Insulin sensitizers in treatment of nonalcoholic fatty liver disease: systematic review
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CRD summary
This review investigated the clinical effectiveness of insulin sensitizers in the treatment of nonalcoholic fatty liver disease (NAFLD). The authors concluded that the use of insulin sensitizers in NAFLD improves insulin resistance and liver function, but further research is required to corroborate histological changes. Given the lack of controlled trials available, the authors' conclusions appear overconfident in relation to the benefits.

Authors' objectives
To summarise the evidence on the clinical effectiveness of insulin sensitizers in the treatment of nonalcoholic fatty liver disease (NAFLD).

Searching
MEDLINE, EMBASE, CINAHL, ERIC, LISTA, the Cochrane Database of Systematic Reviews, the Cochrane Controlled Trials Register, DARE and LILACS were searched up to March 2006 for papers written in English, Spanish, German or French. Dissertations were sought through ProQuest and FirstSearch. Proceedings from the Digestive Disease Week of the American Gastroenterological Association (1999 to 2006) and the American Association for the Study of Liver Diseases Meetings (2003 to 2005) were also searched, and the reference lists of retrieved articles were checked.

Study selection
Study designs of evaluations included in the review
Clinical trials with at least 10 participants at baseline were eligible for inclusion.

Specific interventions included in the review
Studies of insulin sensitizers were eligible for inclusion provided there was no concomitant treatment such as ursodeoxycholic acid or antioxidants. Relevant comparators were placebo and diet. The included studies were of metformin (dose range: 20 mg to 2 g/day), rosiglitazone (8 mg/day) and pioglitazone (30 mg/day). The duration of treatment ranged from 12 to 48 weeks. The included controlled studies used diet as the comparator.

Participants included in the review
Studies of adults with NAFLD or nonalcoholic steatohepatitis (NASH), based on histology or imaging studies (computed tomography, abdominal ultrasound or magnetic resonance imaging) and/or aberrant liver function tests in the absence of alcohol consumption, were eligible for inclusion. In most of the included studies the majority of participants were male and the mean age ranged from 36 to 51 years. Where reported, the proportion of diabetics ranged from none to 13%.

Outcomes assessed in the review
The outcomes reported in the results were insulin resistance, histological changes (e.g. lactic acid), liver histology (e.g. inflammation and fibrosis), NASH score and adverse events.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for relevance and any disagreements were resolved by consensus.

Assessment of study quality
The authors recorded whether studies were randomised or blinded. This appears to have been conducted as part of the data extraction process and two reviewers were involved.
Data extraction
Two reviewers independently extracted the data following standardised procedures, and any disagreements were resolved by referring to the original paper. Attempts were made to contact corresponding authors where data to be extracted were not presented in the published report, and any responses were included in the data extraction.

Methods of synthesis
How were the studies combined?
The studies were discussed in a narrative synthesis, comparing the results for metformin versus diet trials and metformin single-arm trials and thiazolidinediones single-arm trials separately.

How were differences between studies investigated?
Differences between the studies were reported in the tables and in the text.

Results of the review
Nine studies (n=175) were included: one randomised controlled trial (RCT), one non-randomised controlled trial, one RCT from which only one arm was used, and six single-arm trials.

The single RCT (n=36), which compared metformin plus restricted diet with restricted diet alone (1,600 to 1,800 calories per day), reported statistically significant improvements in alanine aminotransferase, aspartate aminotransferase, body mass index and index of insulin resistance for the treatment compared with control. There were no differences between groups in liver biopsies. No patient discontinued metformin because of a lack of tolerance. The non-randomised controlled trial (n=20) reported a statistically significant difference between metformin and diet for alanine aminotransferase. The most common adverse effects were gastrointestinal.

The authors stated there was an improvement in insulin resistance in the four single-arm trials (n=62) of metformin, though this appears to have been statistically significant for two trials only. Three studies reported a reduction in liver function test values and one reported a statistically significant improvement in inflammation, steatosis and NASH score following treatment. One patient had to withdraw because of an increase in serum lactate levels. The most common adverse effects were gastrointestinal.

All three single-arm studies (n=60) of thiazolidinediones reported a statistically significant improvement in insulin resistance and in alanine and aspartate aminotransferase levels from baseline. There was an improvement in liver biopsy criteria in two studies. Weight gain, serum lactate increases, bad dreams and heavy legs were reported.

Authors’ conclusions
Current information indicates that the use of insulin sensitisers in NAFLD improves insulin resistance and liver function. RCTs are required to corroborate histological changes.

CRD commentary
There was a clearly defined review question. A range of sources was searched for relevant studies, including unpublished studies, thus reducing the risk of publication bias. Papers written in three languages other than English were included, thereby reducing the risk of language bias. The authors made reasonable attempts to reduce error and bias in the review processes. The quality assessment was very limited, but it was clear from the fact that single-arm studies was the predominant design that the evidence available was weak. The narrative synthesis was appropriate. Given the paucity of RCTs, the authors’ conclusion is perhaps overconfident in relation to the benefits for insulin resistance and liver function.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that further well-designed trials are required. Four ongoing trials of metformin and three of thiazolidinediones were identified in the review.

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