Endocr (2007) 32:79–82
DOI 10.1007/s12020-007-9012-3

ORIGINAL PAPER

Metformin reduces thyrotropin levels in obese, diabetic women with primary hypothyroidism on thyroxine replacement therapy

M. Luisa Isidro · Manuel A. Penín · Rosa Nemiña · Fernando Cordido

Received: 20 July 2007 / Accepted: 14 September 2007 / Published online: 2 October 2007

Abstract *Context* It has been reported that metformin might modify thyroid hormone economy. In two retrospective studies, initiation of treatment with metformin caused suppression of TSH to subnormal levels. *Objective* To prospectively evaluate if administration of metformin to obese, diabetic patients with primary hypothyroidism on stable thyroxine replacement doses modifies TSH levels. *Patients and methods* Eight obese, diabetic postmenopausal women with primary hypothyroidism participated in the study. They received 1,700 mg of metformin daily for 3 months. Weight, TSH, free T4, and free T3 levels were measured at baseline, 3 months after metformin initiation and 3 months after its withdrawal. *Results* After 3 months of on metformin, mean TSH was significantly lower than basal TSH (3.11 ± 0.50 μUI/ml vs. 1.18 ± 0.36 μUI/ml; $P = 0.01$). Mean TSH 3 months after metformin withdrawal was 2.21 ± 0.37 μUI/ml, significantly higher than TSH after metformin ($P = 0.05$), but not different from basal TSH. Mean fT4 level increased during metformin administration (basal fT4: 1.23 ± 0.06 ng/dl, fT4 after metformin: 1.32 ± 0.04 ng/dl; P = ns), and decreased after its withdrawal (fT4 3 months after metformin withdrawal: 1.15 ± 0.05 ng/dl; vs. 3 months after metformin, $P = 0.04$; vs. basal; P = ns). *Conclusions* In obese, diabetic patients with primary hypothyroidism on thyroxine replacement treatment, short-term metformin administration is associated with a significant fall in TSH.

Keywords Metformin · Thyrotropin · Thyroxine replacement therapy · Hypothyroidism

M. L. Isidro (✉) · M. A. Penín · F. Cordido
Endocrine Department, Hospital Juan Canalejo, As Xubias 84, La Coruna 15006, Spain
e-mail: lisidro@canalejo.org

R. Nemiña
Investigation Department, Hospital Juan Canalejo, As Xubias 84, La Coruna 15006, Spain

F. Cordido
Medicine Department, University of La Coruña, La Coruna, Spain

Introduction

Type 2 diabetes and primary hypothyroidism are two very prevalent diseases and both metformin and thyroxine are widely used drugs. It was not until recently that metformin was reported to be able to modify thyroid hormone economy [1]. In that observational study of four patients, initiation of treatment with metformin caused suppression of TSH to subnormal levels. In another retrospective study performed by Guerrero et al. [2], the authors found a statistically significant decrease in TSH, along with an increase in fT4, after treatment with metformin, although the decrease in TSH seemed to be independent of the fT4 increase. A previous study had not found significant variations in thyroid hormone levels during treatment with metformin in obese, euthyroid patients [3].

The effects of drugs on the pituitary–thyroid axis have been extensively reviewed [4] and no clinically relevant interactions between metformin and most commonly used drugs, apart from folate and B12 vitamin, have been described [5]. If this metformin-induced TSH suppression is confirmed, metformin could be a useful adjunct to post-ablation TSH suppression therapy, on one hand, and this drug–drug interaction should be kept in mind when one of the drugs is added to a patient already taking the other, in order not to cause undesired secondary effects, on the other.

Our aim was to prospectively evaluate if metformin administration to obese, diabetic patients with primary hypothyroidism on thyroxine replacement treatment modified thyrotropin levels.

Results

Patients

All the patients had type 2 diabetes. Four of them were being treated with sulfonylureas and two with insulin. During treatment with metformin the physical exams, except for changes in body weight, did not reveal significant changes. Two patients complained of mild flatulence, which disappeared in spite of metformin maintenance and did not require reductions in its dose. No patients complained of symptoms of thyroid dysfunction.

The mean daily dose of thyroxine per kg of body weight was 1.21 ± 0.13 μg at baseline and 1.29 ± 0.14 μg after three months of treatment with metformin ($P = 0.04$).

TSH

Basal mean TSH was 3.11 ± 0.57 μUI/ml (normal values: 0.35–5.50 μUI/ml). After three months of metformin mean TSH was 1.18 ± 0.36 μUI/ml, statistically lower than basal TSH ($P = 0.01$) (Fig. 1). TSH decreased in all the patients, and was suppressed below normal levels in two. TSH levels 3 months after metformin initiation correlated with fT4 levels at the same moment ($r = –0.71$; $P = 0.04$). We found no correlation between either TSH levels three months after metformin, or the degree of TSH reduction, and either weight at that moment or the degree of weight reduction. The degree of TSH reduction correlated with basal TSH ($r = 0.74$; $P = 0.03$).

Three months after metformin withdrawal TSH levels had increased, when compared to TSH levels after treatment, in all but one patient. Mean TSH 3 months after metformin withdrawal was 2.21 ± 0.37 μUI/ml, significantly higher than mean THS on metformin ($P = 0.05$), and not significantly different from basal TSH.

Individual changes in TSH during the period of study are shown in Table 1.

Free T4

Mean basal fT4 was 1.23 ± 0.06 ng/dl (normal values: 0.85–1.86 ng/dl). The mean free T4 was slightly higher during metformin treatment but the increase was not significant (1.32 ± 0.04 vs. 1.23 ± 0.06 ng/dl, P = ns) (Fig. 1). fT4 increased in all but one patient, but in every case it remained in the normal reference range.

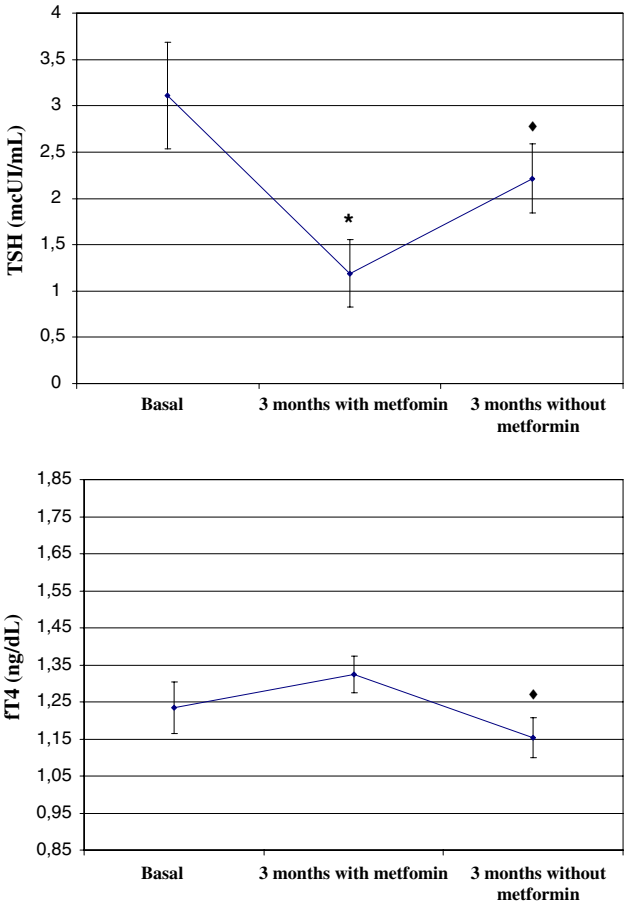

Fig. 1 Changes in TSH and fT4. (*) $P \leq 0.05$ vs. basal. (♦) $P \leq 0.05$ vs. 3 months with metformin

When metformin was withdrawn fT4 levels decreased: mean fT4 3 months after metformin withdrawal was 1.15 ± 0.05 ng/dl, significantly lower than mean fT4 after metformin ($P = 0.04$), but not different from mean basal fT4.

Free T3

After treatment with metformin fT3 levels decreased non-significantly (basal fT3: 2.83 ± 0.23 pg/ml vs. fT3 after metformin: 2.75 ± 0.14 pg/ml; normal values: 2.20–4.70 pg/ml; P = ns). Three months after metformin withdrawal mean fT3 was 2.57 ± 0.12 pg/ml, not statistically different from either mean fT3 after metformin or from mean basal fT3.

Table 1 Individual TSH (μUI/ml) changes during the study

	Basal TSH	TSH 3 months with metformin	TSH 3 months after metformin withdrawal
1	5.50	0.09	2.22
2	1.26	0.16	0.42
3	4.10	1.20	2.31
4	3.96	3.05	1.87
5	1.56	0.63	2.59
6	1.00	0.60	1.30
7	3.70	1.90	3.30
8	3.82	1.88	3.70

Weight

After treatment with metformin mean body weight was significantly lower than basal weight (76.6 ± 4.4 kg vs. 83.6 ± 5.0 kg, $P = 0.04$) (Fig. 2).

All but two patients lost weight during treatment with metformin. Three months after metformin withdrawal mean body weight was 80.0 ± 5.2 kg (significantly higher than weight after metformin, $P = 0.02$; significantly lower than basal weight $P = 0.02$).

HbA1c

Mean basal HbA1c was 7.5 ± 0.7%. After 3 months on metformin mean HbA1c was 6.4 ± 0.4% ($P = 0.02$ vs. basal HbA1c). Three months after metformin withdrawal mean HbA1c was 7.0 ± 0.6% ($P = 0.02$ vs. basal HbA1c; $P = 0.04$ vs. 3 moths on metformin).

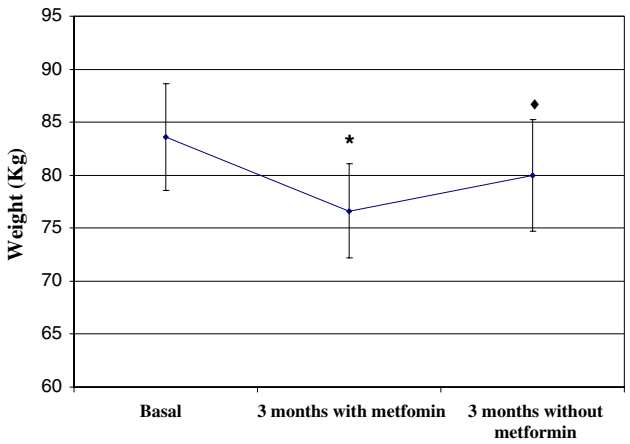

Fig. 2 Changes in weight. (*) $P \leq 0.05$ vs. basal. (♦) $P \leq 0.05$ vs. 3 months with metformin

Discussion

Our results show that in obese, diabetic women with primary hypothyroidism on stable doses of thyroxine replacement treatment, short-term metformin administration is associated with a significant fall in TSH. In the same group of patients, metformin withdrawal is accompanied by a significant rise in TSH. Although the small number of patients included preclude other interpretations, the changes observed in TSH levels were consistent and statistically significant. This fact can be clinically relevant in certain clinical circumstances, particularly given the prevalence of prescription and the overlap in the patient populations taking these drugs.

The explanations for the metformin-induced TSH reduction in hypothyroid patients are speculative at present. Contrary to what Vigersky et al. [6] reported, our patients significantly lost weight during treatment with metformin, which is a well-known effect of this drug. In obese euthyroid subjects weight loss is accompanied by reductions in fT3 levels, but most authors have not found significant changes in fT4 or TSH [7–10]. Several factors may alter the dose of thyroxine needed for adequate replacement in patients with hypothyroidism, body weight being one of them [11]. Since in our patients metformin induced weight loss and the replacement dose of thyroxine was not reduced, after 3 months of metformin they were receiving significantly higher daily doses of thyroxine per kg of body weight than at baseline. Mean free T4 was slightly higher during metformin treatment, although the increase did not reach statistical significance. The relationship between serum TSH and fT4 concentrations is log-linear, so that small changes in serum fT4 concentrations result in substantial changes in serum TSH [12[R1]]. In fact, in our patients mean TSH level three months after metformin treatment showed an inverse correlation with fT4 levels at the same moment.

In some patients of the study by Vigersky et al. not only was weight stable or increased, but also the TSH remained low despite a T4 dose reduction, and there was a lack of change in plasma fT4 levels. In our series the TSH decreased in all the patients, even when two did not lose weight. Guerrero et al. [2] reported significant increases in fT4, although in their study the decrease in TSH seemed to be independent of the changes in fT4. These data would be more consistent with a direct effect of metformin on TSH regulation, rather than suppression by a higher T4 dose. Vigersky et al. reported decreases in serum TSH to subnormal levels, which we only observed in two of our patients. A possible explanation for the lesser degree of TSH reduction in our patients could be attributed to differences in the etiology of hypothyroidism

between the two series. It is possible that in patients with some degree of thyroid function, endogenous thyroid hormone secretion would decrease to compensate for any alteration in T4 and T3 metabolism. That our patients had some degree of residual thyroid function is suggested by the fact that they were receiving lower daily doses of thyroxine than those usually estimated as necessary to achieve euthyroidism.

In conclusion, in obese, diabetic patients with primary hypothyroidism on stable doses of thyroxine replacement treatment, short-term metformin administration is associated with a significant fall in TSH. The fall in TSH might be due to the larger thyroxine replacement dose per kilogram of body weight, but the mechanism remains uncertain.

Patients and methods

Patients and study protocol

Eight obese diabetic postmenopausal women (mean age 64.5 ± 2.9 years; mean BMI 35.1 ± 2.7 kg/m^2), with primary hypothyroidism on stable doses of thyroxine replacement treatment for at least one year, were selected to receive 1,700 mg of metformin daily for 3 months. No other changes in their usual treatments were performed. Thyroxine replacement brand and dose remained unchanged during the study.

The patients were consecutively selected from those attending our outpatient unit, who met the inclusion criteria (being obese, diabetic, and with primary hypothyroidism on stable replacement thyroxine dose for at least one year), in whom metformin was not contraindicated and who were willing to participate.

Patients were seen 1 and 3 months after metformin introduction, and then 3 months after this drug had been withdrawn. A medical interview, a physical examination, and blood analysis for thyroid hormones were performed at every visit. Local Ethics Committee approval was obtained and all the patients gave informed consent for the study.

Hormonal studies

TSH, free T4 (fT4), and free T3 (fT3) were measured after an overnight fast, between 08–09 h, with a chemiluminescent immunometric assay (ADVIA Centaur®, Spain), with intrassay coefficients of variation of 2.48, 2.44, and 2.41% for low, medium and high plasma TSH levels; intrassay coefficients of variation of 4.69, 2.31, and 2.22% for low, medium and high plasma fT4 levels; and intrassay coefficients of variation of 3.08, 2.35, and 2.47% for low, medium and high plasma fT3 levels.

Statistical analysis

Results are presented as mean ± SEM. All comparisons were based on univariate, nonparametric tests. Intragroup comparisons were based Wilcoxon sign-rank test. Numerical correlations were analyzed using the Spearman's correlation test. P values ≤ 0.05 were considered significant. For graphic presentation we use mean values ± SEM.

References

1. R.A. Vigersky, A. Filmore-Nassar, A.R. Glass, J. Clin. Endocrinol. Metab. **91**, 225–227 (2006)
2. A.F. Guerrero, P.M. Williams, R. Vigersky, [abstract] The Endocrine Society, Toronto, p. 650 (2007)
3. S.E. Oleandri, M. Maccario, R. Rosetto, M. Procopio, S. Grotoli, E. Avogadri, C. Gauna, C. Ganzaroli, E. Ghigo, J. Endocrinol. Invest. **22**, 134–140 (1999)
4. M.I. Surks, R. Sievert, N. Engl. J. Med. **333**, 1688–1694 (1995)
5. A.J. Scheen, Drug Saf. **28**, 601–631 (2005)
6. L.R. Harborne, N. Sattar, J.E. Norman, R. Fleming, J. Clin. Endocrinol. Metab. **90**, 4593–4598 (2005)
7. S. Buscemi, S. Verga, R. Maneri, G. Blunda, A. Galluzzo, J. Endocrinol. Invest. **20**, 276–281 (1997)
8. L. Douyon, D.E. Schteingart, Endocrinol. Metab. Clin. North Am. **31**, 173–189 (2002)
9. M. Rosenbaum, J. Hirsch, E. Murphy, R.L. Leibel, Am. J. Clin. Nutr. **71**, 1421–1432 (2000)
10. R. Sari, M.K. Balci, H. Altunbas, U. Karayalcin, Clin. Endocrinol. (Oxf). **59**, 258–262 (2003)
11. O. Olubowale, R. Chadwick, Br. J. Surg. **93**, 57–60 (2006)
12. K.Carr, D.T. McLeod, G. Parry, H.M. Thornes, Clin. Endocrinol. **28**, 325–333 (1988)