The effect of pioglitazone on muscle and liver triglyceride content and total body fat in patients with familial combined hyperlipidaemia

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Background: Combined hyperlipidaemia (CHL) is the most common disorder of lipid metabolism, affecting up to 2% of the population and confers 20% of the risk for premature CHD. Subjects with familial CHL (FCHL) and their first degree relatives frequently display insulin resistance and hyperlipidemia.[1-3] The link between insulin resistance and components of the metabolic syndrome is complex but increased intra-abdominal adiposity and ectopic fat deposition have been implicated as a predominant factor in the pathogenesis of the associated abnormalities and the development of degenerative, metabolic and vascular complications. The role of thiazolidinediones in the treatment of type 2 diabetes is well established,[4,5] however, it is not known whether FCHL patients, who have similar phenotypic presentations and lipid parameters, would respond favourably to the effects of TZDs. The effect of pioglitazone on liver, muscle, regional body fat content and lipid parameters were studied in patients with familial combined hyperlipidaemia (FCHL). The study was a double bind placebo controlled in design.

Methods: 22 male patients with FCHL (mean age 53.5 ± 7.4 yr; BMI 26.7 ± 2.2 kg/m^2) were randomly assigned to receive pioglitazone (n=10) or placebo (n=12) for 4 months in addition to their conventional lipid-lowering therapy with statins+/- fibrates. Patients were started on 30mg pioglitazone/placebo for 4 or 8 weeks at which time the dose was increased to 45md od. MRI and ^{1}H-MRS were performed before and after 16 weeks of treatment.
Fasting blood tests: performed at baseline 4, 8 and 16 weeks, included routine biochemical measurements, lipids, NEFA, insulin, leptin, adiponectin, and AIP (atherogenic index of plasma) calculated.
Total body adipose tissue content: Rapid T_1-weighted MR images (TR 36ms, TE 14ms) were acquired as previously described.[6] Subjects were imaged prone with arms straight above head and were scanned from fingertips to toes acquiring 10mm-thick transverse images with 30mm gaps in arms and legs, and 10mm gaps in the trunk. Images were analysed using SliceOmatic (Tomovision, Montreal, Canada). Total AT, subcutaneous, total internal, subcutaneous abdominal and intra-abdominal AT volumes were measured.
MRS of the liver: ^{1}H MR spectra were were obtained from the right lobe of the liver using a PRESS sequence (TR 1500ms, TE 135ms) without water saturation, with 128 signal averages.[7]
MRS of muscle: IMCL was measured in the soleus (S-IMCL) and tibialis (T-IMCL) muscles by ^{1}H MR with TR 1500ms, TE 135 ms, 256 averages. IMCL were measured relative to the total muscle creatine signal, after correcting for T_1 and T_2.[8]

Results: Significant changes in plasma triglycerides (-26.5%, p=0.006), HDL cholesterol (10.7% p=0.02), AIP (-78.6%, p=0.002), blood glucose (-4.4%, p=0.03) and ALT (-7.7% p=0.005) were observed following pioglitazone treatment. Favourable changes were also observed in CRP (-12.7%, p=0.04) and adiponectin (130.1%, p=0.001). Pioglitazone resulted in a significant increases in both total (5.3%, p=0.02) and subcutaneous (7.1%, p=0.003) AT. The latter was observed in the abdominal (12.0%, p=0.04) and peripheral (5.5%, p=0.008) depots. No significant changes were observed in intra-abdominal AT (p=0.4). There was a significant increase in soleus-IMCL levels (47.4%, p=0.02) but no significant changes in either tibialis-IMCL or IHCL following pioglitazone treatment. However changes in the latter were significantly correlated with alterations in both ALT and AST levels. Indeed multiple regression analysis of the data revealed the only parameters to influence changes in S-IMCL were changes in AIP and CRP. Whereas changes in several AT compartments including total AT, peripheral subcutaneous AT, both intra-abdominal and peripheral internal AT and body weight influenced changes in T-IMCL levels. Changes in IHCL were significantly influenced by changes in plasma triglycerides, and total AT. There was no influence of changes in regional adiposity on IHCL.

Discussion: The aim of this study was to assess whether patients with FCHL, already on lipid lowering medication, would benefit from the addition of pioglitazone. In the one published study of FCHL patients treated with pioglitazone, the subjects were not receiving any conventional lipid-lowering medication.[9] They found no significant effect on BMI, fasting glucose, HbA1c, serum lipid levels, body fat distribution, nor in IMCL, but did observe changes in insulin sensitivity, which we were not able to detect probably because of our use of surrogate markers of insulin sensitivity. Studies in subjects with type-2 diabetes have shown varied responses to pioglitazone therapy. Some have reported similar changes to our study with increases in peripheral and abdominal subcutaneous AT, and no changes in IAAT.[10] Others reported reductions in intra-abdominal AT,[5] or no changes in adiposity.[11,12] Pioglitazone has previously been reported not to change IMCL in subjects with FCHL.[9] We also found no change in T-IMCL, and paradoxically observed a significant increase in S-IMCL. This may be related to changes in fat oxidation and redistribution. A number of studies have reported reductions in IHCL, together with changes in intra-abdominal AT, and IMCL in subjects with type-2 diabetes and NASH following TZD. This may occur since IAAT, IMCL and IHCL tend to be significantly increased in these subjects before pioglitazone treatment. However, in the current study, subjects with FCHL had been on treatment with lipid lowering medication for many years. As a result none of these parameters (IAAT, IMCL and IHCL) were significantly outside the normal range found in our control populations, possibly making a reduction in any of these parameters with pioglitazone more difficult to achieve and/or to detect. In FCHL patients with uncontrolled lipid parameters despite treatment with conventional lipid lowering therapy, the addition of pioglitazone may help to achieve target lipid levels.

References

1. Aitman TJ, Godsland IF, et al. Arterioscler Thromb Vasc Biol 1997 17(4):748-54.
2. Karjalainen L, et al. Arterioscler Thromb Vasc Biol 1998 18(10):1548-53.
3. Shoulders CC, Jones EL, Naoumova RP Hum Mol Genet 2004; S1: R 149-60
4. Kelly IE, Han TS, Walsh K, Lean ME. Diab Care. 1999;22(2):288-93.
5. Miyazaki Y, Mahankali A, et al. JCEM. 2002;87(6):2784-91.
6. Thomas EL, Saeed N, et al. Magnetic. J Appl Physiol. 1998;85(5):1778-85.
7. Thomas EL, Hamilton G, et al. Gut. 2005;54(1):122-7.
8. Rico-Sanz J, Thomas EL, et al. J Appl Physiol. 1999;87(6):2068-72.
9. Abbink EJ, De Graaf J, et al. J Intern Med 2006 259(1):107-16.
10. Smith SR, De Jonge L, et al. Metabolism 2005 54(1):24-32.
11. Hirose H, Kawai T, et al. Metabolism 2002 51(3):314-7.
12. Basu A, Jensen MD, McCann F, et al. Diab Care 2006 29(3):510-4.