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Improvement in hepatic metabolism is associated with reduced conversion to diabetes in IGT subjects treated with pioglitazone (ACT NOW study)

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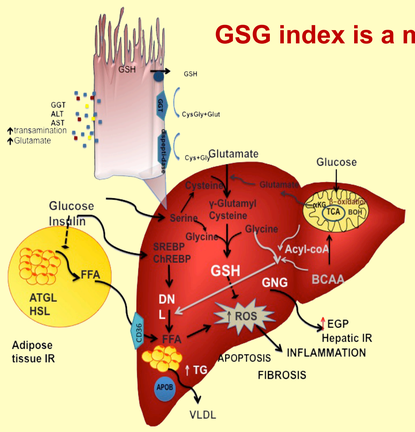
ACT NOW Study:

The ACT NOW is a randomized, double-blind, placebo-controlled study designed to examine whether pioglitazone can reduce the risk of type 2 diabetes mellitus in adults with impaired glucose tolerance. A total of 602 patients were randomly assigned to receive pioglitazone or placebo. The median follow-up period was 2.4 years. Fasting glucose was measured quarterly, and oral glucose tolerance tests were performed annually. Conversion to diabetes was confirmed on the basis of the results of repeat testing.

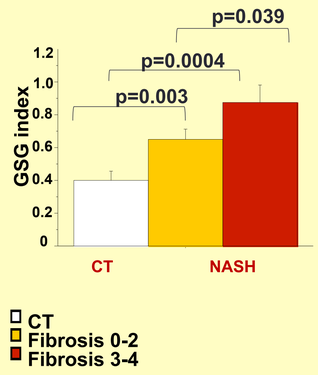
Background and Aims:

Increased liver enzymes are markers of fatty liver disease (FLD) and of progression to type 2 diabetes (T2DM).
Pioglitazone has been shown not only to delay onset of T2DM, but also to ameliorate fatty liver and improve hepatic function. We recently have shown that subjects with FLD have increased plasma amino acid concentrations and that the ratio of glutamate/(serine+glycine) (GSG index) was associated with degree of fibrosis measured by liver biopsy.

GSG index is a marker of liver damage



Gaggini et.al unpublished data



The aim of this study was to evaluate the changes observed in parameters of hepatic function after 2.4 year of pioglitazone treatment in subjects with impaired glucose tolerance (IGT) and the relationship with onset of T2DM.

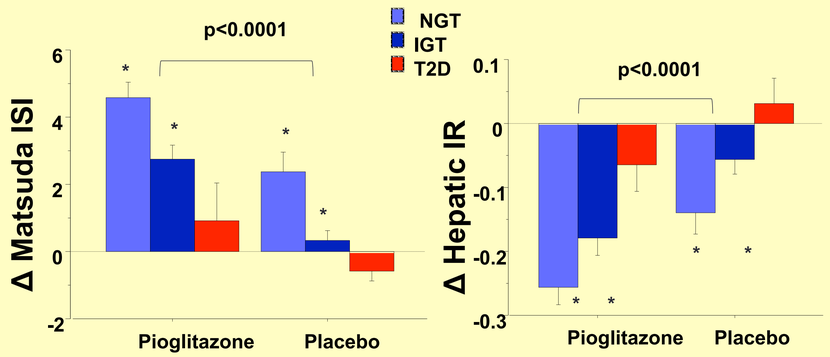
Methods:

441 IGT subjects who participated in the ACT NOW Study and had complete end-of-study metabolic measurements were randomized to receive pioglitazone (45 mg/day) or placebo and were observed for a median of 2.4 years. Indices of insulin sensitivity (Matsuda index [MI]), lipid profile (triglycerides, HDL, LDL), liver enzymes, plasma amino acid concentrations, adipose tissue IR (FFA x Ins), hepatic IR index (Glu 0-30min x Ins 0-30min), and index of hepatic damages, i.e. GSG index and AST/ALT score were measured

Results:

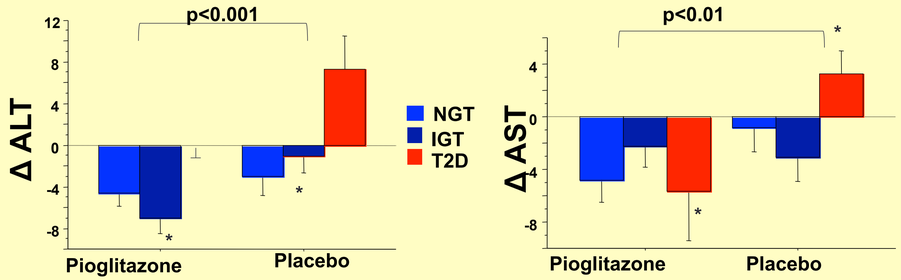
Of the 441 subjects that completed the study 50 (21.9%) PLAC-treated subjects developed type 2 diabetes versus 15 (7.0%) PIO-treated subjects (p<0.005, odds ratio = 0.28 [95% CI] = 0.15-0.49; p<0.0001). 48% of PIO reverted to NGT versus 28% of PLAC (p<0.005).
Pioglitazone significantly improved pheripheral insulin sensitivity, reduced ALT (from 30±1 to 24±1 U/l, p<0.0001), AST (from 26±1 to 22±1 U/l, p<0.0007), AST/ALT (+0.08 vs -0.08) and induced a small but significant improvement in Hep-IR.

Pioglitazone improved insulin sensitivity and decreased hepatic insulin resistance



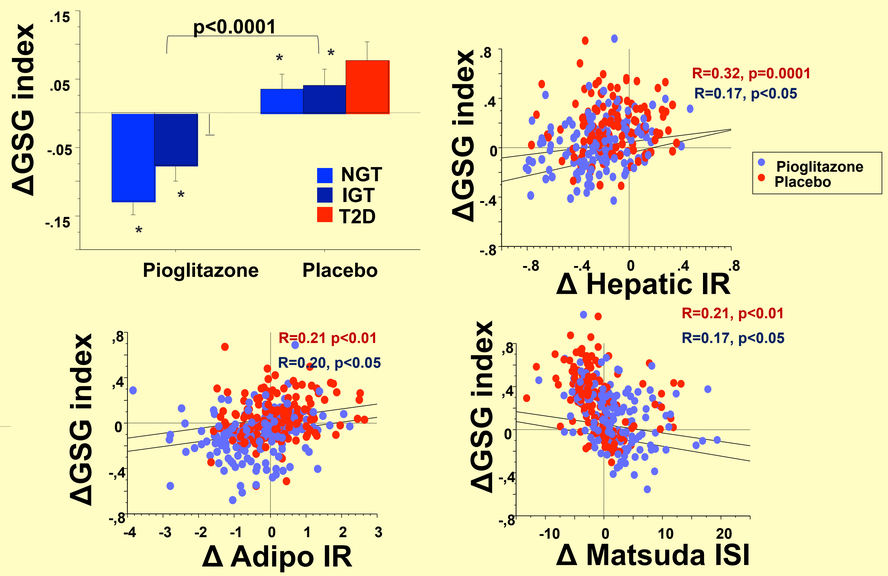
* p<0.05 vs baseline

Pioglitazone decreased AST and ALT showing the improvement in hepatic function



* p<0.05

Pioglitazone decreased GSG index. ΔGSG correlated with changes in hepatic IR, adipose tissue IR and matsuda index



In the pioglitazone group, after 2.4 year, fewer subjects converted to T2DM (n=15 vs 45). New T2DM subjects showed increased or no change (rather than decrease) in GSG index, hepatic IR, AST, ALT and TG concentrations.

Conclusions

Reduced conversion of IGT to T2DM after pioglitazone treatment is strongly related to the improvement in hepatic function.