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Anthropometric indices, lipid profile, and lipopolysaccharide-binding protein levels in metabolic endotoxemia: A case-control study in Calabar Metropolis, Nigeria

Ekong Raymond Eworo[1]✉, Edmund Richard Egbe[2], Zibril A. Okhormhe[1], Bassey K. Offor[1], Bassey Ikoedem Uduak[1], Andeshongkwe Dauda[3]

[1]*Department of Medical Lab. Science, College of Medical Sciences, University of Calabar, Calabar, Nigeria*

[2]*World Health Organization Office, Calabar, Nigeria*

[3]*Federal Medical Centre, Makurdi, Benue State, Nigeria*

ABSTRACT

Objectives: To determine the anthropometric indices, lipopolysaccharide-binding proteins (LBP), and lipid profile in patients with metabolic endotoxemia.

Methods: The study comprised of 47 patients with metabolic endotoxemia (the metabolic endotoxemia group) and 43 controls (the control group). Patients in the metabolic endotoxemia group were categorized further into three subgroups including the normal weight group (n=8), the overweight group (n=12) and the obese group (n=27). Height, weight, waist, and hip circumference were measured, and waist-hip ratio (WHR) and body mass index (BMI) were calculated. LBP was determined by ELISA and total cholesterol, triglycerides, high density lipoprotein by the respective enzymatic colorimetric methods. In addition, low density lipoprotein and very low density lipoprotein were determined by Friedewald's formula.

Results: The mean waist circumference (WC), hip circumference (HC), BMI, total cholesterol, low density lipoprotein, and LBP of the metabolic endotoxemia group were significantly higher (P<0.05) than those of the control group. WHR, TG, high density lipoprotein and very low density lipoprotein of the metabolic endotoxemia group were not significantly different (P>0.05) from those of the control group. The mean WC, HC, WHR, and BMI of the obese group with metabolic endotoxemia were significantly higher (P<0.05) than those of the overweight group and the normal weight group with metabolic endotoxemia. Significant positive correlations were obtained between BMI and LBP (r=0.610, P=0.001), total cholesterol and LBP (r=0.385, P=0.007), TG and LBP (r=0.356, P=0.014) in patients with metabolic endotoxemia.

Conclusions: Metabolic endotoxemia arising from increased circulating level of bacterial derive particles consequent to perturbation in the gut microbial community and the elevated serum level of LBP may precede the development of obesity, characterized by dyslipidemia, dysregulation of gut energy harvest, and metabolic energy imbalance.

KEYWORDS: Metabolic endotoxemia; Gut; Microbiota; Lipopolysaccharide-binding protein; Body mass index; Lipid profile; Anthropometric indices

1. Introduction

Metabolic endotoxemia is the alteration in the gut microbiome that results in the continuing release of lipopolysaccharide (LPS) (endotoxin) from Gram negative bacteria cell walls into circulation, then causes low-level inflammation and metabolic diseases. The gut microbiota supports the intestinal epithelium which acts as a continuous barrier to avoid LPS translocation into circulation under normal physiological conditions[1], so alterations in gut microbiome promote the translocation of microbial products across mucosal barriers. Inappropriate dietary habits like low consumption of fruits and vegetables, high intake of fats, insulinogenic foods, proteotoxins

✉To whom correspondence may be addressed. E-mail: raymondeworo@yahoo.com

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(anaphylatoxins), gluten, and zein, may adversely alter the gut microbial arrangement thereby increasing intestinal permeability and predisposing the individuals to dysfunctional microbiota and dysbiosis[2,3,4]. This can lead to increased production and leakage of endotoxins (which are basically immunogenic) into the circulation and resulting in inflammation[5,6].

The association of gut microbiota dependent mechanism and intestinal permeability is not fully clarified, but metabolic endotoxemia can dysregulate the inflammation and enhance fat absorption, which may elicit body weight gain and obesity[7].

Obesity is a multidimensional disorder that results from an imbalance between energy intake and expenditure[8]. This multifactorial disorder leads to numerous metabolic complications including hypertension, hypercholesterolemia, atherosclerosis, insulin resistance, type II diabetes and fatty liver. Obesity and diabetes are among the metabolic diseases associated with insulin resistance and a low-grade inflammation initiated by bacterial LPS.

Obesity is the metabolic energy imbalance resulting from a complex interaction between genetic and environmental factors, including diet, physical activity. A high-fat diet has negative effect on insulin action and the lipotoxic effect, which disrupts body weight controlling mechanisms[9]. The emerging lifestyle of increased western diets and fast food consumption has great impacts on the gut microbial community of an individual that has been constituted many years back with local diets.

The nutritional value of food may be influenced in part by the assembly and activities of a consumer's gut microbial community ecosystem, and food, in turn, shapes the microbiota and its enormous assortment of the 'gut microbiome'10]. An understanding of the complex relationships among diet, immune system, nutritional status, microbial bionetwork in humans at different points in life, diverse cultural, and socioeconomic backgrounds will explain how dietary habits and lifestyles can result in gut dysbiosis and the associated metabolic aftermaths[11].

The evolving change in lifestyle with increasing dependence on the consumption of fast foods may have an adverse effect on the gut microbial composition of the consumers. This study aims to determine whether metabolic endotoxemia leads to obesity or obesity results in alteration of the gut microbial ecology.

Body mass index (BMI) is a widely used tool to evaluate physical parameters of height and weight as the ratio of weight (kg) to the square of height in meters. BMI=weight (kg)/height (m^2). Overweight and metabolic endotoxemia have been reported as major public health problems across all ages and populations in Western countries[12,13].

The World Health Organization has established recommendations on the reference values (cut-off points), to classify the weight condition of a person (normal, overweight and obese). Although some differences in the values of normal ranges for different populations have been recognized by the World Health Organization, this agency recommends a universal classification of BMI values through a set of cut-off points to classify the weight conditions: <18.50 kg/m^2 underweight; Normal weight 18.50-24.99 kg/m^2, Overweight 25.00-29.90 kg/m^2 and obese ⩾30.00 kg/m2[14]. These universal cut-off points for BMI are based on the probability to acquire obesity and of mortality[15], but it is known that metabolic endotoxemia is just one likely consequence out of a number of disorders associated with obesity, with increased prevalence globally among the adult population in recent times[16,17].

BMI cut-off points are used clinically to identify high-risk individuals for screening; identify individuals for absolute risk assessment; determine the type and intensity of treatment; monitor individuals for effects of treatment over time; determine institutional policies on individuals[18]. Increased BMI is associated with dyslipidemia and insulin resistance during the circulation of lipopolysaccharide, which may lead to increased circulating free fatty acids concentrations[19].

Lipopolysaccharides (endotoxins) make up 80% of Gram negative bacteria cell wall. Their structure contains a polysaccharide part, the O-specific chain (called antigen O) and a lipid part, the lipid A, an extremely conserved section that represents the toxic part of LPS. Once LPS reaches the bloodstream, they are taken up by a transport protein, called the lipopolysaccharide-binding protein (LBP, 60 kDa), secreted mostly by the liver but also by the white adipose tissue[20].

LPS binding protein (LBP) catalyzes the monomerization of LPS and its transfer to CD14 and lipoproteins. In this way, LBP plays a role in the activation pathway of LPS, *i.e.*, activation of monocytes by LPS leading to release of inflammatory mediators and in the neutralization of LPS, *i.e.*, the uptake of LPS by lipoprotein and subsequent clearing. That is, LPS is transferred to the CD14 and TLR4[21]. During metabolic endotoxemia, LBP can transfer LPS to plasma lipoproteins [high density lipoprotein (HDL), chylomicrons, which allows the neutralization of endotoxin activity[22,23]. This neutralization results from the link of lipoproteins to their receptors in the liver, inducing LPS clearance[24].

Systemic exposure to bacterial endotoxin can be determined by measuring plasma LBP. LBP is an acute-phase protein that binds to LPS to induce immune responses. LBP is a type I acute-phase protein that is constitutively produced by the liver and rapidly upregulated during the acute phase response. LBP plays a central role in the response to LPS.

2. Materials and methods

2.1. Study design

This study was a case-control study conducted in Calabar metropolis, Cross River State, between February 2018 and November 2018, to determine whether metabolic endotoxemia is a risk to the development of obesity. Ethical approval was obtained from the Research Ethics Committee of the Cross River State Ministry of Health (approval number lost) and informed consents were obtained from the participants of the study. A total of ninety (90) participants, comprising of (47) subjects with metabolic endotoxemia (the ME group) and (43) normal subjects who served as the control group were recruited into

the study. The ME group was categorized into the normal weight group (BMI: 18.50-24.99 kg/m^2, n=8), the overweight group (BMI: 25.00-29.99 kg/m^2, n=12) and the obese group (BMI: 30.00 kg/m^2, n=27).

2.2. Inclusion and exclusion criteria

Inclusion criteria: This study included apparently healthy obese adults who were between the ages of 23-60 years and gave consent, and were fasting, not on special diets or medication.

Exclusion criteria: Those on special diet, medication, not fasting, and those who smoked tobacco and did not give consent.

2.3. Chemicals and reagents

Lipopolysaccharide-binding protein ELISA kit was obtained from Biotain Hong Kong Company, Fujian, China. Microelisa stripplates, horse raddish peroxidase conjugate reagent, chromogenic solutions A and B, wash solution, sample diluent and stop solution provided in the ELISA kit were used according to the manufacturers instructions. Total cholesterol, triglyceride, and high density lipoprotein cholesterol were determined by enzymatic colorimetric methods, using a reagent kit obtained from Randox INC. Company, USA.

2.4. Samples collection

A standard venipuncture method was used to obtain 5 mL of blood from all the participants in the morning after an overnight fast. The blood was stored into plain containers, and allowed to clot and centrifuged at 3 000 rpm for 5 min. Then the serum was separated into plain serum containers, labeled appropriately and stored at 40 ℃. Participants' height and weight were measured and BMI was calculated. Waist circumference and hip circumference were measured and waist-hip ratios (WHR) were calculated. LBP was determined using the ELISA kit (Biotain Hong Kong Company, Fujian, China). Total cholesterol (TC) and triglycerides (TG), were determined by the respective enzymatic methods. HDL-cholesterol was determined by cholesterol enzyme method using the supernatant obtained by centrifugation, when plasma was treated with polyethylene glycol reagent, to precipitate all beta-lipoproteins, very low density lipoprotein (VLDL), and low density lipoprotein (LDL). Very low density lipoprotein (VLDL) cholesterol concentration was calculated using the formula: VLDL= triglyceride/2.2. Low density lipoprotein (LDL) cholesterol concentration was calculated using the formula: LDL= total cholesterol – (HDL + VLDL).

2.5. Statistical analysis

The data generated were analyzed using SPSS version 23.0 statistical package, differences between groups were analyzed using Student's t-test, variations among groups were analyzed by ANOVA and the relationship between parameters using Pearson's correlation. The significance level of the tests was set at α=0.05.

3. Results

As shown in Table 1, the mean waist circumference (WC), hip circumference (HC), BMI, TC, LDL, and LBP of the ME group were significantly higher (P<0.05) than those of the control group. The mean WHR, TG, HDL, VLDL and age of the ME group were not significantly different (P>0.05) from those of the control group. As shown in Table 2, the mean WC, HC, WHR and BMI of the obese group were significantly higher (P<0.05) compared to those of the overweight group and the normal weight. The mean age, TC, TG, HDL, VLDL, LDL, and LBP did not vary significantly (P>0.05) among the groups.

Significant positive correlations (r=0.610, P=0.001) were observed between BMI and LBP, TC and LBP (r=0.385, P=0.007), as well as TG and LBP (r=0.356, P=0.014) in subjects with metabolic endotoxemia (Figure 1-3).

Table 1. Comparison of age, anthropometric indices, and biochemical parameters between the metabolic endotoxemia group and the control group.

Parameters	Control group[a] (n=43)	ME group[b] (n=47)	t-value	P-value
Age (years)	38.95±7.78	38.87±6.38	0.054	0.957
WC (cm)	36.60±4.15	38.91±4.92	2.395	0.019
HC (cm)	39.16±5.78	42.28±4.37	2.898	0.005
WHR (cm)	0.95±0.09	0.92±0.07	1.662	0.100
BMI (kg/m^2)	26.75±4.28	30.37±5.59	3.427	0.001
TC (mmol/L)	4.38±1.20	5.07±1.43	2.451	0.016
TG (mmol/L)	1.39±0.46	1.20±0.65	1.253	0.213
HDL (mmol/L)	1.39±0.46	1.38±0.53	0.088	0.930
VLDL (mmol/L)	0.67±0.40	0.55±0.29	1.361	0.177
LDL (mmol/L)	2.28±1.18	3.04±1.64	2.528	0.013
LBP (mmol/L)	19.58±5.09	85.13±56.03	7.630	0.001

ME: Metabolic endotoxemia; WC: Waist circumference; HC: Hip circumference; WHR: Waist-hip ratio; BMI: Body mass index; TC: Total cholesterol; TG: Triglycerides; HDL:High density lipoprotein; VLDL: Very low density lipoprotein; LDL: Low density lipoprotein; LBP: Lipopolysaccharide-binding protein; [a]: LBP=2-30 mmol/L; [b]: LBP >30 mmol/L.

Table 2. Comparison of the parameters in the metabolic endotoxemia group.

Parameters	Normal weight group (n=8)	Overweight group (n=12)	Obese group (n=27)	F	P-value
Age (years)	36.75±4.89	37.08±6.37	40.29±6.60	1.630	0.208
WC (cm)	32.13±2.42	37.75±3.59	41.44±3.79	22.003	0.001
HC (cm)	37.13±2.53	41.67±2.50	44.07±4.21	11.664	0.001
WHR (cm)	0.87±0.08	0.90±0.06	0.94±0.07	3.996	0.025
BMI (kg/m^2)	22.21±1.63	28.30±0.84	33.71±4.49	35.318	0.001
TC (mmol/L)	4.97±1.19	4.92±1.37	5.17±1.56	0.143	0.867
TG (mmol/L)	0.98±0.63	1.23±0.82	1.25±0.57	0.552	0.580
HDL (mmol/L)	1.25±0.56	1.49±0.57	1.37±0.52	0.160	0.581
VLDL (mmol/L)	0.44±0.29	0.56±0.37	0.58±0.25	0.665	0.519
LDL (mmol/L)	3.43±1.57	3.48±1.47	2.73±1.72	1.118	0.336
LBP (mmol/L)	64.50±17.53	67.92±43.71	98.89+64.79	2.007	0.146

ME: Metabolic endotoxemia; WC: Waist circumference; HC: Hip circumference; WHR: Waist-hip ratio; BMI: Body mass index; TC: Total cholesterol; TG: Triglycerides; HDL: High density lipoprotein; VLDL: Very low density lipoprotein; LDL: Low density lipoprotein; LBP: Lipopolysaccharide-binding protein.

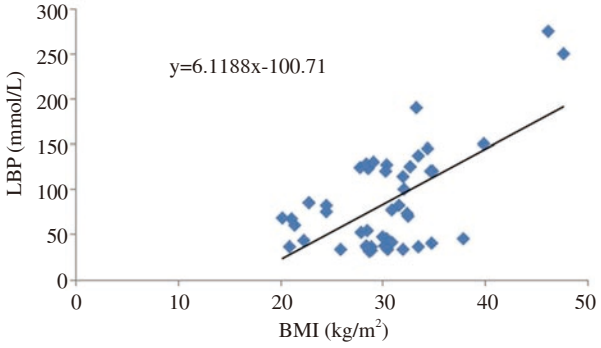

Figure 1. Correlation of BMI against LBP in the metabolic endotoxemia group. BMI: Body mass index; LBP: Lipopolysaccharide binding protein.

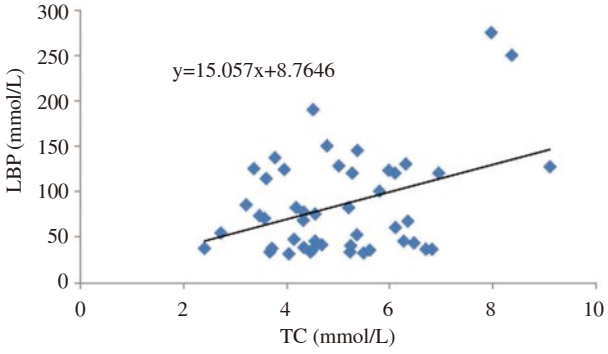

Figure 2. Correlation of TC against LBP in the metabolic endotoxemnia group. TC: Total cholesterol; LBP: Lipopolysaccharide-binding protein.

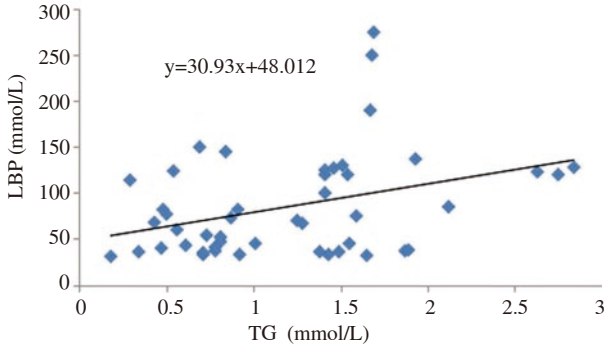

Figure 3. Correlation of TG against LBP in the metabolic endotoxemia group. TG: Triglycerides; LBP: Lipopolysaccharide binding protein.

4. Discussion

This study determined LBP, BMI, and lipid profile in subjects with metabolic endotoxemia in Calabar metropolis. The significantly high levels of WC, HC, and BMI observed in the ME group may be due to the influence of high circulating levels of LBP on lipid absorption and anthropometric indices. LBP is an acute-phase protein that is produced majorly in the liver; it is the main marker of underlying low-grade systemic inflammation due to presence of endotoxins (LPS) from the gut microbial-derived particles, which ultimately leads to increased lipid absorption, amplified gut energy harvest and the development of obesity and metabolic derangements. This finding is in line with that reported by Gonzalez-Quintela *et al.*, and Kim *et al.*, who demonstrated an association between a high level of LBP with metabolic derangement and obesity[25,26]. Awoyemi *et al.*, had equally reported a significantly higher level of LBP in patients with a WC typical of metabolic syndrome[27]. The significantly high BMI of the ME group compared with the control group may be due to the accumulation of lipids and obesity from enhanced lipid absorption. A similar finding had been reported by Citronberg *et al.*, and Nagpal *et al.*, who demonstrated the link between increased levels of bacteria associated with obesity and inflammation, and increased levels of circulating LBP[28,29]. Kong *et al.*, also observed an increased level of LBP with BMI in adult patients with obstructive sleep apnea[30].

The significantly high levels of TC, LDL, and LBP in the ME group may be attributed to the augmented cholesterol absorption with endotoxins derived from changes in the gut microbial community and the corresponding increase in LBP production from the liver for their transport to CD14 and lipoproteins for clearance.

The significantly higher mean BMI, HC and WC in the obese group compared to the overweight group and the normal weight group may suggest an association between anthropometric indices and ME. This observation is in accordance with those reported by Kheirandish-Gozal *et al.*, and Aravindhan *et al.*[31,32]. The association between high LBP with high TG, TC,

and LDL level may suggest that LBP elevation is triggered by concurrent absorption of LPS and TG, TC and LDL from the gut with dysbiosis in its microbial composition. This finding is in accordance with the one reported by Mariann *et al.*, who demonstrated high serum LPS activity with elevated serum triglycerides and low HDL cholesterol concentrations in diabetic patients[33].

The significantly positive correlation between BMI and LBP may suggest increased adiposity with enhanced LBP absorption. This observation agrees with the work done by Gubern *et al.*, who measured anthropometric indices in metabolic endotoxemia[34].

Triglyceride is correlated positively with LBP with metabolic endotoxemia. This may suggest that a high level of triglyceride absorption together with lipopolysaccharide in the bloodstream will trigger the release of a high level of LBP. This agrees with the work by Cardona *et al.*, who reported enhanced LPS transport after a fat diet overload; since the patients with higher increases in triglyceride levels over baseline displayed higher levels of chylomicron[35].

It was concluded from the study that metabolic endotoxemia due to dysbiosis in gut microbiome precedes the development of obesity, characterized by dyslipidemia, dysregulation of gut energy harvest and metabolic energy imbalance. Gut microbiota dependent mechanism for the development of metabolic diseases can be controlled by lowering plasma LPS concentration.

Conflict of interest statement

The authors report no conflict of interest.

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Authors' contribution

E.R.E., E.R.E., Z.A.O., B.K.O., D.A.: Conceived and designed the experiments; performed the experiments; contributed reagents, materials, data acquisition, and data analysis. E.R.E*., B.I.U., E.R.E., Z.A.O., and B.K.O: Analyzed and interpreted the data; contributed reagents, materials and wrote the paper.

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