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Low serum adiponectin predicts 10-year risk of type 2 diabetes and HbA1c independently of obesity, lipids and inflammation – Whitehall II study

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Abstract

Aims—In the present study our aim was to study the effect of serum adiponectin on incident diabetes and HbA1c values.

Methods—We measured baseline serum adiponectin levels in a nested case-control selection (n=140) of the Whitehall II Cohort. Participants (mean[SD] age 50.9[6.3] yrs) had no prevalent diabetes or CHD at baseline. Cases (n=55) had incident diabetes according to an oral glucose tolerance test during follow-up (mean: 11.5±3.0 yrs).

Results—Adiponectin levels were lower among cases (9.3 μg/mL;3.2 [median; IQR] vs. 10.5;3.6, p=0.01). The risk of incident diabetes decreased by 11% (p=0.03) for 1 μg/mL higher adiponectin levels. Higher adiponectin levels were associated with lower HbA1c at follow-up (p<0.05). Both associations were stable to adjustment for age, sex, body mass index, systolic blood pressure, and serum lipids, and for HbA1c also for C-reactive protein (all p<0.05).

Discussion—The observed robust, prospective associations support that adiponectin is an independent predictor of diabetes and the degree of glycemic impairment.

Keywords

Adipokines; Follow-Up Studies; Hemoglobin A; Glycosylated; C-reactive protein

Introduction

A low serum level of adiponectin (which is produced by adypocytes) has repeatedly been associated with type 2 diabetes, cardiovascular disease, and the metabolic syndrome. Further observations, such as the inverse association with lipid levels (except for HDL cholesterol), insulin resistance, inflammatory markers, and more marked secretion by subcutaneous

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compared to visceral fat, are consistent with a protective role of adiponectin in the aetiology of type 2 diabetes [1,2].

We set out to study the nature and strength of the prospective association between adiponectin and incident diabetes in the well-characterised Whitehall II cohort. To explore the potential protective link further [3,4,5,6,7,8,9], we also examined the relation between baseline adiponectin and glycemic control, based on HbA1c. For both outcomes we took account of established risk factors and serum C-reactive protein (CRP), a nonspecific marker of low-grade inflammation.

Materials and Methods

We present results from a nested case-control study within the Whitehall II cohort. The cohort was established in 1985 and included 10,308 non-industrial civil servants aged 35-55 years (6895 men). A detailed description of sampling methods and baseline characteristics has been published previously [10].

Study phase 3 (1991-1994) was the first phase where glucose tolerance was assessed by a 75g oral glucose tolerance test (OGTT) and is the baseline for the current analysis (n=7537). Participants were followed through postal questionnaires at 2.5-year intervals (phases 4-8) and further clinical examinations (including an OGTT) in 1997-1999 (phase 5), and 2003-2004 (phase 7) [10]. The study was approved by the University College London Medical School Committee on the Ethics of Human Research. Informed consent was obtained at baseline and renewed at each contact.

After the exclusion of prevalent diabetes at baseline (n=250), 422 incident cases of diabetes (343 among Caucasian participants) were diagnosed during the average follow-up of 11.5 ± 3.0 [SD] years [11]. Diagnosis of type 2 diabetes was primarily based on a standard 75 g oral glucose tolerance test (OGTT – 56.8%) after ≥5 hours of fasting (≥8 hours in 66% of participants), supplemented by any antidiabetic drug treatment (25.4%), or self-report of doctor diagnosed diabetes mellitus (17.8%).

Age, sex, body mass index (BMI), waist circumference, blood pressure, smoking, physical activity, civil servant employment grade, family history of diabetes mellitus, total cholesterol, triglycerides were determined at baseline. Fasting and 2h glucose was measured using a glucose oxidase method as previously described. [12,10]

CRP and adiponectin were measured in serum (collected at baseline) stored at -80°C, using a high-sensitivity immunonephelometric assay and a Bio-Plex Suspension Array System (Bio-Rad Laboratories, Inc; Hercules, CA, USA; mean intraindividual CV: 4.2%) respectively, with commercially available kits according to manufacturer's instructions [13]. HbA1c was measured at phase 7 on a calibrated HPLC system.

We designed a nested case-control investigation based on 77 Caucasian participants with incident type 2 diabetes. Cases and controls were selected to have available frozen serum samples at baseline, no prevalent or incident coronary heart disease during follow-up, and no longstanding or acute inflammatory diseases at baseline. Controls (n=126) were frequency matched on sex, age (5-year groups), and BMI (5 kg/m^2 groups). After the exclusion of 1 case due to missing fasting glucose measurement and 21 cases due to damaged or missing frozen sample the final number of cases was 55. Similarly we had to exclude 1 control due to missing CRP value, 5 controls due to missing fasting glucose and 35 due to damaged or missing frozen sample. The final dataset thus included 140 participants (68.3% men) with a mean age of 50.9 ±6.3 yrs, BMI 26.7±4.1 kg/m^2, waist circumference 88.2±12.4 cm, total cholesterol 6.6±1.1 mmol/l. Thirteen percent of the participants were regularly engaged in vigorous physical

activity, 7.2% had a positive family history of diabetes mellitus, and 17.4% had a “low” civil servant employment grade (clerical/support).

To assess the effect of the selection process on the characteristics of the cases, we compared cases included in the final analysis to the rest of the cases. Since controls included in the present analysis were different from the rest of the diabetes free participants by design, no similar comparisons were performed for that group. To compare baseline characteristics of cases and controls appropriate univariate statistics were used. Similar binary logistic and multiple linear regression models were built with incident diabetes or HbA1c as respective outcomes and additive block entry of adiponectin and potential confounders. For linear regression CRP and triglycerides were log transformed. Since HbA1c could be modified by drug treatment, we ran a sensitivity analysis excluding all participants on antidiabetic medication. A p-value of <0.05 was considered significant. Analyses were performed with SPSS 14.0 for Windows.

Results

We found no significant differences (all $p>0.1$) between incident diabetes cases of Caucasian origin included or not included into the present analysis regarding all covariates at baseline except that a positive family history of diabetes mellitus was less frequent among included cases ($p=0.014$). (see online Appendix)

Incident diabetes cases had significantly higher triglycerides, fasting plasma glucose, CRP, and lower adiponectin values at baseline compared to controls. Systolic blood pressure tended to be higher among cases. (Table 1)

According to the logistic regression models, the risk of incident diabetes mellitus decreased by 11% for 1 μg/mL higher adiponectin levels. This association remained stable and statistically significant after adjustment for some potential confounders, however lost significance after adjusting for CRP. While CRP only minimally effected the size of the association, further adjustment for fasting glucose also suppressed the size of the effect. The association was independent of physical activity and family history of diabetes. (Table 2)

Higher adiponectin levels at baseline were associated with lower HbA1c values at follow-up 12 years later. This association also remained stable and significant after adjusting for potential confounders including CRP, however lost significance after further adjustment for fasting plasma glucose. The association was independent of the effect of physical activity and family history of diabetes mellitus. (Table 2)

In the sensitivity analysis excluding all cases on antidiabetic treatment at the time of HbA1c measurement (n=11), the magnitude of the association between adiponectin and HbA1c remained almost the same (data not shown).

Discussion and Conclusions

We found a prospective association between adiponectin levels and diabetes incidence and the degree of glycaemic control, which was robust to extensive adjustment for potential confounders. Our findings support the idea that adiponectin is causally involved in the aetiology of diabetes.

Our result on incident diabetes generally confirm the findings of other prospective studies [3, 4,5,6,7,8,9]. Most of these studies found an effect of adiponectin on incident type 2 diabetes independently of age [4,5,6,9], sex [3,4], and blood pressure [4,5,9] with effect magnitudes similar to those observed in our study.

Adiponectin was associated with a lower risk of type 2 diabetes independently of the measure of obesity (BMI or waist circumference) in some [3,5,6,9] but not all of the studies [4,8]. Similarly the role of lipids is somewhat controversial: according to some [5,8] but not all of the studies [9] they attenuated the association between adiponectin and incident diabetes. Our results in this respect are especially robust as the adjustment for BMI and lipids had virtually no effect on the observed risk.

Whether the role of adiponectin is independent of inflammation is controversial. In addition there is a plausible link between adiponectin and low-grade inflammation according to experimental studies [1,2]. It is surprising however that the preventive effect of adiponectin remained independent of a wide range of inflammatory markers in Pima Indians [6], similarly to other ethnicities [3,4,9]. While in our participants the effect of adiponectin became non-significant, the effect size was only attenuated minimally probably reflecting the limited statistical power related to the small sample size.

As observed in our study, blood glucose or insulin have previously been shown to attenuate the strength of the relation between adiponectin and diabetes [4,8,9], although this was not confirmed in Pima Indians and Japanese individuals [3,6].

Physical activity and socioeconomic status were rarely explored in the literature [5,9]. Our findings confirm that adiponectin affects diabetes risk independently of physical activity and employment grade, which is the best marker of socioeconomic status in the Whitehall II population. Family history of diabetes had no effect on this relationship, either in our study or in previous reports [5,8].

While in cross-sectional analyses adiponectin was negatively related to fasting glucose, 2h post load glucose, insulin resistance and HbA1c [3,1,14,6,2], almost no data is available about the temporal relationship between adiponectin and glycemic control. Adiponectin has been linked to deterioration in 2h blood glucose during a 3 year follow-up independently of insulin sensitivity and insulin secretion [15]. Our new finding of an effect of adiponectin on HbA1c values 10 years later extends this observation to a longer follow-up. The relation remained statistically significant after adjusting for CRP, indicating that low grade inflammation does not explain the effect of adiponectin on glycemic control. This is supported also by the fact that no correlation was found between CRP and adiponectin values ($r=-0.048$, $p=0.58$). While the absolute role of adiponectin seems to be minor according to the unstandardized coefficients, it explains a significant proportion (~5%) of the total HbA1c variation in this population. This proportion falls between the variation explained by fasting glucose (11%) and CRP (3%) derived from the same population.

The major weakness of our nested case-control study is that the sample size was lower than the total potentially available number of cases. This was due to a large degree to the predefined exclusion of cases and controls with inflammatory conditions at baseline, or incident CHD. The reduction of available cases and controls due to damaged samples is unlikely to have biased our results, as this would have affected samples equally among cases and controls. This is further confirmed by the observation that no significant differences (all $p>0.1$) were found between all incident diabetes cases of Caucasian origin included or not included into the present analysis regarding all covariates at baseline except that a positive family history of diabetes mellitus was lower among included cases ($p=0.014$). Due to the possibility of a shorter than recommended fasting preceding the OGTT, some controls may have been erroneously classified as cases, however any such misclassification would have only decreased the observed associations towards the null. The long follow-up time, our ability to adjust for a wide range of well characterised covariates and the robustness of our diabetes diagnosis are among the main strengths of our report. Most of our cases were diagnosed on the basis of an OGTT,

making it unlikely that we would have missed incident diabetes cases. Our confirmatory findings on diabetes status and the new observations on HbA1c complement each other, giving further confirmation of a possible role of adiponectin in the development of diabetes mellitus and glycemic control.

Another strength of this nested case control study, is our ability to comprehensively exclude diabetes cases and conditions that might affect inflammation at baseline. Our finding of a prospective association between lower adiponectin levels and the risk of developing diabetes independently of its major risk factors, supports the hypothesis of a causal effect of adiponectin on diabetes development. Moreover, we showed that adiponectin predicts glycemic control 10 years later, independently of diabetes risk factors and low grade inflammation, indicating that mechanisms related to, or mediated by adiponectin may play a role in determining the severity of glycemic impairment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of study participants stratified by case-control status.

Variable	Controls	Incident diabetes	P
N	85	55	
Age (yrs)	50.8 ± 6.2	50.9 ± 6.4	0.91
Male (%)	58 (68.2)	38 (69.1)	1.00
BMI (kg/m2)	26.6 ± 4.1	27.0 ± 4.3	0.61
Waist (cm)	87 ± 12	90 ± 13	0.15
Total cholesterol (mmol/l)	6.7 ± 1.2	6.5 ± 1.1	0.34
Triglycerides (mmol/l)	1.3 [0.9]	1.6 [0.8]	0.047
Systolic blood pressure (mmHg)	121 ± 13	126 ± 13	0.061
C-reactive protein (mg/l)	0.89 [1.26]	1.29 [2.47]	0.032
Fasting glucose (mmol/l)	5.08 ± 0.31	5.49 ± 0.54	<0.0001
Adiponectin (µg/ml)	10.5 [3.6]	9.3 [3.2]	0.014
Physiscal activity			0.87
non/mild	29 (34.5)	21 (38.9)	
moderate	45 (52.4)	26 (48.1)	
vigorous	11 (13.1)	7 (13.0)	
Positive family history (%)	6 (7.1)	4 (7.4)	0.59
Civil servant grade			0.87
administrative	29 (34.5)	21 (38.9)	
executive	40 (47.6)	24 (44.4)	
clerical/support	15 (17.9)	9 (16.7)	

Data with normal and non-normal distribution are given as mean ± standard deviation and median [interquartile range], respectively. Groups were compared using chi-square test, Fisher's exact test, two-sample t-test and Wilcoxon test as appropriate.

Table 2

Multivariate analysis of adiponectin as an independent and incident diabetes or HbA1c as the dependent variables.

Outcome	
Incident diabetes mellitus	**OR (95% CI)**
Adiponectin	0.89 (0.80-0.99)*
+ age, sex, BMI	0.89 (0.79-0.99)*
+ total cholesterol, triglycerides, systolic blood pressure	0.89 (0.79-0.99)*
+ CRP	0.89 (0.79-1.00)
+ fasting plasma glucose	0.94 (0.82-1.07)
Adiponectin, age, sex, BMI, physical activity, fam.hist. of DM, employment grade	0.87 (0.77-0.97)*
HbA1c	**β (95% CI)**
Adiponectin	-0.08 (-0.02 - -0.14)*
+ age, sex, BMI	-0.08 (-0.02 - -0.14)*
+ total cholesterol, triglycerides, systolic blood pressure	-0.08 (-0.02 - -0.14)*
+ CRP	-0.08 (-0.01 - -0.14)*
+ fasting plasma glucose	-0.05 (0.01 - -0.11)
Adiponectin, age, sex, BMI, physical activity, family history of diabetes mellitus, employment grade	-0.10 (-0.04 - -0.16)**

* p<0.05

** p<0.01

For the linear regression analysis triglycerides and CRP were log-transformed.

OR – odds ratio

95% CI – 95% confidence interval