Endotoxemia Is Associated with an Increased Risk of Incident Diabetes

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OBJECTIVE—Diabetes is accompanied with a chronic low-grade inflammation, which may in part be mediated by endotoxins derived from Gram-negative bacteria.

RESEARCH DESIGN AND METHODS—We investigated in a population-based cohort whether endotoxemia is associated with clinically incident diabetes. The serum endotoxin activity was measured by limulus assay from the FINRISK97 cohort comprising 7,169 subjects aged 25–74 years and followed up for 10 years.

RESULTS—Both the subjects with prevalent diabetes (n = 537) and those with incident diabetes (n = 462) had higher endotoxin activity than the nondiabetic individuals (P < 0.001). The endotoxin activity was significantly associated with increased risk for incident diabetes with a hazard ratio 1.004 (95% CI 1.001–1.007; P = 0.019) per unit increase resulting in a 52% increased risk (P = 0.013) in the highest quartile compared with the lowest one. The association was independent of diabetes risk factors: serum lipids, γ-glutamyl transferase, C-reactive protein, BMI, and blood glucose. Furthermore, the association of endotoxemia with an increased risk of incident diabetes was independent of the metabolic syndrome as defined either by the National Cholesterol Educational Program-Adult Treatment Panel III or the International Diabetes Federation. Endotoxin activity was linearly related (P < 0.001) to the number of components of the metabolic syndrome.

CONCLUSIONS—Both prevalent and incident diabetes were associated with endotoxemia, which may link metabolic disorders to inflammation. The results suggest that microbes play a role in the pathogenesis of diabetes.

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Endotoxin (lipopolysaccharide [LPS]) is one of the potent virulence factors of Gram-negative bacterial species and has a major role in both acute and chronic infections. This unique glycolipid is located at the outer membrane of the bacteria, but in the circulation system 80–97% of it is bound to the lipoproteins (1). LPS may be cleared from the circulation system mainly by HDLs, which also neutralize its activity effectively.

Circulating endotoxin may derive from bacteria causing either overt acute infections or common chronic conditions. Additionally, endotoxin is believed to translocate from microbiota in the gut. Experiments in animal models kept in germ-free environments have shown that endotoxin is associated with cardiometabolic abnormalities including obesity, insulin resistance, and diabetes (2). Endotoxin activates both adaptive and innate immune systems characterized by a release of antibodies, cytokines, and other inflammatory mediators, which may promote hepatic insulin resistance. Treatment of rats with an antibiotic specifically targeted against Gram-negative bacteria reduces macrophage tumor necrosis factor-α expression and hepatic steatosis (3).

In humans, energy-enriched diets increasing weight gain and insulin resistance associate with absorption of endotoxin from the gastrointestinal track (4–6). This “metabolic endotoxemia” (7) resulting from the increased intestinal permeability/motility may lead to low-grade inflammation. Severity of inflammation may depend on a complex interplay between specific proteins, receptors, and lipoproteins that mediate the endotoxin bioactivity and metabolic fate.

In two small case-control studies, circulating LPS was higher in both type 1 and type 2 diabetic subjects compared with nondiabetic subjects (8,9). High serum LPS activity also associates with the development of diabetic nephropathy in patients with type 1 diabetes (10). It has been hypothesized that bacterial endotoxins can act as triggers, linking inflammation to metabolic syndrome and thereby diabetes (4,11,12). Studies of this association in humans, however, are scarce as a result of the methodological challenges. Therefore, we investigated in a large population-based cohort followed up for 10 years, if endotoxemia is associated with clinically incident diabetes.

RESEARCH DESIGN AND METHODS—The FINRISK97 involved a population-based sample (n = 7,169) of 25–74-year-old participants of the survey, which was conducted in five geographical areas in Finland (13). The survey included a self-administered questionnaire and a clinical examination with weight, height, and blood pressure measurements as well as blood drawing. The study was approved by the Ethics Committee of the National Public Health Institute and conducted according to the Helsinki Declaration. All subjects gave written informed consent.

Laboratory analyses
Before blood sampling, the participants were asked to fast for 4 h and to avoid heavy meals earlier during the day. The median fasting time was 5 (interquartile range 3–7) hours. All laboratory measurements, except serum glucose (14), were carried out at the Disease Risk Unit in the National Institute for Health and Welfare, Helsinki. Lipids and
γ-glutamyltransferase (GGT) measurements were performed from fresh serum samples on clinical chemistry analyzers: Olli-C (Thermo Scientific, Vantaa, Finland) in 1997 and ultrasensitive C-reactive protein (CRP) from frozen samples (−70°C) on Architect c8000 analyzer (Abbott Laboratories, Abbott Park, IL) in 2005. Total cholesterol, triglyceride, and GGT concentrations were determined enzymatically using commercial reagents (Thermo Scientific). HDL cholesterol concentration was measured after precipitation of apolipoprotein B-containing lipoproteins with dextran sulfate and magnesium chloride. CRP was measured using a latex immunoassay (Sentinel diagnostics, Milan, Italy). LDL cholesterol concentrations were calculated according to the Friedewald formula. For standardizing the measurements, the laboratory has taken part in the World Health Organization Lipid Reference Program (Prague) and External Quality Assessment Schemes organized by Labquality (Helsinki, Finland).

Serum endotoxin activities were determined by kinetic Limulus Amebocyte Lysate (LAL) test kit with a chromogenic substrate (HyCult biotechnology b.v., Uden, the Netherlands) on diluted (1:5, vol/vol in endotoxin-free water) samples. The interassay coefficient of variation was 9.2% (n = 75).

**Diabetes at baseline and follow-up**

Baseline diabetes was defined either from 1) the questionnaire as a doctor-diagnosed disease or impaired glucose tolerance, 2) the drug reimbursement records of purchases of hypoglycemic drugs (ATC-class A10) from the Social Insurance Institution of Finland (SII), 3) the SII records of patients entitled to reimbursed diabetes medication, or 4) the National Hospital Discharge Register for hospitalizations with diabetes (E10-E14/ICD-10; 250/ICD-9) as the main or additional diagnosis.

The follow-up of the cohort was until the end of the year 2007. The cases with incident diabetes were identified from 1) the drug reimbursement records of hypoglycemic drugs (ATC-class A10) from SII, 2) the SII records of patients entitled to reimbursed diabetes medication, 3) the National Hospital Discharge Register for hospitalizations with diabetes (ICD-codes as above), and 4) the National Causes-of-Death Register with diabetes (ICD-codes as above) as the underlying, direct or contributing cause of death.

**Definitions of metabolic syndrome**

The nondiabetic subjects were classified into those with and without metabolic syndrome using two definitions: 1) the National Cholesterol Educational Program-Adult Treatment Panel III (ATP III) (15) and 2) the International Diabetes Federation (16). Missing glucose concentrations (n = 941, 14%) were substituted with the mean observed value, 5.12 mmol/L, and used in the calculations of the prevalence of metabolic syndrome.

**Statistics**

The statistical significance of the differences between the subjects with and without diabetes was tested with t test or $\chi^2$ test. The values with skewed distribution, serum triglyceride and CRP concentrations, and endotoxin activities, were log-transformed before comparisons.

| Table 1—Baseline risk factors of the subjects with and without incident diabetes |
|-----------------|-----------------|-----------------|
|                | No diabetes (n = 6,170) | Incident diabetes (n = 462) | P* |
| Age (years)    | 53.2 (11.0)      | 57.3 (9.4)      | <0.001 |
| Education (years) | 10.8 (4.0)      | 9.4 (3.5)      | <0.001 |
| Cholesterol (mmol/L) | 5.7 (1.0)      | 5.9 (1.1)      | <0.001 |
| HDL cholesterol (mmol/L) | 1.40 (0.36) | 1.21 (0.33) | <0.001 |
| Triglycerides (mmol/L)† | Determined | 1.48 (0.95) | 2.19 (1.30) | <0.001 |
| Corrected for fasting time | 1.34 (0.85) | 2.01 (1.18) | <0.001 |
| LDL cholesterol (mmol/L) | 3.61 (0.91) | 3.81 (0.94) | <0.001 |
| G-GT (U/L)† | 36.4 (58.6) | 58.1 (112) | <0.001 |
| CRP (mg/L)† | 2.47 (5.17) | 4.57 (8.02) | <0.001 |
| Glucose (mmol/L)  | 10.3 (1.1) | 10.9 (1.2) | <0.001 |
| Glucose (mg/dL) | 185 (36) | 200 (42) | <0.001 |
| LDL cholesterol (mg/dL) | 130 (40) | 150 (50) | <0.001 |
| HDL cholesterol (mg/dL) | 50 (10) | 55 (11) | <0.001 |
| Total cholesterol (mg/dL) | 130 (40) | 150 (50) | <0.001 |
| Triglycerides (mg/dL) | 150 (50) | 200 (60) | <0.001 |
| Systolic blood pressure (mmHg) | 138 (20) | 148 (20) | <0.001 |
| Diastolic blood pressure (mmHg) | 83 (18) | 88 (15) | <0.001 |

| n (%) | P‡ |
|-------|----|
| Male | 2,962 (50.5) | 261 (60.1) | <0.001 |
| Female | 2,900 (49.5) | 173 (39.9) | 0.374 |
| Smoking | | | |
| Never | 3,321 (53.8) | 234 (50.6) | 0.374 |
| Former | 1,507 (24.4) | 117 (25.3) | 0.374 |
| Current | 1,342 (21.8) | 111 (24.0) | 0.374 |
| Hypertensive | 3,080 (50.0) | 341 (73.8) | <0.001 |
| Family history of diabetes | 1,278 (20.7) | 129 (27.9) | <0.001 |
| Free-time physical inactivity | 1,271 (20.6) | 169 (36.6) | <0.001 |
| Metabolic syndrome (ATP-III) | 1,175 (20.1) | 269 (62.0) | <0.001 |
| Metabolic syndrome (IDF) | 1,455 (24.9) | 287 (66.1) | <0.001 |

*Significance of the differences between the subjects with and without diabetes was tested with t test or $\chi^2$ test. †Mean value of two measurements. ‡Log transformation before comparisons.
**RESULTS**—The FINRISK97 cohort included 537 (7.9%) subjects with prevalent diabetes at baseline. Their mean (SD) serum endotoxin activity was higher than that in nondiabetic subjects, 70.73 (42.62) vs. 62.18 (36.77) EU/mL, \(P < 0.001\), respectively. This produced odds ratios (95% CI) of 1.005 (1.003–1.008, \(P < 0.001\))/unit increase, or 1.043 (0.759–1.433, \(P = 0.79\)), 1.717 (1.290–2.284, \(P < 0.001\)), and 2.232 (1.689–2.949, \(P < 0.001\)) for prevalent diabetes in the 2nd, 3rd, and 4th quartile of serum endotoxin activity compared with the 1st quartile when adjusted for age and sex. These subjects were excluded from further analyses.

Serum endotoxin activity had a significant positive correlation with CRP, cholesterol, and triglyceride concentration, and a negative correlation with HDL cholesterol concentration. It did not correlate with the fasting time. Characteristics of those with \((n = 462)\) and without \((n = 6,170)\) incident diabetes during the median follow-up time of 10.8 years are summarized in Table 1. The risk factors associated with diabetes and cardiovascular diseases accumulated in those with incident diabetes: all differences were highly significant except that of the smoking habit. Also serum endotoxin activity was higher \((P < 0.001)\) in those who developed diabetes compared with those who did not. It was significantly associated with increased risk for diabetes with a hazard ratio (HR) (95% CI) of 1.008 (1.006–1.010, \(P < 0.001\))/unit, when adjusted for age and sex, and 1.004 (1.001–1.007, \(P = 0.019\))/unit, when adjusted for diabetes risk factors. The regression models for endotoxin quartiles are shown in the table (Table 2, Fig. 1). Replacing determined semifasting triglyceride concentrations with calculated fasting triglyceride concentrations or adding glucose concentrations into the model did not notably change the results.

According to ATP III and IDF definitions, 1,444 (23.0%) and 1,742 (27.7%) had metabolic syndrome, which was more prevalent in those with incident diabetes than in those without (Table 1). Serum endotoxin activity increased linearly \((P < 0.001)\) in the categories of positive metabolic syndrome parameters (Fig. 2). In a Cox regression model, it remained significantly associated with an increased risk for incident diabetes, when the presence of metabolic syndrome was introduced as a covariate: the HRs in the highest endotoxin quartiles were 1.650 (95% CI 1.210–2.250, \(P = 0.002\)) (Table 3) and 1.701 (1.249–2.316, \(P = 0.001\)) depending on the metabolic syndrome definition, ATP III or IDF, respectively.

**CONCLUSIONS**—In this large prospective cohort we show that endotoxemia is associated with increased risk for clinically incident diabetes. Importantly, the risk was independent of established diabetes risk factors, i.e., glucose, lipid, and CRP levels, as well as BMI. It was also independent of factors known to affect serum endotoxin activity, i.e., cholesterol, triglyceride, and HDL cholesterol concentrations, as well as smoking (10,18). Interestingly, despite the linear relation between endotoxemia and the

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**Table 2—Associations between risk factors and incident diabetes**

| Model 1 | 95% CI | 95% CI | Significance |
|---------|--------|--------|--------------|
| **Model 1** | | | |
| Age (years) | 1.046 | 1.036 | 1.056 | <0.001 |
| Male | 1.382 | 1.139 | 1.678 | 0.001 |
| Endotoxin quartiles* | 1.000 | | | |
| Q1 | | | | |
| Q2 | 1.073 | 0.768 | 1.498 | 0.681 |
| Q3 | 1.703 | 1.255 | 2.309 | 0.001 |
| Q4 | 2.751 | 2.071 | 3.654 | <0.001 |
| **Model 2** | | | |
| Age (years) | 1.040 | 1.028 | 1.053 | <0.001 |
| Male | 1.194 | 0.938 | 1.520 | 0.150 |
| Education (years) | 0.989 | 0.958 | 1.022 | 0.512 |
| Family history of diabetes | 1.481 | 1.187 | 1.848 | 0.001 |
| Free-time physical inactivity | 1.370 | 1.094 | 1.715 | 0.006 |
| Cholesterol (mmol/L) | 1.098 | 0.983 | 1.226 | 0.097 |
| HDL (mmol/L) | 0.438 | 0.292 | 0.659 | <0.001 |
| Smoking | | | |
| Never | 1.000 | | | |
| Former | 0.994 | 0.768 | 1.288 | 0.965 |
| Current | 1.335 | 1.028 | 1.734 | 0.030 |
| Triglycerides (mmol/L) | 1.090 | 0.994 | 1.194 | 0.066 |
| GGT (U/L) | 1.001 | 1.000 | 1.002 | 0.001 |
| BMI (kg/m²) | 1.149 | 1.128 | 1.171 | <0.001 |
| Hypertensive | 0.869 | 0.708 | 1.067 | 0.179 |
| CRP (mg/L) | 1.017 | 1.005 | 1.030 | 0.007 |
| Endotoxin quartiles* | | | |
| Q1 | 1.000 | | | |
| Q2 | 0.939 | 0.652 | 1.351 | 0.733 |
| Q3 | 1.233 | 0.885 | 1.718 | 0.216 |
| Q4 | 1.518 | 1.090 | 2.114 | 0.013 |

*Endotoxin quartiles: Q1 2.40–38.10 EU/mL, Q2 38.20–54.10 EU/mL, Q3 54.20–77.0 EU/mL, Q4 77.10–475.8 EU/mL. †P for trend.
number of parameters defining the metabolic syndrome, high serum endotoxin activity was still associated with an increased diabetes risk.

Endotoxins can be found in the serum of apparently healthy subjects (19) because in common chronic infections and subclinical conditions the Gram-negative organisms colonize the human respiratory, genitourinary, and especially the gastrointestinal tract, including the oral cavity and the gut. For example, endotoxemia may arise from the most common chronic oral infection, periodontitis, which has an association with incident cardiovascular disease events and type 2 diabetes (18,20). The limulus assay used presently does not reveal the source of the endotoxin activity which varies greatly between bacterial clones. The assay is not specific to any bacterial species, but responds to the initial phase of the complement activation by LPS. Latest evidence suggests, however, that bacterial LPS deriving from the gut microbiota may trigger inflammation and oxidative stress in response to diets (4,6,21–23). High intake of fat or carbohydrates does not promote only endotoxemia, but also production of LPS transporting proteins and receptors (23). This “metabolic endotoxemia” has been shown to initiate or promote obesity, insulin resistance, metabolic syndrome, and finally diabetes (5). Whatever the sources, the current study clearly indicates for the first time an association between endotoxemia and incident diabetes.

The metabolic fate of endotoxins is highly dependent on serum lipoprotein balance, although it is bound by all lipoprotein classes (1). LPS mainly binds to HDL in health but to VLDL in sepsis, thereby increasing its affinity to lipoproteins with lower density during an infection (1,24). Dietary fat is incorporated from the gut into triglyceride-enriched lipoproteins, chylomicrons, whose formation promotes LPS absorption (23,25). This is in accordance with our present observation that endotoxin activity has a strong positive correlation with serum triglyceride concentration, as also reported earlier (10,18). More basic research, however, is needed to define the role of chylomicron-associated LPS in inflammation because the cellular responses also depend on the equilibrium of multiple endotoxin receptors and transfer proteins.

A clear limitation of the current study is the use of semifasting serum samples in the triglyceride, glucose, and endotoxin determinations. The mean relative change in triglyceride concentration per fasting hour is \(-3.7\% \pm 4.2\% \text{ to } -3.1\%\), and the semifasting results can be converted into fasting ones using a specific factor for the fasting time (17). In the current study, both semifasting and the

Figure 1—Cumulative survival without incident diabetes. The cumulative survival in LPS quartiles was analyzed by Cox regression model adjusted for age, sex, education, family diabetes history, free-time physical inactivity, smoking, hypertension, BMI, serum cholesterol, triglyceride, HDL cholesterol, GGT and CRP concentrations. The HR and 95% CI for the quartiles are shown in Table 2.

Figure 2—Serum endotoxin activities according to number of parameters of metabolic syndrome. Metabolic syndrome was defined according to the ATP III criteria (n = 6,273), and mean endotoxin activities with 95% CI are shown. The number of subjects in the categories is 0 = 1,203, 1 = 2,118, 2 = 1,507, 3 = 934, 4 = 459, and 5 = 52. Linear trend of endotoxin activity vs. number of positive metabolic syndrome parameters was tested using ANOVA with linear contrasts and assuming equal variances.
corrected results were applied, and they
did not have an effect on the main result.
Glucose measurements were used in an
additional Cox model as a covariate, and
they did not affect the association between
endotoxemia and incident diabetes, either.
In the absence of fasting blood glucose values,
however, we did not have a chance to
identify the clinically mild cases of incident
diabetes, i.e., those treated with diet only,
which may have caused an underestima-
tion in the results. In addition, it may have
resulted in some misclassifications of sub-
jects with metabolic syndrome. Fasting
time may also affect plasma endotoxin
concentration (23), although in the cur-
rent study no such correlation was found.
The effect, however, is dependent on the
composition of the meal before (23)—
information which was not within the
scope of our study.

The expanding epidemic of diabetes
in industrialized countries requires more
research on its predictors. Our results
indicate for the first time that endotox-
emia is a key player in the pathogenesis of
diabetes and that microbes may have a
central role.

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tory determinations. V.S. designed the study,
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References
1. Kallio KAE, Buhlin K, Jauhiainen M, et al.
Lipopolysaccharide associates with pro-
atherogenic lipoproteins in periodontitis
patients. Innate Immun 2008;14:247–253
2. Turnbaugh PJ, Ley RE, Mahowald MA,
Magrini V, Mardis ER, Gordon JL. An
obesity-associated gut microbiome with
increased capacity for energy harvest.
Nature 2006;444:1027–1031
3. Pappo I, Becovier H, Berry EM, Freund
HR. Polymyxin B reduces cecal flora, TNF
production and hepatic steatosis during
total parenteral nutrition in the rat. J Surg
Res 1991;51:106–112
4. Cani PD, Amar J, Iglesias MA, et al.
Metabolic endotoxemia initiates obesity and
insulin resistance. Diabetes 2007;56:
1761–1772
5. Cani PD, Neyrinck AM, Fava F, et al. Se-
lective increases of bifidobacteria in gut
microflora improve high-fat-diet-induced
diabetes in mice through a mechanism
associated with endotoxemia. Diabetologia
2007;50:2374–2383
6. Amar J, Burcelin R, Ruidavets JB, et al.
Energy intake is associated with endotoxemia
in apparently healthy men. Am J Clin Nutr
2008;87:1219–1223
7. DiBaise JK, Zhang H, Crowell MD,
Krajmalnik-Brown R, Decker GA, Rittmann
BE. Gut microbiota and its possible rela-
tionship with obesity. Mayo Clin Proc
2008;83:460–469
8. Devaraj S, Dasu MR, Park SH, Jalal I.
Increased levels of ligands of Toll-like re-
ceptors 2 and 4 in type 1 diabetes. Diabetologia
2009;52:1665–1668
9. Creely SJ, McTernan PG, Kusminski CM,
et al. Lipopolysaccharide activates an
innate immune system response in human
adipose tissue in obesity and type 2 di-
abetes. Am J Physiol Endocrinol Metab
2007;292:E740–E747
10. Nyman M, Puusinen PJ, Tuomainen AM,
Forsblom C, Groop PH, Lehto M; Finns-
Diante Study Group. Serum lipopolysac-
charide activity is associated with the
progression of kidney disease in finnish
patients with type 1 diabetes. Diabetes
Care 2009;32:1689–1693
11. Erridge C, Attina T, Spickett CM, Webb
DJ. A high-fat meal induces low-grade
endotoxemia: evidence of a novel mech-
anism of postprandial inflammation. Am J
Clin Nutr 2007;86:1286–1292
12. Manco M. Endotoxin as a missed link
among all the metabolic abnormalities in
the metabolic syndrome. Atherosclerosis
2009;206:36; author reply 37
13. Vartiainen E, Laatikainen T, Peltonen M,
et al. Thirty-five-year trends in cardio-
vascular risk factors in Finland. Int J Epi-
demiol 2010;39:504–518
14. Salomaa V, Havulinna A, Saarela O, et al.
Thirty-one novel biomarkers as predictors
for clinically incident diabetes. PLoS ONE
2010;5:e10100
15. Expert Panel on Detection, Evaluation,
and Treatment of High Blood Cholesterol
in Adults. Executive Summary of The
Third Report of The National Cholesterol
Education Program (NCEP) Expert Panel
on Detection, Evaluation, And Treatment
of High Blood Cholesterol In Adults
(Adult Treatment Panel III). JAMA 2001;
285:2486–2497
16. Alberti KG, Eckel RH, Grundy SM, et al.;
International Diabetes Federation Task
Force on Epidemiology and Prevention;
National Heart, Lung, and Blood Institute;
American Heart Association; World Heart
Federation; International Atherosclerosis
Society; International Association for
the Study of Obesity. Harmonizing the
metabolic syndrome: a joint interim
statement of the International Diabetes
Federation Task Force on Epidemiology
and Prevention, National Heart, Lung,
and Blood Institute; American Heart
Association; World Heart Federation;
International Atherosclerosis Society; and
International Association for the Study
of Obesity. Circulation 2009;120:1640–1645
17. Sundvall J, Laatikainen T, Hakala S, Leiviska J, Alfthan G. Systematic error of serum triglyceride measurements during three decades and the effect of fasting on serum triglycerides in population studies. Clin Chim Acta 2008;397:55–59
18. Pussinen PJ, Tuomisto K, Jousilahti P, Havulinna AS, Sundvall J, Salomaa V. Endotoxemia, immune response to periodontal pathogens, and systemic inflammation associate with incident cardiovascular disease events. Arterioscler Thromb Vasc Biol 2007;27:1433–1439
19. Pussinen PJ, Vilkuna-Rautiainen T, Alfthan G, et al. Severe periodontitis enhances macrophage activation via increased serum lipopolysaccharide. Arterioscler Thromb Vasc Biol 2004;24:2174–2180
20. Demmer RT, Jacobs DR Jr, Desvarieux M. Periodontal disease and incident type 2 diabetes: results from the First National Health and Nutrition Examination Survey and its epidemiologic follow-up study. Diabetes Care 2008;31:1373–1379
21. Grunfeld C, Feingold KR. Endotoxin in the gut and chylomicrons: translocation or transportation? J Lipid Res 2009;50:1–2
22. Deopurkar R, Ghanim H, Friedman J, et al. Differential effects of cream, glucose, and orange juice on inflammation, endotoxin, and the expression of Toll-like receptor-4 and suppressor of cytokine signaling-3. Diabetes Care 2010;33:991–997
23. Ghanim H, Sia CL, Upadhyay M, et al. Orange juice neutralizes the proinflammatory effect of a high-fat, high-carbohydrate meal and prevents endotoxin increase and Toll-like receptor expression. Am J Clin Nutr 2010;91:940–949
24. Levine DM, Parker TS, Donnelly TM, Walsh A, Rubin AL. In vivo protection against endotoxin by plasma high density lipoprotein. Proc Natl Acad Sci USA 1993; 90:12040–12044
25. Ghoshal S, Witt J, Zhong J, de Villiers W, Eckhardt E. Chylomicrons promote intestinal absorption of lipopolysaccharides. J Lipid Res 2009;50:90–97