Is adiponectin and its genetic regulators useful or not for prediction of carotid intima-media thickness and coronary heart disease?

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This editorial refers to ‘Variation in the ADIPOQ gene promoter is associated with carotid intima media-thickness independent of plasma adiponectin levels in healthy subjects’ by S. Patel et al., on page 386

The abdominal adipose tissue is now generally regarded as an important endocrine organ, secreting a wide range of adipokines and other regulatory peptides or hormones. One of these adipokines that has attracted a great deal of interest is adiponectin, which can be detected in various molecular forms. Its synthesis is regulated by the ADIPOQ gene promoter. Adiponectin has been implicated to be a marker of insulin sensitivity and glucose metabolism, as well as being involved in inflammatory processes. Previous studies have shown an inverse correlation between circulating adiponectin levels and measures of insulin resistance, as well as C-reactive protein (CRP) levels. It is still an open question whether or not adiponectin plays a causal and independent role in the development of arterial lesions due to atherosclerosis, resulting in increased risk of cardiovascular events. As atherosclerotic lesions are influenced by the interplay between metabolic abnormalities, haemodynamic factors, and local (peri-)vascular inflammation, it is assumed that adiponectin may play a role in this process because of cross-sectional associations with many of the risk factors involved.

A few studies have investigated adiponectin levels in relation to intima-media thickness (IMT) in the common carotid artery, this being an early marker of atherosclerosis and the consequence of elevated levels of cardiovascular risk factors.

In previous screening studies it was reported that adiponectin levels were inversely correlated with carotid IMT, both in 140 obese young subjects compared with a group of matched controls and in 1515 healthy middle-aged subjects of both genders. More recently, common carotid IMT was shown to be associated with adiponectin levels in a USA-based middle-aged female cohort. Furthermore, a Japanese case–control study reported that adiponectin is associated with increased prevalence of coronary artery disease (CAD) and that adiponectin had a close relationship with CRP levels. It has been suggested that atherogenesis may be associated with a decrease of adiponectin through abnormal glyco- and lipid metabolism induced by inflammation.

However, to what extent this could be explained by other risk factors associated with obesity and the metabolic syndrome has so far been unclear. A population-based study from Malmö, Sweden, showed inverse relationships between circulating adiponectin levels and carotid IMT in men, but not in women. Several other risk factors were also associated with adiponectin, including waist circumference, diastolic blood pressure, high-density lipoprotein (HDL) cholesterol, and haemoglobin A1c (HbA1c). The relationship between IMT and adiponectin was attenuated and non-significant (P = 0.15) after full adjustments for these risk factors. The results thus suggested that traditional cardiovascular risk factors associated with obesity and the metabolic syndrome account for most of the inverse relationship found between adiponectin and carotid IMT in the general population. In particular, the adjustment for glycaemic control (HbA1c) was of considerable importance.

The European Group on Insulin Resistance (EGIR) has reported from the RISC study on cross-sectional associations between adiponectin levels and carotid IMT, as well as between specific genetic polymorphisms and both adiponectin levels and IMT. The study population (n = 1306) was defined middle-aged and health-selected from 13 European countries, and this may be of importance for the limited range of cardiovascular risk factors present when no elevated levels or disease states are included in the screened subjects. Overall, no independent association was shown between plasma adiponectin levels and IMT data based on standardized ultrasound investigations. In contrast, a specific genetic polymorphism [the ADIPOQ gene single nucleotide polymorphism (SNP) in the –11377G allele] was associated with...
greater IMT values compared with C allele homozygotes, even after adjusting for circulating adiponectin levels. On the other hand, some other ADIPOQ SNPs showed associations with lower adiponectin levels, but not with carotid IMT.

This means first that plasma adiponectin does not seem to be an important cross-sectional determinant for early atheroscleroses, as manifested by elevated IMT, in the normal healthy population when diseased or high-risk individuals have been excluded. This is in contrast to what has been documented for adiponectin being associated with risk of myocardial infarction and also being an independent predictor of coronary heart disease (CHD) in a prospective study of 70-year old men in Uppsala, Sweden. In a multivariate analysis including conventional risk factors, serum adiponectin in that study was associated with lower risk for CHD [hazard ratio (HR) 0.81; 95% confidence interval (CI) 0.66–0.99] for one standard deviation increase of adiponectin. The association was independent of body mass index (BMI) and remained significant even after adjustment for the insulin sensitivity index, based on data from a hyperinsulinaemic, euglycaemic clamp. In the elderly population studied, however, one may anticipate that more men had signs of atherosclerosis and risk factors in need of treatment compared with men in the EGIR-RISC population. No carotid IMT measurements were carried out, however. The conclusion is that adiponectin might be more useful as an athero-crotic disease risk predictor in elderly populations as compared with younger populations. No data on prediction in elderly women are, however, available at the moment; gender differences in prediction or in cross-sectional associations remain to be investigated.

Secondly, in the study of Patel et al., we are provided with a complicated pattern of genetic polymorphisms showing relationships with either plasma adiponectin levels or IMT, but not with both clinical variables at the same time. This questions whether the targeted SNPs of the ADIPOQ promoter gene that were investigated in the study are really that important, as the one that influenced adiponectin levels did not influence IMT, and vice versa. Following the discussion of the application of so-called ‘Mendelian randomization’ in genetic epidemiology, it is anticipated that a true role for plasma adiponectin predicting atherosclerosis, IMT, and incident cardiovascular disease would require that the genetic regulator behind it should also be predictive, at least to some degree. This has been tried in another observational study from the Uppsala group, but neither circulating plasma adiponectin levels nor ADIPOQ gene polymorphisms predicted congestive heart failure (CHF) in a longitudinal, community-based cohort of elderly men without CHF at baseline. Polymorphisms in the ADIPOQ gene have been associated with serum adiponectin concentrations and cardiovascular risk in men with diabetes, when significant associations between the adiponectin locus variant (APM1 G276T) and decreased cardiovascular risk were reported, as well as with increased plasma adiponectin levels in 879 diabetic men followed for 14 years. Similar studies should ideally also be carried out in other populations with a broader age range, and also including women. As confounding could be crucial, it is also of importance to have access to data on potential confounders, not only in biology (i.e. hyperglycaemia), but also in lifestyle habits (i.e. diet, physical activity, and smoking).

In conclusion, the present observational study in Europeans from 13 countries might have limitations for showing associations between adiponectin levels, or some genetic polymorphisms, and IMT due to the stated selection bias of healthy individuals. On the other hand, the finding of an association between one polymorphism and plasma adiponectin levels points to the possibility that a longer follow-up period, not only restricted to cross-sectional analyses, might reveal interesting findings. This is a promising future research possibility, in this well-defined cohort, based on a fruitful collaboration across Europe, with the largest sample of data that is currently available, not only on adiponectin and IMT, but also on insulin sensitivity (clamp). Time will tell if baseline plasma adiponectin, or its genetic determinants, are also able to predict changes in IMT during follow-up, as well as incident cardiovascular events.

Finally, the study has shown another very important thing—it is indeed possible to gather researchers, staff, and a large number of screened individuals, based on informed consent, from a substantial proportion of the European countries in a high-tech screening survey. Hopefully, a longer follow-up time will be funded by the EU so that the important long-term prediction analyses can eventually be carried out.

Conflict of interest: none declared.

References


**CLINICAL VIGNETTE**

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**Giant left atrium**

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A 61-year-old woman presented to our department with symptoms of chest distress and shortness of breath that had worsened in the previous 3 months. She had a history of rheumatic heart disease. A chest x-ray revealed a gross enlargement of the cardiac silhouette. An echocardiogram showed a massive dilated left atrium (LA) (16.3 × 13.0 × 8.2 cm) and a thrombus (1.9 × 2.9 cm) in the apical half of left atrium. The mitral valve was moderate-to-severe insufficiency and stenosis. A cardiac MRI was performed and showed a giant LA and compression of the left ventricle (LV), right ventricle (RV), and right atrium (RA) against the anterior chest well. She refused surgery, so digoxin, frusemide, and warfarin were given. Giant LA is defined as that measuring >8 cm or touching the right lateral side of chest wall and has been described almost exclusively in rheumatic mitral valve disease. It may be misdiagnosed to a mass lesion or pleural effusion. Pleuracentesis and biopsy are dangerous and would better be alert before echocardiogram, cardiac MRI, or CT is performed.

 Panels A and B. Chest X-ray demonstrates the gross enlargement of the cardiac silhouette.

 Panel C. Echocardiogram shows the massive dilated left atrium (LA).

 Panel D. Echocardiogram shows the thrombus in the left atrium (LA).

 Panel E. Cardiac MRI shows the giant left atrium (LA) and compression of the left ventricle (LV), right ventricle (RV), and right atrium (RA).