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 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.

Diabetes Care 32:1689–1693, 2009

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.
Serum LPS activity and diabetic nephropathy

**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 (diabetes 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 (normalalbuminuria) 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 progression of kidney disease in 477 patients — 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.

### 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/m²)          | 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 |
| ApoAl (g/l)          | 138 ± 20         | 140 ± 24         | NS  |
| ApoAl (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 χ² 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 n | MA n | NA prog n | MA prog n |
|-------|------|------|-----------|-----------|
| LPS (EU/ml) | 239  | 238  | 159       | 80        |
| 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) |
| 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) |
| 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) |
| 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)* |

*P < 0.05; †P < 0.01; ‡P ≤ 0.001. Aa, A. actinomycetemcomitans; MA, microalbuminuria; NA, normoalbuminuria; non, nonprogressors; Pg, P. gingivalis; prog, progressors.

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, there were no significant differences in antihypertensive (normoalbuminuric nonprogressor 8.2% vs. normoalbuminuric progressor 8.7% of patients), 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 [26–63], 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 IgA 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

| Parameter | Model | Hazard ratio (95% CI) | P |
|-----------|-------|-----------------------|---|
| A1C (%)   | 1     | 1.28 (1.11–1.49)      | 0.001 |
| eGDR (mg · kg⁻¹ · 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 · kg⁻¹ · 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 |
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 \([\ln(\text{LPS-to-HDL ratio}) \text{ vs. } \ln(\text{triglycerides}) \text{, } r = 0.68, P < 0.001]\).

**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 inflammation 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.

Acknowledgments—The study was supported by the Folkhalsan Research Foundation (to P.-H.G.), Wilhelm and Else Stockmann Foundation (to P.-H.G. and M.L.), and the Academy of Finland (grant 118391 to P.J.P.).

No potential conflicts of interest relevant to this article were reported.

Parts of this study were presented in abstract form at the annual meeting of the European Diabetic Nephropathy Study Group in Frascati, Rome, Italy on 29–30 May 2009.

The skilled technical assistance of our laboratory technicians M. Parkkonen, A.-R. Salonen, A. Sandelin, T. Soppela, and J. Tuomikangas is acknowledged. We also acknowledge the physicians and nurses at each study center.

References

1. Andersen AR, Christiansen JS, Andersen JK, Kreiner S, Deckert T. Diabetic nephropathy in type 1 (insulin-dependent) diabetes: an epidemiological study. Diabetologia 1983; 25:496–501
2. Bonnet F, Cooper ME. Potential influence of lipids in diabetic nephropathy: insights from experimental data and clinical studies. Diabetes Metab 2000; 26:254–264
3. Tuomilehto J, Borch-Johnsen K, Molarus A, Forsen T, Rastenye D, Sarti C, Reunalan A. Incidence of cardiovascular disease in type 1 (insulin-dependent) diabetic subjects with and without diabetic nephropathy in Finland. Diabetologia 1998; 41:784–790
4. Saraheimo M, Teppo A-M, Forsblom C, Fagerudd J, Group P-H, the FinnDiane Study Group. Diabetic nephropathy is associated with low-grade inflammation in type 1 diabetic patients. Diabetologia 2003; 46:1402–1407
5. Muller LMAJ, Gorter KJ, Hak E, Goudzwaald WL, Schellevis FG, Hoepelman AIM, Ruteen GEHM. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. Clin Infect Dis 2003; 41:281–288
6. Wendel M, Paul R, Heller AR. Lipoproteins in inflammation and sepsis. II. Clinical aspects. Intensive Care Med 2007; 33:25–35
7. Sarma MJ, Jaber BL. Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. Kidney Int 2000; 58:1758–1764
8. Mealey BL, Oates TW. Diabetes mellitus and periodontal disease. J Periodontol 2006; 77:1289–1303
9. Kshirsagar AV, Offenbacher S, Moss KL, Barros SP, Beck JD. Antibodies to periodontal organisms are associated with decreased kidney function. Blood Purif 2007; 25:125–132
10. Shultis WA, Weil EJ, Looker HC, Curtis JM, Shlosman M, Genco RJ, Knowler WC, Nelson RG. Effect of periodontitis on overt nephropathy and end-stage renal disease in type 2 diabetes. Diabetes Care 2007; 30:306–311
11. Zeledon JI, McKelvey RL, Servilla KS, Hofinger D, Konstantin KN, Kellie S, Sun Y, Massie LW, Hartshorne MF, Tzamaloukas AH. Glomerulonephritis causing acute renal failure during the course of bacterial infections: histological varieties, potential pathogenic pathways and treatment. Int Urol Nephrol 2008; 40:461–470
12. Thorn LM, Forsblom C, Fagerudd J, Thomas MC, Pettersson-Fernholm K, Saraheimo M, Waden J, Rönnback M, Rosengård-Bärlund M, Björkesten C-G, Taskinen M-R, Group P-H, the FinnDiane Study Group. Metabolic syndrome in type 1 diabetes. Diabetes Care 2005; 28:2019–2024
13. Pussinen PJ, Tuomisto K, Jousilahti P, Haivulinna AS, Sundvall J, Salomaa V. Endotoxemia, immune response to periodontal pathogens and systemic inflammation associated with incident cardiovascular disease events. Arterioscler Thromb Vasc Biol 2007; 27:1433–1439
14. Vreugdenhil ACE, Snook AMP, Veer C, Greve J-WM, Buurman WA. LPS-binding protein circulates in association with ApoB-containing lipoproteins and enhances endotoxin-LDL/VLDL interaction. J Clin Invest 2001; 107:229–234
15. Kallio KA, Buhlin K, Jauhiainen M, Keva R, Tuoomainen AM, Klinge B, Gustafsson A, Pussinen PJ. Lipopolysaccharide associates with pro-atherogenic lipoproteins in periodontitis patients. Innate Immun 2008; 14:247–253
16. Tuoomainen MA, Jauhiainen M, Kovanen PT, Metso M, Paju S, Pussinen PJ. Aggregatibacter actinomycetemcomitans induces MMP-9 expression and pro-atherogenic lipoprotein profile in apoE-deficient mice. Microb Pathog 2008; 44:11–117
17. Tolonen N, Forsblom C, Thorl L, Waden J, Rosengård-Bärlund M, Saraheimo M, Heikila O, Pettersson-Fernholm K, Taskinen M-R, Group P-H, the FinnDiane Study Group. Relationship between lipid profiles and kidney function in patients with type 1 diabetes. Diabetologia 2008; 51:12–20
18. Borawski J, Wilczynska-Borawska M, Skokowska W, Mysliwiec M. The periodontal status of pre-diagnosis chronic kidney disease and maintenance of dialysis patients. Nephrol Dial Transplant 2007; 22:457–464
19. Kornum JB, Thomsen RW, Ris A, Lervang H-H, Schonheyder HC, Sorensen HT. Diabetes, glycemic control, and risk of hospitalization with pneumonia. Diabetes Care 2008; 31:1541–1545
20. Ojetti V, Migneco A, Silveri NG, Ghirlanda G, Gasbarrini G, Gasbarrini A. The role of H. pylori infection in diabetes. Curr Diabetes Rev 2005; 1:343–347
21. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, Waget A, Delmece E, Cousin B, Sulpiace T, Chambon D, Ferrieres J, Tanti J-P, Gibson GR, Castella L, Delzenne NM, Alessi MC, Burcelin R. Metabolic endotoxemia induces obesity and insulin resistance. Diabetes 2007; 56:1761–1772
22. Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, Burcelin R. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet–induced obesity and diabetes in mice. Diabetes 2008; 57:1470–1481
23. Amar J, Burcelin R, Ruidavets JB, Cani PD, Fauvel J, Alessi MC, Chambon D, Ferrieres J. Energy intake is associated with endotoxemia in apparently healthy men. Am J Clin Nutr 2008; 87:1219–1223
24. Ghoshal S, Witta J, Zhong J, de Villiers W, Eckhardt E. Chylomicrons promote intestinal absorption of lipopolysaccharides. J Lipid Res 2009; 50:90–97
25. Benfield T, Jensen JS, Nordestgaard BG. Influence of diabetes and hyperglycemia on infectious disease hospitalisation and outcome. Diabetologia 2007; 50:549–554