Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis

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CRD summary
This review concluded that higher adiponectin levels are associated with a lower risk of type 2 diabetes across diverse populations, consistent with a dose-response relationship. This conclusion was based on synthesis of data on a substantial number of individuals and is probably reliable, but the lack of assessment of study validity should be considered when interpreting the conclusion.

Authors' objectives
To assess the association between plasma adiponectin levels and the risk of type 2 diabetes for the prediction of type 2 diabetes and identification of high-risk groups.

Searching
MEDLINE, EMBASE and Science Citation Expanded databases were searched without language restriction up to April 2009. Search terms were reported. References of selected studies were checked. Full publications and abstracts were eligible for inclusion in the review.

Study selection
Prospective studies of plasma adiponectin concentrations and type 2 diabetes with at least one year's follow-up were eligible for inclusion. Studies on populations with specific diseases or using specific medications were excluded from the review. Also excluded were studies that did not report diabetes incidence separately from incidence of impaired glucose tolerance.

Studies were conducted in North America, Europe and Asia. Most included studies were carried out in the general population, but a minority were in people with impaired baseline glucose tolerance. Some studies enrolled only males or only females. In the other studies, the proportion of women ranged from 31 per cent to 68 per cent. A range of ethnic origins was represented. Mean ages ranged from 25 to 74 years. Type 2 diabetes was diagnosed using an oral glucose test, self-reported information or a combination of plasma glucose concentrations and self report. Assays used to measure adiponectin were: enzyme-linked immunosorbent assay; radioimmunoassay; bio-plex suspension assay; and latex turbidimetric assay.

It appeared that three reviewers were involved in selecting the studies for the review.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Medians, ratios of cases to non-cases and relative risks (RR) with 95% confidence intervals (CI) were extracted for each tertile, quartile or quintile of adiponectin concentration as reported. Where medians were not reported they were approximated using midpoints or means of the categories. Where several multivariable-adjusted RRs were reported the estimate (adjusted most fully for potential confounding factors, except for other metabolic biomarkers) was extracted. Continuous results with or without log transformations were also extracted relative to adiponectin concentrations. Two reviewers independently extracted the data using a standardised form.

Methods of synthesis
Dose response associations were estimated using two-stage generalised least-squares trend estimation analysis. Pooled RRs for type 2 diabetes incidence by log-transformed adiponectin level were calculated using DerSimonian and Laird random-effects meta-analyses. A secondary analysis of pooled RR for type 2 diabetes incidence per 5 μg/mL was also conducted. Statistical heterogeneity was assessed using the Cochran Q test and the $I^2$ statistic. Stratified analyses were conducted to explore the effect of ethnic origin, age, sex (proportion of women) and body mass index (BMI) of the
study population, duration of follow-up, year of publication, type of assay, means of determining diabetes status and measure of association (RR versus odds ratio with rare disease assumption). Sensitivity analyses assessed the impact of omitting each individual study, of using a fixed-effect model, modelling adiponectin levels without log transformation and excluding a study that did not adjust for adiposity and included only participants with baseline-impaired glucose tolerance. Publication bias was assessed by visual inspection of funnel plots and using the Egger and Begg tests.

**Results of the review**

Fifteen studies were included in the review: 10 cohort studies; one case-cohort study; and four nested case-control studies. Follow-up ranged from one to 18 years.

Higher adiponectin levels were associated with a lower risk of type 2 diabetes. The RR for type 2 diabetes was 0.72 (95% CI: 0.67, 0.78, p < 0.001, 13 studies, n = 14,398) per 1-log μg/mL increment in adiponectin levels. Absolute risk difference was 3.9 per 1,000 person-years per 1 log μg/mL for elderly white and black individuals and 7.5 per 1,000 person-years per 1 log μg/mL for Japanese Americans. For individuals with impaired glucose tolerance the absolute risk difference was 30.8 per 1,000 person years per 1 log μg/mL . There was evidence of statistically significant heterogeneity ($I^2 = 43\%$, $Q = 22.9$, $p = 0.04$). The sensitivity analyses did not significantly affect the results. Analysis without log transformation gave a pooled RR of type 2 diabetes per 5 μg/mL increment in adiponectin levels of 0.74 (95% CI: 0.68, 0.80, 12 studies, n = 12,802) with evidence of statistically significant heterogeneity ($I^2 = 59\%$, $p = 0.004$). Results of other adjusted analyses were also reported.

There was no evidence of publication bias.

**Authors’ conclusions**

Higher adiponectin levels are associated with a lower risk of type 2 diabetes across diverse populations, consistent with a dose-response relationship.

**CRD commentary**

The review question was clear and was supported by specific inclusion criteria. The authors searched three relevant databases without language or publication restrictions, which reduced the chances of bias and omission of relevant studies. Publication bias was assessed and no evidence was found to support it. The authors reported using methods designed to reduce bias and error in the selection of studies and the extraction of data. No assessment of study validity was reported, which made it difficult to assess the reliability of the included data. However, the authors attempted to control for confounding (which is often the primary risk to data reliability in observational studies) by using the estimate of effect which was best adjusted for confounding factors. The statistical synthesis appeared appropriate. Heterogeneity was assessed and explored. The authors’ conclusions reflected the results of the review, which contained data on a substantial number of individuals. The conclusions are probably reliable, but the lack of an assessment of study validity should be borne in mind when interpreting the conclusions.

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

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

Research: The authors stated that larger studies or individual participant data pooled analyses were needed for the evaluation of modifying factors on the relationship between adiponectin levels and type 2 diabetes risk. They further stated that the predictive value of adiponectin in addition to established risk factors should be evaluated using appropriate statistical techniques.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.