CLINICAL STUDY

Plasma adiponectin and serum advanced glycated end-products increase and plasma lipid concentrations decrease with increasing duration of type 2 diabetes

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Abstract

Objective: To prospectively follow the concentrations of plasma adiponectin (p-adiponectin) and serum advanced glycation end-products (s-AGE) in relation to plasma lipids and retinopathy over 3 years in type 2 diabetic patients.

Design and methods: P-adiponectin, s-AGE, plasma lipids and diabetic retinopathy were prospectively evaluated in 61 type 2 diabetic patients at baseline and at follow up 3 years later.

Results: Mean p-adiponectin (from 8.84 ± 5.14 to 11.05 ± 6.16 $\mu\text{g/ml}$; $P = 0.006$) and s-AGE (from 637 ± 242 to 781 ± 173 ng/ml ; $P < 0.0001$) concentrations had increased at follow up. In addition, HbA1c (7.7 ± 1.7 to $7.4 \pm 1.4\%$; $P = 0.0045$) and fasting C-peptide (1.00 ± 0.38 to 0.81 ± 0.35 nM ; $P = 0.019$) had decreased and all lipid variables had significantly improved at follow up. P-adiponectin correlated inversely with fasting C-peptide ($r_s = -0.273$; $P = 0.045$) and low-density lipoprotein (LDL)/high-density lipoprotein (HDL) ratio ($r_s = -0.362$; $P = 0.011$), and directly with plasma HDL cholesterol ($r_s = 0.381$; $P = 0.005$) at follow up. Analysis of variance with adiponectin and s-AGE as dependent variables and fasting C-peptide, plasma HDL and plasma LDL cholesterol as covariates demonstrated that the increase in s-AGE was independent ($P = 0.001$) and the increase in p-adiponectin dependent on covariate changes ($P = 0.862$). There was a slight correlation between s-AGE at baseline versus the degree of retinopathy at follow up ($r_s = 0.281$; $P = 0.0499$).

Conclusion: Both p-adiponectin and s-AGE increased during the 3 years. The increase in p-adiponectin was explained by improvements in insulin sensitivity and dyslipidaemia, whereas the increase in s-AGE was independent of changes in metabolic covariates. s-AGE increase when the duration of type 2 diabetes increases.

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Introduction

Adiponectin is an adipocyte-specific bioactive protein secreted from adipose tissue (1). In animal models, adiponectin deficiency results in insulin resistance (2). In healthy individuals, adiponectin is negatively correlated with body mass index (BMI) (3) and plasma triglyceride concentrations (4, 5) and positively associated with plasma high-density lipoprotein (HDL) cholesterol concentrations (3–5) and increased insulin sensitivity (6). Among type 2 diabetic patients, cross-sectional studies have shown that low plasma adiponectin (p-adiponectin) concentrations (7) are associated with low plasma HDL cholesterol concentrations (8). There is a need for prospective studies to establish the relationship between plasma adiponectin and lipids among type 2 diabetic patients.

Among diabetic patients, increments of advanced glycation end-products (AGE) (9) have been associated

with disturbed lipid metabolism. AGE-modified low-density lipoprotein (LDL) impairs the LDL receptor-mediated clearance mechanism (10), AGE-modified HDL has disturbed function (11) and AGE may directly inhibit the scavenger receptor class B I-mediated reverse cholesterol transport (12). Possibly as a consequence of this, increased serum AGE (s-AGE) concentrations are associated with increased plasma triglycerides and LDL concentrations in children and adolescents with type 1 diabetes (13). Increased serum concentrations of AGE may in addition contribute to the development of vascular complications by inducing endothelial dysfunction (14) and retinopathy (15, 16). Although irreversible glycation should be increased by prolonged hyperglycaemic exposure, s-AGE concentrations were not increased in children and adolescents with long durations of type 1 diabetes (13, 17). Indeed, s-AGE decreased in a 10-year prospective study of insulin treated, mainly type 1 diabetic

patients (18). It is now important to prospectively follow the progression of s-AGE in type 2 diabetic patients.

The aim of this study was to prospectively follow the development of p-adiponectin and s-AGE in relation to plasma lipids, plasma C-peptide and retinopathy over 3 years in type 2 diabetic patients.

Subjects and methods

Subjects

From a population-based study of the diabetes incidence in Malmö, Sweden, between 1990 and 1992 (19), 61 newly diagnosed patients with type 2 diabetes (all negative for islet antibodies) were investigated with regard to biochemical risk factors 5 years after the diagnosis of diabetes (baseline examination) (20). Their age ranged from 45 to 69 years, with a median value of 59 years. These investigations were repeated 8 years after diagnosis (follow-up examination).

Informed consent was obtained from all subjects. The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Lund University.

Analytical methods

BMI was measured as weight (in kg)/height squared (in m²). Blood pressure (BP) was measured in the supine position with a sphygmomanometer in the right upper arm after 10 min rest. P-adiponectin concentrations were measured using a RIA for human adiponectin (Linco Research, St Louis, MO, USA) (4). s-AGE concentrations were measured using

an N-ε-carboxymethyl-lysine (CML) ELISA system (Roche Diagnostics, Penzberg, Germany) (18).

Retinopathy

An experienced ophthalmologist (M Kangro) assessed diabetic retinopathy from fundus photography. The 11 levels of the alternative classification on the Wisconsin scale were used (21, 22). Level 10 represents no retinopathy, levels 21–51 nonproliferative diabetic retinopathy (NPDR) of increasing severity, and levels 60+ all forms of proliferative diabetic retinopathy (PDR), with and without laser treatment. The eye with the more severe level of retinopathy determined the patient's retinopathy level.

Statistical methods

Differences between groups were evaluated with the Mann–Whitney U test and the χ^2 test. Differences over time within groups were evaluated with the Wilcoxon signed-rank test. In analysis of variance with repeated design p-adiponectin and s-AGE were dependent variables, and correlating variables were covariates. Tests were two-tailed and *P* values <0.05 were considered significant. Results are presented as mean±s.d. StatView 4.5 (SAS Institute, Cary, NC, USA) was used for the statistical calculations.

Results

Adiponectin

There was a significant (*P* = 0.006) increase in mean p-adiponectin from 8.84±5.14 µg/ml at baseline to 11.05±6.16 µg/ml at follow up (Table 1). In parallel

Table 1 Treatment, clinical features, p-adiponectin and s-AGE at baseline and 3 years later in 61 type 2 diabetic patients. Means±s.d. or *n* (%) are shown. P, plasma; Fp-C-peptide, fasting plasma C-peptide.

	Baseline	Follow up	<i>P</i> value
Treatment (<i>n</i> (%))			
Anti-hypertensive	20 (33)	23 (38)	0.5696
Lipid lowering	2 (3)	11 (18)	0.0022
Insulin	3 (5)	7 (11)	0.1811
Sulphonylurea	34 (56)	38 (62)	0.5795
Biguanide	11 (18)	27 (44)	0.0028
Clinical features			
Retinopathy (<i>n</i> (%))	6 (10)	14 (23)	0.0179
BP (mmHg)	139±17/87±10	147±20/89±9	0.1195/0.033
BMI (kg/m ²)	29.3±5.4	28.2±4.6	0.001
Fp-C-peptide (nM)	1.00±0.38	0.81±0.35	0.019
HbA1c (%)	7.68±1.72	7.38±1.44	0.0045
P-cholesterol (mM)	5.78±0.95	5.34±1.04	0.0003
P-LDL (mM)	3.72±0.81	3.17±0.76	<0.0001
P-HDL (mM)	1.08±0.26	1.27±0.36	<0.0001
P-triglycerides (mM)	2.26±1.63	1.92±1.10	0.0431
P-adiponectin (µg/ml)	8.84±5.14	11.05±6.16	0.0055
s-AGE (ng/ml)	637±242	781±173	<0.0001

with this, several variables including BMI indicated improved metabolic control. Table 1 shows that HbA1c, fasting plasma C-peptide and all lipid variables were significantly improved at follow up. There was an increased use of biguanides (baseline 11/61 (18%) versus follow up 27/61 (44%); $P = 0.0028$), and lipid-lowering drugs (baseline 2/61 (3%) versus follow up 11/61 (18%); $P = 0.0022$; Table 1). However, total plasma cholesterol (from 5.74 ± 0.89 to 5.36 ± 0.92 mM; $P = 0.0022$) and plasma LDL cholesterol (from 3.66 ± 0.75 to 3.21 ± 0.78 mM; $P = 0.0001$) decreased significantly in patients without lipid-lowering therapy as well. There were no significant correlations between p-adiponectin and BMI (first study $r = 0.054$, $P = 0.672$; follow-up study $r = 0.015$, $P = 0.938$) or s-AGE. At follow up, p-adiponectin correlated significantly and inversely with fasting plasma C-peptide ($r_s = -0.273$; $P = 0.045$), plasma C-peptide 6 min after a glucagon injection ($r_s = -0.365$; $P = 0.008$; Fig. 1, top panel) and LDL/HDL ratio ($r_s = -0.362$; $P = 0.011$), and directly with plasma HDL cholesterol ($r_s = 0.381$; $P = 0.005$, Table 2).

Figure 1 Top panel: correlation between plasma (P) C-peptide 6 min after glucagon injection versus p-adiponectin at follow up ($r_s = -0.365$; $P = 0.008$) in 61 type 2 diabetic patients. Bottom panel: correlation between plasma LDL cholesterol at baseline versus s-AGE at follow up ($r_s = 0.335$; $P = 0.02$) in 61 type 2 diabetic patients.

Table 2 Spearman's correlation coefficients between p-adiponectin concentration and BPs and metabolic variables at baseline and at follow up 3 years later in 61 type 2 diabetic patients. Significant correlations are shown in bold. P, plasma.

	<i>r</i> value	<i>P</i> value
Baseline		
Age	0.117	0.385
BMI	0.054	0.672
Systolic/diastolic BP	0.058/– 0.316	0.621/ 0.022
Fasting p-C-peptide	–0.237	0.661
HbA1c	0.017	0.891
P-cholesterol	0.191	0.138
P-HDL cholesterol	0.241	0.064
P-LDL cholesterol	0.077	0.564
P-triglycerides	0.008	0.952
s-AGE	0.254	0.067
Follow up		
Age	0.003	0.981
BMI	0.090	0.493
Systolic/diastolic BP	0.075/0.008	0.591/0.954
Fasting p-C-peptide	– 0.273	0.0446
HbA1c	–0.102	0.450
P-cholesterol	0.043	0.751
P-HDL cholesterol	0.381	0.005
P-LDL cholesterol	–0.168	0.235
P-triglycerides	–0.119	0.381
s-AGE	–0.037	0.788

s-AGE

There was a significant ($P < 0.0001$) increase in mean s-AGE from 637 ± 242 ng/ml at baseline to 781 ± 173 ng/ml at follow up. s-AGE correlated significantly with plasma cholesterol, both at baseline and at follow up ($r_s = 0.283$; $P = 0.041$ on both occasions), plasma HDL cholesterol at baseline ($r_s = 0.287$; $P = 0.041$) and with plasma LDL cholesterol at follow up ($r_s = 0.309$; $P = 0.032$) (Table 3). In addition, plasma LDL cholesterol at baseline correlated with s-AGE at follow up ($r_s = 0.335$; $P = 0.02$; Fig. 1, bottom panel). However, there were no significant correlations between HbA1c and s-AGE.

Analysis of variance (repeated design) with p-adiponectin and s-AGE as dependent variables and BMI, diastolic BP, fasting plasma C-peptide, plasma HDL and plasma LDL cholesterol showed that the increase in s-AGE was independent of the changes in covariates ($P = 0.001$), whereas the increase in p-adiponectin was totally dependent on the changes in covariates ($P = 0.862$). Accordingly, the increment in s-AGE at follow up was unrelated to lipid status.

Retinopathy

At baseline, six patients (10%) showed diabetic retinopathy, whereas the prevalence had significantly ($P = 0.0197$) increased to 14 (23%) at follow up. There was a slight but significant correlation between s-AGE at baseline and the severity of retinopathy at follow up ($r = 0.281$; $P = 0.0499$). Concentrations

Table 3 Spearman's correlation coefficients between s-AGE concentrations and BPs and metabolic variables at baseline and at follow up 3 years later in 61 type 2 diabetic patients.

	<i>r</i> value	<i>P</i> value
Baseline		
Age	−0.022	0.890
BMI	− 0.412	0.003
Systolic/diastolic BP	0.022/−0.134	0.845/0.491
Fasting p-C-peptide	− 0.316	0.023
HbA1c	−0.114	0.414
P-cholesterol	0.283	0.041
P-HDL cholesterol	0.287	0.041
P-LDL cholesterol	0.215	0.128
P-triglycerides	−0.010	0.945
Follow up		
Age	−0.183	0.186
BMI	0.030	0.832
Systolic/diastolic BP	−0.080/−0.159	0.570/0.255
Fasting p-C-peptide	−0.088	0.527
HbA1c	−0.038	0.784
P-cholesterol	0.283	0.042
P-HDL cholesterol	0.142	0.305
P-LDL cholesterol	0.309	0.032
P-triglycerides	0.053	0.704

Significant correlations are shown in bold. P, plasma.

of p-adiponectin or s-AGE did not differ significantly between patients with and without retinopathy.

Discussion

This study showed that glycaemic control as reflected by a decrement in HbA1c and dyslipidaemia as reflected by decrements in total plasma cholesterol, plasma LDL cholesterol and plasma triglycerides and increments in plasma HDL cholesterol concentrations had improved at follow up. In parallel with this improvement, p-adiponectin concentration had increased and plasma C-peptide concentrations decreased, indicating that insulin sensitivity had improved. On the other hand, s-AGE, the putative long-term consequences of hyperglycaemia, had increased at follow up.

That the increment in p-adiponectin concentration at follow up was associated with signs of increased insulin sensitivity is in line with the inverse correlation between p-adiponectin concentrations and features of the insulin-resistance syndrome observed in cross-sectional studies (2–5). The previously reported (3–5, 23) association between high p-adiponectin and high plasma HDL cholesterol, an established anti-atherogenic factor, was also found at follow up. It has to be remembered, however, that a decrease in plasma C-peptide might not only be explained by improved insulin sensitivity, perhaps related to the increase in biguanide treatment, but might also reflect progressively decreasing β -cell function with increasing diabetes duration.

The increment of p-adiponectin and improvement in the lipid profile at follow up was not only due to the institution of pharmacological lipid lowering, as this

was also seen in patients without such treatment. Hence, diet and other non-pharmacological intervention had contributed to the improvement in metabolic control as inferred from the decrease in BMI at follow up. Whether the increased p-adiponectin concentration should be considered secondary to improvement in the metabolic syndrome or whether adiponectin has a primary role in this context cannot be concluded from the current study. Although our extended statistical analysis showed that all changes observed in p-adiponectin were related to changes in its covariates, only a randomized study has the utility to clarify whether adiponectin, by decreasing intramyocellular lipid accumulation (24) and hepatic fat content (25), decreases insulin resistance (26, 27).

s-AGE and not only adiponectin concentrations had increased at follow up. When we related the increment in s-AGE to lipid status we found a positive correlation between plasma LDL cholesterol and s-AGE at follow up. Indeed, plasma LDL at baseline correlated with s-AGE at follow up, suggesting that elevated plasma LDL concentrations may predict future elevations in s-AGE. However, further statistical analysis demonstrated that alterations in s-AGE were unrelated to lipids. Hence, the proven increase in s-AGE seemed to be a consequence of an increasing accumulation of AGE during the observation period rather than being a consequence of dyslipidaemia. In this context, it may be appropriate to consider the fact that the patients did not obtain normoglycaemia. Hence, it might be that only slight degrees of hyperglycaemia lead to accumulation of AGE.

Our finding of increments in s-AGE may be considered logical. However, others have recently reported a lack of correlation between s-AGE concentrations and the duration of diabetes in type 1 diabetic patients (13). Indeed, a decrease in s-AGE believed to be secondary to improvement in metabolic control was reported recently (18). In contrast, we found an increase in s-AGE at follow up despite improvement in the glycaemic control, as demonstrated clearly by the decrement in HbA1c at follow up. The discrepancy could be related to the fact that we prospectively followed patients with type 2 and not type 1 diabetes. However, as s-AGE concentrations were not lower in type 1 diabetic patients with long duration compared with those with short duration (13), the finding of a decrease in s-AGE when the duration of type 1 diabetes increases (18) has to be confirmed in new prospective studies of type 1 diabetic patients.

Although our extended statistical analysis showed that s-AGE concentrations were independent from lipid status, it is still possible that glycation of lipids contributes to the unfavourable lipid profile in diabetes (10–12). Indeed, tissue AGE correlates with concentrations of plasma AGE-modified LDL cholesterol (28).

In our prospective study, the prevalence of retinopathy doubled over 3 years. Noteworthy is that we found

a correlation between high s-AGE at baseline and the degree of retinopathy at follow up. Hence, our study indicates that s-AGE concentrations are important for the progression of retinopathy (15). Indeed, AGE have been reported to be elevated in serum (15) and to accumulate in the retina in diabetic retinopathy (29). AGE may have an important role in the development and progression of retinopathy.

In conclusion, concentrations of p-adiponectin and s-AGE increased over 3 years in type 2 diabetic patients. The increment in p-adiponectin was associated with improved metabolic control and reduced insulin resistance, whereas the increment in s-AGE was independent of changes in other metabolic variables.

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