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Review

Metformin and thyroid; a narrative review to current concepts

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Abstract

Metformin has different metabolic effects on diverse tissues through various pathways such as hypothalamic-pituitary-thyroid axis. It is shown that metformin influence on thyroid structure considerably and reduced nodule volume by 30-50% of the first volume in diabetic patients. Besides, metformin shows anti-mitogenic and proapoptotic properties in thyroid cancer cells and enhances the antitumor effect of chemotherapeutic drugs. It prevents cancer growth by reduction of hyperinsulinemia too.

Keywords: Thyroid, Hypothyroidism, Metformin

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Relationship of diabetes and thyroid

An interesting field of investigation of thyroid diseases is the lately found link of insulin resistance with thyroid functional and structural irregularities. Thyroid disorders and diabetes mellitus are strictly associated. Thyroid disorders are more prevalent in diabetic patients than the public people. Recent studies interested to evaluate the effect of thyroid hormone on metabolism of food absorption and its components in certain tissues to elucidate the association of diabetes with hypothyroidism and offer suggestions for evaluating and therapy of this disorder during treatment with anti-hyperglycemia drugs (1).

Method of search

In this review, we analyzed several articles from the international scientific library databases to evaluate the therapeutic efficacy of curcumin in kidney diseases. We searched PubMed/Medline, Scopus and Google Scholar, using the following key words; thyroid, hypothyroidism, metformin, thyroid-stimulating hormone and thyroid disease.

Metformin and thyroid disease

Metformin is well recognized as a first-line drug for the control of diabetes. The report related to thyroid-stimulating hormone (TSH)-lowering effect of metformin in diabetic patients with hypothyroidism for first time was published in 2006 (2). Following reports have recommended that metformin may decrease serum TSH levels in patients with hypothyroidism in either patients treated with levothyroxine or untreated (3). A survey of researches assessing the effect of metformin therapy on thyroid function is reviewed by Pappa and Alevizakia (4). While the TSH reduction is analytically significant, in often studies the amount of decrease is small and not associated with variations in free thyroid hormone level. In two small scale preliminary studies, metformin lowered the increased TSH in patients with hypothyroidism caused by interferon or amiodarone that corresponded with its influence on insulin sensitivity (5,6). These two reports also discovered that the effect of metformin on activity of hypothalamic–pituitary–thyroid axis was partly linked to thyroid function. Moreover, metformin is not alone related to reduction TSH in diabetic patients with intact thyroid axis. The most of existing reports supports that metformin treatment is not associated to important change in TSH levels if there is normal thyroid function.

A meta-analysis on 206 patients evaluated the variations in serum TSH levels in following of metformin treatment against control. It involved seven studies, of which four studies were carried on 119 patients with overt hypothyroidism treating levothyroxine, two studies on 33 patients with subclinical hypothyroidism not treating levothyroxine and one study on 54 subjects with normal thyroid gland without any levothyroxine treating. Six studies involved diabetic patients and one study women with polycystic ovary syndrome (PCOS) treating with metformin. The results indicated that metformin decreases TSH levels in both overt and subclinical hypothyroidism

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Implication for health policy/practice/research/ medical education

Metformin may decrease serum TSH levels in patients with hypothyroidism in either patients treated with levothyroxine or untreated. Metformin may directly influence the thyroid hormones production.

whereas no alteration in TSH levels was detected in subjects with normal thyroid gland or hyperthyroidism (7). More marked investigations are required to explain the mechanisms of metformin action in the subjects with abnormal thyroid axis. While body mass index (BMI) stayed fixed in often studies, obesity and insulin resistance factors should be regarded and checked.

A retrospective study in seven community health center in Spain on 278 euthyroid diabetic subjects was conducted to assess the changes in serum TSH level after one year of metformin administration. In these specific subjects with normal thyroid gland, metformin looked to simulate a 'buffer effect' on thyrotrophic hormone release as it caused a restore in circulating TSH to 2.98 mU/L. In other words, metformin has a thyrotrophin reducing effect when TSH is higher than 2.98 mU/L (8). A retrospective study on 393 diabetic patients and a double-blind placebo-control clinical trial on 89 patients with prediabetes is revealed that metformin had a TSH reducing effect in patients with TSH levels higher than 2.5 mU/L (9,10). Therefore, a serum TSH threshold level of 2.5-3 mU/L can anticipate the effect of metformin on serum TSH.

A double-blind clinical trial, on 60 patients with metabolic syndrome assessed the effect of metformin on thyroid function in patients with subclinical hypothyroidism. Obtained results in this study showed that metformin decreases the TSH level principally in patients with a TSH level upper than 5 mIU/L and positive thyroid peroxidase antibody (TPO-ab positive) and increases free thyroxine. Increasing in free thyroxine level would be due to lose weight that was not detected after regulating data based on gender (11).

A study conducted on diabetic rat models and randomly classified into four groups, based on whether they were prompted to diabetic model or treated with metformin. It is discovered a mainly higher TSH and lesser free thyroxine in diabetic rats group, compared with control group, without significant alteration in free triiodothyronine level. It is detected that rats administered metformin exhibited indications similar to hyperthyroidism, for example weight loss, and a reduction in TSH and a significant increase in free thyroxine and free triiodothyronine levels, independent from whether they were simulated with diabetes disorder or not (12).

A study on overall 80 diabetic or pre-diabetic patients with age higher than 18 years with overt hypothyroid disorder treated with suitable and constant levothyroxine. The results of this study showed that metformin treatment is linked with an important decrease in the serum levels of TSH in overt hypothyroidism patients. TSH reduction is not accompanied with alternative variation in free thyroxine at three months but is associated with significant increase in free thyroxine level at half year and one year periods (13).

Metformin has different metabolic effects on diverse tissues through various pathways such as hypothalamic-pituitary-thyroid axis. The effect of metformin treatment on hypothalamic-pituitary-thyroid axis in 34 diabetic old women with subclinical hypothyroidism treated with antipsychotic agents is compared with not-treated antipsychotic agents. Glucose regulation indicators in addition to TSH levels, free thyroid hormones and prolactin were determined at the start of the study and after six months. Although metformin decreased serum TSH levels in two groups, this effect was further reported in the antipsychotic-treated against non-treated patients. The impact on TSH levels corresponded with enhancement in insulin sensitivity and with a decrease in prolactin levels. Thyroid hormones persisted non-change during the whole of the study (14). TSH-lowering effect of metformin is mainly reported in antipsychotic agents treated elderly women with reduced dopaminergic transmission (14). A recent prospective clinical trial comprising 24 prediabetic patients with PCOS and untreated subclinical hypothyroidism, 12 patients had already been administrated with bromocriptine while all patients treated with metformin during sox months. Metformin showed stronger TSH-lowering effect in patients not administrated with bromocriptine (over 60%) against that in administrated bromocriptine patients (about 30 %) (15).

Mechanism of metformin on thyroid

Numerous mechanisms have been suggested to explain TSH-lowering effects of metformin and there is not a unite theory at present. The relation of metformin-thyroid is complex and its properties are associated to the insulin sensitivity of metformin in target tissues (16). The hypothalamus-pituitary-thyroid axis controls the thyroid hormones production. Dominant effects of metformin on adjustment of hypothalamic-pituitary-thyroid axis might include the adenosine monophosphate-activated protein kinase (AMPK) system while metformin inhibit the activity of AMPK in the hypothalamus in opposition to its peripheral effects, which may influence on the activity of triiodothyronine on the hypothalamus, cause decrease TSH release (17).

Metformin may act on thyroid hormone receptors and on hypothalamic-pituitary-thyroid axis activity. Other the theoretical pathways for the TSH-lowering effect of metformin may be associated to the probable effect on thyroid hormone receptors or the variation of the activity of type II deiodinase at hypothalamus level (18). The type II deiodinase accelerate the transformation of thyroxine to the active triiodothyronine (19). Corresponding with

certain level of insulin resistance, type II deiodinase producing fewer triiodothyronine while metformin might increase activation of type II deiodinase in hypothyroid patients (20). Moreover, metformin may change the hippocampal expression in type III deiodinase and insulin-like growth factor 2 genes and hypothetically regularize the abnormal epigenetic information of them that influence on activity of the thyroid hormones (21,22).

Furthermore, other mechanism of metformin might be variations in the attraction, binding, bioavailability and metabolism of thyroid hormones receptors (4). Some authors opposed that metformin may increase gastrointestinal uptake of levothyroxine but it is not probable due to free thyroid hormones levels were not altered in total clinical studies and TSH values often reduced in individuals who did not administer levothyroxine (23). In several animal experimental studies it has been revealed that metformin can cross through the brain-blood barrier (BBB) and increase its level in the pituitary against other brain regions. However, the brain-blood barrier is well recognized for its extremely selective permeability and metformin has low molecular mass and is soluble in water, therefore, hypothetically is not capable to pass the BBB. So far, there is not report on the diffusion of metformin to the BBB in human body, thus, it persists to be investigated (24).

Interestingly, metformin was found to increase dopaminergic manner in the hypothalamus of obese females with insulin resistance and PCOS. Some studies show that the effect of metformin on pituitary cells function is partly linked with the variations in dopaminergic control of TSH release.

There are important gender variations in the distribution of dopamine receptors binding in the pituitary. Female and male rats varied in number and attraction of dopamine receptor and rate of release of dopamine in pituitary. Additionally, there is important distinction between female and male gender in AMPK activity in the brain that is based on estrogen steroid hormone (25). These differences in dopaminergic regulation may clarify reason that metformin effect on hypothalamic-pituitary-thyroid axis activity be more powerful in women than in men with subclinical hypothyroidism (14). These findings may describe why TSH-lowering effect in metformin was less expressed in bromocriptine treated than bromocriptine-non treated women and why bromocriptine partly avoided the TSH-lowering effect of metformin (26). It is proved that a reduction in TSH level in metformin treated patients at least partly derive from dopaminergic regulation of thyrotropin function. It is probable that action of metformin on functions of endocrine cells in the anterior pituitary is lesser if dopaminergic neurotransmission is increased, such that TSH-lowering effect is oppositely corresponded with level of dopaminergic activity. Cabergoline is a specific agonist for D2 dopamine receptors and its attraction for D1 receptors is very lesser than that of bromocriptine. Likewise, cabergoline fills dopamine binding sites for an extended duration of time against bromocriptine and is very slowly removed from the pituitary. Accordingly, its inducing effect on hypothalamic dopaminergic transmission is more powerful and enduring than that of bromocriptine. In comparison between bromocriptine and cabergoline, only in bromocriptine-treated patients, metformin decreased serum TSH in patients with subclinical hypothyroidism. These results show that the effect of metformin on the activity of hypothalamic-pituitary-adrenal axis is partly controlled by dopaminergic regulation, activity of endocrine cells in the anterior pituitary and insulin sensitivity (27).

Metformin and thyroid nodule and tumor

Current evidence verified that insulin as a growth factor accompanied by TSH induces proliferation of thyroid cells and may be complicated in the pathogenesis of thyroid cancer progress. Thus subjects with excess levels of insulin in blood have greater thyroid gland and a more incidence of thyroid nodules and cancer (28). Meanwhile, it is shown that metformin influence on thyroid structure considerably and reduced nodule volume by 30-50% of the first volume in diabetic patients (29). Besides, metformin shows anti-mitogenic and proapoptotic properties in thyroid cancer cells and enhances the antitumor effect of chemotherapeutic drugs (30). It prevents cancer growth by reduction of hyperinsulinemia and by reducing the mTOR pathway (31).

Sodium-iodide symporter (NIS)-induced iodine uptake is the first step of the synthesis of thyroid hormones. The employment of AMPK activator agents such as metformin may be beneficial for the amelioration expression of NIS and augmentation of iodide absorption by thyrocytes. Therefore, metformin may directly influence the thyroid hormones production of and then reduction the level of TSH (32).

Conclusion

Remarkably, no alterations in TSH levels were detected in individuals with normal thyroid function or hyperthyroidism, while TSH-lowering effect was detected in patients with increased levels of this hormone, deriving from either primary hypothyroidism or resistance to thyroid hormone.

Authors' contribution

Conceptualization, Methodology, Validation, Resources, Data Curation, Visualization, Supervision, Project Management: HN; Investigation: ZR; Writing—Original Draft Preparation: ZR & HN; Writing—Reviewing and Editing: ZR & HN

Conflicts of interest

HN and ZR are the researchers at Nickan Research Institute. The fore, their contributions with the journal have neither influenced the review process nor affected the acceptance of the manuscript.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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