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Serum adiponectin predicts all-cause mortality and end stage renal disease in patients with type I diabetes and diabetic nephropathy

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Adiponectin levels are increased in patients with type I diabetes especially in the presence of microangiopathy. Here we determined the predictive value of serum adiponectin levels and 8 adiponectin gene polymorphisms for mortality, cardiovascular events and end-stage renal disease in type I diabetic patients. This prospective, observational follow-up study of type I diabetics consisted of 438 patients with overt diabetic nephropathy that were compared to 440 type I patients with normal albumin excretion. These two groups were followed an average of 8 years and generally matched for gender, age and duration of diabetes. Cox regression analysis of 373 patients showed a covariate-adjusted hazard ratio for all-cause mortality of 1.46 for a change of one standard deviation in log10 of serum adiponectin. There was no association with cardiovascular events; however, serum adiponectin levels predicted end stage renal disease in a covariate-adjusted analysis. Two of eight gene polymorphisms, found in the 878 patients, were associated with increased serum adiponectin levels but none of the polymorphisms were associated with a renal or cardiovascular outcome. These studies show that high serum adiponectin levels predict mortality and progression to end stage renal disease in type I diabetic patients.

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Proteinuric patients with type I diabetes have an increased mortality compared to the general population, mainly explained by end-stage renal disease (ESRD) and cardiovascular disease (CVD).[1]

The adipocyte secretes a number of peptides labeled adipocytokines or adipokines. The most abundantly secreted adipokine is adiponectin, which is induced during adipocyte differentiation. In experimental studies and in type II diabetic patients, adiponectin has been shown to possess anti-inflammatory, antiatherogenic, and cardioprotective properties.[2] Furthermore, adiponectin has been suggested to enhance insulin action.[3,4]

Recently, two cell surface receptors for adiponectin have been identified. The two receptors are expressed in most tissues, but liver and muscle showed by far the most prominent expression.[5] Receptor activation has been shown to stimulate AMP-activated protein kinase and peroxisome proliferator-activated receptor-γ, fatty-acid oxidation, and glucose uptake.[5,6] These actions suggest a role of adiponectin as an endogenous insulin sensitizer.[3,4]

Low concentrations of adiponectin have been associated with obesity,[7,8] type II diabetes,[7,9] and coronary artery disease.[9–12] In addition, with respect to kidney disease in type I diabetes, serum adiponectin levels are increased and associated with microangiopathy.[11,13–15] The levels of adiponectin are influenced by genetic variations in the *adiponectin* (*ADIPOQ*) gene.[16] However, the relationship between concentrations of adiponectin and microangiopathy is not fully understood, but we have previously shown that genetic variations in the *ADIPOQ* gene are associated with the risk of diabetic nephropathy.[17] This prompted us to investigate whether serum levels of adiponectin and eight polymorphisms in the *ADIPOQ* gene predict all-cause mortality, CVD events, and ESRD in a well-characterized population of type I diabetic patients with or without diabetic nephropathy. Furthermore, we wanted to investigate whether associations with genetic variants are driven through increased adiponectin levels.

RESULTS

Baseline characteristics

This was a prospective observational follow-up study with a median follow-up time until end point or last visit of 8.1 (0.0–12.8) years. From Denmark, 952 patients were originally included in the EURAGEDIC case–control study.[18] In 52 patients no follow-up was possible and 22 individuals had at least one unreported genotype due to technical reasons. The remaining study population included two groups: 438 cases with type I diabetes and diabetic nephropathy and 440 controls with type I diabetes for more than 15 years and persistent normoalbuminuria. Baseline clinical and laboratory characteristics of the 878 patients are shown in Table 1. Patients with nephropathy were younger, received more antihypertensive treatment, had higher HbA_{1c}, blood pressure, serum creatinine and total cholesterol, but lower concentrations of high-density lipoprotein cholesterol than patients with normoalbuminuria ($P<0.05$). There was a correlation between adiponectin and the following parameters: Age ($r=0.17$), serum levels of creatinine ($r=0.41$), weight ($r=-0.28$), urinary albumin excretion rate ($r=0.29$), and high-density lipoprotein cholesterol ($r=0.27$), and all P-values were <0.001. On average, glomerular filtration rate (GFR) was well preserved in patients with diabetic nephropathy, but nevertheless, in type I diabetic patients serum adiponectin was significantly higher in individuals with diabetic nephropathy, as previously published.[13] Furthermore, after adjustment for the presence of nephropathy, patients carrying the minor allele in −11387 and the non-A-allele in +2033 had significant elevated adiponectin concentrations, $P=0.031$ and 0.040. However, associations disappeared after Bonferroni correction for multiple testing. Allele and genotype frequencies for the eight variants in the *ADIPOQ* gene were compatible with the Hardy–Weinberg equilibrium. Allele frequencies for all polymorphisms are shown in Table 2. Interestingly, the two polymorphisms associated with increased adiponectin levels were also nominally associated with diabetic nephropathy in the case–control study: The A-allele in −11387 was associated with diabetic nephropathy (A-allele frequency: 9.4 versus 6.6% in cases and controls, respectively, $P=0.014$), as well as +2033 (the non-A-allele frequency: 37.0 versus 41.3% in cases and controls, respectively, $P=0.050$).

Follow-up data

In 373 patients, circulating levels of adiponectin were measured. Data were evaluated with adiponectin as a continuous variable. During follow-up, 19 (10.9%) patients with normoalbuminuria and 79 (39.9%) patients with macroalbuminuria died. Cox regression analysis revealed an increased risk for all-cause mortality with a hazard ratio (HR) of 1.75 (1.47–2.10, $P<0.001$) for a change of one s.d. (0.21) in $\log_{10}$ of serum adiponectin. Adiponectin remained an independent predictor of all-cause mortality in the Cox regression model (covariate-adjusted (sex, age, ± nephropathy, systolic blood pressure, HbA_{1c}, serum creatinine, serum cholesterol, and antihypertensive treatment) HR 1.46 (1.07–2.00, $P=0.018$)). This association was linear and the interaction term between case–control group and adiponectin level was significant ($P=0.037$). However, no associations were seen when analyzing cases and controls separately in a multivariate Cox regression model ($P=0.428$ and 0.093). In addition, one s.d. increase of $\log_{10}$ of serum adiponectin was associated with an increased risk of the combined end point

Table 1 | Baseline clinical and laboratory characteristics of the 878 patients divided according to nephropathy status

	Nephropathy (*N*=438)	Normoalbuminuria (*N*=440)	*P*-value
Sex (men/women)	267/171	233/207	0.017
Age (years)	42.3 ± 10.4	45.4 ± 11.5	<0.001
Duration of diabetes (years)	28.4 ± 8.8	27.7 ± 10.1	0.29
BMI (kg/m^2)	24.2 ± 3.3	24.2 ± 3.1	0.80
HbA_{1c} (%)	9.4 ± 1.5	8.4 ± 1.1	<0.001
Antihypertensive treatment (%)	77.3	16.6	<0.001
sBP (mm Hg)	145 ± 22	134 ± 19	<0.001
dBP (mm Hg)	83 ± 12	76 ± 10	<0.001
UAER (mg per 24 h)	593 (3–14,545)[a]	7 (1–30)	—
S-creatinine (mmol/l)	103 (52–706)	79 (53–134)	<0.001
GFR (crEDTA, ml/min per 1.73 m^2)	74 ± 34	—	—
eGFR (ml/min per 1.73 m^2)	66 ± 28	87 ± 16	<0.001
S-cholesterol (mmol/l)	5.6 ± 1.2	4.9 ± 1.0	<0.001
S-HDL cholesterol (mmol/l)	1.5 ± 0.6	1.6 ± 0.5	0.002
S-triglycerides (mmol/l)	1.3 (0.3–9.9)	0.8 (0.3–5.4)	<0.001
Smoking (%)	45.8	39.5	0.08
Retinopathy (0/SR/PR)	7/133/298	159/163/118	<0.001
Myocardial infarction (%)	4.5	1.8	0.03
Stroke (%)	7.0	1.6	<0.001
S-adiponectin (mg/l)[b]	24.2 (7.6–117.5)	17.3 (6.1–48.6)	<0.001

BMI, body mass index; dBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PR, proliferative retinopathy; sBP, systolic blood pressure; SR, simplex retinopathy; UAER, urinary albumin excretion rate.
[a]Some patients with previously persistent macroalbuminuria receiving antihypertensive treatment had values <300 mg per 24 h at the time of investigation.
[b]*N*=198 patients with diabetic nephropathy and *N*=175 patients with normoalbuminuria. Data are expressed as *N*, means ± s.d., medians (range).