Metformin and thyroid disease

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Abstract

An intriguing area of research in thyroidology is the recently discovered association of insulin resistance with thyroid functional and morphological abnormalities. Individuals with hyperinsulinemia have larger thyroid gland and a higher prevalence of thyroid nodules and cancer. Accordingly, patients treated with metformin have a smaller thyroid volume and a lower risk of incident goiter, thyroid nodule and cancer. Multiple studies *in vitro* and *in vivo* have demonstrated that metformin can inhibit the growth of thyroid cells and different types of thyroid cancer cells by affecting the insulin/IGF1 and mTOR pathways. Besides, metformin treatment was associated with a decrease in the levels of serum thyroid-stimulating hormone (TSH) in diabetic patients possibly by enhancing the effects of thyroid hormones in the pituitary and activating the adenosine monophosphate-activated protein kinase (AMPK). Based on this evidence, metformin appears to be a promising therapeutic tool in patients with thyroid disease. More clinical studies are necessary to evaluate the clinical significance of metformin for the treatment of thyroid diseases.

Key Words

- ▶ metformin
- ▶ thyroid disease
- ▶ thyroid nodule
- ▶ thyroid cancer
- ▶ thyrotropin

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Introduction

Metformin, the most widely used antidiabetic drug, is considered as the cornerstone of type 2 diabetes treatments. Surprisingly, a few years ago, it has been reported that serum TSH level in hypothyroid patients decreased in response to metformin therapy and increased again when metformin was discontinued (Vigersky *et al.* 2006). Later, this finding has been confirmed by several studies.

The novel effects of metformin on the thyroid were not confined to hypothyroidism. Prospective and retrospective studies showed that patients with prediabetes and type 2 diabetes mellitus (T₂DM) had a significantly increased thyroid volume and a higher prevalence of incident goiter and nodules. Furthermore, diabetic patients treated with metformin had a smaller thyroid volume and a lower risk

for the formation of thyroid nodules when compared with controls (Anil *et al.* 2013, Ittermann *et al.* 2013, Blanc *et al.* 2015). These results suggested that metformin exerts an anti-proliferative activity, providing a rationale for an innovative therapy of thyroid proliferative diseases with metformin.

Metformin and thyroid function

Metformin and hypothyroidism

A retrospective review of 4 patients with chronic hypothyroidism suggested that metformin is involved in reducing TSH level (Vigersky *et al.* 2006). It is worth noting that this was an isolated effect on TSH

without any relevant changes in serum thyroxine (T_4) and triiodothyronine (T_3) levels. After this first report, great interest has aroused in the effects of metformin on thyroid function in patients with T_2 DM. A meta-analysis including 7 studies that evaluated changes in TSH levels in patients receiving metformin, showed a reduction of TSH levels both in overt and in subclinical hypothyroidism, with no change in euthyroid patients (Lupoli *et al.* 2014).

Following these initial findings, a number of studies were performed to elucidate the effect and mechanism of metformin on TSH level (Table 1). In a longitudinal population-based study, 5689 T_2 DM patients treated for hypothyroidism and 59,937 euthyroid patients with T_2 DM were included (Fournier *et al.* 2014). Metformin monotherapy was associated with an increased risk of low TSH levels in patients with treated hypothyroidism, whereas this was not observed in euthyroid patients. In a retrospective clinical study, Distiller *et al.* (2014) revealed an association not only between diabetes and hypothyroidism but also between the metformin therapy and a significantly lower prevalence of diagnosed hypothyroidism.

However, contradictory results have also been reported. A retrospective study was conducted to evaluate the variation in serum TSH level after 1 year of metformin treatment in 278 euthyroid diabetic individuals (Santos-Palacios *et al.* 2015). In this particular population, metformin seemed to induce a 'buffer effect' on TSH secretion as it induced a return in circulating TSH to the middle of its normal range with the threshold point level defined as 2.98 mU/L. In other words, metformin has a lowering effect on TSH level when TSH is higher than 2.98 mU/L, whereas this effect is the opposite in those individuals with a serum TSH level lower than 2.98 mU/L. Karimifar *et al.* (2014) randomly treated 89 people with prediabetes (impaired fasting blood glucose values of 100–125 mg/dL, and/or 2-h postprandial blood glucose values of 140–199 mg/dL during OGTT) with metformin or placebo for a period of 3 months. In this double-blind placebo-control clinical trial, metformin treatment was associated with a decrease in the levels of serum TSH only in those patients with TSH $>2.5 \mu\text{U/mL}$. Furthermore, the aforementioned thyrotropin-lowering effect of metformin was not observed in subclinical hyperthyroid subjects with coexistent T_2 DM (Krysiak *et al.* 2015). Therefore, the clinical consequences of the effect of metformin treatment on TSH level need further investigations.

Mechanism of action on thyroid function

Metformin is the most widely prescribed insulin-sensitizing agent in diabetic patients; however, cellular and molecular mechanism of metformin action is complex and multifactorial. It is active at all sites of impaired insulin action (Giannarelli *et al.* 2003). At the level of the liver, metformin increases insulin-mediated suppression of hepatic glucose production, mainly by reducing gluconeogenesis. In skeletal muscle it promotes insulin receptor phosphorylation, glucose transporter (GLUT)-4 translocation resulting in increased glucose uptake and glycogen synthesis. In adipose tissue, metformin promotes the re-esterification of free fatty acids and inhibits lipolysis, which may indirectly improve insulin sensitivity through reduced lipotoxicity. Thus, many of the metabolic alterations brought about by insulin resistance (IR) are improved by metformin (Giannarelli *et al.* 2003). Although a number of hypotheses have been put forward, no study has so far elucidated the mechanism in detail.

Metformin is hypothesized to change the affinity and/or quantity of thyroid hormone receptors, increase the central dopaminergic tone or induce activation of the TSH receptor, thus enhancing the effects of thyroid hormones in the pituitary (Vigersky *et al.* 2006). In a case report of a 28-year-old male with resistance to thyroid hormone, metformin-induced hyperthyroidism, normalized altered circulating levels of peripheral markers of thyroid hormone action and required a temporary reduction in the levothyroxine dose (Krysiak & Okopien 2011). The interesting finding suggested that metformin may modulate hypothalamic–pituitary–thyroid axis activity at the levels of peripheral tissues and by its impact on the thyroid gland itself.

In a recent prospective clinical trial including 24 prediabetic patients with polycystic ovary syndrome (PCOS) and untreated subclinical hypothyroidism, 12 patients had already been treated with bromocriptine. After metformin treatment of all patients for 6 months, thyrotropin-lowering effect of metformin was stronger in patients not treated with bromocriptine than that in patients receiving bromocriptine. The results indicated that metformin treatment may have an impact on thyrotropin function in hypothyroid patients, in part, associated with the changes in dopaminergic regulation of thyrotropin secretion and is less pronounced in patients receiving bromocriptine treatment (Krysiak & Okopien 2015). Recently, metformin was found to be able to cross the blood–brain barrier (BBB) in rat and

Table 1 Summary of studies on metformin and thyroid function.

Study type	Population	Numbers	Summary of findings	Reference
Retrospective study	Patients with chronic hypothyroidism on fixed doses of L-T ₄	4 individuals	Initiation of treatment with metformin caused suppression of TSH to subnormal levels.	Vigersky et al. 2006
Three-month prospective study	Obese, diabetic postmenopausal women with primary hypothyroidism	8 individuals	Short-term metformin administration is associated with a significant fall in TSH in obese, diabetic patients with primary hypothyroidism on thyroxine replacement treatment.	Isidro et al. 2007
One-year case–control study	Diabetic patients including euthyroid patients on L-T ₄ substitution, subclinical hypothyroid patients who did not receive L-T ₄ treatment and euthyroid patients	101 individuals	A significant TSH decrease associated with metformin administration was observed in diabetic subjects with hypothyroidism who were either treated or untreated with L-T ₄ , but not in euthyroid subjects.	Cappelli et al. 2009
Six-month prospective, placebo-controlled study	Overweight women with PCOS and primary subclinical hypothyroidism	27 individuals	In overweight PCOS patients with primary hypothyroidism, treatment with metformin resulted in a significant fall in TSH.	Morteza Taghavi et al. 2011
Four months case–control study	Patients with PCOS, including hypothyroidism treated with levothyroxine, untreated subclinically hypothyroidism, euthyroid	33 individuals	Metformin administration has a TSH-lowering effect in diabetic patients on L-T ₄ treatment and shows a significant reduction of TSH also in euthyroid patients with higher baseline.	Rotondi et al. 2011
Retrospective study	Euthyroid diabetic patients, including subjects never treated with metformin and L-T ₄ ; subjects started metformin treatment at recruitment; patients on L-T ₄ who started metformin recruitment	393 individuals	Metformin administration has a TSH-lowering effect in diabetic patients on L-T ₄ treatment and shows a significant reduction of TSH also in euthyroid patients with higher baseline.	Cappelli et al. 2012
Retrospective study	Euthyroid patients with T ₂ DM females	828 individuals	Metformin administration has no relationship between TSH values and thyroid function in euthyroid T ₂ DM patients.	Díez & Iglesias 2013
Retrospective study	Overweight and obese subjects with or without diabetes	108 individuals	Metformin treatment seems to affect thyroid function in diabetic patients by maintaining plasma thyrotropin levels to subnormal levels.	Kouidhi et al. 2013
Longitudinal population-based study	T ₂ DM patients with or without hypothyroidism	A total of 5689 patients with treated hypothyroidism and 59,937 euthyroid patients were included in the subcohorts	Metformin use was associated with an increased incidence of low TSH levels in patients with treated hypothyroidism, but not in euthyroid patients. The clinical consequences of this need further investigation.	Fournier et al. 2014
Retrospective study	T ₂ DM patients with or without hypothyroidism	922 individuals	The use of metformin therapy in people with T ₂ DM diabetes was associated with a significantly lower prevalence of diagnosed hypothyroidism.	Distiller et al. 2014

(Continued)

Table 1 Continued.

Study type	Population	Numbers	Summary of findings	Reference
Three-month placebo-controlled clinical trial	Prediabetic people	89 individuals	In prediabetic people, metformin decreases serum TSH, only, in those people with TSH >2.5 µU/mL.	Karimifar <i>et al.</i> 2014
Retrospective study	Patients without hypothyroidism	278 individuals	Metformin seems to induce a 'buffer effect' on TSH secretion in euthyroid diabetic individuals.	Santos-Palacios <i>et al.</i> 2015
Three- and 6-month of prospective study	T ₂ DM patients with subclinical hyperthyroidism	42 individuals	Metformin has a negligible effect on hypothalamic-pituitary-thyroid axis activity in T ₂ DM patients with subclinical hyperthyroidism.	Krysiak <i>et al.</i> 2015
Six-month prospective study	Prediabetic patients with polycystic ovary syndrome and untreated subclinical hypothyroidism	24 individuals	Metformin treatment may have an impact on thyroid function in hypothyroid patients, probably by enhancing the effect of thyroid hormone action in the pituitary.	Krysiak <i>et al.</i> 2015
Six-month prospective study	Amiodarone-treated patients with T ₂ DM patients: patients with treated overt hypothyroidism, patients with untreated subclinical hypothyroidism	48 individuals	The obtained results indicate that the effect of metformin on hypothalamic-pituitary-thyroid axis activity is partially related to thyroid function. Metformin treatment may bring clinical benefits to patients with amiodarone-induced hypothyroidism and poor tolerance of exogenous L-thyroxine.	Krysiak <i>et al.</i> 2016a
Four-month Pilot study	Two matched groups of women with type 2 diabetes and untreated subclinical hypothyroidism	20 individuals	The effect of metformin on serum thyrotropin was stronger in patients with interferon-induced thyroiditis than in patients with Hashimoto's thyroiditis, as well as correlated with its impact on insulin sensitivity.	Krysiak <i>et al.</i> 2016b
Four-month prospective study	Patients with subclinical hypothyroidism	35 individuals	Sex may determine the effect of metformin on hypothalamic-pituitary-thyroid axis activity.	Krysiak <i>et al.</i> 2016c

penetrate the BBB reaching much higher levels in the pituitary than that in other brain regions (Labuzek *et al.* 2010). Impressively, pituitary gland is the brain region with the highest metformin accumulation achieved after its acute and chronic administration. Its concentration in the hypothalamus matched the level in plasma. Another study found that metformin induced upregulation of BBB actions via AMPK activation (Takata *et al.* 2013). However, the BBB is well known for its highly selective permeability, which allows the passage of water, some gases and lipid-soluble molecules by passive diffusion, as well as the selective transport of molecules such as glucose and amino acids that are crucial to neural function. Theoretically, metformin is not able to cross the BBB due

to its low molecular mass (168Da) and water solubility. No studies on the penetration of metformin to the BBB in human body have been performed so far; therefore, it still remains to be determined.

Other authors suggested that TSH-lowering effect of metformin may be explained by a metformin-induced activation of the adenosine monophosphate-activated protein kinase (AMPK), which is involved in a variety of cellular functions and regulates cellular energy metabolism (Duntas *et al.* 2011). Indeed, it may be plausible that any central effects of metformin on the TRH/TSH regulation involve the AMPK system. Metformin is proved to have an inhibitory effect on AMPK activity in the hypothalamus where it opposes T₃ (Alevizaki 2013).

Another link between metformin and TSH may be IR. In a pilot study, metformin reduced elevated thyrotropin level in patients with interferon-induced hypothyroidism, as well as correlated with its impact on insulin sensitivity (Krysiak *et al.* 2016b). However, its clinical relevance is still unknown. A new study has found that in patients with T₂DM and untreated amiodarone-induced hypothyroidism, metformin reduced serum level of thyrotropin and this effect correlated weakly with its action on insulin sensitivity (Krysiak *et al.* 2016a). This study also found that the effect of metformin on hypothalamic–pituitary–thyroid axis activity was partially related to thyroid function. Besides, metformin is not independently associated with TSH in T₂DM patients with normal thyroid axis. More targeted studies are demanded to clarify the mechanisms of metformin action in the cases with activated TSH axis. A recent study has indicated that sex may determine the effect of metformin on hypothalamic–pituitary–thyroid axis activity, and only in women, metformin decreased serum TSH levels (Krysiak *et al.* 2016c).

Furthermore, it seems to be unlikely that metformin enhances gastrointestinal absorption of thyroid hormones in patients with hypothyroidism. In most studies, there was no increase of serum thyroid hormone level in response to metformin, irrespective of thyroxine replacement or not. A clinical study concluded that levothyroxine (L-T₄) absorption is unchanged by concomitant metformin intake (Al-Alusi *et al.* 2015). In addition, metformin is not known to increase the absorption of any other nutrients or drugs.

Clinical implications

If the effect of metformin on TSH suppression is confirmed, metformin may be a useful adjunct for TSH suppression therapy as it appears to suppress serum TSH without causing biochemical hyperthyroxinemia or clinical hyperthyroidism. On the flip side, it increases the complexity of monitoring thyroid functional status in diabetic patients on metformin. Depressed TSH level provides false reassurance or may prompt initiation of therapy or endocrinologists may decrease L-T₄ dosage with spuriously low TSH level. The clinicians should consider the effect of metformin when they interpret thyroid function to avoid any appropriate treatment or adjustment of L-T₄ dosage.

Metformin and thyroid nodule and tumor

The pathogenesis of thyroid nodule

Thyroid gland is a frequent site of abnormal epithelial cell proliferation, as demonstrated by the fact that the incidence of thyroid proliferative disease has risen rapidly over the past few years. Formation of thyroid nodule is due to the local enlargement of the thyroid caused by excessive growth and structural transformation of one or several areas within the normal thyroid gland. The etiology seems to involve complex interactions between environmental, iodine status, genetic and endogenous factors (Derwahl & Studer 2001).

Recent findings demonstrated that insulin as a growth factor along with TSH stimulates thyroid cell proliferation and might be involved in the pathogenesis of thyroid growth and cancer development (Gursoy 2010). Patients with IR have larger thyroid volumes and higher risk for formation of thyroid nodules, and higher circulating levels of insulin are thought to increase thyroid proliferation and formation of thyroid nodules (Ittermann *et al.* 2013, Ogbera *et al.* 2012). One study hereof worth mentioning showed that development of thyroid nodule may depend on IR: in patients with small benign thyroid nodules and IR, metformin therapy was accompanied by a reduction in the nodular size, which was paralleled by a fall in TSH (Rezzonico *et al.* 2011). TSH via cAMP, and various growth factors, cooperated with insulin or insulin growth factor (IGF)-1 stimulates cell cycle progression and proliferation in various thyrocyte culture systems and primary cultures of different thyroid cell types (Kimura *et al.* 2001) (Fig. 1). On the other hand, 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 (Baser *et al.* 2016). This effect, at least in part, is mediated via IGF-I-dependent pathway; therefore, IGF1 might be involved in the pathogenesis of thyroid nodular growth and cancer development.

More importantly, rising world-wide incidence of thyroid cancer is also believed to be related to IR (Rezzonico *et al.* 2009), explained insulin/IGF1-mediated growth stimulation. The insulin growth factors (IGFs) are potent mitogenic and anti-apoptotic factors and play a major role in a variety of human malignancies, including thyroid tumors (Kimura *et al.* 2001). The role of insulin itself in the pathogenesis

Figure 1

TSH and insulin/IGF1 axis in nodule formation. Insulin along with TSH functions as a growth factor and stimulates thyroid cell proliferation and might be involved in the pathogenesis of thyroid morphological abnormalities. The classical TSHR, MAPK and mTOR pathways acts on downstream effectors to modulate regulation of thyroid gene expression and other processes that may relate to thyrocyte proliferation, differentiation, malignant transformation. Arrows represent activation. This schematic overview shows the most important factors of the associated signaling network. Not all members of the signaling pathway are illustrated in order to be simplified.

of cancer is still debated, as insulin is not produced locally in thyroid cancer. However, its receptor may be activated by insulin homologs IGF1 and IGF-2, potent mitogenic factors produced locally in thyroid cancers (Díez & Iglesias 2013). It was observed that expression of insulin receptor was increased in hypofunctioning benign thyroid adenomas, which lost differentiated functions such as iodine uptake. Therefore, overexpression or activation of insulin receptor may be an early event in thyroid tumorigenesis and nodular formation.

Metformin and IR in thyroid nodules

Metformin was found to antagonize the growth-stimulatory effect of insulin *in vitro* (Chen *et al.* 2012). With addition of metformin, the insulin-induced increase of cell proliferation was almost abolished. As stated previously, hyperinsulinemia in patients with T₂DM

and/or prediabetes is associated with a higher incidence of benign and malignant tumors. A recent cross-sectional study also found a significant correlation between glycated hemoglobin and thyroid volume or the number of nodules (Blanc *et al.* 2015). Therefore, as an effective insulin-sensitizing drug, metformin may play a significant role in the adjuvant therapy of proliferative disease.

Given the impact of IR on the thyroid gland, Rezzonico *et al.* (2011) reported a retrospective study on 66 women with IR and nodular hyperplasia. A more pronounced reduction in nodule size was seen in patients treated with both metformin and L-T₄ compared to that in patients on metformin alone. The effect of metformin on shrinkage of thyroid nodule was accompanied by a fall in TSH concentration and normalization of the homeostasis model assessment (HOMA) index. Another randomized aforementioned placebo-controlled clinical trial also indicated that metformin can reduce the size of small solid thyroid nodules and prevent an increase

in the thyroid volume (Karimifar *et al.* 2014). Recently, a preliminary study also found that metformin therapy significantly decreased thyroid volume and nodule size in subjects with IR (Anil *et al.* 2016). Therefore, in patients with IR and nodular goiter, metformin may be a useful drug both to decrease IR and the size of solid nodules. By taking the role of TSH and IR in nodule formation into account, metformin may also be effective on prevention or treatment of thyroid nodule.

Metformin and thyroid carcinoma

Previous epidemiological studies have shown a positive relationship between IR and several common adult cancers, including differentiated thyroid carcinoma (DTC) (Gursoy 2010). Given the metformin-mediated improvements in insulin sensitivity, it was speculated that metformin results in a decreased prevalence of both IR and thyroid carcinoma. In fact, clinical trials have demonstrated that treatment with metformin was associated with higher remission rate and survival in diabetic patients with thyroid cancer (Klubo-Gwiezdzinska *et al.* 2013), and a favorable outcome in diabetic patients with cervical lymph node metastasis of DTC (Jang *et al.* 2015). Another large observational study in Taiwanese patients with T₂DM showed that metformin reduced thyroid cancer risk (Tseng 2014). In a mouse model, metformin could block progression of obesity-activated thyroid cancer (Park *et al.* 2016). An opposite finding from Becker *et al.* (2015) indicated neither use of metformin nor of other antidiabetic drugs was associated with a decreased risk of thyroid cancer in a case-control study. Besides, a recent retrospective analysis found that metformin attenuated a 131I-induced decrease of peripheral blood cells in patients with DTC (Bikas *et al.* 2016).

Metformin was proved to inhibit the TNF- α -induced CXCL8 secretion in primary cultures of human thyroid cells, acting as a further indirect anticancer property of the drug (Rotondi *et al.* 2015). Besides, *in vitro* study, our study showed that metformin exerted a growth-inhibitory effect on primary thyrocytes and thyroid cancer cells by reducing hyperinsulinemia and by a direct cellular action, including inhibition of cell cycle progression and induction of apoptosis (Chen *et al.* 2012). Metformin markedly diminished growth stimulation by insulin on differentiated human thyroid cells, anaplastic thyroid carcinoma cells, a doxorubicin-resistant thyroid carcinoma cell line and thyroid cancer stem cells. In addition, an additive antimitogenic effect on

chemotherapeutics agents was observed. In a recent study, sorafenib, a multikinase inhibitor used as alternative therapy for radioiodine-resistant DTC, combined with metformin synergistically decreased the proliferation of anaplastic thyroid cancer cell lines and the outgrowth of derived cancer stem cells (Chen *et al.* 2015). In papillary thyroid cancer, the therapeutic potential of metformin has also been identified both *in vitro* and *in vivo* (Cho *et al.* 2014). Another study on medullary thyroid carcinoma (MTC) cell lines showed that metformin inhibited growth and induced anoikis in MTC-derived cells, suggesting that metformin inhibits growth and prevents the development of metastases in MTC (Klubo-Gwiezdzinska *et al.* 2012). In addition, metformin may inhibit the growth, migration and mesenchymal transition of thyroid cancer cell lines by the mTOR pathway beyond insulin/IGF1 pathway (Han *et al.* 2015).

The suppressive effect of metformin on TSH level suggests a need for dose reduction of L-T₄ in postoperative hypothyroid patients receiving TSH-suppressive therapy and metformin treatment. In a retrospective clinical study on patients undergoing total thyroidectomy, for TSH suppression, a lower thyroxine dose was observed in patients treated with metformin, when compared to that in patients without metformin (Casteras *et al.* 2013). However, the results of this study were controversially discussed due to different characteristics (greater weight and age) of the patients in metformin-treated and control groups. Another single-blind randomized controlled trial found that adding 500mg of metformin did not enable L-T₄ dose reduction in patients with DTC (Mousavi *et al.* 2014). On the other hand, we have to take this fact with caution as the effect of metformin can be related to changes in the hypothalamus-pituitary axis, and the dose reduction may cause symptoms of hypothyroidism to patients as peripheral tissues may need more L-T₄. Therefore, the exact role of metformin in patients on TSH-suppressive therapy after ablative treatment for thyroid cancer is still the subject of discussion.

Conclusions and future perspectives

In the last decade, several clinical studies demonstrated that metformin may have a TSH-lowering effect. Apart from this, metformin was found to reduce the nodular volume, inhibit the growth of thyroid carcinoma and potentiate the antimitogenic effect of chemotherapeutic agents. 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 associated studies are necessary to analyze the effects of metformin in these patients.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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