Serum Lipopolysaccharide Activity Is Associated With the Progression of Kidney Disease in Finnish Patients With Type 1 Diabetes

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OBJECTIVE — The aim of the study was to investigate whether serum lipopolysaccharide (LPS) activities are associated with the progression of kidney disease in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — For this prospective study, we chose 477 Finnish patients with type 1 diabetes, who were followed for 6 years. At the baseline visit, 239 patients had a normal albumin excretion rate (normoalbuminuria) and 238 patients had macroalbuminuria. Patients were further divided into nonprogressors and progressors based on their albumin excretion rate at follow-up. Eighty normoalbuminuric patients had developed microalbuminuria, and 79 macroalbuminuric patients had progressed to end-stage renal disease. Serum LPS activity was determined with the Limulus amoebocyte lysate chromogenic end point assay.

RESULTS — Serum LPS activity was significantly higher in the macroalbuminuric group than in the normoalbuminuric group ($P < 0.001$). Notably, normoalbuminuric progressor patients had a significantly higher LPS activity at baseline than normoalbuminuric nonprogressor patients (median 49 [interquartile range 34–87] vs. 39 [29–54] EU/ml; $P = 0.001$). The normoalbuminuric progressor patients exhibited features of the metabolic syndrome with higher triglyceride concentrations and lower estimated glucose disposal rate. A high LPS-to-HDL ratio was associated with the progression of kidney disease in both groups. Insulin resistance ($P < 0.001$) and serum LPS activity ($P = 0.026$) were independent risk factors of disease development, when A1C was removed from the regression analysis.

CONCLUSIONS — High serum LPS activity is associated with the development of diabetic nephropathy in Finnish patients with type 1 diabetes.

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Diabetic nephropathy is one of the leading causes of death in patients with type 1 diabetes worldwide. It has been estimated that approximately one-third of patients with type 1 diabetes develop chronic kidney disease during their lifetime (1). Patients with diabetic nephropathy experience dyslipidemia and macrovascular complications, which in turn increases the risk of cardiovascular death (2,3). Although renal dysfunction is often associated with a long duration of diabetes, poor glycemic control, and genetic susceptibility, the etiology of the complication is largely unknown. Recent studies have demonstrated that patients with type 1 diabetes have elevated levels of proinflammatory markers in the serum (4). It should also be noted that type 1 diabetic patients are more prone to infections than nondiabetic subjects (5).

Bacterial infections induce a systemic inflammatory response, which may cause severe organ damage or even death. Bacterial endotoxins/lipopolysaccharides (LPSs) play a central role in acute and chronic inflammations. LPS triggers the innate immune response characterized by cytokine release and immune system activation. LPS is a unique glycolipid located at the outer membrane of Gram-negative bacteria. These potentially harmful bacteria may colonize in different parts of the body including the oral mucosa and gastrointestinal, genitourinary, and respiratory tracts (6).

Bacterial infections may be life-threatening, especially in patients who require dialysis or who have undergone kidney transplantation. In such patients with end-stage renal disease (ESRD), sepsis increases the risk of mortality >100-fold compared with that for the general population (7). Several studies have shown that periodontitis is relatively common among patients with diabetes and impaired kidney function (8–10). Periodontitis refers to inflammation of the supporting tissue of the teeth and is often caused by Gram-negative bacteria. Bacterial infections are also associated with other forms of kidney disease, e.g., IgA nephropathy, the most common form of glomerulonephritis in the world (11). In addition, bacterial endotoxins have been commonly used to induce acute kidney failure in laboratory animals. Given the close association between periodontitis and kidney disease on one hand and periodontitis and Gram-negative bacteria on the other, it can be hypothesized that LPS triggers not only inflammation in patients with periodontitis but also the process that leads to diabetic nephropathy. Thus, we studied whether serum LPS activity is associated with the development of kidney disease in Finnish patients with type 1 diabetes.

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RESEARCH DESIGN AND METHODS

— Patients with type 1 diabetes were recruited and characterized by the Finnish Diabetic Nephropathy (FinnDiane) Study. The FinnDiane Study is a nationwide multicenter survey, initiated in 1997 to elucidate risk factors for diabetic kidney disease in Finnish patients with type 1 diabetes. The study protocol is in accordance with the Declaration of Helsinki, and it has been approved by the local ethics committee at each study center.

A total of 477 patients participated in this study. Type 1 diabetes was defined as an age at onset <35 years and permanent insulin treatment started within 1 year after the diagnosis. Data on medication and smoking were collected with a standardized questionnaire by the attending physician during the patient's visit. Kidney status was assessed by the albumin excretion rate (AER) in at least two of three overnight or 24-h urine collections: normal albumin excretion (AER <20 μg/min or <30 mg/24 h), microalbuminuria (AER ≥20 < 200 μg/min or ≥30 < 300 mg/24-h), macroalbuminuria (≥200 μg/min or ≥300 mg/24 h), and ESRD (dialysis treatment or kidney transplantation). In addition to the urine collections for classification, AER (24 h) was also measured centrally; this result was used for the statistical analysis. Patients with normal AER (normoalbuminuria) and macroalbuminuria were selected for the study based on their kidney status at the time of reexamination. After the prospective follow-up (5.9 ± 2.1 years on average), all available progressors, with a change from one albuminuria category to a higher level, were matched for sex and smoking with a group of nonprogressors that was twice as large. Altogether 239 normoalbuminuric patients and 238 macroalbuminuric patients were included in this study.

Analysis of fasting blood samples (A1C, serum lipids and lipoproteins, and serum creatinine) were performed as described earlier (12). Serum high-sensitivity C-reactive protein concentrations were measured centrally by photometric immunochemistry at the Helsinki University Central Hospital. Estimated glucose disposal rate (eGDR) was calculated as described earlier (12). The AER was measured centrally by photometric immunochemistry at the Helsinki University Central Hospital. Serum LPS activity was determined with a Limulus amoebocyte lysate chromogenic end point assay from 1:5 diluted samples (Hycult Biotechnology, Uden, the Netherlands). HDL is one of the key factors involved in the detoxification of endotoxins and is known to decline with the severity of diabetic nephropathy. The LPS-to-HDL ratio may reflect the severity of the condition. Serum IgA and IgG class antibodies to the periodontal pathogens *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* were determined from serum samples by a multiserotype enzyme-linked immunosorbent assay (13).

Table 1—*Clinical characteristics of 477 type 1 diabetic patients at baseline*

	Normoalbuminuria	Macroalbuminuria	*P*
Subjects (men/women)	239 (150/89)	238 (149/89)	
Age (years)	32 ± 11	41 ± 10	<0.001
Age at onset (years)	16 ± 9	11 ± 7	<0.001
Duration (years)	17 ± 11	29 ± 8	<0.001
Follow-up (years)	6.2 (4.4–7.2)	6.8 (5.7–7.4)	0.001
BMI (kg/m^2)	24.7 ± 3.3	25.8 ± 4.1	0.001
Waist-to-hip ratio	0.86 ± 0.08	0.90 ± 0.09	<0.001
A1C (%)	8.5 ± 1.6	8.9 ± 1.5	0.004
Diastolic blood pressure (mmHg)	79 ± 9	83 ± 10	<0.001
Systolic blood pressure (mmHg)	128 ± 15	144 ± 20	<0.001
Serum creatinine (μmol/l)	84 (75–92)	132 (102–204)	<0.001
Serum C-reactive protein (mg/l)	1.9 (1.2–3.6)	2.7 (1.6–5.4)	<0.001
Cholesterol (mmol/l)	4.8 ± 1.0	5.4 ± 1.1	<0.001
Triglycerides (mmol/l)	1.07 (0.80–1.44)	1.42 (1.03–2.09)	<0.001
HDL cholesterol (mmol/l)	1.33 ± 0.37	1.17 ± 0.38	<0.001
LDL cholesterol (mmol/l)	2.90 ± 0.85	3.44 ± 0.93	<0.001
ApoAI (g/l)	138 ± 20	140 ± 24	NS
ApoAII (g/l)	35 ± 8	34 ± 7	NS
ApoB (g/l)	88 ± 20	103 ± 23	<0.001
AER (mg/24 h)	10 (7–17)	626 (225–1497)	<0.001
eGDR (mg · kg^{-1} · min^{-1})	7.4 (5.7–9.0)	4.1 (3.1–5.0)	<0.001
Adiponectin (mg/l)	10.3 (7.2–13.7)	15.0 (10.4–22.3)	<0.001
Antihypertension medication (%)	10	92	<0.001
Lipid-lowering medication (%)	4	25	<0.001
Current smoking (%)	32	32	NS

Data are expressed as means ± SD or median (IQR).

Statistical analyses

Data are expressed as means ± SD for normally distributed variables. For nonnormally distributed values, data are expressed as median (interquartile range [IQR]). The levels of significance were tested with ANOVA for normally distributed values, and nonnormally distributed values were analyzed with the Mann-Whitney *U* test. Correlations between clinical variables were analyzed by Pearson's correlation coefficient. Nonnormally distributed variables were log transformed for the analysis. Differences between frequencies were tested with Pearson's χ^2 test. The significance of disease-associated variables was tested with multivariate Cox regression analysis. Statistical analyses were performed with SPSS (version 15.0; SPSS, Chicago, IL). $P < 0.05$ was considered statistically significant.

RESULTS

— The principal aim of the study was to investigate whether serum LPS activity is associated with the progression of kidney disease in 477 patients with type 1 diabetes. At the basal visit, 239 patients had a normal AER and 238 had macroalbuminuria. Clinical characteristics of the patients are shown in Table 1.

At baseline, macroalbuminuric patients had significantly higher LPS activity (53 [IQR 38–74] vs. 42 [31–60] EU/ml, $P < 0.001$) than normoalbuminuric patients. LPS activity did not differ between sexes among all patients. However, in the normoalbuminuric group male patients had slightly higher LPS activity than females (44 [33–63] vs. 38 [29–52] EU/ml, $P = 0.037$).

In the normoalbuminuric group, 80 of 239 patients developed microalbuminuria during the follow-up. Clinical characteristics of the normoalbuminuric

Table 2—*Serum LPS activity and antibody levels to periodontal pathogens*

	NA	MA	NA non	NA prog	MA non	MA prog
n	239	238	159	80	159	79
LPS (EU/ml)	42 (31–60)	53 (38–74)‡	39 (29–54)	49 (34–87)‡	50 (35–75)	58 (44–73)
Aa IgA (EU)	1.07 (0.78–1.73)	1.15 (0.81–1.82)	1.04 (0.78–1.70)	1.17 (0.76–1.83)	1.15 (0.81–1.83)	1.15 (0.78–1.75)
Aa IgG (EU)	2.69 (1.94–3.92)	2.30 (1.61–3.47)†	2.70 (2.05–3.95)	2.65 (1.88–3.78)	2.44 (1.68–3.69)	2.07 (1.47–3.33)
Pg IgA (EU)	0.58 (0.32–0.91)	0.81 (0.37–1.40)†	0.56 (0.32–0.88)	0.58 (0.33–1.19)	0.79 (0.33–1.40)	0.85 (0.42–1.89)
Pg IgG (EU)	5.23 (4.25–6.13)	5.27 (4.26–7.05)	5.52 (4.25–6.29)	4.94 (4.24–5.87)*	5.39 (4.38–6.91)	5.12 (4.11–7.51)

*$P < 0.05$; †$P < 0.01$; ‡$P \leq 0.001$. Aa, *A. actinomecetemcomitans*; MA, microalbuminuria; NA, normoalbuminuria; non, nonprogressors; Pg, *P. gingivalis*; prog, progressors.

nonprogressor and the normoalbuminuric progressor patients are presented in supplementary appendix 1 (available at http://care.diabetesjournals.org/cgi/content/full/dc09-0467/DC1). Groups were matched for sex and smoking. At baseline, there were no significant differences in antihypertensive (normoalbuminuric nonprogressor 8.2% vs. normoalbuminuric progressor 12.7%) or lipid-lowering (3.1 vs. 5.0%) medications between the groups. The normoalbuminuric nonprogressor patients had significantly higher A1C (9.4 ± 1.7 vs. 8.0 ± 1.4%, $P < 0.001$), total cholesterol (5.1 ± 1.1 vs. 4.7 ± 0.9 mmol/l, $P = 0.001$), LDL cholesterol (3.15 ± 0.91 vs. 2.78 ± 0.80 mmol/l, $P = 0.002$), apolipoprotein (apo) B (94 ± 21 vs. 85 ± 19 g/l, $P = 0.001$), and triglyceride concentrations (1.11 [IQR 0.88–1.90] vs. 1.06 [0.79–1.33], $P = 0.04$), as well as AER (16.7 [9.7–37.2] vs. 8.3 [5.9–12.3], $P < 0.001$) than normoalbuminuric nonprogressor patients. Normoalbuminuric progressor patients were also more insulin resistant (eGDR 6.5 [4.9–8.1] vs. 8.4 [6.1–9.3], $P < 0.001$). Of note, the normoalbuminuric progressor patients had higher serum LPS activity than normoalbuminuric nonprogressor patients (49 [34–87] vs. 39 [29–54] EU/ml, $P < 0.001$). However, serum antibody levels to the periodontal pathogen *A. actinomycetemcomitans* were not different between the groups. The normoalbuminuric progressor patients had slightly lower IgG levels to *P. gingivalis* than normoalbuminuric nonprogressor patients (Table 2).

In the normoalbuminuric group, variables significantly associated with progression in univariate analysis (A1C, LDL cholesterol, triglycerides, apoB, eGDR, and LPS) were further tested in a Cox regression model. The A1C (hazard ratio 1.28 [95% CI 1.11–1.49], $P = 0.001$) and eGDR (0.89 [0.80–1.00], $P = 0.044$) were independent risk factors for incident microalbuminuria (Table 3, model 1). When A1C was removed from the model, both eGDR (0.83 [0.75–0.91], $P < 0.001$) and lnLPS (1.85 [1.08–3.18], $P = 0.026$) were associated with disease development (Table 3, model 2). Because progression was defined based on a change in AER, it is natural that AER is a strong predictor of disease progression. Hence, we also included this variable into the regression analyses. As expected, the AER itself was the strongest predictor of disease progression in all models (data not shown).

In the macroalbuminuric group, 79 of 238 patients progressed to ESRD during follow-up. Clinical characteristics of the progressors and nonprogressors are presented in supplementary appendix 2. The groups were matched for sex and smoking. At baseline, macroalbuminuric progressor patients were treated more often with lipid-lowering agents than the macroalbuminuric nonprogressor patients (37 vs. 20%, $P = 0.003$). No differences were seen in the frequency of antihypertensive medication between the groups. The macroalbuminuric progressor patients had higher A1C (9.3 ± 1.8 vs. 8.7 ± 1.3%, $P = 0.016$), systolic blood pressure (149 ± 21 vs. 141 ± 19 mmHg, $P = 0.01$), serum creatinine (275 [IQR 157–364] vs. 117 [94–139] μmol/l; $P < 0.001$), serum triglyceride (1.71 [1.13–2.63] vs. 1.27 [0.98–1.70 mmol/l], $P < 0.001$), and serum adiponectin levels (20.4 [13.4–32.1] vs. 13.4 [9.0–19.6], $P < 0.001$) than macroalbuminuric nonprogressor patients. No difference in insulin sensitivity (eGDR) was found between the groups ($P = 0.118$).

A high LPS-to-HDL ratio was associated with both the development of microalbuminuria and with the progression of kidney disease (normoalbuminuric nonprogressor 30 [IQR 21–43] vs. normoalbuminuric progressor 39 [26–65], $P < 0.001$ and macroalbuminuric nonprogressor 47 [28–67] vs. macroalbuminuric progressor 57 [38–82], $P = 0.017$) (Fig. 1). At baseline, macroalbuminuric patients had higher serum levels of *P. gingivalis* IgA antibodies (0.81 [0.37–1.40] vs. 0.58 [0.32–0.91]; $P < 0.01$) than normoalbuminuric patients. The serum levels of *A. actinomycetemcomitans* IgG antibodies were also slightly lower in the macroalbuminuric patients. In the macroalbuminuric group, neither the serum LPS activity nor IgA/IgG antibody

Table 3—*Cox regression analyses of kidney disease–associated parameters in NA patients*

	Model	Hazard ratio (95% CI)	*P*
A1C (%)	1	1.28 (1.11–1.49)	0.001
eGDR ($mg \cdot kg^{-1} \cdot min^{-1}$)	1	0.89 (0.80–1.00)	0.044
ApoB (g/l)	1	0.99 (0.97–1.02)	0.646
LDL cholesterol (mmol/l)	1	1.31 (0.80–2.16)	0.282
ln(triglycerides) (mmol/l)	1	1.05 (0.49–2.22)	0.905
ln(LPS) (EU/ml)	1	1.51 (0.84–2.71)	0.17
eGDR ($mg \cdot kg^{-1} \cdot min^{-1}$)	2	0.83 (0.75–0.91)	<0.001
ApoB (g/l)	2	1.00 (0.97–1.02)	0.865
LDL cholesterol (mmol/l)	2	1.21 (0.74–1.98)	0.447
ln(triglycerides) (mmol/l)	2	1.10 (0.52–2.34)	0.798
ln(LPS) (EU/ml)	2	1.85 (1.08–3.18)	0.026

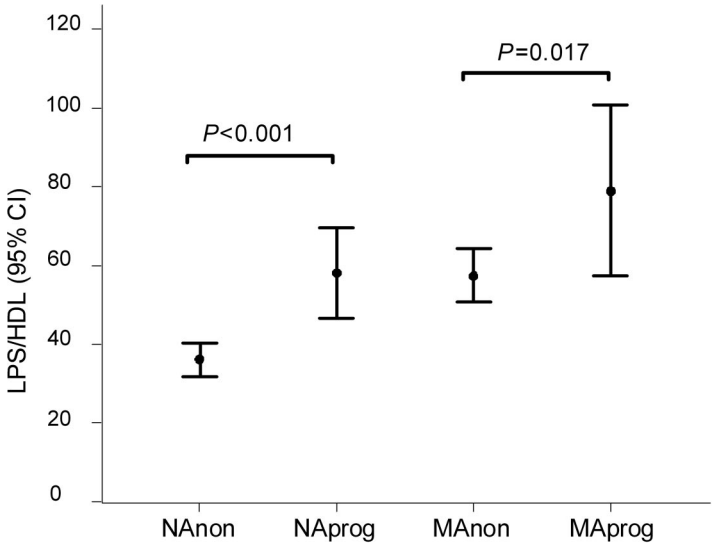

Figure 1—*A high LPS-to-HDL ratio was associated with both the development of microalbuminuria in the normoalbuminuric (NA) group and with the progression of kidney disease in the macroalbuminuria (MA) group. non, nonprogressors; prog, progressors.*

levels to periodontal pathogens were associated with the progression of kidney disease (Table 2).

Serum LPS activity was related to several clinical variables. Among all patients, the best correlations were observed between serum LPS activity and serum lipids: ln(LPS) versus ln(triglycerides) ($r = 0.61$, $P < 0.001$), ln(LPS) versus cholesterol ($r = 0.34$, $P < 0.001$), ln(LPS) versus apoB ($r = 0.34$, $P < 0.001$), and ln(LPS) versus HDL ($r = -0.24$, $P < 0.001$) (supplementary appendix 3). Adjustment of serum LPS activity with HDL concentrations strengthened the correlation with serum triglyceride concentration [ln(LPS-to-HDL ratio) vs. ln(triglycerides), $r = 0.68$, $P < 0.001$].

CONCLUSIONS — Diabetic nephropathy is a devastating health condition that causes morbidity and mortality. It has been estimated that approximately one-third of the patients with type 1 diabetes develop diabetic nephropathy during their lifetime. Although long duration of diabetes and poor glycemic control are associated with the progression of kidney disease, it is evident that other yet-unknown risk factors must exist.

Our living environment is inhabited with viruses and microorganisms, of which some are beneficial and others are detrimental to health. Gram-negative bacteria are considered harmful pathogens, which may colonize in various sites in the human body. In chronic diseases in particular, bacterial infections may cause significant damage to health. Bacterial LPS contributes to acute and chronic inflammations and triggers the innate immune response characterized by cytokine release and immune system activation.

We show here for the first time that high serum LPS activity is associated with the development of microalbuminuria in patients with type 1 diabetes. Although macroalbuminuric patients had a significantly higher serum LPS activity than normoalbuminuric patients, those in the macroalbuminuric group whose disease progressed were no different from those whose disease did not progress. Therefore, other factors seem to play a more important role in the disease progression of macroalbuminuric patients.

LPS has been shown to be associated with various classes of serum lipoproteins. In a normal situation, HDL is thought to be the main factor involved in the detoxification/neutralization of LPS. LPS is released from the cell membranes by HDL and eventually cleared by the liver (6). In certain disease conditions, such as atherosclerosis, periodontitis, and bacterial sepsis, HDL levels can be significantly reduced. This may lead to LPS redistribution toward apoB-containing LDL- and VLDL-rich particles (14–16). In this respect it is understandable that progression of kidney disease has been linked to both dyslipidemia and metabolic syndrome in patients with type 1 diabetes (2,12,17). Normoalbuminuric patients who developed microalbuminuria displayed several features of the metabolic syndrome, including decreased insulin sensitivity, dyslipidemia, and poor glycemic control. Notably, serum LPS activity showed a strong positive correlation with serum triglyceride and apoB concentrations. A concomitant decrease in serum HDL concentrations could indicate that LPS molecules are distributed toward apoB-containing VLDL/LDL particles. We have recently demonstrated that high LPS activity, especially in combination with a low HDL cholesterol concentration increases the risk of incident cardiovascular disease events in the FINRISK study, a survey on risk factors of chronic diseases in the Finnish population (13). Likewise in the present study, a high LPS-to-HDL ratio was associated with the development of kidney disease in normoalbuminuric patients and with progression in macroalbuminuric patients with type 1 diabetes.

Serum LPS activity in itself does not reveal the type or source of infection. Based on previous findings, Gram-negative bacterial infections are relatively common in patients with periodontitis and chronic kidney disease (8–10,18). In the present study, we did not see an association between two common periodontal pathogens (*A. actinomycetemcomitans* and *P. gingivalis*) and the progression of the kidney disease in patients with type 1 diabetes. This does not, however, rule out detrimental effects of periodontal pathogens in patients with diabetic nephropathy. It is also possible that harmful bacterial pathogens may colonize in other parts of the body. Diabetic patients often have respiratory tract infections. A recent study demonstrates that poor glycemic control and a long duration of type 1 diabetes increase the risk of pneumonia-related hospitalization (19). The gastrointestinal tract may also be inhabited by pathogenic bacteria, e.g., *Helicobacter pylori*, which is one of the most common causes of chronic infections in humans (20). Recent studies have also demonstrated that in mice fed a high-fat diet, colonization of Gram-negative bacteria in their gut is increased. Changes in gut microbiota may induce metabolic endotoxemia, which is associated with increased inflammation, obesity, and insulin resistance (21,22). A high-fat diet has also been shown to increase plasma levels of bacterial endotoxins in humans (23). A recent study in mice demonstrated that long-chain fatty acids in particular promote LPS absorption from the gut (24). Based on the above observa-

tions, it seems that both quantity and quality of lipids influence the translocation of LPS from the gastrointestinal tract to the circulation. These results indicate that infections in the gastrointestinal tract may also contribute to the development of bacterial endotoxemia in humans. It is evident that hyperglycemia increases the risk for bacterial infections. In Danish diabetic patients, a 1 mmol/l increase in plasma glucose was associated with a 6–10% increased relative risk of pneumonia, urinary tract infection, and skin infection (25).

In the present study we showed that poor glycemic control and high serum LPS activity are associated with the development of kidney disease in patients with incident microalbuminuria. Further studies are required to elucidate the role of Gram-negative bacterial infections in patients with diabetes. In the future, identification of bacterial pathogens may help us to find more effective treatments for these patients, which may also retard progression of diabetes complications.

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