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Diabetic nephropathy is associated with low-grade inflammation in Type 1 diabetic patients

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Abstract

Aims/hypothesis. Increased concentrations of C-reactive protein and interleukin-6, a finding suggestive of the presence of inflammation, have been observed in Type 2 diabetes. In such patients, C-reactive protein was predictive of diabetic nephropathy. Studies on low-grade inflammatory markers and nephropathy in Type 1 diabetic patients have shown conflicting results. Therefore we studied whether low-grade inflammation is associated with diabetic nephropathy in Type 1 diabetic patients.
Methods. We divided 194 Type 1 diabetic patients into three groups from the Finnish Diabetic Nephropathy Study based upon their albumin excretion rate. Patients with normoalbuminuria (n=67) had no antihypertensive medication or signs of cardiovascular disease, while patients with microalbuminuria (n=64) or macroalbuminuria (n=63) were all treated with an angiotensin-converting enzyme inhibitor, a drug that could attenuate low-grade inflammation. As a measure of insulin sensitivity we used estimated glucose disposal rate. C-reactive protein was measured by radioimmunoassay and interleukin-6 by high sensitivity enzyme immunoassay.
Results. C-reactive protein was higher in micro- and macroalbuminuric patients compared to normoalbuminuric patients (normoalbuminuria 2.0±1.7, microalbuminuria 2.6±1.7, macroalbuminuria 2.9±2.5 mg/l; p=0.016), while interleukin-6 increased in parallel with the severity of the renal disease (1.9±1.5, 2.9±3.3, 3.6±3.1 ng/l; p<0.0001). In multiple regression analysis albumin excretion rate was the only variable independently associated with C-reactive protein (p=0.03), whereas albumin excretion rate (p=0.0003), HDL-cholesterol (p=0.0135) and duration of diabetes (p=0.0176) were independently associated with interleukin-6.
Conclusions/interpretation. Low-grade inflammatory markers are associated with diabetic nephropathy in Type 1 diabetic patients. The predictive value needs to be assessed. [Diabetologia (2003) 46:1402–1407]

Keywords Diabetes, nephropathy, low-grade inflammation, C-reactive protein, interleukin-6.

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Abbreviations: DN, diabetic nephropathy; CRP, C-reactive protein; eGDR, estimated glucose disposal rate; FinnDiane, finnish diabetic nephropathy study; MDRD, modification of diet in renal disease.

Diabetic nephropathy (DN), a devastating late complication of Type 1 diabetes, is characterized by increased arterial blood pressure, progressive proteinuria, a relentless decline in renal function and up to a 37-fold increased risk of cardiovascular death [1].

The pathogenesis of DN is still a matter of debate although strong evidence suggests that it results from an interaction between susceptibility genes and the diabetic milieu. The true pathogenetic mechanism is not known, but there may be a common denominator of micro- and macrovascular complications. Such a factor could be low-grade inflammation and endothelial dysfunction [2, 3].

C-reactive protein (CRP) is an acute-phase protein produced by the liver cells in response to various stimuli. It is also a very sensitive marker of inflammation. In this respect, the fact that CRP is associated with atherosclerosis and the risk of developing myocardial infarction is noteworthy [4].

Interleukin-6 (IL-6) is a proinflammatory cytokine, which is produced by many cells such as adipocytes, activated leucocytes, myocytes and endothelial cells [5, 6, 7, 8, 9]. Expression studies have also shown IL-6 mRNA in the mesangium of renal specimens from diabetic subjects [10]. IL-6 has in fact been shown to be the main stimulus for the hepatic production of CRP, and its gene transcripts are expressed in human atheromatous lesions. CRP itself has been shown to stimulate monocyte release of IL-6 [6]. Interestingly, IL-6 seems to be associated with visceral obesity and insulin resistance, one of the key features of microalbuminuria and macrovascular complications in Type 2 diabetes [11]. In Type 1 diabetic patients insulin resistance has also been shown to play a central role in the pathogenesis of overt nephropathy [12].

In Type 2 diabetes increased concentrations of CRP and IL-6 have been observed, a finding suggestive of the presence of inflammation [11]. Whether this is also the case in Type 1 diabetes is still unclear. There are two studies regarding CRP or IL-6 and diabetic nephropathy in Type 1 diabetes showing conflicting results. The first study failed to detect an increase in CRP in microalbuminuric (n=22) compared to Type 1 diabetic patients with normal albumin excretion rate (AER) (n=17) [13]. The second study, in contrast, depicted an association between CRP and DN, but the authors did not find a difference between normo- and microalbuminuric patients. Furthermore, IL-6 was not measured nor was low-grade inflammation related to features such as smoking, waist-to-hip ratio (WHR), lipids, blood pressure or a history of parental Type 2 diabetes [14].

We therefore addressed the question, whether low-grade inflammation is associated with diabetic nephropathy in Type 1 diabetes.

Subjects and methods

Subjects. We selected 194 Type 1 DM patients from the ongoing nationwide, multi-centre Finnish Diabetic Nephropathy Study (FinnDiane), and divided them into three groups according to their AER in three consecutive overnight or 24-h urine collections. Normal AER (normoalbuminuria) was defined as an AER persistently less than 20 μg/min or less than 30 mg/24 h, microalbuminuria as AER between 20 to 200 μg/min or 30 to300 mg/ 24-h and macroalbuminuria as AER more than 200 μg/min or more than 300 mg/24 h in at least two out of three urine collections.

Type 1 diabetes was defined as an onset of diabetes before the age of 35 years and permanent insulin treatment initiated within 1 year of diagnosis. From the entire study population of 1616 patients complete information about history of hypertension, diabetes, cardiovascular disease and mortality of both parents was available. The patients were then required to have a duration of diabetes of 10 to 30 years. Based on this criteria the number of eligible patients decreased to 882. To assure renal status three complete urine collections were required decreasing the number of eligible patients to 577. Patients with normal AER were further required to have neither antihypertensive medication nor signs of cardiovascular disease, while patients with microalbuminuria or macroalbuminuria were required to be on ACE-inhibitor treatment. A total of 401 Type 1 diabetic patients met all these selection criteria. Thereafter the patient groups were matched for duration of diabetes. Since the shortest disease duration in the macroalbuminuric group was 13 years this cut off point was chosen for all patients. Finally, the patients were matched for sex. This resulted in 194 patients representative of a wide range of AER. At inclusion five microalbuminuric and eight macroalbuminuric patients were treated with statins. None of the patients used acetosalicylic acid.

The ethical committees of all participating centres approved the study protocol. Written informed consent was obtained from each patient.

Methods. Data on medication, smoking, cardiovascular status, diabetic complications and parental history of diabetes, hypertension and cardiovascular disease were registered with a standardized questionnaire, which was completed by the patient's attending physician based upon medical files. Blood pressure was measured twice in the sitting position with a mercury sphygmomanometer after a 10 min rest. Height, weight and WHR were recorded, and blood was drawn for the measurements of HbA_{1c}, lipids, creatinine and inflammatory markers (CRP and IL-6).

HbA_{1c} and lipids were measured by enzymatic methods in the local hospitals. Serum creatinine was determined using a modified Jaffe reaction. As a measure of insulin sensitivity we calculated the estimated glucose disposal rate (eGDR) with an equation developed by another study [15] and modified for HbA_{1c}. To define the severity of renal disease in addition to AER we estimated GFR by an equation derived from the Modification of Diet in Renal Disease (MDRD) Study [16, 17] and also by a known formula [18].

CRP was measured by radioimmunoassay as described [19]. Briefly, CRP standards (Orion Diagnostica, Espoo, Finland) and patients' sera were incubated with sheep CRP antiserum (Code C 4063, Sigma Chemical Co, St. Louis, Mo., USA), and with Sepharose-anti-sheep IgG (Pharmacia, Uppsala, Sweden) for 1 h at room temperature, and thereafter centrifugated. The radioactivity of the pellets was measured, and the standard curve used for the calculations. IL-6 was measured by high sensitivity enzyme immunoassay (Quantikine HS human IL-6 immunoassay, R&D Systems, Minneapolis, Minn., USA). The detection limit for CRP was 0.01 mg/l and for IL-6 0.1 ng/l. We also measured CRP and IL-6 of 66 healthy controls in sera (36 women and 30 men with a mean age of 37.6 years (range 19–63). In these control subjects the concentration of CRP varied from 0.2 to 4.8 mg/l (means ± SD; 1.2±1.0 mg/l) and the IL-6 concentrations from 0.13 to 5.20 ng/l (1.25±1.07 ng/l).

Statistical analysis. Data are expressed as means ± SD for normally distributed values, as median with range for non-normally distributed values, and percentages. Differences between groups for normally distributed variables were tested using ANOVA and non-parametric data with the Kruskal-Wallis test. Frequencies were tested with Pearson Chi-square test or two-tailed Fisher's exact test when appropriate. Correlations were

Table 1. Clinical characteristics of 194 Type 1 diabetic patients

	Normo	Micro	Macro
n	67	64	63
Sex (M/F)	36/31	37/27	34/29
Age (years)	37.1±8.0	36.8±8.0	34.0±7.3[d, g]
Age at onset (years)	14.9±8.2	14.4±8.1	11.6±6.3[e]
BMI (kg/m^2)	24.0±3.0	25.3±2.8[b]	25.2±3.8
WHR	0.85±0.08	0.87±0.09	0.89±0.08[d]
SBP (mmHg)	129±11	136±19[a]	138±18[e]
DBP (mmHg)	78±8	83±11[b]	84±9[f]
eGDR (mg/kg^{-1}·min^{-1})	7.6±2.1	4.5±1.6[c]	3.9±1.6[f, g]
HbA_{1c} (%)	8.1±1.2	8.8±1.5[a]	9.4±1.9[f, g]
Total cholesterol (mmol/l)	4.92±0.79	5.10±0.99	5.66±1.26[f, h]
HDL-cholesterol (mmol/l)	1.63±0.41	1.60±0.48	1.41±0.46[e, g]
Triglycerides (mmol/l)	0.9 (0.4–2.0)	1.0 (0.5–3.4)	1.5 (0.6–9.1)[f, i]
Creatinine (μmol/l)	82 (47–144)	89 (65–194)[a]	110 (70–675)[f, i]
GFR (MDRD) (ml/min/1.73 m^2)	86±14	79±17[b]	59±27[f, i]
GFR (Cockcroft-Gault) (ml/min/1.73 m^2)	101±20	98±24	72±33[f, i]
AER (mg/24 h)	9 (2–85)	97 (3–418)	719 (10–6069)
History of smoking (%)	22	36[b]	30
Statin treatment (%)	0	8	13

Data are mean ± SD or median (range). [a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$ normo vs micro, [d] $p<0.05$, [e] $p<0.01$, [f] $p<0.001$ normo vs macro, [g] $p<0.05$, [h] $p<0.01$, [i] $p<0.001$ micro vs macro

calculated using simple and multiple linear regression analysis. All calculations were carried out with a BMDP statistical package (BMDP Statistical Software, Los Angeles, Calif., USA). A p value of less than 0.05 was considered statistically significant.

Results

Since there were no differences between men and women data are pooled. Age as well as age at onset of diabetes was lower and WHR higher in patients with more advanced disease (macroalbuminuria) compared to normoalbuminuric patients (Table 1). As expected both systolic and diastolic blood pressure values were higher in patients with microalbuminuria and macroalbuminuria compared to those with normal AER. However, pulse pressures were similar in all three groups. The three groups did not differ regarding current smoking, but there were more microalbuminuric than normoalbuminuric patients that had stopped smoking. HbA_{1c} and creatinine values increased, while GFR (MDRD) and eGDR decreased in parallel with the severity of the renal disease. Total cholesterol and triglycerides were higher and HDL-cholesterol lower in macroalbuminuric patients than in normo- and microalbuminuric patients. The three patient groups did not differ regarding parental history of diabetes, hypertension or cardiovascular disease.

Concentrations of CRP and IL-6 were higher in normoalbuminuric diabetic patients than in healthy controls (Figs. 1, 2). Within the diabetic group, patients with micro- and macroalbuminuria had higher concentrations of CRP than normoalbuminuric pa-

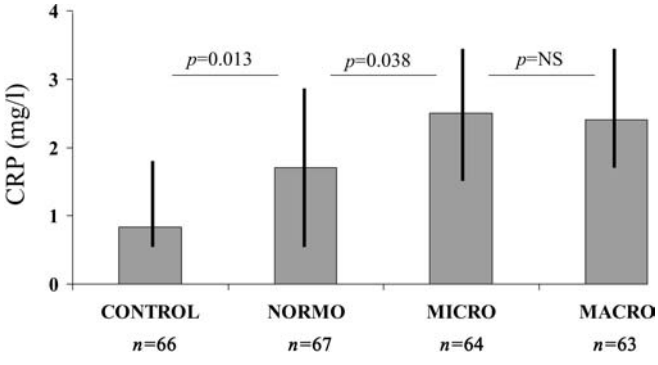

Fig. 1. CRP concentrations in 194 Type 1 diabetic patients with and without diabetic nephropathy as well as in 66 healthy control subjects. Data is median with interquartile range

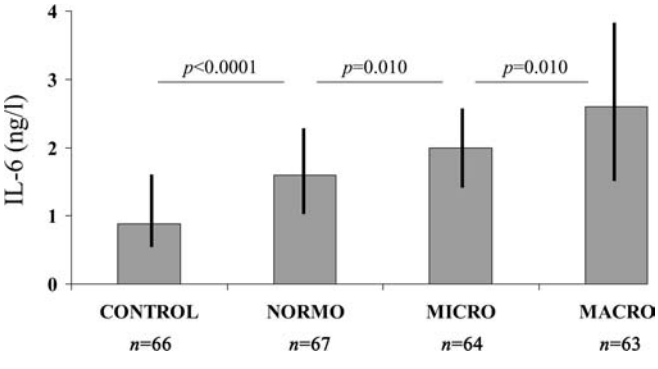

Fig. 2. IL-6 concentrations in 194 Type 1 diabetic patients with and without diabetic nephropathy as well as in 66 healthy control subjects. Data is median with interquartile range

Table 2. Pearson correlation coefficients in 194 Type 1 diabetic patients

	lnIL-6	lnCRP
Duration of diabetes	0.16[a]	–0.06
WHR	0.17[a]	0.02
SBP	0.02	0.11
DBP	0.13	0.15[a]
eGDR	–0.23[b]	–0.15[b]
HbA_{1c}	0.17[b]	0.12
lnCreatinine	0.30[c]	0.14
GFR (MDRD)	–0.36[c]	–0.12
GFR (Cockroft-Gault)	–0.24[c]	–0.10
Cholesterol	0.08	0.08
HDL-chol	–0.16[a]	–0.06
lnTG	0.23[b]	0.19[a]
lnAER	0.21[b]	0.29[c]

[a] $p<0.05$; [b] $p<0.01$; [c] $p<0.001$

tients and IL-6 showed an increase in parallel with the renal engagement. The differences in IL-6 remained pronounced even after adjustment for WHR.

CRP and IL-6 were positively correlated with each other (r=0.3291, $p<0.0001$). IL-6 correlated positively with creatinine, AER, triglycerides, HbA_{1c}, WHR and duration of diabetes and negatively with GFR, HDL-cholesterol and eGDR (Table 2). There were positive correlations between CRP, AER, triglycerides and diastolic blood pressure, while there was an inverse correlation between CRP and eGDR. In a multiple linear regression analysis with duration of diabetes, WHR, eGDR, HbA_{1c}, creatinine, GFR (MDRD), HDL-cholesterol, triglycerides, AER in the model, IL-6 was independently associated with AER (β-coefficient 0.10±SE 0.03, $p=0.0003$), HDL-cholesterol (–0.29±0.12, $p=0.0135$) and duration of diabetes (0.03±0.01, $p=0.0176$). Similarly diastolic blood pressure, eGDR, triglycerides and AER in the model, CRP was independently associated with AER (0.10±0.05, $p=0.0302$).

Discussion

We report an association of inflammatory markers IL-6 and CRP with diabetic nephropathy in Type 1 diabetic patients. The difference in IL-6 concentrations between the groups remained pronounced even after adjustment for WHR suggesting that diabetic nephropathy is truly associated with low-grade inflammation. Interestingly, there was an independent relationship between duration of diabetes and IL-6 as well as between HDL-cholesterol and IL-6. These findings could imply that both the burden of glucose exposure (long duration of diabetes) and decreased insulin sensitivity have a common denominator, low-grade inflammation, and might act in concert in the pathogenesis of diabetic nephropathy.

A finding of our study is that in Type 1 diabetic patients low-grade inflammation is present already at the stage of microalbuminuria. We confirm the previous finding that Type 1 diabetic patients with proteinuria have increased CRP concentrations [14], but extend the finding to increased concentrations of IL-6. This is important since IL-6 is considered to be the main stimulus for the hepatic production of CRP. We included a much larger patient population and this could explain why no significant increase in CRP concentrations could be seen in microalbuminuric Type 1 diabetic patients in a previous small study [13].

The question arises, whether our studied patient population is representative of various degrees of renal involvement, and whether low-grade inflammation really is a key player in the pathogenesis of diabetic nephropathy. All our patients were recruited from the nationwide multi-centre FinnDiane study and matched for sex and duration of diabetes. Patients without nephropathy had no antihypertensive medication, no signs of cardiovascular disease and a duration of diabetes of at least 13 years. The long disease duration suggests that these patients have a rather low risk of developing nephropathy. The patients with microalbuminuria or macroalbuminuria, in contrast, were required to be treated with an ACE-inhibitor to be representative of Type 1 diabetic patients with increased AER in our country. Since these drugs are suggested to reduce the concentrations of CRP and IL-6 [20, 21], ACE-inhibition could actually have diminished the true differences in inflammatory markers between the patient groups. This further underlines that diabetic nephropathy is a state of low-grade inflammation.

The observation that duration of diabetes was independently related to IL-6 suggests that chronic exposure to glucose and possibly advanced glycation-end-products (AGEs) could stimulate the production of IL-6. Activated monocytes/macrophages are besides adipose and muscle tissue important sites of IL-6 production [7, 9, 22]. In this respect the finding that serum-free pentosidine, the first AGE to be shown in tissue and plasma in diabetes, and the monocyte activation marker neopterin has been shown to correlate with the rate of progression of diabetic nephropathy [23], supports the hypothesis that AGEs might activate monocytes to produce IL-6. Furthermore, given the fact that low-grade inflammation has been linked to markers of endothelial dysfunction (von Willebrand factor and soluble form of vascular cell adhesion molecule-1) in Type 1 diabetic patients with macroalbuminuria [14], the source of IL-6 could also reside in the smooth muscle cells of the vasculature and be the result of chronic exposure to AGEs.

Both increased concentrations of IL-6 and CRP were associated with decreased insulin sensitivity, calculated as an estimated glucose disposal rate (eGDR) using a modified formula of another study [15]. Such

a relationship was further strengthened by the observed positive correlation between IL-6 and triglycerides and the negative correlation between IL-6 and HDL-cholesterol. All three variables (low eGDR, high triglycerides, low HDL-cholesterol) are indicators of insulin resistance, and are connected to each other. Therefore, it is not surprising that only one of the variables, HDL-cholesterol, showed an independent relationship with IL-6 in multivariate regression analysis. It is of note that by using the eGDR we could show that insulin resistance worsened in parallel with the severity of the renal disease in our patients. Thus, low-grade inflammation in Type 1 diabetic patients seems to be connected not only to severity of proteinuria but also to insulin sensitivity. This observation is likely to be true since similar results have been obtained in Type 2 diabetic patients with the metabolic syndrome [11]. Furthermore, the results are also in line with the data from the Pittsburgh Epidemiology of Diabetes Complication Study showing that insulin resistance is associated with overt nephropathy [12]. However, that study did not include measurements of inflammatory markers.

During resting conditions roughly 15 to 35% of IL-6 is derived from adipose tissue, and the majority from omental adipose tissue [6, 7]. Given the strong relationship between IL-6 and WHR, the increased IL-6 concentrations in our study could possibly be due to higher WHR. However, even after adjustment for WHR the IL-6 concentrations were higher. Thus, low-grade inflammation seems to be a key finding of diabetic nephropathy, and could even be the reason for the reduced insulin sensitivity in these patients. Such a view is supported by experimental data showing that IL-6 is capable of inducing insulin resistance in mouse hepatocytes and human hepatocarcinoma cell lines by affecting both proximal and distal events in hepatic insulin receptor signal transduction [24].

Interestingly, statins and ACE-inhibitors inhibit mesangial cell nuclear factor-κB activation and expression of pro-inflammatory cytokines such as IL-6, which suggests that some of the beneficial effects of statins and ACE-inhibitors could at least in part be mediated via pro-inflammatory genes [21].

In conclusion, low-grade inflammatory markers are associated with diabetic nephropathy in Type 1 diabetic patients. The predictive value of low-grade inflammatory markers needs to be assessed.

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