Nutrición Hospitalaria

Nutr Hosp. 2012;27(2):382-390
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Revisión

The influence of endotoxemia on the molecular mechanisms of insulin resistance

A. P. Boroni Moreira[1] and R. de Cássia Gonçalves Alfenas[2]

[1]Candidate for doctoral degree in Nutrition Science. Federal University of Viçosa. Minas Gerais. Brazil. [2]Assistant Professor. Nutrition and Health Department. Federal University of Viçosa. Brazil.

Abstract

Introduction: **The reduction in the capacity of insulin to reach its biological effects can lead to a chronic hyperglycemia and hyperinsulinemia, assuming an important role in the pathogenesis of metabolic disorders associated to obesity and diabetes. Insulin resistance is associated to chronic subclinical inflammation, which in part can be mediated by increased plasmatic lipopolysaccharide levels, an endotoxin derived from the membrane of gram-negative bacteria that mainly reside in the gut.**

Objectives: **The aim of this review study is to describe the molecular mechanisms involved in the pathogenesis of insulin resistance due to metabolic endotoxemia and of its connection to obesity and diabetes.**

Results and discussion: **Lipopolysaccharide present in the intestinal lumen can reach the circulatory system causing metabolic endotoxemia. When lipopolysaccharide binds to Toll-like receptor 4, inflammation is activated, changing several stages of insulin signaling. It has been shown that chronic exposure to this endotoxin may contribute to weight gain and type 2 diabetes mellitus manifestation. Obese and diabetic people have increased plasmatic lipopolysaccharide levels. The increase in the number of gram-negative bacteria on gut microbiota, the reduction on gut mucosal integrity, and the consumption of high-fat diets increase the plasmatic lipopolysaccharide levels. Therefore, the type of diet consumed may modulate the composition of gut microbiota and improve gut mucosal integrity, decreasing the occurrence of endotoxemia and its postprandial inflammatory effects, leading to adequate insulin signaling. However, there are very few studies that evaluated the influence of nutrients and/or specific food types on metabolic endotoxemia.**

(*Nutr Hosp.* 2012;27:382-390)

DOI:10.3305/nh.2012.27.2.5543

Key words: *Gut microbiota. Lipopolysaccharide. Endotoxemia. Inflammation. Insulin resistance.*

Correspondence: Ana Paula Boroni Moreira.
Universidade Federal de Viçosa.
Departamento de Nutrição e Saúde.
Av. PH Rolfs, s/n.
36570-000 Viçosa. Minas Gerais. Brazil.
E-mail: apboroni@yahoo.com.br; ana.boroni@ufv.br

Recibido: 26-VI-2011.
1.ª Revisión: 4-X-2011.
Aceptado: 11-X-2011.

LA INFLUENCIA DE LA ENDOTOXEMIA EN LOS MECANISMOS MOLECULARES DE RESISTENCIA A LA INSULINA

Resumen

Introducción: **La reducción de la capacidade de la insulin para alcanzar sus efectos biológicos puede inducir a un processo crónico de la hiperglucemia y la hiperinsulinemia, asumiendo un rol de importância en la patogénesis de las alteraciones metabólicas relacionadas con la obesidade y la diabetes. Esta resistencia a la insulina se conecta a la inflamación crónica subclínica que, en parte, podría estar mediado por el aumento de los niveles plasmáticos de lipopolisacárido, una endotoxina derivada de la membrana de las bactérias gram-negativas que reside principalmente en el intestino.**

Objetivos: **El objetivo de esta revisión es describir los mecanismos moleculares implicados en la patogénesis de la resistencia a la insulina que surgen a partir de la endotoxemia metabólica y la conexión con la obesidad y la diabetes.**

Resultados y discusión: **Lipopolisacárido presente en el lumen intestinal podría tener acceso al sistema circulatorio, generando un cuadro de endotoxemia metabólica. Cuando se conecta a los receptors Toll-like 4, lipopolisacárido activa vías que conducen a la inflamación, alterar la senalización de insulin en varios pasos. Los estudios han demostrado que la exposición crónica a la endotoxina podría contribuir al aumento de peso y la manifestación de la diabetes mellitus tipo 2. Las personas obesas y diabéticas se han incrementado los niveles plasmáticos de lipopolisacárido. El aumento del número de bacterias gram-negativas en la microbiota intestinal, la disminución de la integridad de la mucosa intestinal, y el consumo de dietas ricas en grasa aumentar los niveles plasmáticos de lipopolisacárido. En este contexto, el tipo de dieta ingerida podría modular la composición de la microbiota y mejorar la integridad de la mucosa intestinal, disminuyendo la aparición de endotoxemia y sus efectos inflamatorios posprandial, promoviendo así la señalización de la insulina. Sin embargo, los estudios de lo que se acerca de la influencia de los nutrientes y/o alimentos específicos en la endotoxemia metabólica son aún insuficientes.**

(*Nutr Hosp.* 2012;27:382-390)

DOI:10.3305/nh.2012.27.2.5543

Palabras clave: *La microbiota intestinal. Lipopolisacárido. Endotoxemia. Inflamación. Resistencia a la insulina.*

Abbreviations

α: Alpha.
β: Beta.
γ: Gamma.
μg/mL: Micrograms per milliliter.
Akt: Protein kinase B.
BMI: Body mass index.
CRP: C-reactive protein.
DM: Diabetes mellitus.
ERK: Extracellular signal-related kinase.
EU/mL: Endotoxin Units per milliliter.
FFA: Free fatty acids.
g: Gram.
HDL: High density lipoprotein.
IκB: Inhibitor of kappa B.
IKK: IκB kinase.
IL: Interleukin.
iNOS: Inducible nitric oxide synthase.
IR: Insulin resistance.
IRAK: Interleukin-1 receptor-associated kinase.
IRS: Insulin receptor substrate.
IRβ-subunit: Insulin receptor β subunit.
JNK: c-Jun NH_2-terminal kinase.
kcal: Kilocalories.
kg/m^2: Kilogram/square meter.
LBP: Lipopolysaccharide-binding protein.
LPS: Lipopolysaccharides.
MAPK: Mitogen-activated protein kinase.
MCP-1: Monocyte chemoattractant protein-1.
MD-2: Myeloid differentiation protein-2.
MyD88: Myeloid differentiation primary response gene (88).
NF-κB: Nuclear factor kappa B.
ng/kg: Nanogram per kilogram.
NIK: NF-κB-inducing kinase.
PAI-1: Plasminogen activator inhibitor type 1.
PI3-q: Phosphatidylinositol 3-kinase.
PKC: Protein kinase C.
PPAR: Peroxisome proliferator-activated receptor.
SOCS: Suppressor of cytokines signaling.
TIR: Toll-interleukin-1 receptor.
TLR: Toll-like receptor.
TNF: Tumor necrosis factor.
TRAF6: TNF receptor-associated factor 6.

Introduction

The subclinical inflammatory process impairs insulin biological effects.[1] It is shown that inflammatory mediators absorbed through the gut, such as lipopolysaccharide (LPS), may cause chronic subclinical inflammation. Endotoxemia occurs when LPS reaches the circulatory system. When that happens LPS can induce an immune response, activating pathways that cause inflammation, which in turn inhibits insulin signaling. It is argued that chronic and systemic exposure to slightly increased levels of LPS may cause insulin resistance (IR), disturbing food intake control and energy expenditure,[2,3] which may favor weight gain and the manifestation of type 2 diabetes mellitus (DM).[4,5,6,7]

IR is defined as a clinical condition in which there is subnormal metabolic response to a given concentration of the hormone on the insulin sensitive tissues. It is characterized by changes on the insulin phosphorylation cascade. Genetic and acquired defects, such as obesity (especially visceral obesity), sedentary lifestyle, pregnancy, hepatitis C, polycystic ovary syndrome and corticosteroids treatment reduce insulin sensitivity.[8,9,10,11,12]

IR is an essential component of the physiopathology of several diseases, such as the obesity, type 2 DM, hypertension, non-alcoholic fatty liver disease, cardiovascular disease, renal failure, cancer and Alzheimer disease.[4,5,7,12,13,14]

The identification of all factors that trigger IR and understanding the mechanisms involved in this process is a major challenge to the scientists seeking the development of strategies to reduce its deleterious effects on health. Therefore, the molecular mechanisms involved in the pathogenesis of IR due to metabolic endotoxemia, and its association with obesity and type 2 DM is presented in this paper.

Methods

A literature review was conducted using the Medline, PubMed, Scielo and Lilacs electronic scientific basis. In the search strategy, the words in English, Spanish and Portuguese and their combinations were used as follows: insulin, insulin resistance, lipopolysaccharide, endotoxin, endotoxemia, inflammation, gut microbiota, obesity, diabetes mellitus, pro-inflammatory cytokine, immunologic and inflammatory mediators. The selection of the papers was based on the analysis of the titles and abstracts presented in the manuscripts, regardless of their publication year. Thus, in this review paper, it is presented a critical version of the content of the selected papers.

Insulin signaling pathways

Insulin is an anabolic hormone produced by pancreatic β cells in response to increased postprandial glucose and amino acids levels. Its metabolic effects include the regulation of the glycemic homeostasis, reducing hepatic production of glucose (to inhibit gluconeogenesis and glycogenolysis) and increasing peripheral uptake of glucose, mainly by the muscular and adipose tissues. Insulin also stimulates protein synthesis and inhibits protein degradation, increases hepatic lipogenesis and reduces adipocytes lipolysis. It also affects gene expression, cellular proliferation and differentiation. This hormone stimulates nitric oxide production in the endothelium, prevents apoptosis and it is also responsible for food intake control in the hypothalamus.[9,10]

Insulin signaling starts when it binds to its specific receptor located in the cell membrane, a protein that presents kinase activity. Insulin receptor contains two subunits (extracellular) and two subunits (transmembrane and intracellular). Thus, once insulin binds to the receptor subunit, there is a conformational change on the subunit. This conformational change self-phosphorylates the subunit turning it into tyrosine, activating its tyrosine kinase activity. Once activated, the receptor phosphorylates several protein substrates turning them into tyrosine. Currently, ten receptor substrates have been identified, and four belong to the family of the insulin receptor substrate, the IRS proteins (IRS-1/2/3/4). Other substrates include Shc, Gab-1, $p60^{dok}$, Cbl, JAK2 and APS. The phosphorylation of these proteins turning them into tyrosine creates recognition sites for molecules containing domains with *Src* 2 (SH2) homology, which can enable the following signaling pathways: a) phosphatidylinositol-3-kinase (PI3-q)/protein kinase B (Akt), b) Ras/Raf/mitogen-activated protein kinase (MAPK) and c) JAK/STAT. PI3-q/Akt pathway is responsible for regulating insulin metabolic actions such as glucose uptake, glycolysis, glycogen and protein synthesis, mitogenesis regulation and cellular differentiation. Ras/Raf/MAPK pathway is involved in cellular proliferation and differentiation. JAK/STAT pathway is involved on gene expression regulation.[8,9,10,15,16,17]

Insulin resistance

Besides being phosphorylated and turning into tyrosine, the insulin receptor can also be phosphorylated turning into serine. When that happens, its phosphorylation and tyrosine formation is impaired after insulin stimulation. This type of inhibitory phosphorylation causes a negative feedback on insulin signaling and may cause IR. The inflammation processes can trigger the formation of several inflammatory molecules such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), inhibitor of B (I B) kinase β (IKKβ) and c-Jun NH_2-terminal kinase (JNK). All these molecules can phosphorylate the IRS turning them into serine, which exerts a negative effect on the insulin signaling pathway.[8,18,19,20,21]

IR induces a chronic hyperglycemia process, which in most cases is followed by a compensatory hyperinsulinemia. The chronic hyperglycemia and hyperinsulinemia play a central role on metabolic disorders associated with obesity and type 2 DM.[4,7]

The development of IR is tissue-specific. The hypothalamus and skeletal muscle are the first ones to become resistant to hormone action. Subsequently, insulin fails to act properly on liver cells and endothelial cells. Adipose tissue IR occurs later.[22] The activation of an inflammatory response on rats hypothalamus in response to high-fat diet consumption for example can lead to insulin and leptin molecular and functional resistance, resulting in poor food intake and energy expenditure control.[2,3] It has been claimed that hypothalamus IR may favor weight gain and type 2 DM manifestation.[23] It is worth emphasizing that central IR may also be a consequence of obesity.[24]

When IR occurs, insulin antilipolytic activity is attenuated and there is an increase on free fatty acids (FFA) levels, leading to cellular dysfunction in several tissues (muscle, liver, adipose tissue, pancreas and vascular). This effect is referred to as lipotoxicity.[10,25,26] High levels of FFA may inhibit the IRSs, inducing or enhancing skeletal muscle and liver tissue IR.[27]

IR may be present for several years before the high plasma glucose levels are noticed, because pancreas is constantly stimulated to produce and secrete insulin to maintain blood glucose and metabolic homeostasis. After some time, cells β failure can occur and as IR increases glucose intolerance and ultimately diabetes may manifest. Another metabolic abnormality that can be associated with IR is endothelial dysfunction, since insulin has a vasodilator effect by stimulating nitric oxide production.[7,25,28]

Lipopolysaccharide

It is estimated that human microbiota contains approximately 10^{14} bacterial cells,[29] consisting of more than 1,000 different species, especially anaerobic bacteria.[30] Gut microbiota is the largest and most complex, containing up to 10^{12} cells/g of feces.[29] However, the composition of gut microbiota can vary among humans,[31] according to age, food habits and environmental factors.[32] It is claimed that gut microbiota composition can affect the host homeostasis, modulating subclinical systemic inflammation. Inflammation can be triggered especially by gram-negative bacteria.[33,34] LPS is a major component of the outer membrane of these bacteria. It is considered an endotoxin, which contributes to the structural integrity and protection of that membrane from chemical attack. Once it reaches blood circulation, it causes metabolic endotoxemia, which can induce an immune response leading to inflammation. It can also inhibit insulin signaling, contributing to IR. Therefore, endotoxemia may favor obesity and type 2 DM manifestation.[5,6] It is worth emphasizing that the gut is the main source of LPS.[35] It is estimated that the intestinal lumen has more than 1g of LPS. A small dose of endotoxin in the circulatory system can cause inflammatory reactions.[36,37]

LPS consists of lipid and polysaccharide covalently bound. Three structurally and genetically distinct regions form this glycoconjugate: a portion called lipid A (responsible for endotoxic activity), oligosaccharide core and external region or *O*-antigen.[38]

It has been proposed that the intestinal absorption of LPS includes its internalization by the enterocytes. Within the enterocyte, LPS is transported to the golgi complex, where chylomicrons are synthesized.[5,39] The

consumption of a high-fat diets seems to favor the translocation of LPS through the intestinal mucous.[34] Once LPS is incorporated into the newly synthesized chylomicrons, it crosses the intestinal barrier, reaches the lymphatic system and subsequently the bloodstream. LPS is transported by lipoproteins and by a specific acute phase response protein, called LPS binding protein (LBP). All subclasses of lipoproteins can bind to LPS, and that is dependent on the amount of phospholipids on the surface of the lipoprotein. Under physiological conditions, HDL is the main receptor for LPS.[5,40,41] It has been observed that the binding of LPS to lipoproteins, especially to chylomicrons, partially prevents the activation of monocytes and macrophages, and consequently the secretion of pro-inflammatory cytokines.[5,42] It is worth emphasizing that most of the studies published about this topic so far were conducted in conditions of acute inflammation or sepsis. There are almost no data available on the role of lipoproteins in conditions of modest LPS increase, as it is observed in obesity and in type 2 DM.[5]

The target tissues for LPS are the adipose tissue, liver and endothelium.[5] Thus, the portion responsible for endotoxic activity of LPS (lipid A) binds to the Toll-like receptor 4 (TLR-4) present in the plasma membrane. The recognition of LPS to this receptor is mediated by LBP protein, the CD14 co-receptor of TLR-4 and by the myeloid differentiation protein-2 (MD-2).[43,44,45] The TLR-4 are on the surface of immune cells (monocytes, macrophages, Kupffer cells and preadipocytes) and non-immune cells (adipocytes, hepatocytes and endothelial cells).[5,39,46]

Lipopolysaccharide, inflammation and insulin resistance

The role of LPS and of the consumption of high-fat diet in the development of subclinical inflammation has been shown in wild-type and CD14-/- mice. After chronic infusion (4 weeks) of LPS, the wild-type mice showed increased body, liver, visceral and subcutaneous adipose tissue weights, besides increased fasting and postprandial blood glucose. When wild-type mice were submitted to the consumption of high-fat diet without LPS infusion, there was also an increase in body weight and adipose tissue associated with the establishment of an inflammatory state. However, these effects were not observed on CD14-/- mice. Therefore, the infusion of LPS or the consumption of high-fat diet triggered an inflammatory response in muscle, adipose and liver tissue.[47] According to some authors, the increased levels of circulating FFAs can also activate TLR-4 favoring its binding to LPS and the development of inflammation.[25,48]

The activation of TLR-4, through LPS, can trigger various signaling pathways, and the main ones are: nuclear factor kappa B (NF-κB) and MAPK.[33] The translocation of NF-κB from the cytosol to the nucleus promotes the activation of genes that encode proteins involved in the inflammatory response, such as TNF-α, IL-6, inducible nitric oxide synthase (iNOS) and monocyte chemoattractant protein-1 (MCP-1).[49] MAPK represent a family of kinases that phosphorylate serine and threonine, regulating important cellular processes such as growth, proliferation, differentiation and migration, through modulation of gene transcription in response to changes in the intracellular environment. MAPK signaling pathway includes the extracellular signal-regulated kinases such as JNK, p38 MAPK (p38) and extracellular signal-related kinase (ERK).[5,50,51] JNK, p38 and ERK can induce IR through different mechanisms. Fujishiro et al.[52] showed that the activation of the JNK pathway suppresses phosphorylation on tyrosine of IRS-1 and IRS-2, while the p38 pathway moderately reduces the expression of IRS-1 and IRS-2. Since the ERK pathway suppresses the expression of the insulin receptors, IRS-1 and IRS-2, making its contribution to IR more evident than the other pathway.

After its interaction with LPS, TLR-4 dimerizes and undergoes conformational changes that allow the recruitment of adapter molecules to the intracellular domain Toll-interleukin-1 receptor (TIR). The molecules are: myeloid differentiation primary response gene (MyD88), IL-1 receptor-associated kinase (IRAK), TNF receptor-associated factor 6 (TRAF6), NF-κB-inducing kinase (NIK), culminating in the phosphorylation of the IKK complex. This complex consists of two catalytic subunits IKK-α and IKK-β and a regulatory subunit IKK-γ. In the cytoplasm of non-stimulated cells, NF-κB is in an inactive form because of its association with proteins known as IκB. The phosphorylation of IκB leads to its degradation, releasing NF-κB for translocation to the nucleus and subsequent expression of several pro-inflammatory genes.[5,50,53]

Mice heterozygous IKKβ +/- were protected against the development of IR when submitted to the consumption of high-fat diet and when they were genetically obesity.[54] IKKβ can block insulin signaling, since it directly phosphorylates the IRS-1 on serine residues, and of IκB.[19,55]

The infusion of LPS for 3 hours caused an increase in IL-1 and IL-6 expressions and plasminogen activator inhibitor-1 (PAI-1) in subcutaneous adipose tissue of wild-type mice compared to CD14-/- mice. The concentration of phosphorylated NF- B and IKK also increased in the liver of wild-type mice, while in CD14-/- mice there was no change. There was weight gain and an increase on visceral and subcutaneous adipose tissue only in wild-type mice.[47] Endotoxemia also caused an increase in the expression of TNF-α.[56] The increase in the levels of pro-inflammatory factors such as IL-1, IL-6, PAI-1 and TNF-α is related to the decrease on insulin action.[33,57] TNF-α and IL-6 are responsible for the inhibitory phosphorylation of IRS-1, since they activate JNK and IKK .[58,59] On the other hand, MCP-1 exacerbates inflammation since it recruits monocytes from the circulation, activating them to a pro-inflammatory

macrophage phenotype.[4] In addition, LPS can also activate a protein kinase C (PKC) and consequently, activate JNK and IKK contributing to IR.[1,60]

In adipocytes 3T3-L1, LPS caused the phosphorylation of Akt reduction, while the expression of iNOS increased.[49] The increase of iNOS may increase the production of nitric oxide and consequently the IR by changing glucose uptake. This IR is associated with iNOS is mediated by S-nitrosation of proteins involved in insulin signaling, such as the insulin receptor β subunit (IRβ), IRS-1 and Akt. S-nitrosation of IR reduces its self-phosphorylation and also its tyrosine kinase activity, while S-nitrosation of IRS-1 reduces its tissue expression, possibly by increasing the degradation mediated by proteasome. Akt is also targeted by S-nitrosation, which occurs at the same time it looses its serine kinase activity.[61]

Park et al.[62] developed a model of transgenic mice capable of expressing human resistin. When these animals where exposed to LPS there was an increase in the circulating resistin levels, besides developing liver IR. Resistin can activate NF-κB, increase the expression of pro-inflammatory cytokines and, consequently, impair insulin signaling.[62,63]

Clinical studies

Endotoxemia and insulin resistance

Agwunobi et al.[64] were the first researchers to demonstrate, in humans, the impairment on insulin sensitivity 6-7 h after the administration of low doses of LPS. In this study, LPS also produced significant increases on plasma concentrations of counterregulatory hormones such as cortisol, glucagon and growth hormone, which contribute to the reduction of peripheral and hepatic glucose uptake.

Dandona et al.[65] verified that intravenous administration of LPS (2 ng/kg) resulted in a rapid increase of plasma TNF-α, IL-6, FFA, reactive oxygen species by polymorphonuclear leukocytes, MCP-1, macrophage migration inhibition factor, C-reactive protein (CRP), resistin, visfatin and LBP in healthy individuals with a body mass index (BMI) between 20 and 25 kg/m^2. It is worth emphasizing that the increased levels of TNF-α favors the occurrence of lipolysis, increasing the levels of FFA.[66] The increase in the production of reactive oxygen species can activate several kinase serines.[67] Visfatin has insulin-mimetic properties. In a meta-analysis study, Chang et al.[68] verified that the level of circulating visfatin was positively associated with IR.

Mehta et al.[69] also conducted a study in which healthy individuals with a BMI between 18 and 30 kg/m^2 received intravenous LPS (3 ng/kg). The endotoxemia induced fast and transient increase on plasma of TNF-α, IL-6, resistin, leptin, MCP-1, CRP, cortisol and FFA. It was also verified that the occurrence of endotoxemia induced systemic IR, but β-pancreatic cells function was not affected. Additionally, it was observed that an increase in suppressor of cytokine signaling 1 and 3 expression (SOCS-1 and SOCS-3). It has been suggested that SOCS-1 and SOCS-3 inhibit insulin signaling by interfering with tyrosine phosphorylation of IRS-1 and IRS-2 or by targeting IRS-1 and IRS-2 for proteasome degradation.[70,71]

Pussinen et al.[72] evaluated the relationship between endotoxemia and the incidence of DM in a cohort study involving 7,169 individuals between 25 and 74 years of age. The individuals were followed for 10 years. The authors verified that the levels of LPS were associated with increased risk of DM developing and the occurrence of a negative correlation with HDL levels. Thus, it seems that a chronic exposure to slightly elevated levels of LPS may contribute to IR, and hence to the manifestation of chronic diseases.

Endotoxemia, obesity and type 2 diabetes mellitus

LPS can also be found in the plasma of healthy individuals,[73] since besides colonizing the gut, gram-negative bacteria is also present on the oral cavity and the respiratory and genito-urinary systems. However, clinical studies have shown that the concentrations of circulating LPS and LBP (an endotoxemia marker) are higher in type 1 or 2 diabetic individuals, and in obese,[72,74,75,76,77] strengthening their link with IR and metabolic diseases.

Blood samples from obese, overweight and normal weight afro-american women were collected and stimulated in vitro with various doses of LPS. The obese class III (BMI > 40 kg/m^2) expressed 365% more TNF-α than normal weight (BMI between 20-25 kg/m^2) women when the intermediate concentrations of LPS (20 μg/mL) was tested. When the maximum expression of TNF-α was assessed independently of the dose of LPS, it was verified that the obese class III produced 230% more than the normal weight women. The obese class I (BMI between 30-35 kg/m^2) produced 190% more TNF-α than the normal weight.[78] The results of this study reinforce the effect of the excess of body weight on the expression of inflammation markers such as TNF-α.

Van Dielen et al.[79] evaluated the effect of weight loss on plasma levels of LBP in obese individuals submitted to gastric reduction surgery (BMI 46.7 kg/m^2 before the surgery). During the first six months there was a severe weight loss (42.3% loss of excess weight). Nevertheless, the levels of LBP and of other biomarkers (CRP and soluble TNF-α receptors) did not change, suggesting the occurrence of an inflammatory state. However, at 12 and 24 months after surgery, when body weight stabilized (BMI: ~ 33.0 kg/m^2), LBP levels decreased significantly (107.6 ± 77.4 and 78.9 ± 39.4 μg/ml, respectively), compared to the values presented before the surgery (134.7 ± 98.2 μg/ml). It is worth emphasizing that other inflammatory biomarkers also reduced during this period.

In a study conducted by Creeley et al.[76], individuals with type 2 DM presenting mean LPS values 76% higher than the individuals without the disease. The diabetic patients were treated with rosiglitazone and showed a reduction corresponding to 51% on insulin and 35% on LPS levels. Rosiglitazone is an agonist of peroxisome proliferator-activated receptor (PPAR-γ), which presents anti-inflammatory properties.[80] This antidiabetic agent may attenuate inflammation, favoring the clearance of LPS by reducing the insulinemia and increasing HDL bioavailability. Reductions on plasma insulin concentrations favor the function of Kupffer cells that are, in part, responsible for LPS clearance.[76] When LPS interacts with HDL, the activation of TLRs is impaired.[81] Individuals with low HDL levels showed a greater inflammatory response (TNF-α, IL-1β, IL-6, IL-8) after the infusion of low doses of LPS.[82] Pajkrt et al.[83] verified that the infusion of HDL can reduce the deleterious effects of LPS.

Hyperglycemia and hyperinsulinemia, common conditions in patients with DM, can also be an indirect cause of endotoxemia,[5] since they reduce the motility of the jejunum and the gastrointestinal transit time, favoring bacterial overgrowth in the small intestine and increasing the gut permeability.[84,85,86] It is worth emphasizing that the highest concentration of LPS in diabetics enhances the development of chronic complications inherent to the disease, as observed by Nymark et al.[87] These authors verified a correlation between endotoxemia and the occurrence of diabetic nephropathy in type 1 DM patients.

Although the gut is the main source of LPS, infections by gram-negative bacteria in other parts of the body can also increase the levels of plasma LPS. Pussinen et al.[88] verified the occurrence of endotoxemia from periodontitis.

It is worth emphasizing that the increase of pro-inflammatory cytokines such as IFN-γ, TNF-α, IL-6 and IL-1β, commonly seen in obese and diabetics,[4,76,89,90] is able to affect the expression/distribution of proteins capable to form the tight junctions, such as ocludina and zonular occludens-1, increasing gut permeability.[35] This change in gut permeability may favor the translocation of LPS and, consequently, cause metabolic endotoxemia, thus increasing subclinical inflammation.[4,35]

Effect of the diet on the endotoxemia

The consumption of high-fat diet can change the composition of gut microbiota, increasing gut permeability and/or reduce LPS catabolism favoring the occurrence of metabolic endotoxemia[32,34] and consequently weight gain and IR.[73,91,92]

Mice received LPS orally, diluted in oil or water. Endotoxemia was observed only after the administration of LPS-oil mixture. It was verified that the consumption of a diet with 72% of fat increased endotoxemia 2.7 times when compared to the control diet. When the mice were fed a 40% fat diet, there was a 1.4 times increase in endotoxemia.[47] In healthy men, the level of plasma LPS can increase approximately 50% after a high-fat meal.[92]

In a recently conducted study, healthy individuals were divided into three groups. Each group received one type of drink (water, glucose or orange juice) in combination with a high-fat meal (containing approximately 36% of carbohydrate, 50% of fat and 14% of protein, ~ 900 kcal). The ingestion of glucose or water and the high-fat meal induced oxidative stress and inflammation, as well as the increased expression of TLR-4 and endotoxemia. On the other hand, the consumption of orange juice plus the high-fat meal prevented the occurrence of the previous situation. The beneficial effect of orange juice may be due to its flavonoids content. The chronic occurrence of oxidative stress and inflammation promotes the development of chronic diseases such as obesity and type 2 DM.[93] The results of this study suggest that eating certain types of foods such as orange juice, may act as a protective factor against postprandial endotoxemia.

In the previously mentioned study[93], it was not detected the presence of LPS in the beverage containing glucose. On the other hand, the orange juice had a content of LPS 85 EU/mL, while the water had 21 EU/mL. The total LPS content of the meal was 12,600 EU. It was verified that after the consumption of the meal with glucose or water, plasma concentration of LPS increased above 60% compared to baseline. On the other hand, there is no increase on plasma LPS after the ingestion of the meal with orange juice, despite having a higher content of endotoxin. It is worth emphasizing, however, that compared to the total LPS content present in the gut, the amount present in a food is extremely small. Thus, it is unlikely that the LPS concentration present in the food contributes to an increase in the concentration of plasma LPS.[92,93]

It has been verified that administration of probiotics *(Lactobacillus* and *Bifidobacterium* for example) or prebiotics (inulin and oligofructose for example) can modulate the microbiota and improve gut permeability, thus controlling the occurrence of endotoxemia.[32,34,94,95] The consumption of phytochemicals and polyunsaturated fatty acids also seems to result in beneficial effects on the intestinal environment and microbiota composition.[96] However, it is not fully understood the factors and food components that contribute to the gut microbiota diversity and gut integrity.[29]

There is little information in the literature about the effect of specific nutrients and/or food on metabolic endotoxemia. Therefore, it is necessary to conduct interventional studies in humans to identify dietary strategies capable to modulate gut microbiota, improving gut integrity and/or to reduce postprandial inflammatory effects, in order to avoid the occurrence of endotoxemia and, consequently, of IR.

Conclusion

The chronic exposure to slightly increased LPS levels in the blood is a risk factor for IR, since this endotoxin can induce an immune response and activate pathways leading to subclinical inflammation inhibiting several step of insulin signaling. Thus, IR induced by endotoxemia may contribute to weight gain and the development of type 2 DM. Although gut microbiota is the main source of LPS, the results of the few studies available so far suggests that the type of diet ingested may prevent endotoxemia occurrence and its deleterious effects on insulin signaling.

References

1. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. *J Clin Invest* 2006; 116 (7): 1793-801.
2. Milanski M, Degasperi G, Coope A, Morari J, Denis R, Cintra DE et al. Saturated fatty acids produce an inflammatory response predominantly through the activation of 2009 TLR4 signaling in hypothalamus: implications for the pathogenesis of obesity. *J Neurosci* 2009; 29 (2): 359-70.
3. Moraes JC, Coope A, Morari J, Cintra DE, Roman EA, Pauli JR et al. High-fat diet induces apoptosis of hypothalamic neurons. *PLoS One* 2009; 4 (4): e5045.
4. Ding S, Lund PK. Role of intestinal inflammation as an early event in obesity and insulin resistance. *Curr Opin Clin Nutr Metab Care* 2011; 14: 328-33.
5. Manco M, Putignani L, Bottazzo GF. Gut microbiota, lipopolysaccharides, and innate immunity in the pathogenesis of obesity and cardiovascular risk. *Endocr Rev* 2010; 31 (6): 817-44.
6. Cani PD, Possemiers S, Van de Wiele T, Guiot Y, Everard A, Rottier O, et al. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut* 2009; 58 (8): 1091-103.
7. Shanik MH, Xu Y, Skrha J, Dankner R, Zick Y, Roth J. Insulin resistance and hyperinsulinemia: is hyperinsulinemia the cart or the horse? *Diabetes Care* 2008; 31 (2): S262-8.
8. Carvalho-Filho MA, Carvalheira JBC, Velloso LA, Saad MJA. Cross-talk das vias de sinalização de insulina e angiotensina II: implicações com a associação entre diabetes mellitus e hipertensão arterial e doença cardiovascular. *Arq Bras Endocrinol Metab* 2007; 51 (2): 195-203.
9. Carvalheira JBC, Zecchin HG, Saad MJA. Vias de Sinalização da Insulina. *Arq Bras Endocrinol Metab* 2002; 46 (4): 419-25.
10. Pessin JE, Saltiel AR. Signaling pathways in insulin action: molecular targets of insulin resistance. *J Clin Invest* 2000; 106 (2): 165-9.
11. Shulman GI. Cellular mechanisms of insulin resistance. *J Clin Invest* 2000; 106 (2): 171-6.
12. Hoehn KL, Salmon AB, Hohnen-Behrens C, Turner N, Hoy AJ, Maghzal GJ et al. Insulin resistance is a cellular antioxidant defense mechanism. *Proc Natl Acad Sci* 2009; 106 (42): 17787-92.
13. Laron Z. Insulin and the brain. *Arch Physiol Biochem* 2009; 115 (2): 112-6.
14. Luis DA, Aller R, Izaola O, Sagrado MG, Conde R. Effect of two different hypocaloric diets in transaminases and insulin resistance in nonalcoholic fatty liver disease and obese patients. *Nutr Hosp* 2010; 25 (5): 730-5.
15. Roith DL, Zick Y. Recent advances in our understanding of insulin action and insulin resistance. *Diabetes Care* 2001; 24 (3): 588-97.
16. Saltiel AR, Kahn CR. Insulin signaling and the regulation of glucose and lipid metabolism. *Nature* 2001; 414: 799-806.
17. Velloso LA, Carvalho CR, Rojas FA, Folli F, Saad MJ. Insulin signalling in heart involves insulin receiver substrates-1 and -2, activation of phosphatidylinositol 3-kinase and the JAK 2-growth related pathway. *Cardiovasc Res* 1998; 40 (1): 96-102.
18. Hotamisligil GS. Inflammatory pathways and insulin action. *Int J Obes Relat Metab Disord* 2003; 27: S53-5.
19. Gao, Z, Hwang D, Bataille F, Lefevre M, York D, Quon MJ et al. Serine phosphorylation of insulin receiver substrate 1 by inhibitor kappa B kinase complex. *J Biol Chem* 2002; 277: 48115-21.
20. Hirosumi J, Tuncman G, Chang L, Gorgun CZ, Uysal KT, Maeda K, Karin M, HotamisligiL GS. A central role for JNK in obesity and insulin resistance. *Nature* 2002; 420 (6913): 333-6.
21. White MF. IRS proteins and the common path to diabetes. *Am J Physiol Endocrinol Metab* 2002; 283: E413-22.
22. Prada PO, Zecchin HG, Gasparetti AL, Torsoni MA, Ueno M, Hirata AE et al. Western diet modulates insulin signaling, c-Jun N-terminal kinase activity, and insulin receiver substrate-1ser307 phosphorylation in a tissue-specific fashion. *Endocrinology* 2005; 146 (3): 1576-87.
23. Lin X, Taguchi A, Park S, Kushner JA, Li F, Li Y et al. Dysregulation of insulin receiver substrate 2 in beta cells and brain causes obesity and diabetes. *J Clin Invest* 2004; 114 (7): 908-16.
24. Tschritter O, Preissl H, Hennige AM, Stumvoll M, Porubska K, Frost R et al. The cerebrocortical response to hyperinsulinemia is reduced in overweight humans: a magnetoencephalographic study. *Proc Natl Acad Sci USA* 2006; 103 (32): 12103-8.
25. DeFronzo RA. Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009. *Diabetologia* 2010; 53: 1270-87.
26. Weinberg JM. Lipotoxicity. *Kidney Int* 2006; 70: 1560-6.
27. Shah A, Mehta N, Reilly MP. Adipose Inflammation, insulin resistance, and cardiovascular disease. *J Parenter Enteral Nutr* 2008; 32 (6): 638-44.
28. Carvalho MHC, Colaço AL, Fortes ZB. Citocinas, disfunção endotelial e resistência à insulina. *Arq Bras Endocrinol Metab* 2006; 50 (2): 304-12.
29. Hattori M, Taylor TD. The human intestinal microbiome: a new frontier of human biology. *DNA Res* 2009; 16 (1): 1-12.
30. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* 2010; 464 (7285): 59-65.
31. Phillips ML. Gut reaction: environmental effects on the human microbiota. *Environ Health Perspect* 2009; 117 (5): A198-205.
32. Delzenne NM, Cani PD. Gut microbiota and the pathogenesis of insulin resistance. *Curr Diab Rep* 2011; 11: 154-9.
33. Cani PD, Delzenne NM. The gut microbiome as therapeutic target. *Pharmacol Ther* 2011; 130: 202-12.
34. Cani PD, Neyrinck AM, Fava F, Knauf C, Burcelin RG, Tuohy KM et al. Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. *Diabetologia* 2007a; 50 (11): 2374-83.
35. Brun P, Castagliuolo I, Leo VD, Buda A, Pinzani M, Palù G, Martines D. Increased intestinal permeability in obese mice: new evidence in the pathogenesis of nonalcoholic steatohepatitis. *Am J Physiol Gastrointest Liver Physiol* 2007; 292: G518-25.
36. Ghoshal S, Witta J, Zhong J, Villiers W, Eckhardt E. Chylomicrons promote intestinal absorption of lipopolysaccharides. *J Lipid Res* 2009; 50: 90-7.
37. Berg RD. The indigenous gastrointestinal microflora. *Trends Microbiol* 1996; 4: 430-5.
38. Raetz CRH, Whitfield C. Lipopolysaccharide endotoxins. *Annu Rev Biochem* 2002; 71: 635-700.
39. Neal MD, Leaphart C, Levy R, Prince J, Billiar TR, Watkins S et al. Enterocyte TLR4 mediates phagocytosis and translocation of bacteria across the intestinal barrier. *J Immunol* 2006; 176: 3070-9.
40. Schwartz YSH, Dushkin MI. Endotoxin-lipoprotein complex formation as a factor in atherogenesis: associations with hyperlipidemia and with lecithin:cholesterol acyltransferase activity. *Biochemistry Mosc* 2002; 67: 747-52.

41. Levels JH, Abraham PR, van den Ende A, van Deventer SJ. Distribution and kinetics of lipoprotein-bound endotoxin. *Infect Immun* 2001; 69 (5): 2821-8.
42. Harris HW, Grunfeld C, Feingold KR, Read TE, Kane JP, Jones AL et al. Chylomicrons alter the fate of endotoxin, decreasing tumor necrosis factor release and preventing death. *J Clin Invest* 1993; 91: 1028-34.
43. Peri F, Piazza M, Calabrese V, Damore G, Cighetti R. Exploring the LPS/TLR4 signal pathway with small molecules. *Biochem Soc Trans* 2010; 38 (5): 1390-5.
44. Araki Y, Katoh T, Ogawa A, Bamba S, Andoh A, Koyama S, Fujiyama Y, Bamba T. Bile acid modulates transepithelial permeability via the generation of reactive oxygen species in the Caco-2 cell line. *Free Radic Biol Med* 2005; 39: 769-80.
45. Shimazu R, Akashi S, Ogata H, Nagai Y, Fukudome K, Miyake K et al. MD-2, a molecule that confers lipopolysaccharide responsiveness on toll-like receiver 4. *J Exp Med* 1999; 189: 1777-82.
46. Grimaldi E, Donnarumma G, Perfetto B, De Filippis A, Melito A, Tufano MA. Proinflammatory signal transduction pathway induced by shigella flexneri porins in caco-2 cells. *Braz Journal Microbiol* 2009; 40: 701-9.
47. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* 2007b; 56 (7): 1761-72.
48. Lee JY, Soh KH, Rhee SH, Hwang D. Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase 2 mediated through Toll-like receiver 4. *J Biol Chem* 2001; 276 (2001): 16683-9.
49. Song MJ, Kim KH, Yoon JM, Kim JB. Activation of Toll-like receiver 4 is associated with insulin resistance in adipocytes. *Biochem Biophys Res Commun* 2006; 346 (3): 739-45.
50. Bastos DHM, Rogero MM, Arêas JAG. Mecanismos de ação de compostos bioativos dos alimentos no contexto de processos inflamatórios relacionados à obesidade. *Arq Bras Endocrinol Metab* 2009; 53 (5): 646-56.
51. Pan ZK. Toll-like receivers and TLR-mediated signaling: more questions than answers. *Am J Physiol Lung Cell Mol Physiol* 2004; 286: L918-20.
52. Fujishiro M, Gotoh Y, Katagiri H, Sakoda H, Ogihara T, Anai M, et al. Three mitogen-activated protein kinases inhibit insulin signaling by different mechanisms in 3T3-L1 adipocytes. *Mol Endocrinol* 2003; 17 (3): 487-7.
53. Wang Q, Dziarski R, Kirschning CJ, Muzio M, Gupta D. Micrococci and peptidoglycan activate TLR2→MyD88→ IRAK→TRAF→NIK→IKK→NF-kB signal transduction pathway that induces transcription of interleukin-8. *Infect Immun* 2001; 69 (4): 2270-6.
54. Yuan M, Konstantopoulos N, Lee J, Hansen L, Li ZW, Karin M et al. Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of Ikkbeta. *Science* 2001; 293 (5535): 1673-7.
55. Kim JK, Kim YJ, Fillmore JJ, Chen Y, Moore I, Lee J et al. Prevention of fat-induced insulin resistance by salicylate. *J Clin Invest* 2001; 108: 437-46.
56. Cani PD, Bibiloni B, Knauf C, Waget A, Neyrinck AM, Burcelin RG et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* 2008; 57 (6): 1470-81.
57. Ma LJ, Mao SL, Taylor KL, Kanjanabuch T, Guan Y, Zhang Y et al. Prevention of obesity and insulin resistance in mice lacking plasminogen activator inhibitor 1. *Diabetes* 2004; 53 (2): 336-46.
58. Shoelson SE, Lee J, Yuan M. Inflammation and the IKKbeta/ IkappaB/NF-kappaB axis in obesity- and diet-induced insulin resistance. *Int J Obes Relat Metb Disord* 2003; 27: S49-52.
59. Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. Protection from obesity induced insulin resistance in mice lacking TNF-α function. *Nature* 1997; 389 (6651): 610-4.
60. Comalada M, Xaus J, Valledor AF, López-López C, Pennington DJ, Celada A. PKC epsilon is involved in JNK activation that mediates LPS-induced TNF-alpha, which induces apoptosis in macrophages. *Am J Physiol Cell Physiol* 2003; 285 (5): 1235-45.
61. Carvalho-Filho MA, Ueno M, Carvalheira JBC, Velloso LA, Saad MJA. Targeted disruption of iNOS prevents LPS-induced -nitrosation of IR /IRS-1 and Akt and insulin resistance in muscle of mice. A*m J Physiol Endocrinol Metab* 2006; 291: E476-82.
62. Park HK, Qatanani M, Briggs ER, Ahima RS, Lazar MA. Inflammatory induction of human resistin causes insulin resistance in endotoxemic mice. *Diabetes* 2011; 60 (3): 775-83.
63. Luis DA, Sagrado MG, Conde R, Aller R, Izaola O. Resistin levels and inflammatory markers in patients with morbid obesity. *Nutr Hosp* 2010; 25 (4): 630-4.
64. Agwunobi AO, Reid C, Maycock P, Little RA, Carlson GL. Insulin resistance and substrate utilization in human endotoxemia. *J Clin Endocrinol Metab* 2000; 85 (10): 3770-8.
65. Dandona P, Ghanim H, Bandyopadhyay A, Korzeniewski K, Ling Sia C, Dhindsa S, et al. Insulin suppresses endotoxin-induced oxidative, nitrosative, and inflammatory stress in humans. *Diabetes Care* 2010; 33 (11); 2416-23.
66. Souza SC, Palmer HJ, Kang YH, Yamamoto MT, Muliro KV, Paulson KE et al. TNF-alpha induction of lipolysis is mediated through activation of the extracellular signal related kinase pathway in 3T3-L1 adipocytes. *J Cell Biochem* 2003; 89 (6): 1077-86.
67. Kim J, Wei Y, Sowers JR. Role of mitochondrial dysfunction in insulin resistance. *Circ Res* 2008; 102: 401-14.
68. Chang YH, Chang DM, Lin KC, Shin SJ, Lee YJ. Visfatin in overweight/obesity, type 2 diabetes mellitus, insulin resistance, metabolic syndrome, and cardiovascular diseases: A meta-analysis and systemic review. *Diabetes Metab Res Rev* 2011.
69. Mehta NN, McGillicuddy FC, Anderson PD, Hinkle CC, Shah R, Pruscino L et al. Experimental endotoxemia induces adipose inflammation and insulin resistance in humans. *Diabetes* 2010; 59: 172-81.
70. Ueki K, Kondo T, Kahn CR. Suppressor of cytokine signaling 1 (SOCS-1) and SOCS-3 cause insulin resistance through inhibition of tyrosine phosphorylation of insulin receiver substrate proteins by discrete mechanisms. *Mol Cell Biol* 2004; 24: 5434-46.
71. Rui L, Yuan M, Frantz D, Shoelson S, White MF. SOCS-1 and SOCS-3 block insulin signaling by ubiquitin-mediated degradation of IRS1 and IRS2. *J Biol Chem* 2002; 277: 42394-8.
72. Pussinen PJ, Havulinna AS, Lehto M, Sundvall J, Salomaa V. Endotoxemia is associated with an increased risk of incident diabetes. *Diabetes care* 2011; 34 (2): 392-7.
73. Amar J, Burcelin R, Ruidavets JB, Cani PD, Fauvel J, Alessi MC, Chamontin B, Ferriéres J. Energy intake is associated with endotoxemia in apparently healthy men. *Am J Clin Nutr* 2008; 87: 1219-23.
74. Sun L, Yu Z, Ye X, Zou S, Li H, Yu D, et al. A marker of endotoxemia is associated with obesity and related metabolic disorders in apparently healthy Chinese. *Diabetes Care* 2010; 33 (9): 1925-32.
75. Devaraj S, Dasu MR, Park SH, Jialal I. Increased levels of ligands of Toll-like receivers 2 and 4 in type 1 diabetes. *Diabetologia* 2009; 52 (8): 1665-8.
76. Creely SJ, McTernan PG, Kusminski CM, Fisher M, Da Silva NF, Khanolkar M et al. Lipopolysaccharide activates an innate immune system response in human adipose tissue in obesity and type 2 diabetes. *Am J Physiol Endocrinol Metab* 2007; 292: E740-7.
77. Ruiz AG, Casafont F, Crespo J, Cayon A, Mayorga M, Estebanez A et al. Lipopolysaccharide-binding protein plasma levels and liver TNF-alpha gene expression in obese patients: evidence for the potential role of endotoxin in the pathogenesis of non-alcoholic steatohepatitis. *Obes Surg* 2007; 17: 1374-80.
78. Kueht ML, McFarlin BK, Lee RE. Severely obese have greater LPS-stimulated TNF-α production than normal weight african-american women. *Obesity* 2009; 17 (3): 447-51.
79. Van Dielen FM, Buurman WA, Hadfoune M, Nijhuis J, Greve JW. Macrophage inhibitory factor, plasminogen activator inhibitor-1, other acute phase proteins, and inflammatory mediators normalize as a result of weight loss in morbidly obese subjects treated with gastric restrictive surgery. *J Clin Endocrinol Metab* 2004; 89 (8): 4062-8.

80. Abranches MV, Oliveira FCE, Bressan J. Peroxisome proliferator-activated receptor: effects on nutritional homeostasis, obesity and diabetes mellitus. *Nutr Hosp* 2011; 26 (2): 271-9.
81. Khovidhunkit W, Kim MS, Memon RA, Shigenaga JK, Moser AH, Feingold KR et al. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. *J Lipid Res* 2004; 45 (7): 1169-96.
82. Birjmohun RS, van Leuven SI, Levels JH, van 't Veer C, Kuivenhoven JA, Meijers JC, et al. High-density lipoprotein attenuates inflammation and coagulation response on endotoxin challenge in humans. *Arterioscler Thromb Vasc Biol* 2007; 27: 1153-8.
83. Pajkrt D, Doran JE, Koster F, Lerch PG, Arnet B, van der Poll T et al. Antiinflammatory effects of reconstituted high-density lipoprotein during human endotoxemia. *J Exp Med* 1996; 184 95): 1601-8.
84. Cuoco L, Montalto M, Jorizzo RA, Santarelli L, Arancio F, Cammarota G et al. Eradication of small intestinal bacterial overgrowth and oro-cecal transit in diabetics. *Hepatogastroenterology* 2002; 49: 1582-6.
85. Byrne MM, Pluntke K, Wank U, Schirra J, Arnold R, Goke B et al. Inhibitory effects of hyperglycaemia on fed jejunal motility: potential role of hyperinsulinaemia. *Eur J Clin Invest* 1998; 28: 72-8.
86. Yang SQ, Lin HZ, Lane MD, Clemens M, DiehlAM. Obesity increases sensitivity to endotoxin liver injury: implications for the pathogenesis of steatohepatitis. *Proc Natl Acad Sci USA* 1997; 94: 2557-62.
87. Nymark M, Pussinen PJ, Tuomainen AM, Forsblom C, Groop PH, Lehto M et al. Serum lipopolysaccharide activity is associated with the progression of kidney disease in finnish patients with type 1 diabetes. *Diabetes Care* 2009; 32: 1689-93.
88. 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: 1433-9.
89. Geraldo JM, Alfenas RCG. Papel da dieta na prevenção e no controle da inflamação crônica – evidências atuais. *Arq Bras Endocrinol Metab* 2008; 52 (6): 951-67.
90. Kohen VL, Candela CG, Fernández CF, Rosa LZ, Milla SP, Urbieta M, López LMB. Parámetros hormonales e inflamatorios en un grupo de mujeres con sobrepeso/obesidad. *Nutr Hosp* 2011; 26 (4): 884-9.
91. Ghanim H, Abuaysheh S, Sia CL, Korzeniewski K, Chaudhuri A, Fernandez-Real JM et al. Increase in plasma endotoxin concentrations and the expression of toll-like receivers and suppressor of cytokine signaling-3 in mononuclear cells after a high-fat, high-carbohydrate meal. *Diabetes Care* 2009; 32 (12): 2281-7.
92. Erridge C, Attina T, Spickett CM, Webb DJ. A high-fat meal induces low-grade endotoxemia: evidence of a novel mechanism of postprandial inflammation. *Am J Clin Nutr* 2007; 86: 1286-92.
93. Ghanim H, Sia CL, Upadhyay M, Korzeniewski K, Viswanathan P, Abuaysheh S, et al. Orange juice neutralizes the proinflammatory effect of a high-fat,high-carbohydrate meal and prevents endotoxin increase and Toll-like receiver expression. *J Clin Nutr* 2010; 91: 940-9.
94. De Bandt JP, Waligora-Dupriet AJ, Butel MJ. Intestinal microbiota in inflammation and insulin resistance: relevance to humans. *Curr Opin Clin Nutr Metab Care* 2011,14: 334-40.
95. Romeo J, Nova E, Wärnberg J, Gómez-Martínez S, Ligia LED, Marcos A. Immunomodulatory effect of fibres, probiotics and synbiotics in different life-stages. *Nutr Hosp* 2010; 25 (3): 341-9.
96. Laparra JM, Sanz Y. Interactions of gut microbiota with functional food components and nutraceuticals. *Pharmacol Res* 2010; 61: 219-25.