



Mini Review

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Obesity, Insulin Resistance and Vitamin D Deficiency may be Reversible Risk Factors for Thyroid Cancer



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Abstract

Background: The incidence of thyroid cancer has been rising significantly over the past few decades; insulin resistance (IR), obesity and vitamin D deficiency (VDD) are found to be associated with many cancer types, this paper introduce a review for papers done in this field to show the association between IR, obesity, and VDD as reversible risk factors for thyroid cancer.

Methods: This paper was designed to review the previous studies in this field to evaluate the possible association between IR, obesity, VDD and thyroid cancer, possible mechanisms and the clinical applications.

Conclusion: Obesity, IR, and VDD are proved to be implicated in thyroid cancer incidence, but there relation to thyroid cancer aggressiveness still controversial, and whether vitamin D3 supplementation, physical activity, Drugs that decrease insulin resistance and diet may affect thyroid cancer prognosis and incidence still raw area for more researches.

Keywords: Thyroid nodules; Thyroid cancer; Vitamin D deficiency, Insulin resistance; Obesity

Abbreviations: IR: Insulin Resistance; VDD: Vitamin D Deficiency

Introduction

Thyroid cancer is the comments endocrine malignancy, it's incidence is rapidly increasing among all other malignancies, This rise may partly due to increase detection of thyroid cancers from enhanced usage of ultrasonography and fine-needle biopsies [1], and changes in exposure to environmental factors as ionizing radiation, and a family history of thyroid cancer. The aim of this paper is discuss if obesity, IR and Vitamin D deficiency (VDD) are possible risk factors for thyroid cancer and if so can we prevent thyroid cancer through weight control, Diet, Vitamin D supplementations, usage of metformin to decrease insulin resistance?

Main Content

Obesity and thyroid cancer

Obesity is proved to be associated with the development and progression of many malignancies as endometrial cancer, breast cancer, esophageal cancer, colon, adenocarcinoma, liver cell carcinoma, prostate cancer, leukemia, melanoma, and non-Hodgkin lymphoma [2]. Recently, several studies have suggested a positive association between obesity and the prevalence of thyroid cancer [2-5], the underlying mechanism has not been

confirmed. IGF-1, IR, cytokines, TSH, adiponectin, estrogens and leptin have been suggested as associated factors [6,7]. Obesity leads to a pro-inflammatory state, decrease adiponectin, and IR, which, leads to hyperinsulinemia and increase IGF1 levels, that may increase the risk for thyroid malignancies

Several studies have been done to show the relationships between obesity and clinical outcomes of thyroid cancer especially PTC [8-10]. There results remain still controversial. Some studies showed an association between obesity and more aggressive tumor stages [8,11,12], they suggested that overweight or obese patients with (PTC) more than 1cm in size had more risk of developing recurrent disease or loco-regional persistence [8]. However, other studies showed a higher body mass index (BMI) was not accompanied with more aggressive pathological features, or the recurrence or persistence of disease [9,13]. Other one reported that obesity might be associated with less aggressive tumor invasion [9].

So as these studies have not shown consistent results, and whether or not the severity of obesity influences the prognosis and the aggressiveness of pathological stages of thyroid cancer so we need more studies to uncover this issue.

Insulin resistance as a risk factor for thyroid cancer

IR is a characteristic finding of most patients with simple obesity, impaired glucose tolerance, type 2 diabetes mellitus, as well as other disorders [14]. Insulin stimulates proliferation of thyroid cells in culture. The presence of insulin resistance (IR) is associated with larger thyroid gland volume and an increased prevalence of thyroid nodules. [15,16] and may be involved in the pathogenesis of thyroid cancer development [17]. It was noticed that insulin receptors are overexpressed in most thyroid tumors as an early stage in thyroid carcinogenesis [18].

IR may be due to chronic activation of the pro-inflammatory pathway [19]. Chronic activation of the NF- κ B pro-inflammatory pathway and/or JNK1 have been implicated [19]. IGF-IR is usually expressed at high levels in thyroid cancer cells [20], Vella et al. [18] showed that thyroid cancers overexpress IGF-I, IGF-IR, and IGF-II and IR [18]. The concomitant increase expression of IGF-IR and IR in thyroid cancer cells causes over expression of IR/IGF-IR hybrid receptors that, in most cases, exceed the IGF-IR content so in cells with a high IR/IGF-IR content, blocking antibodies specific to these receptors inhibit IGF-I-induced cell growth [21].

So changes in the IGF system and the association with high circulating levels of insulin/IGFs have been reported in thyroid cancer, which may have important implications in endocrine cancer prevention and treatment [21].

TSH itself is a major regulator of growth and differentiation of thyroid cells, and plays a role in nodule formation. In the presence of insulin in cell cultures, TSH is a well-known mitogen and also suppresses apoptotic cell death in response to various stimuli [22]. This effect, is mediated in part via IGF-I dependent pathway; therefore, IGF-1 might be expression of insulin receptor was increased in hypo functioning benign thyroid adenomas which lost differentiated functions such as iodine uptake. Therefore, over expression or activation of insulin receptor may be an early event in thyroid tumorigenesis and nodular formation [22]. So, hyperinsulinemia may act by enhancing thyroid proliferation, independently of the patient BMI

Metformin and thyroid cancer

Patients using Metformin had a lower risk for formation of thyroid nodules and a smaller thyroid volume [23-25]. Also Karimifar et al. [26] reported that metformin can reduce small solid thyroid nodules size and prevent an increase in the thyroid volume [26].

Metformin have complex effects that include not only lowering IR but also direct effects on cancer cells [27], Benveng et al. [28] noticed reduction in overall cancer incidence or mortality when metformin is used in the treatment of diabetes [28].

Metformin was found to antagonize the growth-stimulatory effect of insulin in vitro and inhibition of cell cycle progression and induction [29]. A recent cross-sectional study also reported a significant correlation between glycosylated hemoglobin and thyroid volume or the number of nodules [23].

Metformin also has indirect anticancer property as Rotondi et al. proved that metformin inhibit the TNF- α -induced CXCL8 secretion in primary cultures of human thyroid cells, Rotondi et al. In addition to in vitro study done by Chen et al. [29] showed that Rezzónico et al. [27] found that nodule size marked decreased in patients treated with both metformin and L-T4 compared to patients' receiving metformin alone. The shrinkage of thyroid nodule was accompanied by decrease in TSH level and normalization of the homeostasis model assessment HOMA index [27].

Clinical trials showed that metformin therapy was associated with higher remission rate and survival in diabetic patients with thyroid cancer [28], and a favorable outcome in diabetic patients with cervical lymph node metastasis of DTC [13].

Another large observational study in Taiwanese patients with T2DM showed that metformin reduced thyroid cancer risk [30]. In a mouse model, metformin could block progression of obesity-activated thyroid cancer [31]. On the other hand Becker et al. [32] indicated neither use of metformin nor of other antidiabetic drugs was associated with a decreased risk of thyroid cancer [32].

Recently retrospective analysis found that metformin attenuated a 131I-induced decrease of peripheral blood cells in patients with DTC [33]. Chen et al. [29] reported that sorafenib, a multikinase inhibitor used as alternative therapy for radioiodine-resistant DTC, combined with 2 metformin synergistically decreased the proliferation of anaplastic thyroid cancer cell lines and the outgrowth of derived cancer stem cells [29].

In papillary thyroid cancer the therapeutic potential of metformin has also been identified both in vitro and in vivo Cho et al. Another study on medullary thyroid carcinoma (MTC) cell lines showed that metformin inhibited growth in 2 MTC-derived cells, suggesting that metformin inhibits growth and prevents development of metastases in MTC [28]. In addition, 2 metformin may inhibit the growth, migration, and mesenchymal transition of thyroid cancer cell lines by the mTOR pathway beyond insulin/IGF-1 pathway [34].

In conclusion several studies demonstrated that metformin was found to reduce the nodular volume and thyroid nodules size, inhibit the growth of thyroid carcinoma and potentiate the antimetogenic effect of chemotherapeutic agents and also may have a TSH-lowering effect. So these findings suggest a broader use of this drug not only for type 2 diabetics with or without

proliferative thyroid disease but also for those with metabolic syndrome and obesity. However, more studies are required to show the effects of metformin in these patients.

Vitamin D and thyroid cancer

Recently the researchers give attention to the relationship between cancer and vitamin D levels, and the potential use of vitamin D receptor as a therapeutic target, a correlation between vitamin D and cancer prevention has been shown in breast, prostate, and colorectal cancer [35].

Several studies strongly suggest that vitamin D3 deficiency (VDD) increases the risk of developing malignancies [36-38], while others studies reported that there is no association between VDD and thyroid cancer incidence [39,40], prognosis and aggressiveness [40,41]. However, Mawer et al. [42] suggest that adequate vitamin D3 levels may provide protection against cancer and may improve cancer prognosis [42]. Expression of the VDR gene and 25-hydroxyvitamin D3 1- α -hydroxylase, the rate limiting enzyme in the production of active vitamin D3, has been found in several tissues and tumor types [43]. The active form of vitamin D3, 1,25-dihydroxyvitamin D3 (1,25D), exerts antitumor activity by binding to the vitamin D receptor (VDR). The antitumor activities of 1,25D include inhibition of cancer cell proliferation and angiogenesis, promotion of cell differentiation and apoptosis [44,45].

Şahin et al. [46] discovered that increased risk of thyroid cancer in patients with more IR than with Vitamin D3 deficiency and Whether they are coexisting or contributing is controversial [46] but this study involved a small number of thyroid cancer patients. Low vitamin D levels have been observed in autoimmune thyroid diseases, [47] with no correlation of thyroid autoantibodies and vitamin D levels.

Izkhakov et al. [48] showed that VDR mRNA expressed much more in malignant thyroid tissues than in normal thyroid tissues, that indicates a possible correlation between thyroid cancer prognosis and VDR gene expression [48]; however, there were no clinic pathological differences between patients with low levels of gene expression and those with high levels of gene expression. Clinckspoor et al. [49] reported that lower vitamin D3 metabolism was associated with the progression of thyroid cancer of follicular [49].

The very recent study Choi et al. [50] showed that overexpression of VDR mRNA correlates with subtypes of papillary thyroid carcinoma that have the worse prognosis, classic and tall cell variant, and factors associated with poor prognosis such as extra thyroidal extension, lateral neck node metastasis, BRAF V600E mutation and tumor recurrence [50].

So VDD may be implicated in increasing thyroid cancer incidence but whether it affect aggressiveness of the cancer or

not still controversial, and its deficiency should be associated with IR to cause thyroid malignancy still also not known [51].

Conclusion

Obesity, IR, and VDD are proved to be implicated in thyroid cancer incidence, but there relation to thyroid cancer aggressiveness still controversial, and whether vitamin D3 supplementation, physical activity, Drugs that decrease insulin resistance and diet may affect thyroid cancer prognosis and incidence still raw area for more researches

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