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Treatment with a thiazolidinedione increases eye protrusion in a subgroup of patients with type 2 diabetes

Pioglitazone induced eye protrusion

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Summary

Objective. Changes in eye protrusion in patients treated with pioglitazone

Design. Open-label prospective.

Patients. Thirty-six patients with type 2 diabetes and HbA1c \geq 6.5% were included in a study where pioglitazone was added to previous therapy with metformin and sulfonylurea.

Measurements. The degree of eye protrusion before and 26 weeks after treatment with pioglitazone was measured according to Krahn.

Results. Thirteen patients (group A) exhibited an increase of \geq 2 mm and 23 patients (group B) exhibited an increase of $<$ 2 mm ($p_{\text{between groups}}=0.036$). Patients of group A vs. group B had the same BMI, HbA1c and mean doses of pioglitazone but had lower levels (mean \pm SD) of adiponectin in $\mu\text{g/ml}$ at start (4.9 ± 2.1) vs. (7.1 ± 2.5), $p=0.017$ and at the end of study (10.2 ± 4) vs. (14.9 ± 5), $p=0.007$. Patients with thyroid disturbance were more frequent in group A (5 vs. 1), $p=0.02$. In a logistic regression analysis thyroid disturbance, low adiponectin levels and pioglitazone dose predicted a significant change in eye protrusion.

Conclusions. A subgroup of patients with type 2 diabetes treated with pioglitazone responded with increased eye protrusion. This subgroup showed decreased plasma concentration of adiponectin and more frequent thyroid disturbance and were treated with higher doses of pioglitazone. The relationship between insulin resistance, thyroid disturbance and TZD induced eye protrusion should be further studied.

Introduction

Activation of peroxisome proliferator-activated receptor gamma (PPAR γ) with synthetic ligands, e.g. thiazolidinediones (TZDs), has been demonstrated to improve glucose tolerance and to decrease insulin-resistance in patients with type 2 diabetes (1-3). The positive effect on insulin resistance may be explained by selective effects on visceral adipose tissue, which decreases in volume. This is in contrast to subcutaneous adipose tissue, which increases in parallel to an increase in body weight in patients treated with TZDs (4). It may thus seem paradoxical that TZDs despite increase in body weight improve insulin sensitivity. However, it has been clearly demonstrated that TZDs can promote adipose tissue growth by activating the PPAR γ receptor in predominantly subcutaneous preadipocytes (5).

It was recently reported that a type 2 diabetic patient with stable and inactive Graves' ophthalmopathy experienced worsening of ophthalmopathy after treatment with pioglitazone (6). The clinical activity score increased from 1 to 6 including soft tissue enlargement and eye muscle symptoms as well as increased eye protrusion. These symptoms were ameliorated three months after withdrawal of pioglitazone. Starkey et al suggested that treatment with PPAR γ agonists might be contraindicated in patients with a previous history of thyroid autoimmune disease (6). To address the question whether treatment with a glitazone increases eye protrusion we measured eye protrusion in patients with type 2 diabetes receiving pioglitazone in addition to previous antidiabetic therapy with sulfonylureas and metformin. To obtain a quantitative measurement of the degree of improvement of insulin sensitivity by pioglitazone serum adiponectin concentrations were measured.

Subjects and methods

Thirty-six poorly controlled Caucasian type 2 diabetic patients were included in a study where pioglitazone was added to previous therapy with sulfonylurea and metformin. The study has been conducted in accordance with the guidelines in The Declaration of Helsinki and approved by the local ethics committee and informed consent was obtained from all subjects. The degree of eye protrusion was measured by use of a Krahn exophthalmometer before and six months after treatment with pioglitazone. Six patients had a history, clinical signs and/or laboratory indicators of thyroid disturbance (Table 1). Dose adjustment of levothyroxine was performed in two patients. All patients completed the study.

The study was open-labeled and prospective with 26 weeks of follow up. Patients received 30 mg pioglitazone once daily in addition to therapy with metformin and sulfonylurea. The pioglitazone dose was increased to 45 mg/day (n=12) after 16 weeks if HbA1c was $\geq 6.5\%$.

The degree of eye protrusion was measured at inclusion and at the end of study i.e. after 26 weeks of therapy with pioglitazone. The measurements were performed by the same investigator (MD), using the same Krahn's exophthalmometer. Also the same inter-eye distance of the instrument was used for both measurements in given patient. At the second measurement the investigator was not aware of the previous measures of eye protrusion. The coefficient of variation (CV%) for repeated measurements in the same patient for the investigator (MD) was 3.7% for the right eye and 3.4% for the left eye.

Serum concentration of adiponectin was analyzed using The Linco Research Adiponectin RIA assay, St. Charles, Missouri, USA according to the manufacturers description. The limit of sensitivity for the assay was 1 ng/ml and both the inter- and intra-assay coefficients of variation were < 10%.

Statistics

Clinical characteristics are shown in Table 2. Significance of differences in patients' characteristics (age, BMI, HbA_{1c}, adiponectin) between subgroups was analyzed by non-parametric Wilcoxon test. All tests were two-tailed and a p value of less than 0.05 was considered statistically significant. The Wilcoxon signed ranks test was used to compare increase in eye protrusion before and after six months of treatment with pioglitazone. A ≥ 2 mm change in eye protrusion measured by the Krahn exophthalmometer was considered as a significant change (7-9). Logistic regression analysis was used to determine factors that predicted a significant change in eye protrusion. Change in eye protrusion of ≥ 2 mm was considered as dependent variable and baseline characteristics (age, sex, BMI, smoking, presence of thyroid disturbance and adiponectin levels) as well as pioglitazone dose as independent variables. Statistical analyses were carried out using the SPSS version 12.02 and Eviews version 4.0 statistical software.

Results

In all subjects there was a median change in eye protrusion of 1 mm (interquartile range 2 mm) for the right eye, $p < 0,001$ and 1 mm (interquartile range 1 mm) for the left eye, $p = 0,011$. Patients were divided into two subgroups based upon whether they showed an increase in eye protrusion of 2 mm or more (Group A, $n=13$) or not

(Group B, N=23)(Table 2). The increase in eye protrusion (mean \pm SD) was significantly larger in group A (17.3 ± 3 to 19.5 ± 3.1 mm in right eye and 17.4 ± 2.9 to 18.9 ± 2.8 mm in left eye) than in group B (17.5 ± 2.5 to 17.7 ± 2.3 mm in right eye and 17.6 ± 2.5 to 17.6 ± 2.5 mm in left eye) ($p_{\text{right}} < 0.001$, $p_{\text{left}} = 0.001$). As illustrated in figure 1, in 13 patients (group A) eye protrusion increased by 2 mm or more in right or left eye ($p_{\text{right}} = 0.001$, $p_{\text{left}} = 0.002$) while the change in eye protrusion in 23 other patients (group B) was not significant ($p_{\text{right}} = 0.433$, $p_{\text{left}} = 0.928$), ($p_{\text{between groups}}=0.036$). There was a strong correlation between the degree of changes in eye protrusion between right and left eye ($r = 0.66$, $p < 0.001$). None of the patients noticed changes in the appearance of their eyes, nor did they report any other eye symptoms.

Group A and B did not differ regarding weight gain, glycemic control measured as HbA1c or the dose of pioglitazone. The group with the greatest increase in eye protrusion (group A) had lower adiponectin levels at baseline as well as after treatment with pioglitazone. The sex-adjusted increases in adiponectin levels in group A and B were similar after six months (118%). In group A, patients with previous or present thyroid disturbance were more frequent.

Logistic regression analysis, including change in eye protrusion of ≥ 2 mm as dependent variable and baseline characteristics (age, sex, BMI, smoking, presence of thyroid disturbance and adiponectin levels) as well as pioglitazone dose as independent variables was applied. When both thyroid disturbance and smoking were used in the logistic regression, the algorithm did not converge in solution. Therefore we tested to exclude presence of thyroid disturbance and investigate the

effect of smoking. This did not result in significance for smoking and did not affect the other parameters' significance; therefore smoking was excluded in the continuing analyses. Presence of thyroid disturbance, low adiponectin levels and pioglitazone dose were factors that predicted a significant change in eye protrusion (Table 2&3).

Discussion

In this study of patients with type 2 diabetes receiving pioglitazone for 6 months on top of treatment with sulfonylurea and metformin we observed an overall small but significant increase in the degree of eye protrusion as measured by exophthalmometry according to Krahn. None of the patients developed other signs of ophthalmopathy like soft tissue or eye muscle symptom, as described in one patient with type 2 diabetes and a previous history of Graves' ophthalmopathy (6). Our findings are supported by a recent case report of a patient with congenitally prominent globes –but without thyroid disease - who responded with increased proptosis when receiving treatment with rosiglitazone (10).

Who is at risk of increased eye protrusion during treatment with a glitazone? In our study the increase in eye protrusion was neither related to BMI at baseline nor to a difference in weight gain during TZD treatment. However, a low adiponectin level at baseline predicted an increase in eye protrusion suggesting that insulin resistance may be a risk factor for the effect of glitazones on eye protrusion. The relative increase of adiponectin in response to treatment with TZD was similar in both groups, as well as the decrease in HBA1c levels, suggesting that the observed effect was not a reflection of a general enhanced effect of glitazones.

The low adiponectin levels hardly reflect latent hyperthyroid disease as previous studies have shown elevated adiponectin levels in hyperthyroidism compared with hypothyroidism (11).

In orbital adipogenesis, a characteristic in Graves' disease, mitogenic activation of preadipocytes is a prerequisite to fulfil differentiation to mature adipocytes (12). In vitro it has been demonstrated that mitogen (insulin) stimulated orbital preadipocytes responded with an enhanced adipogenesis in the presence of rosiglitazone (13, 14). In vivo a type 2 diabetic patient responded with activation of Graves' ophthalmopathy when treated with pioglitazone (6). In addition it has also been demonstrated that the effect of glitazones can be depot-specific and that orbital fibroblasts are heterogeneous in their response to glitazones (5, 14). Thus the increase in eye protrusion might be the result of an enhanced mitogenic response due to a pre-existing hyperinsulinemic state in this subgroup of patients and when exposed to glitazones they respond with an enhanced adipogenesis.

It is well known that both hypothyroidism and hyperthyroidism can affect glucose tolerance in patients with diabetes (15, 16). In this study, there was an overrepresentation of thyroid disturbance in the group with increased eye protrusion (Group A). The role of this observation is unclear but in earlier studies of thyroid disturbance, adiponectin concentration has been determined in peripheral blood and found to be increased in the hyperthyroid state compared to the hypothyroid state of Graves' patients (11). In two other studies comparing hyperthyroid patients with hypothyroid patients there was no significant difference between the groups in the adiponectin levels (17, 18).

Treatment with TZD has been suggested as a risk factor of developing ophthalmopathy in Graves' disease (6). Graves' ophthalmopathy results from an increase in the volume of orbital adipose / connective tissue and eye muscles (8). There is evidence for an enhanced orbital de novo adipogenesis in Graves' ophthalmopathy with increase in mRNA of immediate early genes in the initial proliferation phase followed by increased expression of PPARgamma, preadipocyte factor-1, adiponectin, leptin as well as stearyl-CoA desaturase (12, 19, 20). Whether this is true for orbital adipogenesis in patients with type 2 diabetes is not known but similar mechanisms have been delineated in subcutaneous adipose tissue of healthy subjects (5). In Graves' ophthalmopathy orbital fibroblasts have been demonstrated to differentiate into mature adipocytes when treated with rosiglitazone (13, 14). Another well-known risk factor for developing ophthalmopathy is exposure to tobacco (21-23) but in our study material the difference in number of current or previous smokers between group A and B was not significant.

In conclusion, we describe a subgroup of type 2 diabetic patients responding with increased eye protrusion when treated with the TZD, pioglitazone.

A low plasma adiponectin, present or previous thyroid disturbance and pioglitazone dose were risk factors for eye protrusion associated with TZD treatment. Obesity and type 2 diabetes are associated with low plasma adiponectin concentrations and the degree of hypoadiponectinemia is closely related to the degree of insulin resistance and hyperinsulinemia (24). With these findings in mind one could speculate if environmental factors like TZD in combination with a pre-existing susceptibility, for example increase in insulin resistance, may result in remodeling of orbital tissue and in the end cause increased eye protrusion in patients with type 2 diabetes.

The clinical importance of our findings and whether these patients are at risk of developing Graves' ophthalmopathy needs to be addressed in future studies.

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Table 1. Characteristics of patients with present or previous thyroid disturbance

Age	64	63	59	49	66	51
Sex	M	M	M	F	F	F
Smoking	Yes	Previously	No	No	No	No
Diagnosis	GD ^a	S.Hyper ^b	S.Hyper ^c	AIT ^d	S.Hypo ^e	NG ^f
TSH ^g , week 0	6.7	0.14	0.19	3.7	4.1	0.07
TSH, week 26	3.8	0.1	0.65	3.7	3.6(0.4-3.5)	0.5
TSH-R ^g		Neg.	Neg.		Neg.	
TPO ab		Neg.	Neg.		Neg.	
Levothyroxine	Yes	No	No	Yes	No	Yes

a. Graves' disease diagnosed and treated with antithyroid drugs at the age of 14.

Hypothyroidism since 1998, treated with levothyroxine. Dose adjustment of levothyroxine at week 0.

b. Peripheral thyroid hormones were normal, no clinical signs of hyperthyroidism.

c. Peripheral thyroid hormones were normal and TSH was gradually normalised during the study. This was the only patient with thyroid disturbance in group B.

d. Autoimmune hypothyroidism, treated with levothyroxine. Year 2001 elevated TPO antibodies.

e. Peripheral thyroid hormones were normal, no clinical signs of hypothyroidism.

f. Uninodular atoxic goitre, dose adjustment of levothyroxine at week 0.

g. Normal range 0.4 -4 mIU/L if not other stated in parenthesis. The normal range references changed during the study.

S.Hypo=Biochemical, subclinical hypothyroidism, **TSH-R**=Thyrotropin-receptor antibodies

S.Hyper=Biochemical, subclinical hyperthyroidism, **TPO ab**=Thyroid peroxidase autoantibodies

Table 2

Patient characteristics before and six months after treatment with pioglitazone in two subgroups according to changes in eye protrusion

Changes in eye protrusion	Increase \geq 2mm	Increase < 2 mm	p
	Group A	Group B	
N (%)	13 (36%)	23 (64%)	
Age (years)	59 \pm 8	60 \pm 8	0.7
Gender-female/male (%)	4/9 (44%)	9/14 (64%)	
Proptosis ^a at start, right eye	17.3 \pm 3 (12-23)	17.5 \pm 2.5 (13-23)	
Proptosis ^a at start, left eye	17.4 \pm 2.9 (13-24)	17.6 \pm 2.5 (13-22)	
Proptosis ^a at study end, right eye	19.5 \pm 3.1 (14-25)	17.7 \pm 2.3 (14-22)	
Proptosis ^a at study end, left eye	18.9 \pm 2.8 (14-24)	17.6 \pm 2.5 (13-22)	
BMI at start	30.4 \pm 5	31 \pm 3.7	0.7
BMI after six months	31.6 \pm 5.3	32.3 \pm 3.7	0.5
Current or previous smokers (%)	10 (77%)	13 (56%)	0.3
Thyroid disturbance	5 (38%)	1 (4%)	0.02
HbA _{1c} % at start	7.4 \pm 0.5	7.6 \pm 0.8	0.7
HbA _{1c} % after six months	6.2 \pm 0.7	6.4 \pm 1.1	0.9
Pioglitazone dose, high/low ^b (%)	5/13(38%)	7/23(30%)	0.001
Adiponectin at start (μ g/ml)	4.9 \pm 2.1	7.1 \pm 2.5	0.017
Adiponectin at study end (μ g/ml)	10.2 \pm 4	14.9 \pm 5	0.007

Values are means \pm SD if not stated otherwise

^a The degree of proptosis by exophthalmometri reading shown in mean \pm SD (range) mm.

^b High dose = 45 mg/day, low dose = 30 mg/day

Table 3. Logistic Regression Analysis

	Coefficient	Std. Error	p
(Constant)	9,70763	7,013262	0,1663
Gender	-1,045414	0,655234	0,1106
Age	0,000471	0,03498	0,9893
BMI	-0,034296	0,089444	0,7014
Inter-eye distance	-0,107785	0,068092	0,1134
Pioglitazone dose	0,084178	0,037542	0,0249
Adiponectin	-0,282401	0,108385	0,0092
Thyroid disturbance	2,721454	0,961764	0,0047

a. Dependent variable: Group

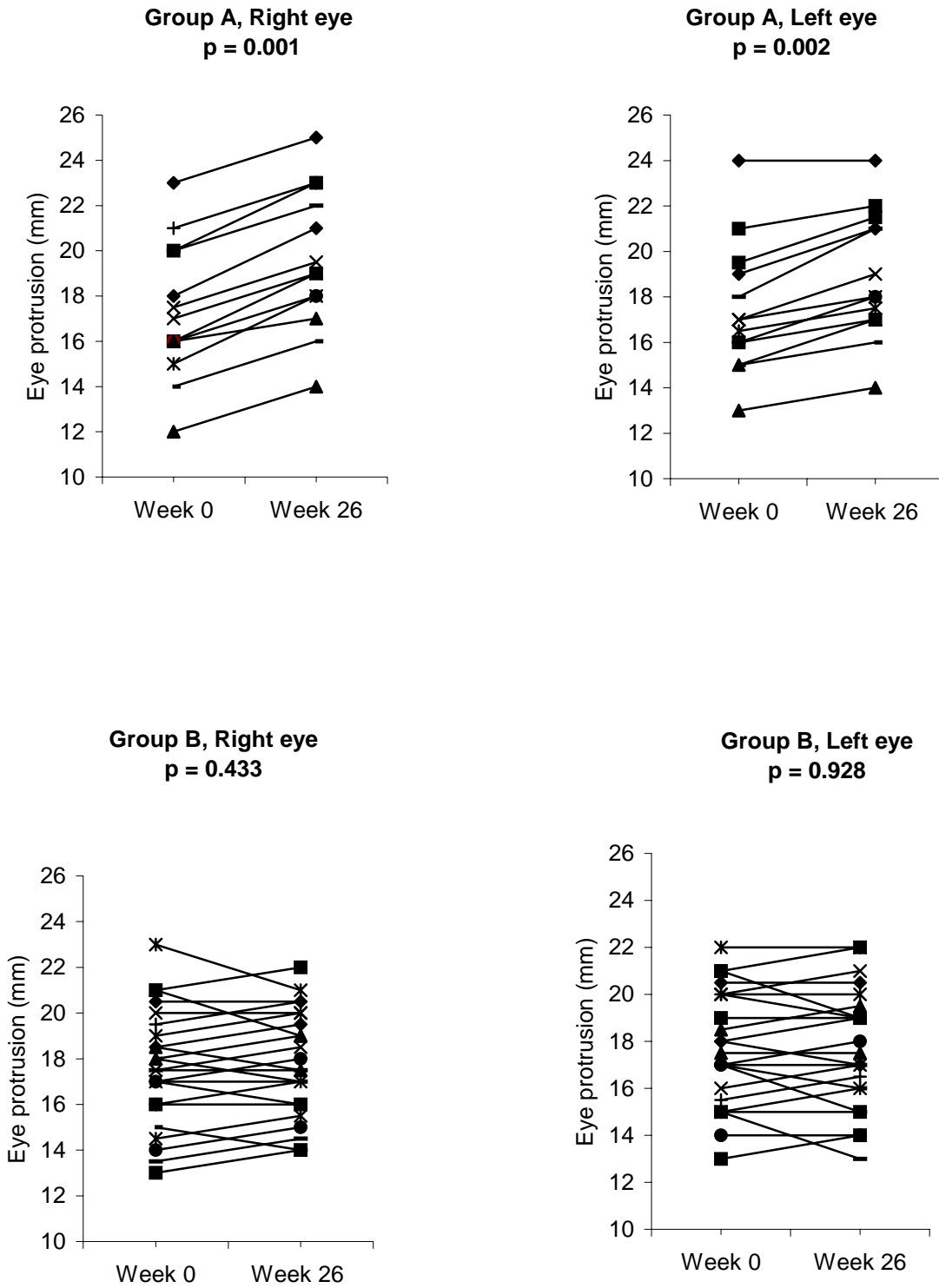


Fig.1. Exophthalmometry according to Krahn in patients with type 2 diabetes. Data are shown as eye protrusion (mm) at start and after 26 weeks of treatment with pioglitazone.

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