Insulin sensitisers in the treatment of non-alcoholic fatty liver disease: a systematic review

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Executive summary

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Executive summary

Background

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of disease, ranging from an increased fat content in the liver (steatosis) to inflammatory change (non-alcoholic steatohepatitis – NASH), and potentially to fibrosis and cirrhosis. By definition, it is seen in people whose alcohol intake is not increased (such as < 10 g a day for women, < 20 g a day for men).

Population-based screening studies suggest that the prevalence of NAFLD is in the region of 17–33% in the Western world. The prevalence of NASH is not known because it currently requires a liver biopsy to confirm the diagnosis, but it has been estimated to be around 3% in the total population. We lack good data on the natural history of NAFLD and progression, partly because there are few long-term follow-up studies of well-defined patient cohorts.

The first stage of NAFLD is hepatic steatosis – accumulation of fat in liver cells. NAFLD is strongly linked with insulin resistance and, hence, with obesity and type 2 diabetes. Most people with NAFLD are obese. Because obesity and diabetes have been increasing in the UK, we can expect to see an increase in NAFLD. Steatosis alone does not cause problems. It is the development of NASH, and progression to fibrosis and cirrhosis, which causes the morbidity and mortality in the NAFLD spectrum.

Many treatments have been tried in NAFLD. Because of the link between NAFLD and insulin resistance, two types of drug, which are sometimes called 'insulin sensitisers', have been tried. These are biguanides (metformin) and the glitazones (rosiglitazone and pioglitazone). This review was commissioned by the UK Health Technology Assessment programme to help decide whether or not a trial or trials of the insulin sensitisers was necessary.

Methods

A systematic review of the clinical effectiveness of metformin, rosiglitazone and pioglitazone was carried out. The review included reviews and randomised controlled trials (RCTs). The databases searched were MEDLINE, 1950 to June 2010; EMBASE, 1980 to June 2010; Science Citation Index Expanded, June 2010 (limited to meeting abstracts only); Conference Proceedings Citation Index-Science June 2010; The Cochrane Library 2005–10. No language restriction was applied.

Abstracts retrieved by the searches were screened independently by two researchers for inclusion or exclusion. Data were extracted from the included studies by two researchers with cross-checking. The quality of trials was assessed using seven criteria. Meta-analysis was not considered appropriate.

The original remit for this review did not include a review of diagnostic methods. However, a rapid narrative review of diagnostic methods was carried out, starting with reviewing previous reviews. The aim of this review was to look for non-invasive alternatives to liver biopsy, which could be used in a large trial of the insulin sensitisers.

Results

Clinical effectiveness

A total of 1842 studies were retrieved by the searches, of which 49 were considered possible inclusions. After reading the full texts of these studies, 34 were excluded. The review therefore included 15 RCTs (one available only in abstract form). Four RCTs used pioglitazone, one used rosiglitazone, eight used metformin, two compared metformin and rosiglitazone, and one used both metformin and rosiglitazone. The rosiglitazone results are reported for completeness in the main text. It has been withdrawn from use in Europe.

Five systematic reviews were identified, but none included all of the trials now available.

The quality of the trials was mixed, with a range of scores from '1' to '7' out of a possible seven. The lower scores often reflected a lack of detail as to how the trials were conducted.

Many of the trials had a small number of patients. Four had fewer than 40 recruits. The duration of most trials was between 6 and 12 months.

Pioglitazone

All four pioglitazone studies involved liver biopsies. Pioglitazone was found to improve all parameters of liver histology, was better than placebo, or diet and exercise, or hypocaloric diet, but was no better than vitamin E. It should be noted that the control group on hypocaloric diet lost only 0.5 kg.

Pioglitazone reduced alanine aminotransferase (ALT) levels. In six trials reporting glycosylated haemoglobin (HbA_{1c}), four of which were in patients with diabetes or impaired glucose tolerance, HbA_{1c} level was reduced, by 0.2–0.7%. Weight gain ranging from 2.5 to 4.7 kg was observed with pioglitazone. Results for insulin resistance were mixed, with both increases and decreases reported.

Metformin

Of the eight metformin studies, five involved liver biopsy and three relied on ultrasound. Most showed no clear benefit from the addition of metformin to diet or (in one case) rosiglitazone. Four trials reported ultrasound changes in steatosis, of which two found no difference and two some advantage with metformin. The lack of benefit was in some cases because patients in the control arm improved on diet.

The two trials that compared metformin and rosiglitazone had mixed results. One found significant improvements in histology when the metformin and rosiglitazone groups were combined and then compared with the diet group, but not when the metformin and rosiglitazone groups were considered individually. The other found improvements with rosiglitazone alone, and the combination of rosiglitazone and metformin, but not with metformin alone.

Hence, there is a lack of evidence that metformin improves liver histology at the NASH stage.

Alanine aminotransferase levels improved on metformin. Reductions in HbA_{1c} levels ranged from 0.23% to 1.2% with metformin.

Unlike with pioglitazone, patients on metformin tended to lose weight (by 4.3 kg, based on only one trial). Measures of insulin resistance tended to improve on metformin.

Diagnosis

There is a growing consensus that NAFLD can be diagnosed without liver biopsy, using combinations of clinical history, laboratory tests (full blood count, liver function tests) and ultrasound. A form of ultrasound known as 'transient elastography' may be useful but further research is needed, especially in obese patients. Computerised tomography (CT) scanning may be better than ultrasound, but there are issues around radiation dose and access. Magnetic resonance spectroscopy may be the best of the non-invasive methods, but is expensive and not readily available.

However, distinguishing steatosis from NASH by non-invasive means is proving more difficult, with doubts that this can be done by ultrasound or CT. New methods of magnetic resonance imaging may be more useful, but remain unproven.

Implications for research

The greatest need for drug trials is probably at the NASH stage. However, at present, any trial in the more advanced forms of NAFLD would have to use liver biopsy. The highest priority for research may, therefore, be in the diagnosis of NAFLD and the differentiation between steatosis and NASH.

Further trials of insulin sensitisers may not be the highest priority. Rosiglitazone has now been taken off the market because its cardiovascular safety was less than that of pioglitazone. However, pioglitazone has other adverse effects: weight gain, oedema and fractures. Metformin is safer, but had little effect on liver histology. The newer agents, the glucagon-like peptide-1 analogues, such as liraglutide, may be more worthy of a trial.

One high priority is for research into the ways of preventing people from becoming obese, and into the ways of ensuring weight loss in those who become obese, so that we can reduce the prevalence of NAFLD.

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Publication

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 09/16/01. The contractual start date was in March 2010. The draft report began editorial review in January 2011 and was accepted for publication in May 2011. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

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