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BRIEF REPORT

Thyrotropin Suppression by Metformin

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Context: Drug-drug interactions are common but often are discovered only long after initial drug release. Metformin has been available in the United States for 9 yr and elsewhere for many years, but as of yet there are no reports that the drug modifies thyroid hormone economy.

Objective: The objective of the study was to describe the clinical and biochemical findings of four patients with chronic hypothyroidism, previously euthyroid on fixed doses of L-T_4 for several years, in whom the metformin was initiated.

Design: This was a retrospective review.

Setting: The study was conducted at a tertiary care military hospital providing care to active-duty soldiers, sailors, and marines, retirees of the armed forces, and their eligible dependents.

Participants: Four patients with chronic hypothyroidism who were placed on metformin participated in the study.

Intervention, Main Outcome Measure: Serum TSH, free T_4, and free T_3 levels were measured during metformin treatment.

Results: Initiation of treatment with metformin (three for diabetes mellitus and one for nonalcoholic steatohepatitis) caused suppression of TSH to subnormal levels without clinical symptoms of hyperthyroidism in any patients. There was no change in free T_4 or free T_3 in patient 1.

Conclusions: No other potential causes of TSH suppression, including medication changes or interference in the TSH assay, could be identified. The mechanism of the fall in serum TSH in these four patients is unclear at this time. Should these findings be confirmed in larger prospective studies, metformin's ability to suppress TSH without causing clinical or chemical hyperthyroidism might render this drug a useful adjunct to the treatment of patients with thyroid cancer. **(*J Clin Endocrinol Metab* 91: 225–227, 2006)**

DRUG-DRUG INTERACTIONS are common but often are discovered only long after initial drug release. Metformin has been available in the United States for almost a decade and elsewhere for many more years, but as of yet there are no reports that the drug modifies thyroid hormone economy. We fortuitously observed a reversible metformin-induced suppression of TSH, without a change in free T_4 (fT4) or free T_3 (fT3) or clinical signs of hyperthyroidism, in a patient with nonalcoholic steatohepatitis (NASH) who was on L-T_4 after radioactive iodine treatment for Graves' disease. Once the first patient was identified, we identified three additional stable hypothyroid patients (two postsurgical and one with Hashimoto's disease) over approximately a 3-month time span who had also developed TSH suppression when they were placed on metformin for treatment of diabetes mellitus.

Patients and Methods

Serum fT4 was measured by equilibrium dialysis [Nichols Institute, San Juan Capistrano, CA; fT4 kit, catalog no. 40-2211/40-2210; analytical sensitivity 1.93 pmol/liter; intraassay coefficient of variation (CV) 10.7% at 19.3 pmol/liter; interassay CV 15.1% at 16.7 pmol/liter] in patients 1, 2, and 4 or by an electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN; assay kit, catalog no. 11731297; analytical sensitivity 0.023 ng/dl; intraassay CV 2.6% for 1.31 ng/dl; interassay CV of 3.3% for 1.64 ng/dl) in patient 3. Serum fT3 was measured by solid-phase RIA (Diagnostic Products Corp., Los Angeles, CA; catalog no. TKF31; analytical sensitivity 0.31 pmol/liter; intraassay CV 5% at 2.8 pmol/liter; interassay CV 6.8% at 4.7 pmol/liter). Serum TSH was measured by a third-generation chemiluminescence immunoassay (Nichols; TSH-Third Generation, catalog no. 60-4100; analytical sensitivity 0.003 μIU/ml; functional sensitivity 0.01 μIU/ml; intraassay CV 12.5% at 0.01 μIU/ml, 4.6% at 1.28 μIU/ml, and 5.1% at 8.35 μIU/ml; interassay CV 15.2% at 0.02 μIU/ml, 5.8% at 1.22 μIU/ml, and 7.3% at 8.52 μIU/ml) in patients 1, 2, and 4 or by an electrochemiluminescence immunoassay (Roche Diagnostics; TSH assay kit, catalog no. 11731459122; analytical sensitivity 0.005 μIU/ml; functional sensitivity 0.014 μIU/ml; intraassay CV 7.2% at 0.04 μIU/ml, 3.2% at 0.092 μIU/ml, and 3.3% at 9.37 μIU/ml; interassay CV 8.7% at 0.034 μIU/ml, 3.3% at 0.91 μIU/ml, and 3.6% at 3.96 μIU/ml) in patient 3. The former assay was used to measure serum the TSH concentration of normal serum to which metformin was added in concentrations from 0.195 to100 μg/ml [the therapeutic range of metformin is 0.465–2.5 μg/ml (1)].

Case reports

Patient 1 is a 58-yr-old nonsmoking, nondrinking Caucasian man who was previously healthy until he developed Graves' disease in 1997. After treatment with 15.6 mCi of radioactive iodine-131, his fT4 fell to 3.8 pmol/liter and TSH rose to 7.67 μIU/ml and L-T_4 treatment was initiated and titrated. He remained clinically and biochemically euthyroid on L-T_4 150 μg daily for the next 4 yr. In 1998 he developed elevated transaminase levels; a liver biopsy performed in 2001 showed steatosis and fibrosis diagnostic of NASH. Because of increasing serum transaminase levels, metformin XR 1500 mg daily was begun in December 2001. Metformin was continued for the next 8 months until suppression of serum TSH was noted (Table 1). At that point, metformin was discontinued, and serum TSH progressively returned to baseline over the next

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Abbreviations: CV, Coefficient of variation; fT3, free T_3; fT4, free T_4; NASH, nonalcoholic steatohepatitis.

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TABLE 1. Thyroid and liver function tests in patient 1

Patient 1	Status	fT4 (pmol/liter)	fT3 (pmol/liter)	TSH (μU/ml)	ALT (U/liter)	AST (U/liter)
Normal		10.3–30.6	1.5–6.9	0.43–4.7	21–72	17–59
August 1998 to December 2001	Baseline	15.3–23.9 (n = 5)		1.60–1.90 (n = 5)	102–205 (n = 18)	61–118 (n = 18)
August 17, 2002	On M 8 months	13.4	4.1	0.11	130	71
October 10, 2002	Off M 2 months	13.2	3.7	1.4	155	92
September 26, 2003	On M 12 months	18	6.6	0.11	135	72
September 16, 2004	Off M/on R 11 months	14.3	5.4	0.93	210	132

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; R, rosiglitazone; M, metformin.

6 wk. To confirm this presumed relationship between metformin administration and serum TSH suppression, the drug was readministered, with the patient's informed consent, from October 2002 until October 2003 in the same dose as before. Once again, serum TSH suppression was noted, and after discontinuation of metformin and substitution of rosiglitazone (4 mg twice daily), serum TSH rose back into the normal range. During both periods of metformin administration, there were no changes in fT4 or fT3 levels, and there was no weight loss or symptoms consistent with hyperthyroidism. The suppression and recovery of serum TSH was not associated with changes in medications other than metformin. Medication compliance was verified by the patient and confirmed by reviewing refill frequency in the integrated military electronic record.

Patient 2 is a 67-yr-old Caucasian woman who had type 2 diabetes mellitus for 12 yr complicated by mild nephropathy. Treatment of diabetes with neutral protamine Hagedörn (NPH) (NovoNordisk, Princeton, NJ) and regular insulin taken twice daily resulted in moderate glycemic control (A1c 7.8%). Primary hypothyroidism due to Hashimoto's thyroiditis had been treated with L-T_4 224 μg daily, a dose that was stable for 5 yr. Other medical problems include breast cancer stage 1, hypertension, hyperlipidemia, and osteoarthritis. Her other medications were lisinopril, fenofibrate, and aspirin. Metformin XR 500 mg daily was added to her diabetic regimen in October 2002, and 2 months later her serum TSH had fallen from 0.64 μIU/ml to a subnormal level of 0.31 μIU/ml (Table 2). Increasing the dose of metformin XR to 1000 mg daily led to a further decrease in serum TSH (0.17 μIU/ml). Her weight had increased 4 lb while on metformin 500 mg daily but then decreased 3 lb when the drug was increased to 1000 mg daily.

Patient 3 is a 66-yr-old man who had been treated for 4 yr with T_4 125 μg daily for hypothyroidism resulting from a thyroidectomy for multinodular goiter. His past medical history includes hypertension, hyperlipidemia, and, since 1998, type 2 diabetes mellitus. His nondiabetic medications were aspirin, lisinopril, simvastatin, amlodipine, and diltiazem. Initial treatment of diabetes with glipizide led to modest glycemic control (A1c 7.2% in June 2002), and addition of metformin in July 2002 led to further improvement (A1c 6.6%) despite a 15-lb weight gain to 190 lb over that time. After administration of metformin, serum TSH fell from 1.30 to 0.14 μIU/ml over a 6-month period despite a reduction in the dose of L-T_4 (from 125 μg daily to 125 μg 6 d/wk or 107 μg daily average). A premetformin fT4 was not obtained. Serum fT4 fell during metformin treatment from 1.65 to 1.06 ng/dl (Table 2).

Patient 4 is a 75-yr-old woman treated with L-T_4 175 μg daily for many years after hypothyroidism developed after a thyroidectomy for papillary thyroid cancer 50 yr previously. She also has hypertension and osteoarthritis. Her other medications were aspirin, calcium, verapamil, hydrochlorothiazide, gabapentin, lisinopril, and furosemide. After diagnosis of type 2 diabetes mellitus in 1998, treatment with insulin was initiated, resulting in moderate control (A1c 7.6%). Addition of metformin XR (500 mg daily) in February 2003, did not improve glycemic control (A1c 8.5% after 3 months) but was associated with a fall in serum TSH from 1.91 to 0.39 μIU/ml over 3 months. Five and 14 wk after discontinuation of metformin, serum TSH increased to 0.54 and 1.17 μIU/ml, respectively. The patient's weight did not change while on metformin.

Metformin addition to normal serum

When metformin was added to normal serum whose baseline serum TSH was 1.20 μIU/ml, the serum TSH concentration varied from 1.06 to 1.20 μU/ml.

Results and Discussion

All four hypothyroid patients described in this report had decreases in serum TSH to subnormal levels after the administration of metformin. We are unaware that this finding has been previously reported. By contrast, Oleandri *et al.* (2) found no differences in thyroid function tests among 28 patients with no known thyroid disease who were treated for obesity with short-acting metformin (500 mg twice daily), dexfenfluramine, or placebo for 3 months in a randomized, controlled trial; weight loss was similar in each group.

Generally, serum TSH levels in a patient on a stable dose

TABLE 2. TSH responses of patients 1–4 to the administration of metformin

Patient	Age (yr)/gender	Underlying disease	Dose of L-T_4 (μg)	Duration of DM (yr)	Metformin (mg/d)	Baseline fT4 (pmol/liter)	Post-Met fT4 (pmol/liter)	Baseline TSH (μU/ml)	Post-Met TSH (μU/ml)
Normal						10.3–30.6	10.3–30.6	0.43–4.7	0.43–4.7
1	58/M	Graves' disease treated with I-131	150	N/A	1500	15.3–23.9 (n = 5)	13.4	1.19–1.90 (n = 5)	0.11
			150		1500	13.2	18.0	1.4	0.11
2	67/F	Hashimoto's	224	14	500	N.D.	N.D.	0.64	0.31
			224		1000	N.D.	29.6	0.31	0.17
			200		1000	29.6	18.7	0.17	0.21
3	66/M	Thyroidectomy for MNG	125	5	1000	N.D.	1.65[a]	1.3	0.36
			107		1000	1.65[a]	1.06[a]	0.36	0.14
4	75/F	Thyroidectomy for PTC	175	5	500	N.D.	35.6	1.91	0.39
			175		0	35.6	24.7	0.39	1.17

M, Male; F, female; DM, diabetes mellitus; MNG, multinodular goiter; PTC, papillary thyroid carcinoma; Met, metformin; N.D., not done.
[a] Analog assay with normal range 1.01–1.79 ng/dl.

of L-T_4 change only when there is a change in absorption, alteration in the dose (or brand) or its bioavailability, a substantial change in weight, or variability in compliance. Reciprocal changes in T_4 levels are usually seen in these circumstances. In patient 1, however, marked changes in serum TSH to subnormal levels were observed without any reciprocal change in serum thyroid hormone levels. In the other three patients, a baseline fT4 was not available. However, TSH remained suppressed in patients 2 and 3 despite lower doses of L-T_4 and lower fT4 levels. These observations were not due to interference in the TSH assay because metformin did not change the TSH value when added to normal serum in concentrations up to 40 times higher than the therapeutic range.

There are several possible mechanisms for the metformin-induced TSH suppression in our patients, but these should be considered speculative at the present time. Metformin may have changed the affinity and/or number of thyroid hormone receptors, increased dopaminergic tone, or induced constituent activation of the TSH receptor. These hypotheses would require that metformin be able to cross the blood-brain barrier. Although metformin is a low-molecular-mass, water-soluble molecule (168 Da), its penetration of the blood-brain barrier has not been studied. The mechanism of action of metformin at a cellular level is not completely understood but is likely to be multifactorial (3–5). The mechanism of thyroid hormone action has been better defined and is quite complex (6). Whether metformin may affect any of the steps in thyroid hormone action that have been defined to date remains to be determined.

If metformin produced subtle increases in the absorption of L-T_4 from the gastrointestinal tract, then suppression of serum TSH might be predicted. However, we believe that this is unlikely because there was no increase in serum thyroid hormone levels in our most completely studied subject (patient 1). Furthermore, whereas metformin inhibits the absorption of vitamin B12 and folate (7, 8), it is not known to increase the absorption of nutrients or medications. We cannot exclude the possibility that the TSH suppression in our patients was the result of a subtle, sustained increase in T_4 absorption and consequent rise in free serum thyroid hormone levels that was too small to be detected. In our small retrospective case series, such factors as interassay variation, biological variability of T_4 absorption, or changes in the volume of distribution may have contributed to our findings.

Could our findings be explained by a metformin-induced change in the bioavailability of circulating thyroid hormones? In some circumstances the free fraction of circulating hormones may not be the same as the level of bioavailable hormones in the circulation, *e.g.* both the free testosterone and non-SHBG-bound testosterone are bioavailable and the combination of both best correlates with the clinical state of the patient (9, 10). It is of interest in this regard that hormone transport proteins, such as transthyretin, facilitate the passage of T_4 across the cellular barrier, specifically the blood-brain barrier in the choroid plexus (11, 12).

In summary, we report four patients in whom metformin appeared to suppress serum TSH to subnormal levels without resulting in biochemical or clinical hyperthyroidism. If our findings are verified and the effect of metformin is central and not peripheral, metformin could be used as an adjunct for the treatment of patients with thyroid cancer because it appears to suppress serum TSH without causing biochemical hyperthyroxinemia or clinical hyperthyroidism.

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References

1. **Al-Jebawi AF, Lassman MN, Abourizk NN** 1998 Lactic acidosis with therapeutic metformin blood level in a low-risk diabetic patient. Diabetes Care 21:1364–1365
2. **Oleandri SE, Maccario M, Rossetto R, Procopio M, Grottoli S, Avogadri E, Gauna C, Ganzaroli C, Ghigo E** 1999 Three-month treatment with metformin or dexfenfluramine does not modify the effects of diet on anthropometric and endocrine-metabolic parameters in abdominal obesity. J Endocrinol Invest 22:134–140
3. **Owen MR, Doran E, Halestrap AP** 2000 Evidence that metformin exerts it anti-diabetic effects through inhibition of the complex 1 of the mitochondrial respiratory chain. Biochem J 348:607–614
4. **Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, Wu M, Ventre J, Doebber T, Fujii N, Musi N, Hirshman MF, Goodyear LJ, Moller DE** 2001 Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest 108:1167–1174
5. **Davidoff F, Berolini D, Haas D** 1978 Enhancement of the mitochondrial Ca^{2+} uptake rate by phenethylbiguanide and other organic cations with hypoglycemic activity. Diabetes 27:757–765
6. **Glass CK, Rosenfeld MG** 2000 The coregulator exchange in transcriptional functions of nuclear receptors. Genes Dev 14:121–141
7. **Wulffele MG, Kooy A, Lehert P, Bets D, Ogterop JC, Borger van der Burg B, Donker AJ, Stehouwer CD** 2003 Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B12 in type 2 diabetes mellitus: a randomized, placebo-controlled trial. J Intern Med 254:455–463
8. **Stocker DJ, Vigersky RA,** The effects of metformin and rosiglitazone on vitamin B12, folate and homocysteine in patients with poorly controlled type 2 diabetes. Program of the 87th Annual Meeting of The Endocrine Society, San Diego, CA, 2005, p 693 (Abstract P3-604)
9. **Manni A, Partridge WM, Cefalu W, Nisula BC, Bardin CW, Santner SJ, Santen RJ** 1985 Bioavailability of albumin bound testosterone. J Clin Endocrinol Metab 61:705–710
10. **Vermeulen A, Verdonck L, Kaufman JM** 1999 A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 84:3666–3672
11. **Robbins J, Lakshmanan M** 1992 The movement of thyroid hormones in the central nervous system. Acta Med Austriaca 19(Suppl 1):21–25
12. **Schreiber G, Richardson SJ** 1997 The evolution of gene expression, structure and function of transthyretin. Comp Biochem Physiol B 116:137–160

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