

# Serum insulin levels and the degree of thyroid dysfunction in hypothyroid women

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## Abstract

**OBJECTIVES.** Among the peripheral effects of thyroid hormone action, their influence on insulin is of great interest and conflicting data on this subject are available. Despite various studies already performed, of concern is whether insulin levels change in line with a deterioration of thyroid function. In this study, we investigated serum insulin levels and their correlations with thyroid-stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) in hypothyroid women.

**DESIGN AND METHODS.** Study group consisted of 22 women with a history of total thyroidectomy and radioiodine ablation performed for thyroid cancer, without diabetes or glucose intolerance. After six-weeks of thyroxine withdrawal, subjects were admitted to the Department of Endocrinology of the Poznań University of Medical Sciences to perform this study.

**RESULTS.** Plasma glucose and insulin were respectively:  $4.76 \pm 0.47$  mmol/L and  $7.19 \pm 4.22 \mu\text{U/mL}$ . Serum TSH, FT4 and FT3 were respectively:  $91.66 \pm 58.59 \mu\text{U/mL}$ ,  $2.65 \pm 2.19$  pmol/L, and  $1.53 \pm 1.00$  pmol/L. Correlations were:  $r$  of  $-0.4381$  and  $P$  of  $0.0414$ ,  $r$  of  $-0.2368$  and  $P$  of  $0.2887$ , and  $r$  of  $0.3954$  and  $P$  of  $0.0686$  for insulin and FT4, insulin and FT3, and insulin and TSH, respectively. The only significant correlation was an inverse correlation between insulin and FT4.

**CONCLUSIONS.** In profound hypothyroidism insulin concentrations correlate with FT4 only, but not with FT3 or TSH.

## INTRODUCTION

Hypothyroidism is a clinical syndrome resulting from deficiency of thyroid hormones. An overall heat production and oxygen consumption are decreased with a subsequent generalized slowing down of all metabolic processes. Thyroid hormones deficiency affects every tissue in the body, including brain function, muscles and the cardiovascular system (Caiozzo & Haddad, 1996; Klein

& Ojama, 2001; Bernal *et al.*, 2003). Furthermore, hypothyroidism influences concentrations of a number of enzymes and blood constituents. Some of these effects are well known: serum cholesterol is elevated, and sex hormone-binding globulin are decreased in hypothyroidism. Some effects are more confusing, and among the peripheral effects of thyroid hormone action, their influence on insulin is of great interest. Conflicting data on this subject are available. Despite various studies al-

ready performed, of concern is whether insulin levels change in line with a deterioration of thyroid function.

Therefore in this study, we examined the *in vivo* influence of hypothyroidism on serum insulin levels in a group of totally thyroidectomized women.

## MATERIALS AND METHODS

The study group consisted of 22 consecutive female hypothyroid patients (mean age  $49.9 \pm 15.0$ ). Prior to this study, all subjects had undergone total thyroidectomy and radioiodine ablation for differentiated thyroid cancer. Then, they were admitted to the Department of Endocrinology for control search for tumor rests and this study was performed under these circumstances. In none of the subjects recurrence was demonstrated. Each subject ceased levothyroxine treatment six weeks prior to admission to enable radioiodine tests. None of the subjects showed the features of the metabolic syndrome according to IDF criteria, or presented with diabetes mellitus. None had a history of alcohol overconsumption. None of the subjects was completely sedentary, or involved in athletics. All subjects were examined in the morning (at 08:00 a.m.) after an overnight fast.

All subjects were examined physically, and their body mass index (BMI) was measured with the formulation: body mass (kg) divided per square height (m). Physical signs confirming thyroid hypofunction included facial appearance, heart rate and rhythm, skin temperature and texture of the skin and hair, as well as a scar on the neck related to previous thyroidectomy, and lack of the thyroid gland in ultrasound examination. Hypothyroidism was diagnosed on the basis of a history of thyroid ablation, clinical symptoms and a laboratory evaluation: in each case the serum thyrotropin (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) were measured and confirmed the diagnosis. All the hormonal assays were performed with an ELISA method, and a routine hospital biochemical analyzer Modular E-170 by Roche was used for all the measurements. Insulin was measured according to the manufacturer's recommended protocol, with a sensitivity of  $0.20 \mu\text{U/mL}$ . An intra-assay and inter-assay coefficients of variation were 1.2 % and 3.4 %, respectively.

Statistical analysis was performed with the STATISTICA software by Statsoft. The correlations between FT4, FT3, TSH and resistin levels were calculated with the Spearman's correlation test. The values are given as the mean  $\pm$  SD.

The study was conducted in accordance with the guidelines in The Declaration of Helsinki and was approved by the ethics committee of the Poznań University of Medical Sciences. All subjects gave informed consent to participate.

## RESULTS

The mean age of the patients was  $49.9 \pm 15$  years, with the median of 52.5 yrs. Their mean body mass index (BMI) was  $28.05 \pm 6.39 \text{ kg/m}^2$ , median  $26.95 \text{ kg/m}^2$ . Waist and hip circumferences were respectively (mean and median):  $86.6 \pm 13.44 \text{ cm}$ ,  $84.50 \text{ cm}$ , and  $100.95 \pm 8.95 \text{ cm}$ ,  $100.50 \text{ cm}$ . The clinical status of the subjects was typical for hypothyroidism. In all patients, symptoms of hypothyroidism included cold intolerance, easy fatigability, muscle cramps, memory problems, constipation and face edema. In physical examination, the average heart rhythm of 50 beats per minute, cold, rough and dry skin, the "dirty elbows sign", puffy edema of the face, and slowed intestinal peristalsis were present.

The mean and median fasting plasma glucose and insulin concentrations were as follows:  $4.76 \pm 0.47 \text{ mmol/L}$ ,  $4.55 \text{ mmol/L}$ , and  $7.19 \pm 4.22 \mu\text{U/mL}$ ,  $5.87 \mu\text{U/mL}$ , for glucose and insulin, respectively. Mean serum TSH was  $91.66 \pm 58.59 \mu\text{U/mL}$ , with the median of  $81.35 \mu\text{U/mL}$ . Mean and median serum FT4 and FT3 were as follows, respectively:  $2.65 \pm 2.19 \text{ pmol/L}$ ,  $2.10 \text{ pmol/L}$ , and  $1.53 \pm 1.00 \text{ pmol/L}$ ,  $1.43 \text{ pmol/L}$ .

To investigate the influence of thyroid status on the serum concentrations of insulin, correlations between insulin levels and FT4, FT3 and TSH were estimated. Results for correlations were as follows:  $r$  of  $-0.4381$  and  $P$  of  $0.0414$ ,  $r$  of  $-0.2368$  and  $P$  of  $0.2887$ , and  $r$  of  $0.3954$  and  $P$  of  $0.0686$  for insulin and FT4, insulin and FT3, and insulin and TSH, respectively. Thus, the only significant correlation was an inverse correlation with FT4. The data are illustrated in Figures 1, 2 and 3, for FT4, FT3 and TSH, respectively.

## DISCUSSION

Apart from clinical signs and symptoms, the main features of hypothyroidism include a variety of biochemical disturbances. Decreased metabolism and diminished energy consumption result in slower glucose utilization, and a decreased metabolism of insulin, the hormone of key importance in carbohydrate homeostasis.

The action of insulin in hypothyroidism has been controversial historically, and the impaired action of insulin in hypothyroid patients was questioned already in the mid 1970s (Shah *et al.*, 1975), with numerous conflicting studies that have been published until today. Nonetheless, of concern is whether insulin concentrations change in line with a decrease of thyroid function. Since the function of the thyroid gland can be measured by an assessment of the serum FT4, FT3 and TSH, an estimation of correlations between their values and insulin levels should bring an answer to this research question.

As shown in this clinical study, the serum levels of insulin only depend on free thyroxine concentrations in hypothyroid women, but are independent from FT3 and TSH. This fact is somewhat striking for clinicians, espe-

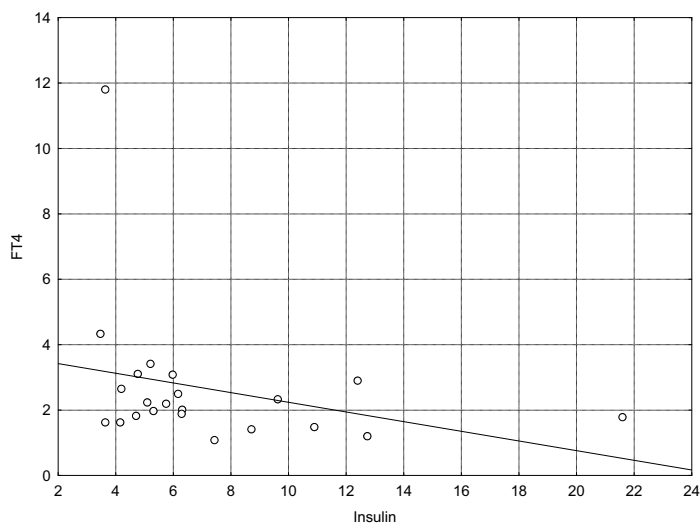
cially as for an assessment of thyroid hypofunction and results of levothyroxine supplementation TSH is the laboratory means most commonly used in clinical practice. However, TSH is secreted by the pituitary gland in response to a high demand for thyroid hormones in the body. Thus, it is an indirect measure of thyroid function. Under these circumstances, although practically useful, TSH does not reflect the degree of thyroid hypofunction completely. Moreover, its levels may vary between individuals due to various sensitivities of the pituitary to thyroid hormone deficiency.

One may argue about the negative results for FT3 in our study. Undoubtedly, FT3 is the acting form of the thyroid hormone, since it, but not FT4, binds to a nuclear receptor and exerts the effect. In contrast, FT4 needs to be converted into FT3 before it starts its action. In this setting, one would expect a correlation between insulin and FT3 rather than FT4. Only partially, our contrary results can be explained by varying degrees of FT4 into FT3 conversion in our patients. This, however, solely explains the discrepancy between FT4-insulin and FT3-insulin correlations but not the fact of the lack of a correlation between FT3 and insulin in the presence of a correlation between FT4 and insulin.

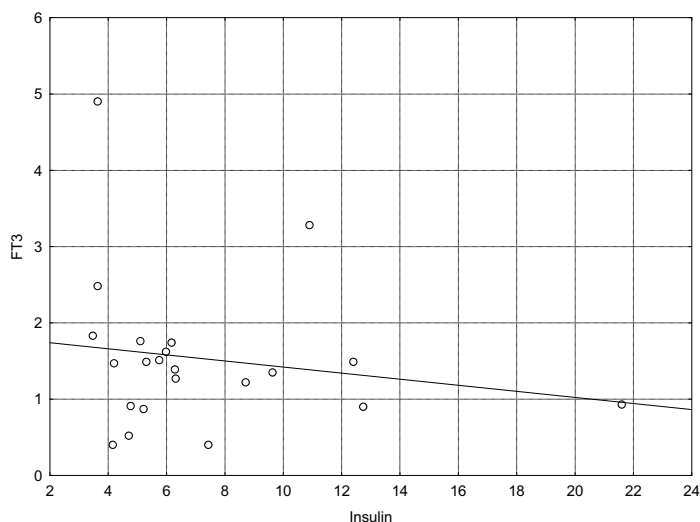
Nonetheless, our finding suggests that FT4 is a very useful tool in the assessment of thyroid hypofunction and in the prediction of increased insulin levels, perhaps even better than TSH and FT3.

Several other studies examined the interactions between insulin and thyroid action, although very few were performed in hypothyroidism *in vivo*, and, in majority, they focused on interactions other than we have. The results of these studies are contradictory: whereas some demonstrate an influence of hypothyroidism on insulin (Dessein *et al.*, 2004; Al Sayed *et al.*, 2006), others do not (Krassas *et al.*, 2006; Brenta *et al.*, 2007). Fasting hyperinsulinemia without true insulin resistance was reported in 77 patients with isolated subclinical hypothyroidism (Tuzcu *et al.*, 2005). In another study, Bakker *et al.* (2001) conducted a research to test the hypothesis that TSH, insulin sensitivity, and levels of low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) are interdependent in euthyroid subjects. TSH was not significantly correlated with insulin sensitivity or fasting triglyceride concentrations. The authors did not evaluate the interdependence of thyroxine and insulin sensitivity, however.

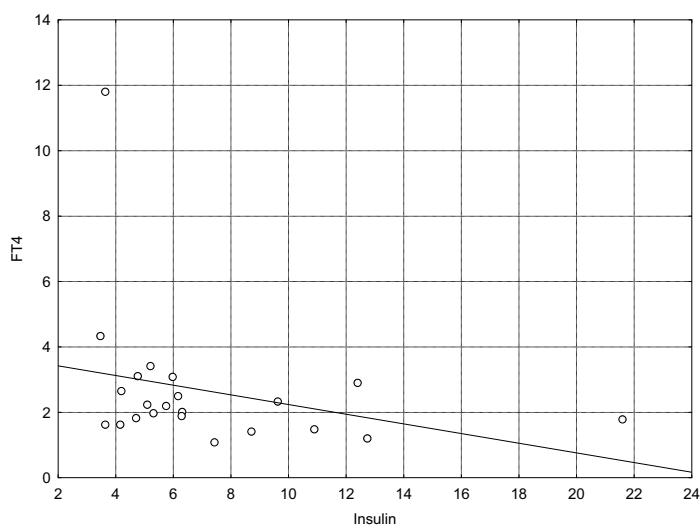
In another *in vivo* study, in 5 patients with exogenous thyrotoxicosis increased basal production and consumption of glucose, increased hepatic glucose synthesis and diminished capability of insulin binding by the erythrocyte were



**Figure 1.** Correlation between the concentrations of insulin (values expressed in  $\mu\text{U}/\text{mL}$ ) and free thyroxine (abbr. FT4, values expressed in  $\text{pmol}/\text{L}$ ) in the group of 22 hypothyroid women examined.



**Figure 2.** Correlation between the concentrations of insulin (values expressed in  $\mu\text{U}/\text{mL}$ ) and free triiodothyronine (abbr. FT3, values expressed in  $\text{pmol}/\text{L}$ ) in the group of 22 hypothyroid women examined.



**Figure 3.** Correlation between the concentrations of insulin (values expressed in  $\mu\text{U}/\text{mL}$ ) and the plasma thyrotropin (abbr. TSH, values expressed in  $\mu\text{U}/\text{mL}$ ) in the group of 22 hypothyroid women examined.

demonstrated. Insulin sensitivity was not decreased however, and this finding is somehow consistent with our present results, although conducted in the opposite, *ie* hyperthyroid state. (Laville *et al.*, 1984)

The mechanisms of the interactions of thyroid hormones and insulin were also investigated. Insulin receptor activity and its relationship with catecholamines in rat erythrocytes were evaluated in experimental hypothyroidism and hyperthyroidism. Down regulation of insulin receptors and alterations in membrane bound catecholamines were demonstrated in both situations. However, the research was not conducted in the humans, and thus it cannot be directly compared to our results. (Azam *et al.*, 1990)

In conclusion, one should admit that the current knowledge about the metabolism of insulin in humans remains still unclear. It may be even more confusing in several clinical conditions which would interfere with insulin metabolism, and hypothyroidism is undoubtedly the case. As shown in our study, only FT4 correlates with insulin concentrations in hypothyroid women, whereas FT3 and TSH do not. A plausible cause of this phenomenon could be an impaired rate of conversion of FT4 into FT3, but this tempting hypothesis needs further research to be proved.

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