Metformin and Thyroid: An Update

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Key Words

Metformin · Thyroid · Diabetes · TSH · Polycystic ovarian syndrome · Thyroid cancer

Abstract

Background: Metformin is one of the most widely prescribed antidiabetic medications with a favorable safety profile. In the last decade, several studies have reported a TSH-lowering effect of metformin in patients with diabetes mellitus. **Objective:** To review literature data on the role of metformin use on thyroid function tests and the course of thyroid cancer. **Methods:** We performed a search in the PubMed database using the terms: 'metformin', 'thyroid', 'TSH', 'diabetes', 'polycystic ovarian syndrome (PCOS)' and 'thyroid cancer'. **Results:** The majority of available evidence suggests that metformin therapy results in a modest reduction of TSH levels in diabetic and/or PCOS patients with thyroid disorder, while thyroid hormone levels remain unaltered. It appears that this effect is independent of thyroid autoimmunity and thyroxine treatment. However, metformin use in subjects with an intact thyroid axis is not associated with a significant change of TSH levels. Concerning thyroid cancer, there is experimental evidence showing antimetastatic properties of metformin in differentiated and medullary thyroid cancer cells. On the other hand, there is also data supporting that metformin administration inhibits iodine uptake by thyroid cells and thus may limit the effectiveness of radioactive iodine treatment. **Conclusions:** Most studies suggest a TSH suppressive action of metformin in subjects with overt or subclinical thyroid dysfunction, while

this is not apparent in euthyroid individuals. It appears that metformin has antimetastatic properties against various thyroid cancer types; however, experimental evidence of reduced efficacy of radioactive iodine treatment following metformin administration may limit its use in the management of differentiated thyroid cancer.

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Introduction

Metformin is well established as a first-line pharmacotherapy for the management of diabetes mellitus (DM). This biguanide is an insulin sensitizer mainly in the liver, but also in the muscle, that activates AMP-activated protein kinase (AMPK), an intracellular sensor of nutrient availability and regulator of energy homeostasis. This results in reducing hepatic gluconeogenesis and enhancing skeletal muscle glucose uptake [1]. Metformin is considered one of the safest antihyperglycemic agents. The main side effect is gastrointestinal (GI) intolerance, including diarrhea, nausea, dyspepsia, and abdominal pain. Although GI symptoms may be observed in up to 28% of patients, they are rarely the cause of discontinuation of therapy (in less than 2% of patients) [2–4]. The risk of lactic acidosis is considered negligible and seems to be associated with other comorbidities rather than the use of metformin [5].

In the last decade, several studies have reported a decrease in TSH levels following the administration of metformin in patients with DM or polycystic ovary syn-

drome (PCOS). The clinical implication of a TSH-lowering property for metformin could be important as an adjunct in the pharmacological treatment of thyroid cancer. In patients receiving thyroxine therapy for TSH suppression, the risk of arrhythmias and bone loss is a hindering factor and the use of a medication with TSH-lowering effects and a more than acceptable safety profile would be an attractive alternative. Furthermore, the increased prevalence of hypothyroidism in patients with DM is another factor illustrating the clinical relevance of metformin's effect on thyroid function tests [6].

In addition, various reports have linked metformin use with decreased cancer incidence and mortality [7–9]; however, the pathophysiologic pathways are not fully elucidated and some skepticism has been raised about observation bias, thus indicating the need for randomized controlled trials. Data on thyroid cancer is lacking, although such an effect might be of paramount interest as the incidence of the latter is rising rapidly.

This review provides a summary of the available data on studies linking metformin with thyroid profile alterations, and possible hypotheses explaining the underlying mechanisms are presented. Existing evidence on the role of metformin in the course of thyroid cancer is briefly discussed.

Clinical Studies

The majority of studies exploring the effect of metformin therapy on thyroid function have been performed in patients with type 2 DM and hypothyroidism. One of the first reports involved a retrospective study of 4 hypothyroid patients who received metformin for DM and non-alcoholic steatohepatitis. Metformin therapy resulted in a decrease of TSH, whereas free thyroid hormone (TH) levels remained steady and no subject experienced hyperthyroid symptoms [10]. Similar findings were shown in the study of Isidro et al. [11] in obese diabetic women with primary hypothyroidism; metformin treatment led to a significant reduction of TSH levels that was reversed when metformin was discontinued, whereas TH levels were unaltered. Interestingly, the degree of TSH reduction was associated with baseline TSH concentration. Since obesity and weight loss are known to interfere with thyroid function tests [12–14], the authors speculated that the fall of TSH might be associated with the significant weight reduction observed in the study participants.

In their recent studies, Cappelli et al. [15, 16] evaluated the effect of metformin in diabetic patients according to their thyroid status. In a study assessing 101 diabetic pa-

tients, short-term metformin therapy was associated with a significant decrease of TSH both in hypothyroid patients on thyroxine replacement and in patients with subclinical hypothyroidism who did not receive thyroxine therapy [15]. However, this was not the case in the group of euthyroid patients without any thyroid disorder, in which TSH concentration remained unchanged. In all groups, no significant alteration in free TH levels was reported. These findings were reproduced in their recent larger study of 393 euthyroid diabetic patients who were categorized into three age- and BMI-matched groups: 119 patients received neither metformin nor thyroxine treatment, 203 started only metformin therapy, and 71 patients were on both metformin and thyroxine [16]. TSH levels remained stable in the first group without any therapy, whereas a significant decline was shown in patients on metformin and thyroxine treatment independently of the baseline TSH concentration. Of note, in patients receiving metformin but not thyroxine, TSH levels were significantly reduced only in the subgroup with basal TSH levels over 2.5 mU/l and this was not associated with thyroid autoimmunity. Additionally, TSH decline was independently related to metformin treatment in the multivariate regression model. In all study groups, no change in free TH levels or BMI was reported.

In the same line, two studies have examined the result of metformin use in patients with PCOS, a population where the prevalence of hypothyroidism may be increased [17]. In the study of Rotondi et al. [18] short-term metformin therapy was associated with a significant reduction of TSH in PCOS women with overt or subclinical hypothyroidism regardless of thyroxine treatment, whereas no change in TSH levels was observed in euthyroid PCOS patients. Consistent with most previous studies, free TH concentration and BMI were steady in all groups. Likewise, in another study, after 6 months of metformin treatment TSH levels were markedly decreased in PCOS women compared to the placebo group, while free TH concentration were similar to baseline [19].

Of interest, in the case report of Krysiak and Okopien [20], metformin administration in a diabetic patient with generalized resistance to TH hormone led to a marked fall of TSH and TH levels along with laboratory evidence of enhanced sensitivity to TH action, i.e. increased heart rate and basal metabolic rate, as well as sex hormone binding globulin level. Given the ability of metformin to cross the blood-brain barrier and its high concentration in the pituitary, it was hypothesized that metformin may augment TH action centrally, while an effect also in the periphery cannot be excluded [21].

In summary, there is clinical data supporting a TSH suppressive effect of metformin in diabetic and/or PCOS patients with thyroid disorder independently of treatment with thyroxine. Although the fall in TSH levels is statistically significant, in most reports the degree of reduction is modest and not accompanied by alterations in free TH concentration. Furthermore, thyroid autoimmunity and obesity do not seem to be important factors in the interplay between metformin and thyroid profile. The retrospective nature of study methodology and the small number of participants, as well as the special population of diabetic and PCOS patients that these studies are performed in, represent limiting factors that should be considered in the interpretation of their findings.

There is some recent evidence that the relation between TSH values and metformin treatment may not be independent. In their cross-sectional study, Díez et al. [22] assessed 828 euthyroid diabetic patients without known thyroid dysfunction, 250 of whom were under metformin. TSH levels were significantly higher in patients on metformin treatment compared to metformin-naïve patients, a finding possibly attributed to the higher BMI of metformin-treated subjects. This finding was also confirmed when the analysis was performed separately in the group of patients without thyroid autoimmunity, but it was not reported for the remaining classes of antihyperglycemic medication. Furthermore, in the multivariate model TSH values were not related to metformin therapy. In the same direction, 3-month treatment with metformin did not result in a significant variation of TSH and TH levels in a study evaluating patients with abdominal obesity [23]. Of note, metformin treatment was recently identified as an independent risk factor for newly diagnosed hypothyroidism – either overt or subclinical – in patients with DM, along with thyroid autoimmunity and the presence of macroangiopathy; however, the diagnosis of hypothyroidism in that study was based on a single TSH and thyroxine measurement [24].

The majority of available evidence supports that in the presence of an intact thyroid axis, metformin treatment is not related to significant modification of TSH values. A summary of studies evaluating the effect of metformin treatment on thyroid function is presented in table 1.

Underlying Mechanisms

Several hypotheses have been addressed to interpret the association of metformin treatment with the decline in TSH levels; however, a unifying theory is currently

missing. The possibility that metformin might increase thyroxine absorption from the GI tract is not likely because free TH levels were unchanged in all clinical reports and TSH values also declined in subjects who did not receive thyroxine.

It has been demonstrated that metformin crosses the blood-brain barrier and a central mechanism of TSH inhibition could thus be an attractive explanation [21]. Even though it activates AMPK in the periphery, metformin suppresses AMPK activity in the hypothalamus and possibly counteracts hypothalamic T3 action on TSH secretion [25, 26]. There is also evidence that metformin treatment increases hypothalamic dopaminergic tone in association with improved insulin sensitivity [27].

Other hypotheses include changes in the affinity of TH receptors, TH binding, bioavailability and metabolism, induced constitutive activation of the TSH receptor, and interference with the TSH assay [10, 11, 15]. Additionally, it cannot be excluded that elevated TSH values may not necessarily reflect hypothyroidism, but could represent recovery from a nonthyroidal illness, mild resistance to TH, or obesity, as is the case in many patients with DM receiving metformin [28]. Against the latter hypothesis is the stable BMI on follow-up in most studies reporting a decrease of TSH levels after metformin administration.

Despite the absence of clear-cut data, merging the hypothesis of a central action of metformin to enhance dopaminergic tone and taking into account the relevance of insulin resistance, which is a common component in diabetes, PCOS and possibly hypothyroidism, might be a rational approach to further investigate this association.

Metformin and Thyroid Cancer

There is accumulating literature data on the beneficial role of metformin in the prevention and management of cancer. Two major hypotheses explaining the potential anticancer properties of metformin include the improvement of insulin sensitivity and thus the inhibition of an insulin-induced mitogenic pathway, as well as the activation of AMPK, which induces catabolism and downregulates cell proliferation by mimicking a state of caloric deprivation [7, 29]. A recent review has provided an update on the potential role of metformin against cancer and a summary of metformin's suggested anticancer mechanisms of action is briefly presented in table 2 [30–33].

Table 1. Summary of clinical studies evaluating the result of metformin therapy on thyroid function tests

Author	Study type	Study population	Indication for metformin treatment	Effect of metformin on TSH levels	Effect of metformin on thyroid hormone levels
Vigersky et al. [10]	retrospective	4 hypothyroid patients	DM and nonalcoholic steatohepatitis	decrease	no change
Isidro et al. [11]	prospective 3-month follow-up	8 obese hypothyroid postmenopausal women	DM	decrease associated with baseline TSH; reversal after metformin withdrawal	no change
Cappelli et al. [15]	prospective 1-year follow-up	29 hypothyroid patients on thyroxine treatment 18 patients with subclinical hypothyroidism without treatment 54 euthyroid subjects without thyroid dysfunction	DM	decrease in patients with overt and subclinical hypothyroidism; no change in euthyroid subjects	no change
Cappelli et al. [16]	retrospective	119 patients not receiving metformin or thyroxine 203 patients under metformin therapy 71 patients under metformin and thyroxine therapy	DM	no change in patients not receiving any treatment; decrease in patients under metformin only in the subgroup with baseline TSH over 2.5 mIU/l; decrease in patients under metformin and thyroxine independent of baseline TSH	no change
Rotondi et al. [18]	prospective 4-month follow-up	7 hypothyroid women on thyroxine 2 women with subclinical hypothyroidism without treatment 24 euthyroid women	PCOS	decrease in women with overt and subclinical hypothyroidism; no change in euthyroid women	no change
Morteza Taghavi et al. [19]	case-control 6-month follow-up	15 overweight hypothyroid women receiving metformin 12 overweight hypothyroid women on placebo	PCOS	decrease only in the group receiving metformin	no change
Krysiak et al. [20]	case report	28-year-old male with resistance to thyroid hormone	DM	decrease	decrease
Díez et al. [22]	retrospective cross-sectional	828 euthyroid patients 250 patients under metformin therapy	DM	higher TSH levels in patients on metformin compared to patients without metformin treatment; no independent relation of TSH with metformin therapy	not evaluated
Oleandri et al. [23]	prospective 3-month follow-up	28 normotensive patients receiving metformin (n = 10), dextfenfluramine (n = 10), or placebo (n = 8)	abdominal obesity	no change	no change
Díez and Iglesias [24]	case-control	1,112 diabetic patients 911 patients without DM	DM	metformin treatment an independent risk factor for newly diagnosed hypothyroidism	

Concerning the effect of metformin on thyroid tumors, it is worth mentioning that metformin treatment resulted in a significant decrease in the nodular size (30–55%) in insulin-resistant patients with thyroid nodules, possibly through its action on the insulin signaling pathway [34]. Interestingly, it was recently reported that metformin exerts an antimitogenic and proapoptotic effect in thyroid carcinoma cell lines and augments the antiproliferative effect of chemotherapeutic agents, such as doxorubicin and cisplatin. Furthermore, it was found to inhibit insulin-induced growth stimulation

not only in differentiated and undifferentiated thyroid carcinoma, but also in thyroid cancer stem cells; it appears that these actions are mediated via interference with the insulin/IGF signaling and the AMPK/mTOR pathway [35]. Similarly, treatment with metformin suppressed growth and metastatic potential in medullary thyroid carcinoma cells by downregulating the mTOR pathway [36]. These observations suggest that metformin might have a role as an adjuvant therapy in the management of thyroid cancer, especially in diabetic patients.

Table 2. Summary of metformin's potential mechanisms of action against cancer

	Suggested anticancer mechanisms
Obesity	prevention of weight gain
Cellular energy stress	reduction of hepatic gluconeogenesis→ lower hepatic glucose output→ decrease of hyperinsulinemia → reduction of cell proliferation; decline in ATP and oxygen consumption → AMPK activation → downregulation of energy consumption → reduced growth; cell cycle arrest and apoptosis in the absence of tumor-specific compensatory mechanisms; reduction of reactive oxygen species→ decreased DNA damage and mutation; mTOR inhibition → downregulation of the growth factor signaling pathway
Breast cancer	mTOR inhibition → reduction of HER-2 protein expression
Prostate cancer	combination of metformin with androgen deprivation therapy may lower castration-induced hyperinsulinemia and inhibit the stimulating effect of insulin on intratumoral androgen synthesis, tumor growth, and eventually castration resistance [32]
Interaction with other drugs	cotreatment with a statin may be necessary for a significant antineoplastic action; protein pump inhibitors may limit metformin's uptake in the cells

However, there is some experimental data that should also be taken into account. In an animal model it was shown that the activation of AMPK results in decreased Na^+/I^- symporter activity and iodine uptake by the thyroid gland and that TSH suppresses AMPK phosphorylation and activation [37]. This was also confirmed by other researchers and this process appears to be regulated at the transcriptional level [38, 39]. In addition, Andrade et al. [40] found that AMPK activation enhances glucose uptake in thyroid cells by upregulating GLUT1 content and hexokinase activity independently of TSH. Altogether, these findings pose skepticism on the possible hampering effect of metformin on radioactive iodine treatment of differentiated thyroid cancer. It is rather premature to draw definite conclusions whether the promising evidence of metformin's antiproliferative action on thyroid cancer cells outweighs the potential limitation of its clinical application due to reduced radioactive iodine effectiveness. One cannot exclude the possibility that in the future metformin might have a role in iodine refractory thyroid cancer. However, further studies are needed before this possibility is considered.

Conclusions

The majority of studies reviewed in this update suggest a TSH suppressive action of metformin in subjects with overt or subclinical thyroid dysfunction regardless of thyroxine treatment and the presence of thyroid autoimmunity. Of note, the decline of TSH values is not ac-

companied by a change in free THs. It seems that in euthyroid individuals, metformin has no significant impact on thyroid function tests. Although BMI remained steady in most studies, obesity and insulin resistance are factors that should be considered and controlled for. Various explanations have been proposed to provide a pathophysiological background of the relation between metformin and TSH decline, and pathways implicating central effects of metformin should be further explored. Concerning the clinical relevance of the metformin-induced effects on TSH levels, thyroid function surveillance in diabetic and/or PCOS patients with hypothyroidism starting treatment with metformin should probably be applied in everyday practice. Furthermore, the possible adjunctive role of metformin in the TSH suppression therapy of patients with thyroid cancer in order to minimize bone and heart side effects induced by high thyroxine doses is a very appealing approach and merits further investigation.

Concerning thyroid cancer, it cannot be excluded that metformin has antimitogenic properties against various cancer types that could be used in the clinical setting; however, experimental evidence of diminished efficacy of radioactive iodine treatment following metformin administration requires investigation and may limit this possibility in the care of thyroid cancer.

Disclosure Statement

The authors have nothing to disclose.

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