Differing effect of statins on insulin sensitivity in non-diabetics: a systematic review and meta-analysis

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CRD summary
The authors concluded that statins did not produce a class effect in terms of insulin sensitivity in non-diabetic patients and there were differences in effect between individual statins. Although there was a possibility of publication bias, this was a largely well-conducted review and the authors' conclusions seem likely to be reliable.

Authors' objectives
To determine whether individual statins have differing effects on insulin sensitivity in patients without pre-existing diabetes mellitus.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched without language restrictions from 1966 to 2008. Search terms were reported. Reference lists of relevant trials and review articles were scanned for additional studies.

Study selection
Trials that compared pravastatin, atorvastatin, rosuvastatin or simvastatin to placebo or control in non-diabetic patients were eligible for inclusion in the review. The eligible outcome was insulin sensitivity measured by euglycaemic clamp, minimum model (MIDMOD), fasting sampled intravenous glucose tolerance test (FSIVGTT), insulin suppression test, quantitative insulin sensitivity check index (QUICKI), homeostasis model assessment (HOMA), Matsuda index, Stumvoll index or Avignon index. Studies that used the reciprocal of fasting insulin and the glucose-insulin ratio were excluded.

Most of the included patients had either metabolic syndrome or hypercholesterolaemia. Most studies used the HOMA-IR (homeostasis model assessment-insulin resistance) insulin sensitivity test; other tests included QUICKI, euglycaemic clamp (M value) and MINMOD.

Two independent reviewers carried out the study selection.

Assessment of study quality
The authors did not state that they assessed the quality of included trials; randomisation and blinding were reported in the study details.

Data extraction
Data were extracted to enable the calculation of mean differences and 95% confidence intervals (CI).

Two independent reviewers carried out data extraction. Disagreements were resolved with a third reviewer.

Methods of synthesis
Standardised mean differences (SMDs) with 95% CIs were pooled in a random-effects meta-analysis (DerSimonian and Laird), using the inverse variance weighting method. The direction of change was standardised so that increases in standardised mean differences suggested improvements in insulin sensitivity. Statistical heterogeneity was assessed using the $I^2$ statistic. Where trials evaluated multiple statin treatment arms individually, pair-wise comparisons were considered separately with placebo/control groups divided between the comparisons.

Subgroup and sensitivity analyses were conducted to explore the impact of including only patients with the metabolic syndrome, different measures of insulin sensitivity and trials that used parallel and crossover designs.
**Results of the review**

Sixteen randomised controlled trials (n=1,146, median sample size 206, range 10 to 401) were included in the review. Ten trials used a parallel design and six used a crossover design. Eleven trials were reported to be double-blind. Most trials were placebo-controlled. Median follow-up duration appeared to be 14 weeks (range four to 24).

Overall, statins had no significant effect on insulin sensitivity when compared with placebo or control. Considered separately, a statistically significant improvement in insulin sensitivity followed treatment with pravastatin (SMD 0.342, 95% CI 0.032 to 0.621, I²=0%; three trials). There was a significant worsening of insulin sensitivity with simvastatin (SMD -0.321, 95% CI -0.526 to -0.117; eight comparisons from five trials) and similar trends were noted for atorvastatin and rosuvastatin. The combined effect of atorvastatin, rosuvastatin and simvastatin compared with placebo or control produced a significant worsening of insulin sensitivity (SMD -0.149, 95% CI -0.284 to -0.013; 19 comparisons).

Results of subgroup and sensitivity analyses did not materially alter the above findings. The authors reported that statistical publication bias could not be assessed.

**Authors' conclusions**

Statins do not produce a class effect in terms of insulin sensitivity in non-diabetic patients. There are differences in effect between different statins.

**CRD commentary**

The review question was clear and the inclusion criteria were sufficiently detailed to enable replication. The search strategy accessed some relevant major data sources. Attempts were made to minimise language bias. There was no apparent use of methods to minimise publication bias. The review process for study selection and data extraction were conducted with efforts to minimise error and bias. There was no formal validity assessment, but the authors reported on the presence of randomisation and blinding. This, together with the inclusion of largely placebo-controlled trials, signalled that study quality was reasonable. Statistical heterogeneity was assessed and explored. An appropriate method of synthesis was chosen. Study details were provided, although patient characteristics were sparse.

With a caveat regarding potential publication bias (acknowledged by the authors), the authors’ conclusions seem likely to be reliable.

**Implications of the review for practice and research**

**Practice**: The authors did not state any implications for practice.

**Research**: The authors stated that further research was needed to determine the incidence of new-onset diabetes arising from different statins and evaluate the relationship between statin properties and their impact on insulin sensitivity.

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