Pharmacological interventions for nonalcoholic fatty liver disease in adults and in children: a systematic review

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CRD summary
This review assessed effectiveness and safety of pharmacological and dietary supplement interventions for non-alcoholic fatty liver disease and concluded that limited data precluded firm conclusions on their efficacy. In light of the variability among study populations and interventions, small study sizes and uncertainty over parts of the review process and methodology, this conclusion should be interpreted with caution.

Authors’ objectives
To assess the effectiveness and safety of pharmacological and dietary supplement interventions for non-alcoholic fatty liver disease (NAFLD).

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for peer-reviewed English-language studies to December 2006; search terms were reported. Cross-references from original articles and reviews were used to identify additional studies.

Study selection
Randomised controlled trials (RCTs) that assessed pharmacological and dietary supplements for patients with NAFLD or non-alcoholic steatohepatitis were eligible for inclusion. Interventions in included studies comprised: vitamin E, metformin, ursodeoxycholic acid (UDCA), pioglitazone, Yo Jyo Hen Shi Ko, probucol, n-acetylcysteine, carnitine, amitine and orlistat. In most studies the control group received placebo; some comparisons were with vitamin E or no treatment. Included studies were undertaken in both adults and children; most were in adults. The primary outcome measures were the normalisation of serum alanine transaminase and/or serum aspartate aminotransferase levels, as well as histological changes in liver biopsy specimens; additional outcomes included incidence and severity of adverse events. The duration of intervention ranged from two to 24 months; in most studies it was six months or less.

Two reviewers independently assessed the studies for inclusion in the review. Discrepancies were resolved by discussion.

Assessment of study quality
Two reviewers independently assessed study quality using the Cochrane criteria based on the presence/absence of: allocation concealment; randomisation; blinding; intention-to-treat analysis; and follow-up.

Data extraction
Data for binary outcomes were extracted to calculate risk ratios (RR) and 95% confidence intervals (CI) using a standardised form. Authors were contacted (unsuccessfully) for additional clarification.

Two reviewers independently performed the data extraction.

Methods of synthesis
Data was pooled in a meta-analysis to calculate a pooled risk ratio with 95% CI. Statistical heterogeneity was assessed using the $X^2$ and $I^2$ tests. The number needed to treat (NNT) was calculated.

Results of the review
Fifteen RCTs were included (n=796, range eight to 126); there was some discrepancy in patient numbers between the tables and the text. Allocation concealment was adequate in nine studies. Follow-up was adequate in 13 studies. Ten studies were double-blind and 10 undertook intention-to-treat analysis.
Normalisation of alanine transaminase (11 studies):

A significant effect on normalization of alanine transaminase in patients was found for those treated with: metformin compared with placebo (RR 2.00, 95% CI 1.23 to 3.24; two studies) or with vitamin E (RR 3.14, 95% CI 1.16 to 8.47; one study); and high-dose (3g) carnitine versus diet (RR 5.75, 95% CI 1.45 to 22.74; one study). There was no significant difference in the proportion of patients with a normal ALT level in those treated with vitamin E compared with placebo (three studies). There was no evidence for statistical heterogeneity.

Normalisation of aspartate aminotransferase (four studies):

Aspartate aminotransferase normalisation was significantly higher in those treated with UDCA combined with vitamin E versus UDCA alone (RR 1.72, 95% CI 1.04 to 2.84; one study) or placebo (RR 2.98, 95% CI 1.30 to 6.85; one study) and in those treated with metformin compared with no treatment (RR 2.81, 95% CI 1.16 to 6.82; one study).

Biopsy specimens (seven studies):

Seven RCTs assessed biopsy specimens, but most had methodological limitations. Pioglitazone was associated with reduced liver necrosis and inflammation (one study).

There was no significant difference for the frequency of adverse effects between the groups.

Authors' conclusions
It was not possible to draw firm conclusions on the efficacy of various treatments for NAFLD due to limited data.

CRD commentary
The review question and inclusion criteria were clear and specific, although the inclusion criteria for interventions were broad. The authors searched the main medical databases and other sources for peer-reviewed publications in English; language bias could have been present and some studies may have been missed. No assessment of publication bias was undertaken due to the small number of included studies. Procedures to minimise reviewer bias and error were reported for study selection and quality assessment, but it was unclear whether these extended to data extraction. The validity assessment used appropriate criteria; most studies appeared to be of poor quality. The type of model used in the meta-analysis was unclear; given the diversity of the included studies a narrative synthesis may have been more appropriate. It appeared that reasonable steps appear were used to assess and explore statistical heterogeneity. A large number of interventions were considered, some compared to placebo and others to other interventions, with findings usually based on a small number of studies and yielding wide confidence intervals. Most studies were conducted in adults and so, as acknowledged by the authors, there may be issues with the generalisability of the findings. The authors' cautious conclusions reflected the results of the review. However, given the variability among study populations and interventions, small study sizes and uncertainty over parts of the review process and methodology, this conclusion should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that findings related to the pathophysiology of NAFLD should be reviewed.

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