasome activation in keratinocytes in psoriatic arthritis: ROS as trigger or effector? Antioxid Redox Signal (2019) 30(6):668–80. doi: 10.1089/ars.2018.6678

15. Wynn TA, Chawla A, Pollard JW. Macrophage biology in development, homeostasis and disease. Nature (2013) 496(7446):445–55. doi: 10.1038/nature12034

16. Dombrowski Y, Peric M, Koglin S, Kammerbauer C, Götz C, Anz D, et al. Cytoplasmic DNA triggers inflammasome activation in keratinocytes in psoriatic lesions. Sci Transl Med (2011) 3(82):82ra38. doi: 10.1126/scitranslmed.3002001

17. Bergsbaken T, Fink SL, Cookson BT. Pyroptosis: Host cell death and inflammation. Nat Rev Microbiol (2009) 7(2):99–109. doi: 10.1038/nrmicro2070

18. He Y, Zeng MY, Yang D, Motoyama K, Nüesch G. NLRC4 is an essential mediator of NLRP3 activation downstream of potassium efflux. Nature (2016) 530(7590):354–7. doi: 10.1038/nature16959

19. Okondo MC, Johnson DC, Sridharan R, Go EB, Chiu AJ, Wang MS, et al. DPP8 and DPP9 inhibition induces pro-caspase-1 dependent monocyte and macrophage pyroptosis. Nat Chem Biol (2017) 13(1):46–53. doi: 10.1038/nchembio.2229

20. Mariño G, Pietrocola F, Eisenberg T, Kong Y, Malik SA, Andryushkova A, et al. Regulation of autophagy by cytosolic acetyl-coenzyme a. Mol Cell (2014) 53(5):710–25. doi: 10.1016/j.molcel.2014.01.016

21. Pietrocola F, Galluzzi L, Bravo-San Pedro JM, Kroemer G. Acetyl-coenzyme a: A central metabolite and second messenger. Cell Metab (2015) 21(6):805–21. doi: 10.1016/j.cmet.2015.05.014

22. Kelley N, Jehnma D, Yuan Y, He Y. NLRP3炎症小体的激活和调控机制概述. Int J Mol Sci (2019) 20(13):1–24. doi: 10.3390/ijms20133328

23. Rocha VZ, Libby P. Obesity, inflammation, and atherosclerosis. Nat Rev Cardiol (2009) 6(6):399–409. doi: 10.1038/nrcardio.2009.55

24. Camell CD, Günther P, Lee A, Goldberg EL, Youm Y, Bartke A, et al. Aging induces an NLRP3 inflammasome-dependent expansion of adipose B cells that impairs metabolic homeostasis. Cell Metab (2019) 30(6):1024–39. doi: 10.1016/j.cmet.2019.10.006

25. Ahais JM, Xia M, Zhang Y, Roini KM, Li PX. Redox regulation of NLRP3 inflammasomes: ROS as trigger or effector? Antioxid Redox Signal (2015) 22(13):1111–29. doi: 10.1089/ars.2014.5994

26. Weetman AP. An update on the pathogenesis of hashimoto’s thyroiditis. J Endocrinol Invest (2021) 44(5):883–90. doi: 10.1007/s40618-020-01477-1

27. Song RH, Wang B, Yao QM, Li Q, Liu X, Zhang JA. The impact of obesity on thyroid autoimmunity and dysfunction: A systematic review and meta-analysis. Front Immunol (2019) 10:2349. doi: 10.3389/fimmu.2019.02349

28. Biordi B. Thyroid and obesity: An intriguing relationship. J Endocrinol Invest (2010) 33(6):588–92. doi: 10.1530/ijid.1.125

29. Ferrabreschi P, Pinchera A, Martinelli S, Scartabelli G, Salveti G, Giannetti M, et al. Prevalence of endocrine diseases in morbidly obese patients scheduled for bariatric surgery: Beyond diabetes. Obes Surg (2011) 21(1):54–60. doi: 10.1007/s11695-010-0297-6

30. Hollówéll JG, Staebling NW, Dana Flanders W, Harry Hannon W, Gunter EW, Spencer CA, et al. Serum TSH, T4, and thyroid antibodies in the united states population (1988 to 1994): National health and nutrition examination survey.
pyroptosis of thyroid follicular cells mediated by enhanced NLRP3, NLRP1, upregulates macrophage DPP4 expression by viral infection and reversed by phenylmethimazole and is associated with Thyrocytes express a functional toll-like receptor 3: Overexpression can be induced changing concepts in thyroid autoimmunity. comprehensive review.

Innate immune activation and thyroid autoimmunity. Demonstration of innate immune responses in the thyroid gland: Potential to sense danger and a possible trigger for autoimmune reactions.лированы на лицам с итальянским происхождением. Thyroid function, and autoimmunity: The multifold role of leptin. Raised serum TSH levels in patients with morbid obesity: Is it enough to diagnose subclinical hypothyroidism? Horm Metab Res (2015) 47(10):773–8. Bahn RS. Current insights into the pathogenesis of graves’ ophthalmopathy. Hornef Metab Res (2015) 47(10):773–8. Bahn RS. Graves’ ophthalmopathy. N Engl J Med (2010) 362(8):726–38. doi: 10.1056/NEJMra0905750. Stein JD, Chlaiders D, Gupta S, Talwar V, Nan B, Lee BJ, et al. Risk factors for developing thyroid-associated opthalmopathy among individuals with Graves’ disease. JAMA Ophthalmol. (2015) 133(3):290–9. doi: 10.1001/jamaophthalmol.2014.5103. Kalmann R, Moursip M. Diabetes mellitus: A risk factor in patients with Graves’ orbitopathy. Br J Ophthalmol (1999) 83(4):463–5. doi: 10.1136/bjo.83.4.463-a. Le Moïl R, Muscia V, Tumminia A, Frittitta L, Buscema M, Palermo F, et al. Type 2 diabetic patients with Graves’ disease have more frequent and severe orbitopathy. Nutr Metab Cardiovasc Dis (2015) 25(5):452–7. doi: 10.1016/j.numecd.2015.01.003. Zheng L, Grennan-Jones F, Dorman MS, Lane C, Morris D, Dayan CM, et al. Possible targets for nonimmunosuppressive therapy of graves’ orbitopathy. J Clin Endocrinol Metabol (2014) 99(7):1183–90. doi: 10.1210/jc.2013-4182. Sciacca L, Vigneri R, Tumminia A, Frasca F, Squatrito S, Frittitta L, et al. Clinical and molecular mechanisms favoring cancer initiation and progression in diabetic patients. Nutr Metab Cardiovasc Dis (2013) 23(9):808–15. doi: 10.1016/j.numecd.2013.05.016. Smith TJ, Huguet GF, Hedges L, Douglas RS. Role of IGF-1 pathway in the pathogenesis of graves’ orbitopathy. Best Pract Res Clin Endocrinol Metabol (2012) 26(7):929–937. doi: 10.1016/j.bpem.2011.03-007. Zhang L, Grennan-Jones F, Lane C, Rees DA, Dayan CM, Ludgate M. Adipose tissue depot-specific differences in the regulation of hyaluronan production of relevance to Graves’ orbitopathy. J Clin Endocrinol Metab (2012) 97(2):653–62. doi: 10.1210/jc.2011-1209. Valtysvei BW, Erickson ZZ, Harteneck DA, Dutton CM, Hefsefeld AE, Jaynesous CH, et al. Differentiation of human orbital preadipocyte fibroblasts induces expression of functional thyrotropin receptor. J Clin Endocrinol Metab (1999) 84(7):2527–56. doi: 10.1210/jcem.84.7.7557. Mathies F, Muller PA, Graves CL, Galabranty J, Zachary J, Costa-borges D, et al. Adrenergic signaling in muscularis macrophtages limits infection-induced neuronal loss. Cell (2021) 180(1):64–78. doi: 10.1016/j.cell.2019.12.002.
iodine therapy in patients with Graves 

10.1089/thy.2018.0731 

Thyroid 
treatment of hyperthyroidism due to inadequate thyroid hormone therapy? 

The POUNDS LOST trial. 

Dongen EPA, et al. In 

91. doi:10.1210/clinem/dgaa754 

Eur J Endocrinol (2020) 2020:8894792. doi:10.1155/2020/8894792 

innate immune cells. 

10.1210/en.2014-1090 

Journal of inflammatory markers. 

Coope A, et al. Defective regulation of the ubiquitin/proteasome system in the 

85. Torlinska B, Nichols L, Mohammed MA, McCabe C, Boelaert K. Patients 

84. Yotsapon T, Waralee C, Hussamon P, Panita S, Siriwan B, Soontaree N, et al. 

83. Huynh CN, Pearce JV, Kang L, Celi FS. Weight gain after thyroidectomy: A 

82. Baranowska-Bik A, Bik W. The association of obesity with autoimmune 

81. Liu G, Liang L, Bray GA, Qi L, Hu FB, Rood J, et al. Thyroid hormones and 

75. Janssen JAMJL, Smith TJ. Lessons learned from targeting IGF-I receptor in 

74. Tall AR, Westerterp M. In 

73. Santini F, Pinchera A, Marulli A, Ceccarini G, Castagna MG, Valeriano R, et al. Lean body mass is a major determinant of levothyroxine dosage in the treatment of thyroid diseases. J Clin Endocrinol Metab (2005) 90(1):124-7. doi:10.1210/jc.2004-1300 

72. Xu-valita P, Cordido M, Outeiriño-blanco E, Pertega S, Ureñas P, Garcia-brao MJ, et al. Evaluation of thyroid hormone replacement dosing in morbidly obese hypothyroid patients after bariatric surgery-induced weight loss. J Clin Endocrinol Metab (2016) 101(6):3685. doi:10.1210/jc.2016-36685 

71. Dixon JB, Staatsdijk NE, Lambert EA, Schlaich MP, Lambert GW. Surgical approaches to the treatment of obesity. Nutr Rev Gastroenterol Hepatol (2013) 8(8):429-37. doi:10.1093/ngrastro/nst012 

70. Braun G, Chen YY, Yang J, Yang W, Cunchuan W. Effect of bariatric surgery on thyroid function in obese patients: a systematic review and meta-analysis. Obes Surg (2017) 27(12):3292-305. doi:10.1007/s11695-017-2965-2 

69. Su X, Peng D. Adipokines as novel biomarkers of cardio-metabolic disorders. Clin Chem Acta (2020) 507:31-8. doi:10.1016/j.cca.2020.04.009 

68. Valenzano R, Tartaglia N, Ambrosi A, Tafuri D, Mondia M, Messina A, et al. The metabolic rearrangements of bariatric surgery: Focus on estrogen and the adipoconnect system. J Clin Endocrinol Metab (2020) 95(10):1-11. doi:10.1210/jc.2020-03132 

67. Zhang C, Zhang J, Liu Z, Zhou Z. More than an anti-diabetic bariatric surgery, metabolic surgery alleviates systemic and local inflammation in obesity. Obes Surg (2018) 28(11):3658-68. doi:10.1007/s11695-018-3400-z 

66. Herrera-Arguyo V, Saiz-Martinez P, Canovas JL, Prados-Carmona J, Alcantara-Laguna M, Lopez F, et al. Dysregulation of components of the inflammatory machinery after bariatric surgery: Novel targets for a chronic disease. J Clin Endocrinol Metab (2015) 91(11):4917–34. doi:10.1210/jc.2015-2965 

65. Gupta G, Sharma P, Kumar P, Itagappa M. Study on subclinical hypothyroidism and its association with various inflammatory markers. J Clin Diag Res (2015) 9(11):BO4-6. doi:10.3778/jcr.2015.1460.0806 

64. Zhu C, Gao J, Mei F, Lu L, Zhou D, Qu S. Reduction in thyroid-stimulating hormone correlated with improved inflammation markers in Chinese patients with morbid obesity undergoing laparoscopic sleeve gastroectomy. Obes Surg (2019) 29(12):3954-65. doi:10.1007/s11695-019-04063-4 

63. Reinehr T, De Sousa G, Andler W. Hyperthyrotropinemia in obese children is reversible after weight loss and is not related to lipids. J Clin Endocrinol Metab (2006) 91(8):3088-91. doi:10.1210/jc.2006-0095 

62. HU Y, Zeng J, Ye X, Song Y, Wu X. Association between elevated thyroid peroxidase antibody and abdominal fat distribution in patients with type 2 diabetes mellitus. Diabetes Metab Syndr Obes Targets Ther (2015) 22:683-71. doi:10.2147/DMOS.S345507 

61. Rotondi M, Magri F, Chiavoto I. Thyroid and obesity: Not a one-way interaction. J Clin Endocrinol Metab (2011) 96(2):344-6. doi:10.1210/jc.2010-2153 

60. Kyrou I, Adesanya O, Hedley N, Wayte S, Grammatopoulos D, Thomas CL, et al. Improved thyroid hypochromatosis following bariatric-induced weight loss in euthyroid adults with severe obesity: a pilot study. Front Endocrinol (Lausanne) (2018) 9:488. doi:10.3389/fendo.2018.00488 

59. Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. Ann Rev Physiol (2009) 71:219–46. doi:10.1146/annurev-physiol-021208-141140 

58. Deng T, Lyon CJ, Bergin S, Caliguari MA, Hsuue WA. Obesity, inflammation, and cancer. Ann Rev Pathol Mech Dis (2016) 11:421–49. doi:10.1146/annurev-pathol-021615-044359 

57. Avergoumi K, Spyrou N, Mantzoros CS, Dalalama M. Obesity and cancer risk: Emerging biological mechanisms and perspectives. Metabol Clin Exp (2019) 92:121-35. doi:10.1016/j.metabol.2018.11.001 

56. Guo B, Su F, Zhang J, Liu B, Li Z. Targeting inflammation/IL-1 pathways for cancer immunotherapy. Sci Rep (2016) 6:1–12. doi:10.1038/srep16107 

54. Wen H, Gra D, Lei Y, Jia S, Zhang L, Huang MTH, et al. Fatty acid-induced NLRP3-ASC inflammasome activation interferes with insulin signaling. Nat Immunol (2011) 12(5):408–15. doi:10.1038/ni.2022
119. Cnop M, Foufelle F, Vellioso LA. Endoplastic reticulum stress, obesity and diabetes. Trends Mol Med (2012) 18(1):59–68. doi: 10.1016/j.molmed.2011.07.010

120. Grivennukou SI, Gorton FR, Karin M. Immunity, inflammation, and cancer. Cell (2010) 140(6):883–99. doi: 10.1016/j.cell.2010.01.025

121. Ferrari SM, Fallahi P, Gallardo MR, Ruffilli I, Elia G, Ragusa F, et al. Immune and inflammatory cells in thyroid cancer microenvironment. Int J Mol Sci (2019) 20(18):1–22. doi: 10.3390/ijms20184413

122. Zhao ZG, Gao XG, Ba CX, Wang W, Yang YY, Wang J, et al. Overweight, obesity and thyroid cancer risk: A meta-analysis of cohort studies. J Int Med Res (2012) 40(6):2041–50. doi: 10.1177/030006051240000601

123. Schmid D, Ricci C, Behrens G, Leitzmann MF. Adiposity and risk of thyroid cancer: A systematic review and meta-analysis. Obes Rev (2015) 16 (12):1042–54. doi: 10.1111/obr.12231

124. Kim WG, Park JW, Willingham MC, Cheng SY. Diet-induced obesity increases tumor growth and promotes anaplastic change in thyroid cancer in a mouse model. Endocrinology (2013) 154(8):2936–47. doi: 10.1210/en.2013-1128

125. Park JW, Han CR, Zhao L, Willingham MC, Cheng SY. Inhibition of stat3 activity delays obesity-induced thyroid carcinogenesis in a mouse model. Endocr Relat Cancer (2016) 23(1):53–63. doi: 10.1530/ERC-15-0417

126. Dias Lopes NM, Mendonça Lens HH, Armani A, Marinello PC, Cecchini AL. Thyroid cancer and thyroid autoimmune disease: A review of molecular disorders: Autoimmune thyroid disorders (Hashimoto’s disease), diabetes mellitus and obesity. TRENDS IMMUNITY (2010) 140(6):883–99. doi: 10.1016/j.cell.2010.01.025

127. Schmid D, Ricci C, Behrens G, Leitzmann MF. Adiposity and risk of thyroid cancer: A systematic review and meta-analysis. Obes Rev (2015) 16 (12):1042–54. doi: 10.1111/obr.12231

128. Ryder M, Ghossein RA, Ricarte-Filho JCM, Knauf JA, Fagin JA. Increased density of tumor-associated macrophages is associated with decreased survival in advanced thyroid cancer. Endocr Relat Cancer (2008) 15(4):1069–74. doi: 10.1677/ERC-08-0036

129. Zhou D, Li Z, Bai X. Braf v600e and RET/PTC promote the activity of nuclear factor-κb, inflammatory mediators, and lymph node metastasis in papillary thyroid carcinoma. A study of 50 patients in inner mongolia. Med Sci Monit (2018) 24:6795–808. doi: 10.12659/MSM.909205

130. Feng C, Gao Y, Wang C, Yu X, Zhang W, Guan H, et al. Aberrant overexpression of pyruvate kinase m2 is associated with aggressive tumor features and the BRAF mutation in papillary thyroid cancer. J Clin Endocrinol Metab (2013) 98(9):1–10. doi: 10.1210/jc.2012-4258

131. Xie M, Yu Y, Kang R, Zhi S, Yang L, Zeng L, et al. PKM2-dependent glycolysis promotes NLRP3 and AIM2 inflammasome activation. Nat Commun (2016) 7:1–13. doi: 10.1038/ncomms13280

132. Altieri B, Muscogiuri G, Barrea L, Mathieu C, Valentini C, Mascielli L, et al. Does vitamin d play a role in autoimmune endocrine disorders? A proof of concept. Rev Endocr Metab Disord (2017) 18(3):335–46. doi: 10.1007/s11554-016-9405-9

133. Rao Z, Chen X, Wu J, Xiao M, Zhang J, Wang R, et al. Vitamin d receptor inhibits NLRP3 activation by impeding its BRCC3-mediated deubiquitination. Front Immunol (2019) 10. doi: 10.3389/fimmu.2019.02783

134. Sadeghi K, Wessner B, Lagger U, Polder M, Tamandl D, Friedl J, et al. Vitamin D3 down-regulates monocyte TLR expression and triggers hyporesponsiveness to pathogen-associated molecular patterns. Eur J Immunol (2006) 36(2):361–70. doi: 10.1002/eji.200425995

135. Chao G, Zhu Y, Fang L. Correlation between hashimoto’s thyroiditis-related thyroid hormone levels and 25-hydroxyvitamin d. Front Endocrinol (Lauanne) (2020) 11:4. doi: 10.3389/fendo.2020.00004

136. Martini LA, Wood RJ. Vitamin d status and the metabolic syndrome. Nutr Rev (2006) 64(11):479–86. doi: 10.1111/j.1753-4887.2006.tb00180.x

137. Green TJ, Skeaff CM, Rockell JEP, Venn BJ, Lambert A, Todd J, et al. Vitamin d status and its association with parathyroid hormone concentrations in women of child-bearing age living in Jakarta and Kuala Lumpur. Eur J Clin Nutr (2008) 62(3):373–8. doi: 10.1038/sj.ejcn.1602696

138. Alkharfy KM, Al-Daghri NM, Yakout SM, Hussain T, Mohammed AK, Krahnawarny S. Influence of vitamin d treatment on transcriptional regulation of insulin-sensitive genes. Metab Syndr Relat Disord (2013) 11(4):283–8. doi: 10.1089/metd.2012.0068

139. Tsugawa Y, Jena AR, Orav EJ, Blumenthal DM, Tsai TC, Mehtsun WT, et al. Age and sex of surgeons and mortality of older surgical patients: observational study. BMJ (2018) 361:k1343. doi: 10.1136/bmj.k1343

140. Talaei A, Mohamadi M, Adgi Z. The effect of vitamin d on insulin resistance in patients with type 2 diabetes. Diabetol Metab Syndr (2013) 5(8). doi: 10.1186/1758-5996-5-8

141. Galaçoğlu D, Popovicu MS, Babek EE, Vidican M, Zaha AA, Babek VV, et al. Vitamin d implications and effect of supplementation in endocrine disorders: Autoimmune thyroid disorders (Hashimoto’s disease and grave’s disease), diabetes mellitus and obesity. Med (2022) 58(2):194. doi: 10.3390/medicina58020194