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Bacterial endotoxin, *Staphylococcus aureus* nasal carriage and obesity among type two diabetes mellitus patients

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Abstract

This study aims to investigate the relationship among the concentrations of circulating LPS, high Body Mass Index (BMI) values and T2DM; furthermore, to investigate an association among NCSA, BMI values and T2DM in comparison with control individuals. T2DM patients and control subjects, who were selected from outpatient of "The Specialist Center for Diseases of Endocrine and Diabetes" in Baghdad. The subjects were divided into four groups: Group I included 21 obese T2DM patients; Group II included 20 lean T2DM patients; Group III included 20 obese as a control group and Group IV included 21 lean as a control group. The study included 82 study populations, male and female, with ages ranged from 35 to 75 years. The patients were not on any kind of anti-type two diabetic treatments and they were resistant to the insulin therapy. The results revealed that the higher circulating levels of LPS were found in the T2DM patient groups in comparison with the control groups with a highly significant difference ($P < 0.01$). The mean of the LPS concentrations for T2DM patient groups were 1.076 ± 0.13 (EU/ml), whereas the mean of the LPS concentrations for controls were 0.611 ± 0.06 (EU/ml). The results of the statistical analysis showed the presence of a significant difference ($P < 0.05$) for the nasal carriage *Staphylococcus aureus* with total isolates of 38, of them 23 *S. aureus* (56.10%) were isolated from the groups of patients with T2DM and 15 *S. aureus* isolates (36.58%) were isolated from the control groups. Collectively, this new finding suggests that high levels of serum LPS and chronic exposure to *S. aureus* superantigens dysregulates the inflammatory tone and triggers body weight gain and T2DM development.

Keywords: Lipopolysaccharide; Body Mass Index; Type two diabetes mellitus; *Staphylococcus aureus* nasal carriage; Obesity

1. Introduction

Staphylococcus aureus is a Gram-positive coccus, facultative anaerobic and an opportunistic pathogen that colonizes the skin and the mucosal surface of the human host [1,2]. In contrast, endotoxin [Lipopolysaccharide (LPS)] is one of the powerful virulence factors of Gram-negative bacterial species and has an important role in both acute and chronic infections [3]. LPS is a glycolipid molecule present in the outer membrane of Gram-negative bacterial cell wall, which is composed of a hydrophobic region, lipid A, through which it is inserted into the outer leaflet of the outer membrane of the bacterial cell wall, a core oligosaccharide and a distal oligosaccharide [4,5]. Obese individuals with insulin resistance were characterized by changes in composition

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of gut microbiota, particularly an elevated Firmicutes/Bacteroidetes ratio compared with the healthy lean individuals [6,7]. It was thought that these changes were associated with the increase in the amount of energy extracted from the diet, which in turn encourages the development of obesity [6,8,9]. Previous studies suggested that the bacterial products (LPS) are translocated across the gut, either in association with a high-fat diet or because of gut damage due to the changing in the gut microbiota may participate in the control of the development of metabolic diseases associated with obesity [10−12]. These bacterial products can result in inducing the inflammation, so-called 'Metabolic endotoxemia' (ME) [10,11]. ME may lead to chronic low-grade systemic inflammation in several tissues (adipose tissue, liver and muscle), that could activate a Toll-like receptor (TLR) pathway to induce metabolic dysfunction and predisposes to insulin resistance and diabetes [13,14]. Furthermore, the rates of *S. aureus* nasal colonization and infection are also significantly increased in overweight and obese individuals in comparison with lean subjects [15,16]. It is possible that the *S. aureus* existence in the obese individuals has an influence on the development of T2DM [16]. Hence, considering a major human pathogen that causes a variety of infections in both healthy and immunocompromised individuals and this can lead to numerous complications and in some cases to death [17]. Carriage of *S. aureus* in the nose appears to play a key role in the epidemiology and pathogenesis of infection. Earlier studies recorded the mean carriage rate in the general population as 37.2% and in non-insulin dependent diabetic patients as 29.0% [18]. In other studies, which were conducted by Kutlu et al. [19] was found that the *S. aureus* colonization in DM patients was 41.9%. Persistent nasal colonization of *S. aureus* (NCSA) ranged from 20 to 30% of healthy adults indicates a major risk factor for infections with the bacterium [16]. This should be considered seriously among bacterium producers of several virulence factors and superantigens (SAgs) that stimulate cytokine production [20]. Long time exposure to SAgs possibly happened through recurrent *S. aureus* colonization and infection in obese individuals, may lead to an inflammation, impaired glucose metabolism and the development of T2DM in the overweight and obese [21]. It is known that there is a strong evidence between T2DM and genetics, but obesity contributes 55% of T2DM cases [22,16]. Therefore; the aim of this study was to: investigate the relationship among NCSA, obesity and T2DM, furthermore to investigate the association among high levels of circulating LPS, obesity and T2DM. For the best general knowledge, this is the first local investigation, presenting the correlation between diabetic patients, obesity, chronic body presence of *S. aureus* with its superantigen and serum LPS.

2. Materials and methods

2.1. Subjects

The clinical (nasal and serum) samples were collected from each T2DM patient and control groups (n = 82) with the age range from 35 to 75 years. The samples were collected from outpatients of "The Specialist Center for Diseases of Endocrine and Diabetes" in Baghdad during the period of 16th November 2015 to 9th February 2016.

2.2. Diagnosis of diabetes

Diagnosis of diabetes was based on the criteria indicated by the American Diabetes Association (ADA) (2012) [23] fasting blood sugar level (FBS) ≥126 mg/dl. Subjects in healthy control groups have FBS below 110 mg/dl.

2.3. Measurement of Body Mass Index (BMI)

The BMI is defined as the individual's weight divided by the square of their height. In accordance with the World Health Organization (WHO) (2013) [24] the BMI ≥ 30.0 kg/m^2 considered as obese.

2.4. Serum sample preparation

Serum sample preparation was carried out in accordance with LPS ELISA Kit manufacture's (HCUSABIO) instructions at the following:

The blood samples were collected under aseptic conditions by using a sterile tube and allowed to clot for 1 h at room temperature or overnight at 4 °C before centrifugation for 15 min at 2200−2500 RPM. Thereafter, serum was transferred to a fresh polypropylene tube and stored at −20 °C until use.

2.5. Isolation and identification of nasal carriage S. aureus

Nasal samples were collected from each subject under aseptic conditions using a sterile nasal swab. The nasal swab was inserted into the nose at approximately 1-inch and rotated three times clockwise and three times counter clockwise [17]. The swabs were immediately cultured onto mannitol salt agar and incubated at 37 °C for 18−24 h. Biochemical identification was

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