

Goserelin-induced transient thyrotoxicosis in a hypothyroid woman on L-thyroxine replacement

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ABSTRACT

An increase in free thyroxine (fT₄) and a decrease in thyroid-stimulating hormone (TSH) was observed in a hypothyroid woman on levothyroxine treatment after implantation of goserelin, a gonadotropin-releasing hormone (GnRH) analogue. In the literature no data are available that describe a drug interaction between GnRH analogues and thyroid hormone replacement. Our hypothesis to explain this observation is that goserelin decreased serum thyroxine-binding-globulin (TBG), resulting in an increase in fT₄ and thereby a decrease in serum TSH.

KEYWORDS

GnRH analogue, hypothyroidism, sex hormones, thyroid function

INTRODUCTION

Sometimes patients ask their doctors questions about drug interactions, which are hard to answer because the literature contains insufficient data on the particular topic. In our case, the question was if there was a known drug interaction between thyroxine and goserelin, a gonadotropin-releasing hormone (GnRH) analogue. Nothing could be found in the literature on such an interaction. Subcutaneous implantation of goserelin will suppress luteinising hormone (LH) and follicle-stimulating hormone (FSH) via sustained delivery of GnRH, resulting in a decrease in oestrogens and chemical castration. The question from our patient, who was on levothyroxine replacement because of primary hypothyroidism, led us to hypothesise that in her case

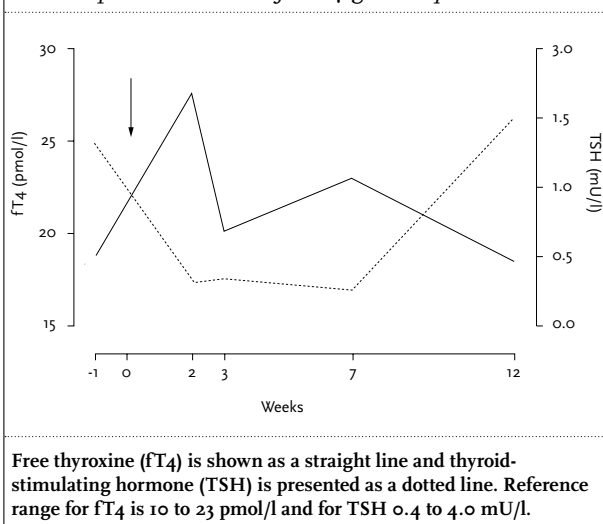
goserelin administration could indeed have an adverse interaction with thyroxine treatment. For, the fall in serum oestrogens will decrease the serum concentration of thyroxine-binding globulin (TBG), the major transport protein for thyroid hormones in serum. Consequently less thyroid hormone is needed for TBG binding. If the thyroid gland is unable to decrease its thyroxine secretion (as in our patient), continuation of the exogenous dose of thyroxine might result in an increase of serum free thyroxine (fT₄). This case report tests our hypothesis that this indeed might happen.

CASE REPORT

A 41-year-old woman with Hashimoto's hypothyroidism, euthyroid on 100 mg thyroxine for several years, was seen at our outpatient clinic. She suffered from metrorrhagia and had tried several hormonal treatment modalities without success. The next step would be subcutaneous implantation of goserelin to induce chemical castration. She was concerned about a possible interaction between thyroxine and goserelin (Zoladex), a GnRH analogue. In view of our hypothesis that the thyroxine replacement dose might become too high we decided to control her thyroid function two weeks after implantation and planned a visit one week thereafter. The thyroxine replacement dose was not changed. One week after administration of goserelin, she complained of tingling in arms and neck, flushes and hyperhidrosis. The general practitioner administered nitroglycerine, the tingling in the arms wore off and she was admitted to a cardiac care unit elsewhere. Ischaemic cardiac disease was not diagnosed; thyroid function was not measured.

Figure 1 shows the results of her thyroid function during a follow-up of 12 weeks after implantation of goserelin. Two weeks after implantation the fT₄ had increased to 27.4 pmol/l with a fall of thyroid-stimulating hormone (TSH) to 0.31 mU/l. The TBG was reduced from 330 nmol/l to 290 nmol/l and serum oestradiol was suppressed below 0.04 nmol/l. Three weeks after implantation of goserelin, the fT₄ was normal (20 pmol/l); TSH was still decreased and normalised later. TBG and oestradiol were not measured at that time. After seven weeks of implantation, the TBG concentration was 300 nmol/l and the oestradiol normalised to 0.16 nmol/l. Triiodothyronine (T₃) did not change during the observation period. The goserelin implantation was not repeated because of her symptoms.

Figure 1. Thyroid function before and after goserelin implantation (arrow) in a hypothyroid patient on a stable replacement dose of 100 µg levothyroxine



DISCUSSION

We hypothesised that an elevated fT₄ might occur after implantation of goserelin which might necessitate a lowering of the thyroxine replacement dose. Our observation in the patient supported the hypothesis: fT₄ levels increased and TSH became suppressed. The causal role of the decrease in serum TBG is supported by data from the literature. Baha and Arafah studied two groups of women with breast cancer: women with normal thyroid function and hypothyroid women who were adequately substituted with levothyroxine replacement.¹ Both groups were treated with the oral androgen, fluoxymesterone. Serum TBG and total T₄ decreased significantly in both groups within four and two weeks, respectively. In the control group fT₄ levels remained unchanged and TSH decreased slightly. In the hypothyroid group on levothyroxine replacement fT₄ levels

increased and TSH decreased within two weeks. These biochemical changes were associated with complaints of tachycardia, hyperhidrosis and insomnia. Thyroid hormone doses had to be reduced by between 25 and 50% to maintain euthyroidism. After discontinuation of the androgens, the TSH levels increased and fT₄ levels decreased when patients continued on the same thyroxine dose. TBG levels returned to normal after eight to ten weeks after therapy was discontinued.

The opposite study was done several years later.² Thirty-six postmenopausal women were given oral oestrogens. In both groups TBG and total T₄ became significantly elevated after 12 weeks but in the healthy group TSH and fT₄ did not change. In the hypothyroid women on thyroxine replacement fT₄ and TSH were significantly decreased and elevated, respectively, at 12 weeks; one woman had symptoms of hypothyroidism and needed an increase in levothyroxine replacement dose. This effect persisted during the whole study period. No data were shown after discontinuation of oestrogens.

The difference in fT₄ and TSH between the control groups and the women on thyroxine is explained by the notion that subjects on levothyroxine replacement are not able to adjust their serum fT₄ concentration via changes in the TSH secretion. For example, administration of androgens will decrease TBG, in all likelihood due to a decrease of glycosylation of TBG and thereby an increase in the clearance of TBG.³ According to the law of mass action, the reduction in TBG will increase the free fraction of circulating thyroxine (fT₄), followed by a decrease in TSH secretion. Under physiological conditions the lower TSH secretion will reduce thyroxine secretion by the thyroid gland, and the equilibrium between bound and fT₄ in the circulation is restored under normalisation of serum fT₄. In hypothyroid patients on a fixed dose of exogenous thyroxine the adaptation to changes in serum TBG via the negative feedback of thyroid hormones on the pituitary is failing.

Upon administration of androgens to women the decrease in TBG concentration as reported by Arafah is between 9 to 13 mg/l (167 to 241 nmol/l).¹ The TBG level in our patient decreased by only 40 nmol/l upon suppression of endogenous oestrogens. Thus the decrease in our patient was modest and may explain the limited increase in fT₄ and minimal decrease in TSH. The effect of sex hormone therapy on thyroid function depends on the route of administration. Transdermal oestrogens or testosterone therapy do not raise serum TBG and therefore do not alter the fT₄ level, because transdermal sex hormones do not have a hepatic first-pass effect in contrast to oral sex hormones.^{4,5} Thus the transdermal route is preferable in women receiving thyroid-hormone replacement.

TBG and T₄ are also influenced by tamoxifen, droloxifene⁶ and by intramuscular testosterone⁷ (table 1). No data of alterations in fT₄ due to tamoxifen or intramuscular

Table 1. *The effect of exogenous oestrogens and androgens on thyroid function tests*

	TBG	T ₄	Free T ₄	TSH
Oral oestrogens	↑	↑	= ↓ (Hypo on T ₄)	= ↑ (Hypo on T ₄)
Transdermal oestrogens	=	=	=	=
Tamoxifen, droloxifene	↑	↑	No data	No data
Oral androgens	↓	↓	= ↑ (Hypo on T ₄)	= ↓ (Hypo on T ₄)
Intramuscular testosterone	↓	↓	=	=
Transdermal testosterone	=	=	No data	No data
Goserelin	↓	↓	↑ (Hypo on T ₄)	↓ (Hypo on T ₄)

TBG = thyroxine-binding globulin; T₄ = thyroxine; TSH = thyroid-stimulating hormone.

testosterone are known in patients with hypothyroidism. But it can be assumed that fT₄ levels would change in substituted hypothyroidism. The clinical relevance of these changes is minor in many but not all patients as shown by Arafah.^{1,2} The symptoms in our patient after goserelin implantation are, in our opinion, non-thyroid-related side effects. First TSH was not completely suppressed and second, T₃ remained unchanged.

CONCLUSION

Our advice is to check thyroid function regularly in patients on thyroid hormone substitution therapy who are being treated with sex hormones.

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