Adiponectin isoforms and cardiovascular disease: the epidemiological evidence has just begun

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This editorial refers to 'Atherogenic dyslipidaemia but not total- and high-molecular weight adiponectin are associated with the prognostic outcome in patients with coronary heart disease',† by M. von Eynatten et al., on page 1307

Adiponectin, also known as Acrp30, AdipoQ, or gelatin-binding protein of 28 kDa (GBP28), is a hormone secreted exclusively by adipocytes.1 Since its discovery in 1995, adiponectin has been the centre of intense debate regarding its prognostic significance for coronary heart disease (CHD) in healthy populations (primary prevention) and in coronary patients (secondary prevention). This is partly due to the apparent paradox between experimental data suggesting a vascular protective effect, and epidemiological evidence failing to confirm this effect and even suggesting an increased risk in some high-risk groups. However, a new research step has just been reached since it is now possible to measure accurately adiponectin isoforms and the high molecular weight (HMW) isoform in particular. This leads to reconsideration of the existing epidemiological evidence of the relationship between adiponectin and cardiovascular disease, heretofore based on total adiponectin.

Epidemiological evidence of the link between adiponectin and cardiovascular disease

Total adiponectin

In the context of primary prevention, the inverse association of total adiponectin with CHD was observed in some but not all population-based studies of healthy subjects. In middle-aged men, higher total adiponectin was associated with a significantly decreased risk of myocardial infarction during 6 years in the Physicians Health Professional Study, and of CHD during 18 years in the Augsburg MONICA Survey.2,3 In elderly participants in the Rancho Bernado Study, a cardioprotective effect of total adiponectin was reported, but only in men and only for non-fatal myocardial infarction.4 In contrast, total adiponectin failed to be associated with cardiovascular disease in British middle-aged men, in British elderly women, or in adult American Indians.5–7 Differences in population characteristics, statistical adjustments, or analytical methods might explain part of those apparent discrepancies between studies.

In secondary prevention studies, the situation might be even more complex since the results diverged according to the study design (cross-sectional vs prospective) and the studied subgroups. For instance, in cross-sectional studies, total adiponectin was found to be lower in patients with acute coronary syndrome (ACS) than in patients with stable coronary artery disease (CAD), and to be inversely related to the complexity of the vessel lesion.8,9 In two recent prognostic studies total adiponectin was shown to increase the risk of recurrent cardiovascular disease.10,11 In the Atherogene registry, however, the association of total adiponectin with cardiovascular disease became marginally non-significant (P = 0.06) after subsequent adjustment for CRP (C-reactive protein) and BNP (brain-derived natriuretic protein).11 In addition, subgroup analyses in these two prognostic studies yielded opposite conclusions since the observed increased risk was seen solely in patients with unstable CAD [unstable angina and non-ST-elevation myocardial infarction (NSTEMI)]10 in the first study and in patients with stable angina in the Atherogene registry.11

Taken together, the existing epidemiological evidence linking total adiponectin and cardiovascular disease remains unclear. Moreover, in coronary patients, the counterintuitive finding that higher total adiponectin was associated with an increased risk of recurrent cardiovascular disease should be interpreted cautiously. In fact, higher adiponectin might reflect a counterbalancing mechanism of the body, trying for instance to alleviate the inflammatory process surrounding an acute coronary event. Similarly, a higher circulating adiponectin level might be due to peripheral adiponectin resistance. Therefore, it remains unlikely that higher adiponectin in itself carries an increased risk of cardiovascular disease in those populations.

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

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Isoforms of adiponectin

Adiponectin circulates in plasma under three forms: a trimer (low molecular weight), a hexamer (trimer–dimer) of medium molecular weight, and a larger multimeric high molecular weight (HMW) form. Previous measurement of HMW necessitated multimer separation (velocity sedimentation/gel filtration) and thereafter quantification of the HMW isoform by western blotting, which was time-consuming and inappropriate for assessment in large sample size studies. A novel enzyme-linked immunosorbent assay (ELISA), which uses a monoclonal antibody raised against human HMW adiponectin antigen (GBP28), was recently developed specifically to measure the HMW isoform.12

The different isoforms might play different roles, but some arguments have suggested that the HMW isoform might be the active protein. Indeed, change in serum HMW adiponectin, but not total adiponectin, was associated with improvement in hepatic insulin sensitivity after treatment with thiazolidinedione, and HMW was reported to suppress apoptosis in cultured endothelial cells.13 Alternatively, HMW adiponectin might represent a precursor pool that can be activated, with the cleaved form, i.e. the low molecular weight isoform, being responsible for the effect on AMP-kinase activity.13

HMW isoform and cardiovascular disease

The epidemiological evidence of an association between adiponectin isoforms and cardiovascular disease is scarce, based on the HMW isoform only, and is supported by studies of small sample sizes conducted in CAD patients. In a cross-sectional study of 249 subjects with type 2 diabetes, HMW adiponectin or the ratio of HMW to total adiponectin was significantly lower in patients with CAD compared with those without, especially in men.14 A more recent study extended those results in 149 patients without type 2 diabetes.15 In that study, HMW was cross-sectionally lower in patients with CAD (n = 137) compared with controls with chest pain (n = 12), and HMW was inversely related to the disease severity of CAD. In longitudinal analysis, low HMW was the strongest predictor of recurrent cardiovascular disease events over 7 years. However, neither total adiponectin nor non-HMW adiponectin were measured in that study.15 Therefore, these few studies of small sample size conducted in CAD patients suggest an inverse association between the HMW adiponectin isoform and CAD, in accordance with experimental evidence.

The present study in perspective

von Eynatten et al. investigated the prognostic value of total and HMW adiponectin in the setting of secondary prevention.16 The study included 1051 patients aged 30–70 years who were engaged in a rehabilitation programme a mean of 43 days after a CHD event. After discharge from the rehabilitation centre, patients were followed-up sequentially over 4.5 years, during which 95 cardiovascular events (cardiovascular death, non-fatal myocardial infarction, and ischaemic stroke) were registered. Cross-sectionally, there was a strong correlation between the HMW isoform and total adiponectin (Spearman correlation was 0.915).

In longitudinal analysis, neither HMW adiponectin nor total adiponectin were predictors of recurrent cardiovascular events, and they were also not associated with mortality. In addition, the study confirmed existing knowledge that dyslipidaemia, low high-density lipoprotein (HDL)-cholesterol, and high triglycerides were associated with recurrent cardiovascular events.

What does this study add?

This was the largest study ever performed on the prognostic value of HMW adiponectin in coronary patients. In addition, the study benefited from being prospective in its design, allowing (a priori) temporal inference to be made. Some limitations should be mentioned however before interpreting the present results. First, adiponectin measurements were performed at the end of a 3-week rehabilitation programme, a period during which patients had been advised to change their lifestyle and their diet, to lose weight, and had received medications for the management of their global cardiovascular risk. Those interventions, which have been shown to reduce significantly the recurrence of cardiovascular events, may therefore mask the beneficial effect of adiponectin, if any, on the recurrence of cardiovascular disease. In addition, all those interventions including medications (angiotensin-converting enzyme inhibitors) increased the circulating adiponectin level, meaning that the contrast of adiponectin between subjects was not strong enough to put forward any association of adiponectin with cardiovascular disease. Secondly, and as acknowledged by the authors, the rates of cardiovascular disease events were low, suggesting that the statistical power of the study was inadequate, especially if the difference to be detected had to be small. Thirdly, one might have expected subgroup analysis according to gender, total adiposity level, heart failure severity, and renal function stage. Fourthly, coronary patients undergoing a rehabilitation programme may not be representative of patients who suffered from an acute CHD regarding social background and disease severity, which may limit the generalizability of the present results to patients with CHD.

What remains to be done?

From an epidemiological point of view, there clearly is a need for prospective studies sufficiently powered to clarify and quantify better the contribution of adiponectin isoforms to cardiovascular disease risk. Therefore, no such studies have been published in healthy populations. It should be kept in mind, however, that results obtained in primary prevention and in secondary prevention should be interpreted separately because in these two settings, the disease process (atherosclerosis) is at a different stage, and one might expect that association of adiponectin with cardiovascular disease differs according to the disease progression. From a pathophysiological view, the pathway mechanisms in which adiponectin and its isoforms are involved remain to be complemented. Finally, from a pragmatic point of view and based on the existing literature, the use of total adiponectin or its isoforms as predictive (primary prevention) and prognostic (secondary prevention) markers of cardiovascular disease might be premature.

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References


