Original Paper

Medical Principles and Practice

Med Princ Pract 2016;25:233–236
DOI: 10.1159/000442821

Received: October 12, 2014
Accepted: November 29, 2015
Published online: November 30, 2015

Metformin Decreases Thyroid Volume and Nodule Size in Subjects with Insulin Resistance: A Preliminary Study

Cuneyd Anil[a] Altug Kut[b] Berna Atesagaoglu[a] Asli Nar[a]
Neslihan Bascil Tutuncu[a] Alptekin Gursoy[a]

Departments of [a]Endocrinology and Metabolism and [b]Family Medicine, Baskent University Faculty of Medicine, Ankara, Turkey

Key Words
Insulin resistance · Metformin · Thyroid volume · Nodule size

Abstract
Objective: The aim of this study was to investigate the effects of metformin on thyroid volume and nodule size. ***Subjects and Methods:*** Prospective data were gathered on 100 newly diagnosed subjects with insulin resistance (68 female, 32 male) between August 2008 and May 2010. Each subject followed a standard diet and exercise program, and received 1,700 mg/day of metformin therapy for 6 months. The height, weight, waist circumference (WC) and thyroid hormone levels of each subject were measured. Additionally, the dimensions of the thyroid lobes and maximum diameter of each thyroid nodule were determined by ultrasonography. BMI and thyroid volumes were also calculated. Insulin resistance was estimated by homeostasis model assessment. All these parameters were measured at the beginning and at the end of the treatment period. ***Results:*** BMI and WC decreased significantly after metformin therapy (34.5 ± 5.1 vs. 32.7 ± 4.8, $p < 0.0001$, and 106.3 ± 11.8 vs. 101.8 ± 19.0 cm, $p = 0.008$, respectively). Insulin resistance also decreased after metformin therapy (4.5 ± 1.9 vs. 2.9 ± 1.7, $p < 0.0001$). The mean thyroid volume (22.5 ± 11.2 vs. 20.3 ± 10.4 ml, $p < 0.0001$) and mean thyroid nodule size (12.9 ± 7.6 vs. 11.7 ± 7.2 mm, $p < 0.0001$) also decreased after treatment. ***Conclusion:*** In subjects with insulin resistance, metformin therapy significantly decreased thyroid volume and nodule size.

Introduction

Previous studies have reported the effect of insulin resistance (IR) on thyroid volume and nodule prevalence [1, 2]. The concept that insulin concurrently functions with thyroid-stimulating hormone (TSH) as a growth factor and stimulates thyroid cell proliferation [3] has also been reported. This proliferative effect on thyrocytes is partially mediated via insulin-like growth factor 1 (IGF-1)-dependent mechanisms; therefore, IGF-1 might be involved in the pathogenesis of thyroid morphological abnormalities [3, 4]. There is now considerable evidence that these hormones and the signal transduction mecha-

KARGER

E-Mail karger@karger.com
www.karger.com/mpp

Cuneyd Anil
Department of Endocrinology and Metabolism
Baskent University Faculty of Medicine, 5 Sokak No. 48
TR–06490 Bahcelievler, Ankara (Turkey)
E-Mail cuneydanil@yahoo.com

nisms they regulate are modulated by metformin therapy [5–7]. Preclinical and clinical data supporting the antiproliferative effects of metformin provide the rationale to study its role in thyroid morphology [8, 9]. This may lead to metformin becoming a potential therapeutic agent for benign and malignant thyroid overgrowths. The objective of the current study was to examine the effects of metformin therapy on thyroid volume and nodule size.

Subjects and Methods

Study Subjects

This was a single-center, prospective interventional trial in euthyroid subjects with IR. The Baskent University Ethics Committee for Human Studies approved the protocol and all participants provided written informed consent. The study population consisted of 100 subjects with IR (68 females and 32 males, age range 22–74 years) referred to our institution for workup of obesity between August 2008 and May 2010.

Euthyroidism was defined as TSH (reference range 0.35–4.0 mIU/l), free tri-iodothyronine (FT3; reference range 1.71–4.71 pg/ml) and free tetra-iodothyronine (FT4; reference range 0.8–1.9 ng/dl) within the normal reference range. The inclusion criterion was age between 18 and 75 years. Exclusion criteria were subjects with a history of thyroid disease, overt or subclinical hyperthyroidism and hypothyroidism (as defined by suppressed or elevated TSH levels, respectively), previous thyroxine suppression therapy at any time, high thyroid autoantibody titers or a history of neck irradiation or surgery.

Subjects with the following confounding factors on thyroid ultrasonography were ruled out as an important step in achieving a more homogenous study population: retrosternal goiter, thyroid volume more than 40 ml, and coalescent thyroid nodules (not suitable for size analysis). The smallest thyroid nodule considered for size analysis was ≥5 mm in the maximum diameter at baseline. Colloid cysts and pure thyroid cysts were not included in the size analysis. Patients were also excluded if they exhibited endocrine obesity, diabetes mellitus, pregnancy or lactation, hepatic or renal dysfunction, and a history of heart failure or significant neurological or psychological illness (depression, epilepsy, schizophrenia) that would have an impact on thyroid function tests.

The study subjects were prescribed a standard hypocaloric diet and regular standard aerobic exercise under the supervision of a dietician who monitored them periodically. Each subject received 1,700 mg/day of metformin therapy during the study period.

Anthropometric Measurements

The height, weight and waist circumference (WC) of each subject were recorded by the same physician (A.G.). WC was measured with a folding tape at the natural waistline (the level of the umbilicus) in a horizontal plane. BMI was calculated by the body weight in kilograms divided by the square of the height in meters (kg/m^2).

Thyroid Function and Morphology

Thyroid ultrasonography was performed by a single physician (A.G.), who was blinded to patient diagnosis and therapy, using a 10-MHz linear probe (Logiq 5 Pro, GE Medical Systems, Waukesha, Wis., USA) before and 6 months after metformin therapy. Thyroid gland volumes were calculated according to the ellipsoid formula: volume (ml) = depth (cm) × width (cm) × length (cm) × π/6 [10]. The diameters of 65 nodules were measured in three dimensions and the largest diameter was recorded for each thyroid nodule.

Laboratory Analysis

Venous blood samples were drawn after a minimum fasting period of 12 h at baseline and 6 months after metformin therapy. All blood samples were collected between 08:00 and 09:00 h. Thyroid function was evaluated by measuring FT4, FT3 and TSH using immunochemiluminescent assays by an automated analyzer (Immulite 2000; Diagnostic Products Corp., Los Angeles, Calif., USA). Thyroid antibodies (antithyroid peroxidase, normal range <50 U/ml, and antithyroglobulin, normal range <40 U/ml) were measured by immunochemiluminescent assays using commercial kits (Diagnostic Products Corp.). IR was estimated based on the calculation of the homeostasis model assessment (HOMA) index for each patient. This was done using the formula: fasting plasma insulin (IU/ml) × fasting plasma glucose (mmol/l)/22.5 [11].

Serum glucose was measured by the glucose oxidase technique (Roche Diagnostics GmbH, Mannheim, Germany). The serum insulin level was assayed with a solid-phase competitive chemiluminescent enzyme immunoassay (Diagnostic Product Corp.).

Statistical Analysis

All continuous data were expressed as the mean ± SD. Data were analyzed with SPSS software (Statistical Package for the Social Sciences, version 11.0, SSPS Inc., Chicago, Ill., USA). Statistical comparisons were performed by means of independent-sample t tests for data with a normal distribution and χ^2 tests for percentages. Pearson's correlation test was performed for the correlation analysis. A p value <0.05 was considered statistically significant.

Results

Anthropometric, biochemical and thyroid ultrasonography data are summarized in table 1. The mean BMI and WC decreased significantly after metformin therapy (34.5 ± 5.1 vs. 32.7 ± 4.8, $p < 0.0001$, and 106.3 ± 11.8 vs. 101.8 ± 19.0 cm, $p = 0.008$, respectively). IR as estimated by HOMA also decreased after metformin therapy (4.5 ± 1.9 vs. 2.9 ± 1.7, $p < 0.0001$).

Thyroid Function and Morphology

After metformin therapy, mean serum concentrations of TSH decreased (1.8 ± 1.0 vs. 1.5 ± 0.8 mIU/l, $p < 0.0001$) and mean serum concentrations of FT3 increased (2.7 ± 0.7 vs. 3.0 ± 0.8 pg/ml, $p = 0.03$) significantly. Mean FT4 values were similar before and after metformin therapy (1.4 ± 0.6 vs. 1.5 ± 1.3 ng/dl, $p > 0.5$).

Table 1. Clinical, laboratory and thyroid ultrasonography characteristics of study subjects before and after metformin therapy

	At baseline	After metformin	p value
Male/female	32/68	–	–
Age, years	52.5±10.3	–	–
BMI	34.5±5.1	32.7±4.8	<0.0001
WC, cm	106.3±11.8	101.8±19.0	<0.01
HOMA-IR	4.5±1.9	2.9±1.7	<0.0001
Thyroid volume, ml	22.5±11.2	20.3±10.4	<0.0001
Mean nodule size, mm	12.9±7.6	11.7±7.2	<0.0001
TSH, mIU/l	1.8±1.0	1.5±0.8	<0.0001
FT3, pg/ml	2.7±0.7	3.0±0.8	<0.05
FT4, ng/ml	1.4±0.6	1.5±1.3	>0.5
Nodule (≥5 mm), %	65.0	56.0	<0.01

The mean thyroid volume was significantly reduced after metformin therapy (22.5 ± 11.2 vs. 20.3 ± 10.4 ml, $p < 0.0001$). The mean thyroid nodule size was also significantly decreased after metformin therapy (12.9 ± 7.6 vs. 11.7 ± 7.2 mm, $p < 0.0001$); 65 patients had thyroid nodules ≥5 mm (satisfying one of the inclusion criteria for admission) at the beginning, which decreased to 56 after metformin therapy ($p = 0.004$). There was no significant correlation between TSH and thyroid volume and nodule prevalence before and after metformin therapy ($p > 0.05$, $r = 0.2$).

Discussion

In this study, thyroid volume and probably the nodule prevalence decreased after metformin therapy. At baseline and after metformin therapy, there was no significant correlation between TSH and thyroid volume which could suggest that TSH-independent mechanisms might be involved in thyroid cell proliferation in subjects with IR.

In a previous report by Rezzonico et al. [1], patients with IR had larger thyroid volumes and a higher risk for the formation of thyroid nodules. They concluded that the higher circulating levels of insulin cause increased thyroid proliferation and thyroid nodules.

Our current and previous data suggest that IR and hyperinsulinemia per se may contribute to an increased thyroid volume and nodule prevalence and an improvement of insulin sensitivity by metformin therapy acting to ameliorate these morphological abnormalities [2]. IGF-1 is actively involved in the TSH-mediated proliferation of thyrocytes. The insulin/IGF-1 signaling pathway has long been known to modulate the regulation of thyroid gene expression and might be considered an additional important factor in thyrocyte proliferation and differentiation [3, 4]. It cannot be excluded that metformin has a direct, antiproliferative effect on the thyroid, possibly by suppressing mTOR activity, which might contribute to these observed effects [8].

In a similarly designed study by Rezzonico et al. [9], 66 women with IR and nodular goiter were assigned to one of four interventional groups which consisted of treatment with metformin alone, metformin and levothyroxine, levothyroxine alone, and a control group. Significant reductions in nodule size were observed in the groups treated with metformin in parallel with improvements in IR, and the other two groups demonstrated no change.

Vigersky et al. [6] reported for the first time that treatment with metformin caused suppression of TSH to subnormal levels without clinical symptoms of hyperthyroidism, which was confirmed in the present study. Although the mechanism of the fall in serum TSH is unclear at this time, similar observations have been reported in the literature [7]. However, in a retrospective but large cohort of euthyroid diabetic patients, Díez and Iglesias [12] did not find any significant relationship between TSH and metformin treatment.

IR increases visceral fat accumulation and this visceral fat increases TSH secretion as a result of a resetting of the hypothalamic-pituitary thyrostat operated by the adipose tissue [13]. There is evidence in the literature indicating that a possible relationship exists between leptin and the thyroid hormones via an influence of leptin on the negative feedback regulation of thyroid hormones and TRH expression [13, 14]. Leptin secretion increases exponentially with increasing fat mass and insulin also increases total leptin levels [14]. Thus, increased fat mass along with IR may contribute to increased serum TSH levels via effects on serum leptin concentrations [13, 14]. Serum FT3 concentrations are also lower in leptin-deficient subjects [13]. In animal studies, metformin increased the leptin receptor gene expression in the arcuate nucleus, suggesting that the TSH- and possibly FT3-modulating effect of metformin is potentially mediated via an increase in the central sensitivity to leptin [15]. The major limitation of this study was the lack of a control group. However, this research was designed as a preliminary study due to its unique layout.

Conclusion

This preliminary study showed that metformin administration in subjects with IR was associated with a significant reduction in thyroid volume and nodule size. The drug therapy also decreased the serum levels of TSH and increased the serum levels of FT3, with no change in FT4. Future studies could reveal some novel aspects of the pathophysiology of goiters.

Disclosure Statement

The authors have no conflicts of interest to declare.

References

1 Rezzonico J, Rezzonico M, Pusiol E, et al: Introducing the thyroid gland as another victim of the insulin resistance syndrome. Thyroid 2008;18:461–464.

2 Ayturk S, Gursoy A, Kut A, et al: Metabolic syndrome and its components are associated with increased thyroid volume and nodule prevalence in a mild-to-moderate iodine-deficient area. Eur J Endocrinol 2009;161:599–605.

3 Kimura T, van Keymeulen A, Golstein J, et al: Regulation of thyroid cell proliferation by TSH and other factors: a critical evaluation of in vitro models. Endocr Rev 2001;22:631–656.

4 Deleu S, Pirson I, Coulonval K, et al: IGF-1 or insulin, and the TSH cyclic AMP cascade separately control dog and human thyroid cell growth and DNA synthesis, and complement each other in inducing mitogenesis. Mol Cell Endocrinol 1999;149:41–51.

5 Seibel SA, Chou KH, Capp E, et al: Effect of metformin on IGF-1 and IGFBP-1 levels in obese patients with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 2008;138:122–124.

6 Vigersky RA, Filmore-Nassar A, Glass AR: Thyrotropin suppression by metformin. J Clin Endocrinol Metab 2006;91:225–227.

7 Cappelli C, Rotondi M, Pirola I, et al: Thyreotropin levels in diabetic patients on metformin treatment. Eur J Endocrinol 2012;167:261–265.

8 Dowling RJO, Goodwin PJ, Stambolic V: Understanding the benefit of metformin use in cancer treatment. BMC Med 2011;9:33.

9 Rezzonico J, Rezzonico M, Pusiol E, et al: Metformin treatment for small benign thyroid nodules in patients with insulin resistance. Metab Syndr Relat Disord 2011;9:69–75.

10 Brunn J, Block U, Ruf G, et al: Volumetric analysis of thyroid lobes by real-time ultrasound. Dtsch Med Wochenschr 1981;106:1338–1340.

11 Matthews DR, Hosker JP, Rudenski AS, et al: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–419.

12 Díez JJ, Iglesias P: Relationship between serum thyrotropin concentrations and metformin therapy in euthyroid patients with type 2 diabetes. Clin Endocrinol 2013;78:505–511.

13 Mantzoros CS, Ozata M, Negrao AB, et al: Synchronicity of frequently sampled thyrotropin (TSH) and leptin concentrations in healthy adults and leptin-deficient subjects: evidence for possible partial TSH regulation by leptin in humans. J Clin Endocrinol Metab 2001;86:3284–3291.

14 Mantzoros CS, Moschos SJ: Leptin: in search of role(s) in human physiology and pathophysiology. Clin Endocrinol 1998;49:551–567.

15 Aubert G, Mansuy V, Voirol MJ, et al: The anorexigenic effects of metformin involve increases in hypothalamic leptin receptor expression. Metabolism 2011;60:327–334.