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Review

Metabolic endotoxemia and diabetes mellitus: A systematic review

Júnia Maria Geraldo Gomes[a,*], *Jorge de Assis Costa*[b], *Rita de Cássia Gonçalves Alfenas*[b]

[a] *Instituto Federal do Sudeste de Minas Gerais, Campus Barbacena, Rua Monsenhor José Augusto, 204, Bairro São José, Barbacena, Minas Gerais, Brazil. CEP 36205-018*

[b] *Nutrition and Health Department, Federal University of Viçosa (Universidade Federal de Viçosa), Avenida PH Rolfs, s/n, Viçosa, Minas Gerais, Brazil. CEP 36570-000*

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ABSTRACT

In this systematic review we analyzed studies that assessed serum concentrations of lipopolysaccharide (LPS) and/or lipopolysacharide-binding protein (LBP) in diabetic patients compared with healthy people. Articles were selected using PubMed and Scopus. Search terms used were endotoxemia, endotoxins, LPS, LBP, diabetes mellitus (DM), type 1 (T1DM), type 2 (T2DM), insulin resistance, humans, epidemiologic studies, population-based, survey, representative, cross-sectional, case–control studies, observational, and clinical trials. Two authors independently extracted articles using predefined data fields, including study quality indicators. There was a great variability in the estimates of metabolic endotoxemia among the studies. Most of the studies observed higher LPS or LBP concentrations in diabetic subjects than in healthy controls. T1DM and T2DM subjects presented higher mean fasting LPS of 235.7% and 66.4% compared with non-diabetic subjects, respectively. Advanced complications (e.g. macroalbuminuria) and disease onset exacerbate endotoxemia. Antidiabetic medications decrease fasting LPS concentrations. Among these medications, rosiglitazone and insulin present higher and lower effects, respectively, compared with other treatments. T1DM and T2DM seem to increase metabolic endotoxemia. However, some confounders such as diet, age, medication, smoking and obesity influence both diabetes and endotoxemia manifestation. A better understanding of the interaction of these factors is still needed.

1. Introduction

Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. Type 1 diabetes (T1DM) results from beta-cell destruction, usually leading to absolute insulin deficiency [1]. Type 2 diabetes (T2DM) occurs due to the progressive loss of insulin secretion and/or insulin action, usually with a contribution from insulin resistance (IR) [1]. The prevalence and incidence of DM have increased during recent decades, especially in Western countries [1]. Short and long-term complications due to uncontrolled glycemia lead to high human, social, and economic burdens [1]. Therefore, understanding the features involved in the

* *Corresponding author at:* Nutritionl and Health Department, Federal University of Viçosa (Universidade Federal de Viçosa), Minas Gerais, Avenida PH Rolfs, s/n, CEP 36570-000, Viçosa, Minas Gerais, Brazil. Fax: +55 31 38992541.
E-mail address: junianut@yahoo.com.br (J.M.G. Gomes).

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pathophysiology of DM is of considerable value to treat DM and prevent its progression.

Increased intestinal permeability may contribute to low-grade inflammation, leading to insulin resistance, and DM [2]. The intestinal epithelial monolayer is an important barrier between the organism and the external environment [3]. A healthy intestinal barrier allows the passage of water, nutrients and bioactive compounds, and avoids the passage of harmful substances such as microbial and dietary antigens [3]. Evidence, largely from animal studies, indicates that DM favors endotoxin (especially lipopolysaccharide (LPS)) translocation across the intestinal barrier, leading to its mild increase in concentration in the bloodstream [4]. LPS is the major component of the outer membrane of the Gram-negative bacteria. This endotoxin is composed of three modules: a highly variable O-antigen constituted of repeating oligosaccharide units, a core oligosaccharide and lipid A [5]. Lipid A component is responsible for much of LPS toxicity. Toll-like receptors (TLR) of the innate immune system recognize lipid A and then trigger immune and inflammatory responses [5].

Integrity breakdown and increased intestinal permeability favor LPS translocation from the intestinal lumen to the bloodstream, causing metabolic endotoxemia [2,4]. LPS has a short half-life, so LPS-binding protein (LBP) has been used as a metabolic endotoxemia marker [6,7]. LBP is an acute-phase protein synthesized in the liver [6,7]. The binding of LBP–LPS complex to cluster of differentiation 14 (CD14), which is mainly expressed by macrophages and neutrophils, mediates signal transduction, including nuclear factor kappa B (NF-κ B) activation via TLR4, leading to the activation of innate and adaptive inflammatory responses [6,7]. Considering that LBP represents the innate immune response triggered by LPS, assessing LBP concentrations is an indirect way to evaluate active LPS. Consequently, LBP is a good marker of metabolic endotoxemia [6,7].

Animal and human studies indicate LPS as an antigen that activates the immune system, playing an important role in the pathogenesis of metabolic chronic diseases related to subclinical inflammation, such as obesity, IR, T2DM, and dyslipidemia [2,8,9]. However, the influence of LPS concentrations on glucose homeostasis in humans is not well understood. In this context, new links between endotoxemia and DM should be highlighted to better treat and prevent DM complications. Therefore, in this systematic review we examined the studies that assessed serum concentrations of LPS and/or LBP in diabetic patients compared with healthy controls. We also discuss existing evidence for the proposal of possible mechanisms linking metabolic endotoxemia and DM.

2. Methods

2.1. Protocol and Registration

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10] (S1 Appendix-Checklist) and was registered in PROSPERO (registration number: CRD42015020532).

2.2. Literature Search

Two authors (JMGG and JAC) independently searched for original articles on endotoxemia status in diabetes mellitus type 1 (DM1), DM2 or impaired glucose tolerant (IGT) patients in the following electronic databases: PubMed (www.pubmed.com) and Scopus (www.scopus.com). Keywords were chosen from the Medical Subject Headings terms using the following search strategy: (Endotoxemia OR Endotoxins OR Lipopolysaccharides or Lipopolysaccharide-binding protein) AND (Diabetes Mellitus, Type 2 OR Diabetes Mellitus, Type 1 OR Insulin Resistance) AND humans AND (epidemiologic studies OR population-based OR survey OR representative OR cross-sectional OR case–control studies OR observational OR clinical trials) NOT (reviews).

The search strategies had no date restrictions and included articles published in English, Portuguese, and Spanish. The date last searched was October 30, 2016. References from the extracted articles were also consulted to complete the data bank.

2.3. Studies Selection

We included all published randomized controlled trials (RCTs), cross-sectional and cohort studies comparing fasting plasma LPS or LBP concentrations in diabetic human patients versus healthy non-diabetic controls (at baseline). Studies were included in the present review if they met the following criteria defined a priori: (1) Population: T1DM, T2DM or IR subjects; (2) Control group: non-diabetic healthy subjects; (3) Exposure: presence of T1DM, T2DM or IR; (4) Main outcomes: report of mean or median plasma LPS or LBP concentrations; (5) Study design: cross-sectional comparison of endotoxemia; (6) Measurement of circulating LPS concentrations by chromogenic kinetic limulus amebocyte assay (LAL assay) or LBP concentrations by enzyme-linked immunosorbent assays (ELISA).

We excluded reviews, case reports, letters, commentaries, abstracts, and unpublished articles. We excluded studies that did not have a control group (healthy non-diabetic subjects), did not include diabetic patients or RI or those that did not discriminate diabetic subjects compared with controls, animal studies, studies that did not indicate LPS values or in which LPS values were not adequately described (e.g. only in graphs, only correlation data), studies with LPS infusion, in vitro assays, and other systemic diseases other than diabetes and obesity (e.g. metabolic syndrome, hypertension, periodontitis and AIDS).

2.4. Data Extraction

All studies were independently screened and evaluated for selection by two authors (JMGG and JAC). After all abstracts were reviewed, data comparisons between investigators were conducted to ensure completeness and reliability. We did not contact authors of the original articles in the case of missing data. The inclusion criteria were independently applied to all identified studies. Differing decisions were resolved by consensus. For each included article, we extracted information of the title, authors, publication year, name of the study,