

## Effect of Pioglitazone on Thyroid Hormones and IGF-I in Patients with Type 2 Diabetes

Lisa Arnetz<sup>1\*</sup>, Mikael Lantz<sup>2</sup>, Kerstin Brismar<sup>1</sup>, Neda Rajamand Ekberg<sup>1</sup>, Michael Alvarsson<sup>1</sup> and Mozghan Dorkhan<sup>2</sup>

<sup>1</sup>Department of Molecular Medicine and Surgery, Department of Endocrinology, Metabolism and Diabetes, Karolinska University Hospital, Stockholm, Sweden

<sup>2</sup>Department of Clinical Sciences, Division of Diabetes & Endocrinology, Lund University, Malmö University Hospital, Sweden

### Abstract

**Background:** Thyroid hormones cause insulin resistance. Pioglitazone is a peroxisome proliferator activated receptor gamma (PPAR $\gamma$ ) agonist, used as treatment of type 2 diabetes (T2D) to increase insulin sensitivity. PPARs and thyroid hormone receptors (TRs) induce intracellular effects through similar molecular mechanisms, and the former may inhibit activation of the latter. Pioglitazone has been shown to increase eye protrusion, a symptom linked both to disturbed thyroid hormone levels and orbital edema secondary to increased IGF-I.

**Aims:** We investigated whether attenuation of insulin resistance with pioglitazone affects thyroid hormone status and IGF-I.

**Methods:** 48 patients with T2D were treated with pioglitazone for 26 weeks. Thyroid hormones and IGF-I were analyzed before and after treatment.

**Results:** After treatment, free T4 decreased (from  $14.2 \pm 0.4$  to  $13.3 \pm 0.3$  pmol/L,  $p=0.009$ ) and TSH increased (from  $190 \pm 200$  to  $220 \pm 200$  U/L,  $p = 0.004$ ). IGF-I also increased (from  $0.5 \pm 0.2$  to  $1.0 \pm 0.2$  SD,  $p<0.001$ ).

**Conclusion:** Pioglitazone lowers free T4 and increases IGF-I in T2D. This may be due to impeded activation of the TR due to PPAR activation. Increased TSH is most likely secondary to reduce T4 activity. Increased IGF-I may cause orbital edema, as previously noted in patients treated with pioglitazone.

**Keywords:** Pioglitazone; Type 2 diabetes; IGF-I; Thyroid hormone; TSH; Eye protrusion; PPAR $\gamma$

### Introduction

Changes in thyroid function affect insulin sensitivity, although the studies on the nature of this relationship show somewhat conflicting results. Hyperthyroidism is associated with increased hepatic glucose output, resulting in hyperinsulinemia and insulin resistance [1]. However, insulin resistance is also seen in hypothyroidism [2]. Few studies have examined the effect of improved insulin sensitivity on thyroid hormone status in humans.

The peroxisome proliferation activated receptors (PPAR $\alpha$ ,  $\beta$  and  $\gamma$ ) are a group of nuclear receptors involved in regulation of lipid metabolism and adipose tissue differentiation. Like PPARs, thyroid hormone receptors (TR) belong to the nuclear receptor super family, and act by binding to DNA and modulating gene expression [3]. Both are co-expressed in the brain, liver and adipocytes. In order to bind to DNA and activate transcription, both PPAR and TR require heterodimerization with the retinoid X receptor (RXR). In addition to activating transcription through its own response elements, PPAR $\alpha$  is able to selectively down-regulate the transcriptional activity of TR through competitive binding to RXR [4].

PPAR agonists and T3 have been found to act either in a synergistic or opposing manner on various genes involved in lipid metabolism. Their signaling pathways converge through their mutual competition for heterodimerization with RXR. Chu et al. have demonstrated such an interaction in animal studies [5].

Pioglitazone is a PPAR $\gamma$ -activator used in the treatment of type 2 diabetes (T2D). It increases insulin sensitivity in various tissues, partly by redistributing fatty acids from those tissues to the subcutaneous adipose tissue. It also has some agonistic effects on PPAR $\alpha$  [6]. In our earlier studies we have noted an increase in eye protrusion in a subgroup

of patients with T2D treated with pioglitazone [7]. This phenomenon was more pronounced in patients with lower levels of adiponectin, reflecting a higher degree of insulin resistance. Given the known effects of PPAR $\gamma$  agonists on adipose tissue differentiation, it is possible that treatment induces orbital adipogenesis. This has been indicated in one study on endogenous PPAR $\gamma$  ligands [8]. In a study on insulin resistant women with polycystic ovary syndrome, pioglitazone increased GH but not total IGF-I [9], whereas in our previous studies on patients with T2D total IGF-I was increased [10,11]. Increased levels of IGF-I are associated with edema, especially in the face and orbita [12,13]. Stimulation of the IGF-I receptor may contribute to ophthalmopathy in Grave's disease, at least in those patients with elevated levels of TSH-binding inhibitory immunoglobulins [14]. We investigated whether attenuation of insulin resistance with pioglitazone affects thyroid hormone status and IGF-I.

### Materials and Methods

The parameters in seen in Table 1 were analyzed before and after six months of treatment with pioglitazone in 48 patients with t T2D diabetes [11,15]. Samples for IGF-I and thyroid hormones were stored in  $-80^{\circ}\text{C}$  and analyzed in the same run.

**\*Corresponding author:** Lisa Arnetz, Department of Molecular Medicine and Surgery, Karolinska Institutet D2:04 Karolinska University Hospital, 17176 Stockholm, Sweden, Tel: 08-524 800 00; E-mail: [lisa.arnetz@ki.se](mailto:lisa.arnetz@ki.se)

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	Baseline	Week 26	Δ	P
Age	61 (45 – 76)	na	na	na
Gender (n male: n female)	28:20	na	na	na
Duration of diabetes (years)	11 (3 – 30)	na	na	na
HbA <sub>1c</sub> (mmol/mol)	70 ± 7	56 ± 7	6 ± 7	<0.001
Weight (kg)	90.2 ± 2.2	94 ± 1 ± 2.3	4 ± 0	<0.001
BMI (kg/m <sup>2</sup> )	31.0 ± 0.6	32.3 ± 0.6	1.3 ± 0.1	<0.001
Waist circumference (cm)	111 ± 2	112 ± 2	1 ± 1	0.132
IGF-I (µg/L)	171 ± 6	199 ± 8	28 ± 4	<0.001
IGF-I (SD)	0.5 ± 0.2	1.0 ± 0.2	0.5 ± 0.1	<0.001
TSH (IU/L)	1.9 ± 0.20	2.2 ± 0.2	0.3 ± 0.2	0.004
Free T4 (pmol/L)	14.2 ± 0.4	13.3 ± 0.3	-0.8 ± 0.3	0.009
Adiponectin (µg/ml)	6.2 ± 0.4	13.2 ± 0.9	7.1 ± 0.6	<0.001

**Table 1:** Clinical characteristics and laboratory analyses at baseline and after 26 weeks of pioglitazone treatment. Data presented as mean ± SEM except for age and duration of diabetes, presented as mean (range). Δ = change in the variable after treatment compared with baseline, na = not applicable.

## Assays

HbA<sub>1c</sub> was analyzed with the Variant II chromatographic method [15] and IGF-I with in-house radio-immunoassay (RIA) [16]. Adiponectin was analyzed using RIA (Research Adiponectin Assay, Linco, St. Charles, Missouri, USA). The limit of sensitivity for the assay was 1 ng/ml and both the inter- and intra assay coefficients of variation were < 10%. TSH and free T4 were analyzed using chemiluminescence (UniCelDxl 800 97, DxI Beckman Coulter, Brea, CA, USA), total CV 6.2 and 3.4% respectively.

## Statistics

Paired t-tests were used to compare IGF-I (SD and µg/L) at baseline and after treatment as it was normally distributed; all other parameters were compared using non-parametric tests as they were not normally distributed. Pearson's correlation coefficients were calculated between continuous variables. P<0.05 was considered statistically significant. All data are presented as means ± SEM unless otherwise stated.

## Results

Clinical characteristics and laboratory analyses before and after treatment are summarized in Table 1. During pioglitazone treatment, HbA<sub>1c</sub> decreased (p<0.001) and adiponectin increased (p<0.001), despite increased weight and BMI (p<0.001 for both; table 1) [15]. Concurrently, TSH increased (p=0.004) while free T4 decreased (p=0.009). The change in (Δ) adiponectin and ΔTSH were correlated (r=0.402, p=0.005). IGF-I increased (p<0.001), and was ΔIGF-I was negatively correlated with ΔHbA<sub>1c</sub> (r=-0.328, p=0.023) but not correlated with Δ adiponectin.

## Discussion

Pioglitazone improved glycemic control (HbA<sub>1c</sub>) and insulin sensitivity (adiponectin). There was an increase in IGF-I, which regression analysis showed was partially related to improved glycemic control. Based on previous studies [9], increased GH may also have contributed to this increase.

After pioglitazone treatment, TSH increased while free T4 decreased. We hypothesize that pioglitazone's binding of PPARγ, which increases formation of PPAR-RXR dimers, impedes formation of TR-RXR complexes and thus reducing thyroid hormone function. The increased TSH most likely reflects pituitary response to feedback signals of reduced free T4 levels and TR activation, with the purpose restore thyroid hormone homeostasis. A concomitant increase in

thyrotropin releasing hormone (TRH) may contribute to increased growth hormone and thereby IGF-I. Increased eye protrusion is more likely related to increased adipogenesis due to pioglitazone, and orbital edema secondary to increased IGF-I, to than changes in thyroid hormone status.

## Significance of this Paper

Pioglitazone is a PPARγ agonist used in the treatment of type 2 diabetes, as it increases insulin sensitivity. Treatment is associated with increased eye protrusion, a condition often seen in Graves' disease. Given this, and the association of IGF-I with orbital edema, we studied the effect of pioglitazone treatment on thyroid hormones and IGF-I. We here report, for the first time, that pioglitazone decreases free T4, secondarily increasing TSH. We also report an increase in IGF-I. Especially the latter finding may explain the increased orbital protrusion seen in patients on pioglitazone therapy.

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