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Anti-inflammatory effects of troglitazone in nondiabetic obese subjects independent of changes in insulin sensitivity

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ABSTRACT

Background: Obesity is characterised by insulin resistance and by elevated levels of proinflammatory markers. We investigated whether, in the absence of changes in glucose, thiazolidinediones (TZDs) have anti-inflammatory effects and whether improvement of insulin sensitivity correlates with suppression of inflammatory markers.

Methods: We performed a randomised double-blind placebo-controlled crossover study with troglitazone (400 mg daily for eight weeks) in 15 normoglycaemic obese subjects. We measured plasma high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), leptin, tissue-type plasminogen activator (tPA), plasminogen activator inhibitor-1 (PAI-1) and tumour necrosis factor-α (TNF-α) after each of the two treatment periods and in 13 age- and sex-matched lean individuals.

Results: Obese subjects were insulin resistant (decreased glucose infusion rate (GIR) during euglycaemic hyperinsulinaemic clamp) and had higher plasma levels of hsCRP, IL-6, leptin, tPA, and PAI-1 compared with lean subjects. TNF-α also tended to be higher. Troglitazone improved insulin sensitivity (mean increase in whole body glucose uptake 23.1 ± 10.5% (p=0.047)) and normalised plasma concentrations of hsCRP, tPA and TNF-α, whereas it did not significantly change IL-6, leptin and PAI-1. Changes in GIR did not correlate with changes in inflammatory markers.

Conclusion: Troglitazone induces suppression of some of the inflammatory markers that are elevated in normoglycaemic obese subjects. The suppression of inflammatory markers, however, does not correlate with improvement in insulin sensitivity, suggesting involvement of partially differential mechanisms in these effects of TZDs.

KEYWORDS

Inflammation, insulin sensitivity, obesity, thiazolidinediones, trial

INTRODUCTION

Insulin resistance, which is a common feature of obesity, appears to be central to the pathogenesis of type 2 diabetes.[1-3] Insulin resistance is hypothesised to develop in obesity mainly as a result of adverse effects of elevated plasma levels of free fatty acids (FFA).[4,5] FFA or their metabolites can impair insulin action and inhibit glucose transport activity by stimulation of protein kinase C isoforms. Furthermore, by increasing the level of oxidative stress, FFA activate stress-sensitive signalling pathways such as the nuclear transcription factor κB (NFκB) pathway, which plays an important role in inflammation.[6] In addition to FFA, chemical messengers synthesised and secreted by adipocytes, such as tumour necrosis factor-α (TNF-α) and leptin, may influence insulin sensitivity.[1,4]

Recent studies have indeed confirmed a role for inflammation in the pathogenesis of insulin resistance. Plasma concentrations of the inflammatory mediators interleukin-6 (IL-6), TNF-α and TNF-receptor and plasminogen activator inhibitor-1 (PAI-1) were elevated in the obese.[7-12] Moreover, some markers of subclinical vascular inflammation, in particular high-sensitivity C-reactive protein (hsCRP) and IL-6, correlated with insulin sensitivity[7,8,13,14] and were shown to be powerful independent predictors of development of type 2 diabetes.[15,16]

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Thiazolidinediones (TZDs), peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonists, improve insulin sensitivity.[17-19] PPAR-γ regulates the transcription and expression of specific genes that affect fat in adipose tissue, skeletal muscle and the liver.[17] TZDs induce a redistribution of fat out of skeletal muscle and liver into peripheral adipocytes[20-22] resulting in a sustained decrease in plasma FFA[23,24] and hence an improvement in insulin sensitivity and a reduced activation of stress-sensitive signalling pathways. Activation of PPAR-γ receptors may also directly contribute to reduction of chronic subclinical inflammation.[25,26] Several studies have shown that TZDs reduce NFκB activation and decrease elevated levels of PAI-1 and hsCRP, but most of these studies were performed in subjects with diabetes.[27-31] However, it is uncertain whether a decrease in plasma glucose levels contributes to the decreases in inflammatory parameters. Therefore, we investigated effects of troglitazone on plasma levels of hsCRP, IL-6, leptin, tissue-type plasminogen activator (tPA), PAI-1 and TNF-α in nondiabetic obese subjects characterised by insulin resistance.

MATERIALS AND METHODS

Subjects

The study groups consisted of 15 obese and 13 lean normotensive, healthy volunteers on no medication. Inclusion criteria were age between 25 and 50 years, nonsmokers, normal fasting glucose concentration, stable body weight, and a body mass index (BMI) between 27 and 36 kg/m^2 for the obese and between 19 and 25 kg/m^2 for the lean. All gave written informed consent. The experimental protocol was approved by the hospital ethics committee.

Protocol

After inclusion, the obese subjects received either troglitazone (2x200 mg daily) or placebo for eight weeks in a randomised double-blind crossover design. Participants were strictly advised to maintain their weight and not to change their diet. At the end of each of the two treatment periods and after an overnight fast, 30 ml of blood was collected in EDTA-containing tubes and plasma was isolated by centrifugation at 4°C and stored in aliquots at -80°C. Subsequently, a euglycaemic-hyperinsulinaemic clamp (insulin [Actrapid; Novo-Nordisc], infusion rate 430 pmol x m^{2}x min^{-1} [60 mU/dl/min]) was performed for 120 minutes. Body weight, waist-hip measurements, ECG, fat skinfold thickness, possible side effects, and serum chemical and haematological profiles were determined as a safety precaution. Between the treatment periods there was a two-week washout phase. Compliance was monitored by pill counts and amounted to over 90%.

Analytical measurements

Plasma glucose was measured by the glucose oxidation method (Beckman Glucose Analyser 2; Beckman Instruments, Fullerton, CA, USA). Plasma insulin was measured with a double antibody radioimmunoassay (interassay coefficient of variation 6.2%). FFAs (nonesterified fatty acids, NEFAs) were analysed with an enzymatic method (ACS-ACOD, NEFA C-kit; Waco, Neuss, Germany). Cholesterol and triglycerides were determined by enzymatic methods (Boehringer-Mannheim, Mannheim, Germany) on a Hitachi 747 analyser (Hitachi, Tokyo, Japan). HsCRP[32] was measured by an ELISA from Kordia (Leiden, the Netherlands); serum leptin by a RIA kit from Linco Research Inc. (St. Louis, MO, USA); IL6[33] by the Pelikine Compact human IL6 ELISA kit from CLB (Amsterdam, the Netherlands); and TNFα, tPA and PAI-1 were determined by specific ELISAs as described elsewhere.[34]

Statistical analysis

Data are presented as mean ± SE and evaluated by using Student's t-test for paired and unpaired data. Linear regression analysis was performed to examine the relationship between (changes in) variables. Significance was set at a p value of less than 0.05. The computer programme ASTUTE (Microsoft Ink, Redmond, WA, USA) was used for the analysis.

RESULTS

Characteristics of the two study groups are presented in *table 1*. The groups were properly matched for age and sex. Fat percentage, waist-hip ratio, fasting plasma insulin, triglycerides and NEFAs, but not fasting glucose and cholesterol, were significantly higher in the obese than in the lean control subjects. The obese had higher diastolic blood pressure than the lean; no difference was seen for systolic blood pressure. Compared with the values for insulin sensitivity of lean subjects, the obese were clearly insulin resistant: whole-body glucose uptake during euglycaemic hyperinsulinaemic clamp was significantly lower in the obese than in the lean control subjects. Insulin sensitivity (i.e. glucose infusion rate (GIR) during euglycaemic hyperinsulinaemic clamp) correlated strongly with BMI (r=-0.67, n=26, p=0.0002).

Plasma levels of hsCRP, IL-6, leptin, tPA, and PAI-1 were significantly higher in the obese compared with the lean group (*table 2*). Plasma level of TNF-α tended to be higher in the obese subjects, but this difference did not attain statistical significance (*table 2*). HsCRP, IL-6 and leptin were strongly associated with BMI (r=0.53, 0.48, and 0.70, respectively) and with GIR (r=-0.51, -0.55, and -0.57, respectively; *figure 1*). TPA was weakly associated with

Table 1 *Characteristics of study groups*

	Lean	Obese	P value
Number (m/f)	13 (7/6)	15 (9/6)	
Age (year)	38.3 ± 2.1	37.4 ± 1.2	NS
BMI (kg/m²)	21.9 ± 0.6	31.7 ± 0.8	<0.001
Fat (%)	22.6 ± 1.7	35.8 ± 1.8	<0.001
Waist/hip	0.86 ± 0.02	1.01 ± 0.02	<0.001
Total cholesterol (mmol/l)	4.61 ± 0.27	4.91 ± 0.26	NS
Triglycerides (mmol/l)	0.82 ± 0.10	2.11 ± 0.59	0.05
NEFAs (mmol/l)	0.38 ± 0.05	0.65 ± 0.08	0.01
Glucose (mmol/l)	5.2 ± 0.1	5.5 ± 0.1	NS
Insulin (pmol/l)	40.9 ± 1.4	85.6 ± 2.1	<0.001
GIR (μmol/kg/min)	53.9 ± 4.3	27.0 ± 2.9	<0.001
Systolic BP (mmHg)	118 ± 3	123 ± 3	NS
Diastolic BP (mmHg)	73 ± 4	82 ± 2	<0.05

BMI = body mass index; NEFAs = nonesterified fatty acids; GIR = glucose infusion rate; BP = blood pressure; NS = not significant.

Table 2 *Plasma concentrations of markers of inflammation in lean subjects and in obese subjects treated with placebo or troglitazone*

	Lean (n=13)	Obese (n=15)	
		Placebo*	Troglitazone*/†
HsCRP (mg/l)	1.06 ± 0.32	4.53 ± 1.28‡	2.23 ± 0.61ns/‡
TNF-α (ng/l)	3.37 ± 0.39	4.54 ± 0.51ns	3.67 ± 0.49ns/§
IL-6 (ng/l)	1.08 ± 0.15	1.60 ± 0.13‡	1.57 ± 0.19‡/ns
Leptin (μg/l)	6.0 ± 1.4	17.2 ± 3.2§	16.5 ± 3.3§/ns
tPA (μg/l)	1.02 ± 0.10	1.58 ± 0.13§	1.15 ± 0.12ns/§
PAI-1 (μg/l)	9.2 ± 1.0	19.5 ± 3.0§	17.2 ± 2.3§/ns

HsCRP = high-sensitivity C-reactive protein; TNF-α = tumour necrosis factor-α; IL-6 = interleukin 6; tPA = tissue-type plasminogen activator; PAI-1 = plasminogen activator inhibitor-1. *T-test *vs* values of lean control subjects; †paired t-test *vs* values of placebo-treated obese subjects; ‡p<0.05; §p<0.01; ns = not significant.

GIR (r=0.44) but not with BMI. TNF-α was not associated with GIR but correlated weakly with BMI (r=0.40). PAI-1 was not associated with GIR or BMI.

Troglitazone was well tolerated. No changes were observed for body weight, plasma triglycerides, total cholesterol, and fasting plasma glucose concentration (data not shown). A nonsignificant decrease was observed for plasma NEFAs (from 0.65 ± 0.08 to 0.48 ± 0.06 mmol/l, p=0.08). Fasting insulin concentrations tended to decrease but remained elevated compared with those in the lean control subjects (data not shown). Insulin sensitivity improved, as evidenced by increased whole-body glucose uptake during euglycaemic hyperinsulinaemic clamp: mean percentage increase in whole body glucose uptake amounted to 23.1 ± 10.5% (p=0.047).

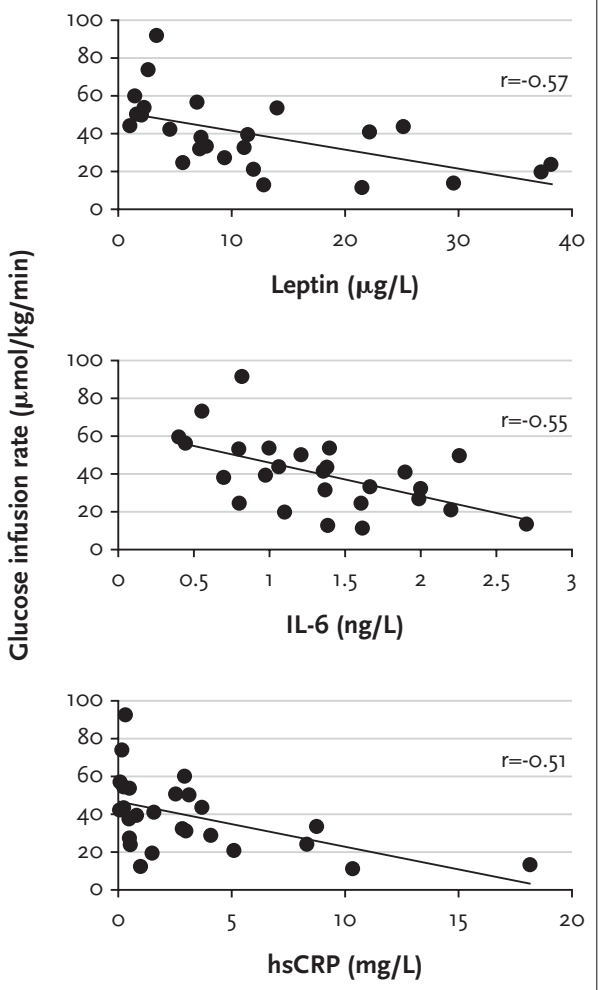
During troglitazone treatment, plasma concentrations of hsCRP, TNF-α and tPA of the obese decreased significantly (*table 2*). Consequently, after treatment these values were not different from those of the lean control subjects. Plasma levels of IL-6, leptin and PAI-1 in the obese did not significantly change during troglitazone treatment and remained elevated compared with the lean subjects.

Troglitazone-induced changes in hsCRP, TNF-α and tPA did not correlate with changes in GIR (data not shown).

DISCUSSION

In line with previous reports, we confirmed the presence of a proinflammatory state in insulin-resistant obese subjects,[15,16,35] as levels of hsCRP, IL-6, leptin, tPA, and PAI-1 were significantly higher in the obese than in the lean. Moreover, levels of hsCRP, IL-6, and leptin inversely correlated with insulin sensitivity. This is consistent with

Figure 1 *Association of insulin sensitivity with plasma levels of leptin, interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hsCRP)*



the hypothesis that chronic subclinical inflammation is involved in the pathogenesis of insulin resistance.[16] The eight-week treatment with troglitazone normalised plasma levels of hsCRP, TNF-α and tPA in obesity but did not affect levels of IL-6, leptin and PAI-1. Since the obese were insulin resistant but did not have diabetes, the observed troglitazone-induced changes in inflammatory markers cannot be caused by changes in blood glucose metabolism.[36]

Plasma TNF-α was not significantly elevated in our obese, insulin-resistant study group. Earlier reports on plasma concentrations of TNF-α in obesity are not uniform. Whereas Hauner *et al.* observed normal plasma levels of TNF-α in obesity,[10] others reported markedly elevated plasma TNF-α concentrations in obese subjects when compared with lean controls.[12] The latter suggested that circulating TNF-α in obesity reflects the level of expression of TNF-α message and protein synthesis in adipose tissue.[12] However, recently, Kern *et al.* demonstrated that despite markedly increased TNF-α secretion from adipose tissue in obesity, plasma levels of TNF-α need not deviate from normal.[8] In their study it was the adipose-secreted form of TNF-α that displayed the strongest relationships with obesity and insulin resistance. They and others suggested that adipose tissue-derived TNF-α and leptin (a messenger molecule produced solely by adipose tissue) induce the production of IL-6 and hsCRP, thus contributing to the development of a proinflammatory state with increasing body weight in obesity.[37,38] The strong relationships that we observed between BMI and insulin sensitivity and plasma hsCRP, IL-6 and leptin but not plasma TNF-α, are in agreement with this hypothesis.

It was previously shown that in prediabetics, troglitazone reduced plasma concentrations of hsCRP[39] and rosiglitazone suppressed the generation of reactive oxygen species by mononuclear cells *ex vivo* and reduced plasma hsCRP and MCP-1.[40] In both studies only nondiabetic obese subjects (7 for troglitazone and 11 for rosiglitazone) and no healthy lean controls were included. More recently, other studies have also shown that rosiglitazone decreased markers of inflammation and endothelial activation (CRP, PAI-1 and von Willebrand factor) in nondiabetic subjects with stable coronary artery disease,[41] hypertension,[42] or metabolic syndrome.[43] It is unclear whether these decreases correlated with an improvement in insulin sensitivity. Our study included 15 obese well-characterised insulin-resistant subjects and 13 healthy lean controls and had a double-blind placebo-controlled crossover design. We have demonstrated that plasma levels of all studied inflammatory parameters are elevated in obesity and that some of them normalise during troglitazone treatment. Thus, there was a distinct though selective beneficial effect of troglitazone on the inflammatory status. To our knowledge, effects of TZDs on tPA and leptin have not been investigated before and IL-6 has not been previously studied in prediabetics. In our study, as with rosiglitazone in patients with type 2 diabetes,[27] troglitazone did not significantly change plasma levels of IL-6. Furthermore, the observed decreases in the levels of the inflammatory proteins hsCRP, TNF-α and tPA did not correlate with troglitazone-induced improvement in insulin sensitivity. In addition, despite some improvement in insulin sensitivity by troglitazone, the obese group remained quite insulin resistant as compared with the lean group. In contrast, troglitazone almost normalised the levels of the proinflammatory cytokines. Together, these observations suggest that troglitazone exerts its action, at least partially, via different pathways. Troglitazone may affect inflammation directly by activation of PPAR-γ present on monocytes,

monocyte-derived macrophages, vascular endothelial cells, and vascular smooth muscle cells,[25] or, via antioxidant properties of the α-tocopherol structure contained in troglitazone, reduce oxidative stress and inhibit activation of NFκB.

Although troglitazone has been withdrawn from most markets because of liver toxicity,[44] details on its effects and mechanisms of action are of interest with respect to the other members of the TZDs, as rosiglitazone and pioglitazone.

Previously we reported an increase in the ratio of large buoyant to small dense LDL, a decrease in LDL *in vitro* oxidisability, and an increase in plasma Lp(a) concentration in obese subjects treated with troglitazone.[45,46] We now add to this the selective anti-inflammatory effects of troglitazone in obesity: plasma levels of hsCRP, IL-6, leptin, tPA, PAI-1 and TNF-α (borderline significant) were elevated in the obese compared with those in lean controls, but troglitazone only reduced CRP, TNF-α and tPA. Considering the fact that low-grade inflammation is increasingly recognised as a key process in the aetiology and pathogenesis of insulin resistance and cardiovascular disease, the anti-inflammatory effects of TZDs may contribute to primary prevention of diabetes and result in improved cardiovascular outcomes. Long-term prospective studies with clinical endpoints, such as the ongoing DREAM trial that evaluates the ability of rosiglitazone to delay progression of type 2 diabetes in a nondiabetic population with impaired glucose tolerance, and RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes), will hopefully answer this question.

In conclusion, our data confirm the association between increased inflammation/fibrinolysis and insulin resistance, and show that TZDs selectively suppress plasma markers of inflammation, independent of changes in glucose control and, at least in part, independent of their effect on insulin sensitivity.

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