High serum adiponectin is associated with favorable lipoprotein subclass profile in 6.4-year follow-up

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Abstract

Objective: Adiponectin is linked to a favorable lipoprotein profile, but potential longitudinal associations are not known.

Design: A population-based follow-up study of all inhabitants born in 1942, 1947, 1952, and 1957 (n = 1294) in Pieksämäki, a town in Finland. Of the 690 subjects participating in both the check-ups, 228 subjects with diabetes or any medication for dyslipidemia, high blood pressure, or diabetes were excluded. The final study population consisted of 462 (182 men and 280 women) apparently healthy subjects.

Methods: Main outcome measures were lipoprotein particle sizes and concentrations, apolipoprotein A-1 (APOA1) and APOB levels at baseline and follow-up across baseline adiponectin tertiles. Serum adiponectin concentrations were determined using an enzyme immunoassay, and lipoprotein subclasses using proton nuclear magnetic resonance spectroscopy.

Results: At the second health check-up 6.4 years later, the very low-density lipoprotein particle concentration decreased across the baseline adiponectin tertiles in men from 1.04 (0.28) to 0.91 (0.29) nmol/l (P for linearity = 0.011) and in women from 0.92 (0.32) to 0.80 (0.24) nmol/l (P = 0.002). Correspondingly, the mean high-density lipoprotein particle size increased from 9.78 to 9.90 nm in men (P < 0.006) and from 10.00 to 10.14 nm in women (P < 0.001).

Conclusion: The favorable links between adiponectin and lipoproteins are detectable 6.4 years later.
nearest 0.5 cm and 0.1 kg respectively. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

Fresh serum samples were drawn after an overnight fast. Plasma was separated by centrifugation for the determination of glucose, lipids, and fasting insulin, and the samples were frozen immediately and stored in −75°C. Plasma insulin was determined using the Phadeseph Insulin RIA 100 method (Pharmacia Diagnostics AB). Plasma glucose concentration was measured by automated colorimetric method (Peridochrom Glucose GOD-PAP, Boehringer, Germany), and the quantitative insulin sensitivity check index (QUICKI) was calculated as follows: \( \text{QUICKI} = 1 / (\log \text{FPI} + \log \text{FBG}) \), where FPI is the fasting plasma insulin level expressed as mU/l, and FBG is the fasting plasma glucose level expressed as mg/dl (5). Serum adiponectin was determined in 2002 with an enzyme immunoassay (Human Adiponectin ELISA Kit, B-Bridge International, Inc., Mountains View, CA, USA) (6). Proton NMR spectroscopy was used to quantify lipoprotein subclasses and particle concentrations in native serum samples in 2009 (7). The lipoprotein subclasses are calibrated according to HPLC and defined according to the following criteria: i) as one of six VLDL subclasses – extremely large (with particle diameter from ~75 nm upward and possibly containing chylomicron particles), very large (average particle diameter of 64.0 nm), large (53.6 nm), medium (44.5 nm), small (36.8 nm), and very small (31.3 nm); ii) as intermediate-density lipoprotein (IDL) (28.6 nm); iii) as one of three LDL subclasses, including large (25.5 nm), medium (23.0 nm), and small (18.7 nm); and iv) as one of four HDL subclasses – very large (14.3 nm), large (12.1 nm), medium (10.9 nm), and small (8.7 nm). The mean size for VLDL, LDL, and HDL particles was calculated by weighting the corresponding subclass diameters with their particle concentrations. HDL particles were included in the LDL measure. The results are expressed as the mean ± s.d.

In the statistical analyses, subjects were divided into sex-specific groups according to adiponectin tertiles. Generalized linear models were used to compare baseline and follow-up data between groups. Age, BMI, QUICKI, and baseline values were introduced into the models as covariates. Correlation coefficients were calculated by the Spearman method, using Sidak-adjusted probabilities.

**Results**

The apparently healthy study population included 182 men and 280 women (mean age at baseline 44.5 ± 6.0 and 44.9 ± 6.0 years respectively). The mean time between the two health check-ups was 6.4 years for both genders.

Table 1 shows the age, BMI, and QUICKI across the gender-specific baseline adiponectin tertiles. In the first check-up, 41 women (14.4%) had hormonal contraception and 15 (5%) had estrogen replacement therapy. At the second health check-up, none of the women had contraceptive hormones, but 78 (27.5%) of them had estrogen replacement therapy. Hormonal contraception or replacement therapy did not vary across adiponectin tertiles.

At baseline, across adiponectin tertiles, the mean HDL particle size and particle concentration as well as APOA1 concentration increased, and VLDL particle concentration and APOB level decreased in both genders statistically significantly (data not shown). LDL particle size or particle concentration did not associate with adiponectin tertiles.

Baseline adiponectin concentration correlated positively with the mean HDL particle size in men \((r = 0.25, P < 0.05)\) and in women \((r = 0.25, P < 0.001)\) measured in the second health check-up 6.4 years later. In women, baseline adiponectin correlated inversely with VLDL particle size \((r = −0.22, P < 0.01)\). There was no correlation between adiponectin and the future LDL particle size or concentration.

The mean HDL particle size measured in the second health check-up increased across the baseline adiponectin tertiles from 9.78 to 9.90 nm in men \((P < 0.006)\) and from 10.00 to 10.14 nm in women \((P < 0.001)\). Negative associations were found for the baseline adiponectin tertiles and VLDL particle concentration in both genders \((P = 0.011 \text{ for men and } < 0.001 \text{ for women})\), and VLDL particle size \((P < 0.001)\) and APOB \((P = 0.040)\) in women. These associations were present

| Table 1 Basic characteristics of the 462 apparently healthy middle-aged men and women across gender-specific adiponectin tertiles. |
|---------------------------------|-----------------|-----------------|-----------------|
| Adiponectin tertiles            |                 |                 |                 |
|                                 | I               | II              | III             |
| **Male**                        |                 |                 |                 |
| Adiponectin range               | <3.5 µg/l       | 3.5–5.5 µg/l    | >5.5 µg/l       |
| Number                         | 60              | 61              | 61              |
| Age, years, mean (s.d.)         | 43 (6)          | 45 (6)          | 46 (6)          |
| BMI, kg/m², mean (s.d.)         | 27.1 (3.3)      | 25.7 (2.5)      | 25.2 (3.1)      |
| QUICKI, mean (s.d.)             | 0.33 (0.02)     | 0.34 (0.02)     | 0.35 (0.02)     |
| **Female**                      |                 |                 |                 |
| Adiponectin range               | <5.7 µg/l       | 5.7–8.4 µg/l    | >8.4 µg/l       |
| Number                         | 92              | 93              | 95              |
| Age, years, mean (s.d.)         | 43 (6)          | 45 (7)          | 46 (6)          |
| BMI, kg/m², mean (s.d.)         | 25.6 (3.9)      | 25.6 (4.4)      | 24.6 (6)        |
| QUICKI, mean (s.d.)             | 0.34 (0.02)     | 0.34 (0.02)     | 0.35 (0.02)     |

For linearity

| **P for linearity** |<|0.05 |<|0.001 |<|0.001 |<|0.001 |<|0.001 |<|0.001 |
|-------------------|---|-----|-----|-----|-----|-----|-----|-----|
Male influencing APOA secretion (8, 9). Our results showing been reported to reduce hepatic APOB release without previous studies.

of adiponectin with APOA1 level, is in line with the health check-up, as well as the longitudinal association the highest baseline adiponectin tertile in the second almost statistically significant) lower APOB is present in that in women a statistically significantly (and in men increased synthesis of APOB(3). Adiponectin has also the accumulation of intraperitoneal fat, resulting in these kinds of changes have lead to an increase in hepatic secretion and delayed catabolism 6.4 years later.

baseline adiponectin and VLDL particle size and APOB statistically significant inverse association between adiponectin tertile. In women, there was also a statistically significant (and in men baseline value of the variable in question).

Model 1, crude; Model 2, adjusted for age, BMI, and QUICKI; Model 3, adjusted for age, BMI, QUICKI, and baseline value of the variable in question.

Conclusion

The novel finding in our apparently healthy study population is that the association between high baseline adiponectin level and favorable lipid profile was observed 6.4 years later. The inverse linear association across baseline adiponectin tertiles with follow-up VLDL particle concentration, as well as a positive association with HDL particle size in both genders, suggests a healthy future lipid profile in the highest baseline adiponectin tertile. In women, there was also a statistically significant inverse association between baseline adiponectin and VLDL particle size and APOB 6.4 years later.

Obesity is associated with a low adiponectin level and an increase in hepatic secretion and delayed catabolism of VLDL APOB. These kinds of changes have lead to the accumulation of intraperitoneal fat, resulting in increased synthesis of APOB (3). Adiponectin has also been reported to reduce hepatic APOB release without influencing APOA secretion (8, 9). Our results showing that in women a statistically significantly (and in men almost statistically significant) lower APOB is present in the highest baseline adiponectin tertile in the second health check-up, as well as the longitudinal association of adiponectin with APOA1 level, is in line with the previous studies.

Adiponectin reduces plasma triglycerides by increasing VLDL triglyceride catabolism via increased lipoprotein lipase (LPL) activity (10, 11). High LPL activity has been shown to result in the production of large HDL particles that are antiatherogenic and anti-inflammatory, and protect from atherosclerosis. Adiponectin has been suggested to lead to other antiatherogenic changes in lipoprotein profiles by decreasing the synthesis of VLDL, resulting in smaller VLDL and larger HDL particles (12–14). High plasma adiponectin has shown to predict insulin sensitivity of lipid metabolism resulting in a positive association with HDL cholesterol concentration and an inverse association with triglyceride concentration (15, 16). This is in line with our longitudinal results showing that adiponectin was inversely correlated with VLDL particle concentration and linearly with HDL particle size in both genders, and that this association weakened after adjusting for age, BMI, and QUICKI.

Contradictory to some other studies (1, 2, 12), we could not find any association between LDL particle size or concentration and adiponectin, not as a continuous variable nor in the tertiles. On the other hand, Shin & Kim (17) have shown that after taking triglyceride level into account, adiponectin does not associate with LDL size, and that the most significant associations are between adiponectin and VLDL and HDL lipoproteins. The possibly explanation is in our apparently healthy study population not having dyslipidemia, hypertension, or diabetes, which all are known to associate with the presence of the small, dense LDL particles.

Recent findings have indicated that adiponectin levels are quite stable over a time period of years. Mascarinec et al. (18) have recently published a soy intervention study showing that adiponectin levels changed neither
in 90 women of intervention group nor in 93 women of control group, regardless of a slight BMI increase during the 2-year follow-up. Our finding of the longitudinal association of adiponectin with lipoprotein particle sizes and concentrations as well as with APOA1 and APOB 6.4 years later might be due to the stability of individual adiponectin concentration over the follow-up period.

The strengths of this study are longitudinal population-based design and NMR analyses performed contemporarily for both the baseline and the follow-up serum samples. Adiponectin levels were not measured at the second health check-up, which may be considered a limitation as the relative small number of study subjects.

We conclude that high adiponectin levels mirror favorable lipid profile 6.4 years later in a population-based apparently healthy cohort.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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