

Topic: TREATMENT OF TYPE 2 DIABETES & OPHTHALMOPATHY

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

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SUMMARY

Context: Activation of peroxisome proliferators-activated receptor gamma (PPR γ) with synthetic ligands such as thiazolidinediones (TZD) has been demonstrated to improve glucose tolerance and decrease insulin resistance in patients with type 2 diabetes. It has been demonstrated that TZD can increase the amount of adipose tissue by activating the PPR γ receptor in predominantly subcutaneous preadipocytes. Recently, a type 2 diabetic patient, with stable & inactive Graves' ophthalmopathy (GO), experienced worsening of GO after treatment with pioglitazone.

Objective: This open-label prospective study addresses the question of whether treatment with a glitazone could change eye protrusion in type 2 diabetic patients.

Setting: The degree of eye protrusion was measured before and 26 weeks after treatment with pioglitazone, using Krahn's exophthalmometer.

Patients: Thirty-six Caucasian patients with poorly controlled type 2 diabetic patients were included in a study where pioglitazone was added to current therapy with sulphonylurea and metformin. The study was open-labelled and prospective with 26 weeks of follow-up. The pioglitazone dose was increased to 45mg/d (n = 12) after 16 weeks if HbA1c was > 6.5 %.

Results: Thirteen patients (group A) exhibited a > 2 mm increase of proptosis and 23 patients (group B) exhibited a < 2 mm increase of proptosis. Patients in group A *versus* group B had the same BMI, HbA1C and mean dose of pioglitazone, but lower levels of adiponectin at the start (4.9 ± 2.1 vs 7.1 ± 2.5 μ g/ml) and at the end of the study (10.2 ± 4 vs 14.9 ± 5 μ g/ml). Patients with thyroid disturbances were more frequent in group A (5 vs 1). In a logistic regression analysis, thyroid disturbance, low adiponectin levels and pioglitazone dose predicted a significant change in eye protrusion.

Conclusion: A subgroup of patients with type 2 diabetes, treated with pioglitazone, responded with increased eye protrusion. This subgroup had decreased plasma concentration of adiponectin and more frequent thyroid disturbances, and was treated with higher dose of pioglitazone. The relationship between insulin resistance, thyroid disturbance and thiazolidinedione-induced eye protrusion should be studied further.

COMMENT

In present study of type 2 diabetic patients who received pioglitazone for 6 months (in addition to sulphonylurea and metformin), the authors observed an overall small but significant increase in the degree of eye

protrusion. No imaging (with MRI or CT-scan) was performed to measure more accurately the degree of eye protrusion and examine possible changes in extra-ocular muscles or orbital adipose tissue. No other

clinical sign of ophthalmopathy was observed in these patients.

Obesity and type 2 diabetes are associated with low plasma levels of adiponectin and hypo-adiponectinemia is closely related to the degree of insulin resistance and hyperinsulinemia. An hypothesis to explain present results might be that environmental factors, such as TZD combined with a pre-

existing susceptibility (insulin resistance), may result in remodelling of orbital tissue and lead ultimately to increased eye protrusion in patients with type 2 diabetes. This observation needs confirmation but it seems prudent not to treat patients with Graves' disease with a thiazolidinedione. (*Chantal Daumerie, M.D.; Ph.D.*)

See Table below

Patients' characteristics before & 6 months after treatment with pioglitazone in 2 subgroups according to changes in eye protrusion

Changes in eye protrusion	Increase \geq 2 mm: Group A	Increase < 2 mm: Group B	P
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* at start, right eye	17.3 \pm 3 (12–23)	17.5 \pm 2.5 (13–23)	
Proptosis* at start, left eye	17.4 \pm 2.9 (13–24)	17.6 \pm 2.5 (13–22)	
Proptosis* at study end, right eye	19.5 \pm 3.1 (14–25)	17.7 \pm 2.3 (14–22)	
Proptosis* 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 6 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
HbA1c percentage at start	7.4 \pm 0.5	7.6 \pm 0.8	0.7
HbA1c percentage after 6 months	6.2 \pm 0.7	6.4 \pm 1.1	0.9
Pioglitazone dose, high/low † (%)	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.

*The degree of proptosis by exophthalmometric reading shown in mean \pm SD (range) mm.

†High dose = 45 mg/day, low dose = 30 mg/day.