STRESS-TOLERANCE TESTS AND POSTPRANDIAL LOW-GRADE INFLAMMATION RESPONSE

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ABSTRACT

Both tumor necrosis factor alpha (TNF alpha) and interleukin 6 (IL-6) are considered as proinflammatory cytokines which display marked daily and postprandial variations. The low-grade inflammation is known to contribute to the development of certain states such as type 2 diabetes, metabolic syndrome and related disorders. Oral glucose tolerance test (OGTT) is applied to diagnose diabetes and is widely used to estimate the insulin sensitivity in the postprandial phase. Application of tolerance tests with high lipid content such as oral lipid tolerance test (OLTT), high-fat meal (HFM) and mixed-meal tests are informative for the metabolic response to complex diets. Postprandial hyperlipidemia and hyperglycemia are important and residual risk factors especially in patients with diabetes mellitus and related metabolic disturbances. There are data suggesting that low-grade inflammation could be mediated by hyperglycemia and dyslipidemia. The aim of the review is to summarize how different challenge tests influence the postprandial circulation levels of IL-6 and TNF alpha.

Keywords: *postprandial inflammation, IL-6; TNF alpha, oral glucose tolerance test, oral lipid tolerance test, high-fat meal*

INTRODUCTION

Repeated episodes and prolonged periods of hyperglycemia, hypertriglyceridemia or hyperinsulinemia may play an important role in the initiation and progression of certain states such as atherosclerosis, diabetes, cardiovascular diseases, etc. Postprandial periods are characterized also by higher oxidation rates in the body which in turn may induce nuclear factor kappa B (NFkB) activation. NFkB-related pathways are involved in the expression of various proinflammatory cytokines, including interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF alpha).

Nowadays, there are many studies that present the adverse postprandial effects of a high- fat meal (HFM). Postprandial hyperlipidemia is an important and residual risk factor especially in patients with diabetes mellitus and related metabolic disturbances (23). Vascular endothelial dysfunction is generally associated with an increase in the proinflammatory markers (1,7).

Postprandial state, especially the one characterized by high levels of triglycerides in the plasma is considered to directly induce the levels of proinflammatory molecules such as IL-6 and MCP1 secreted by adipocytes (13).

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AIM

The aim of the present study is to review the effects of different challenge tests on the postprandial circulation levels of IL-6 and TNF alpha.

MATERIALS AND METHODS

The following literature database was used as a source for the review: http://journals.plos.org/plosone; http://www.ncbi.nlm.nih.gov/pubmed. The keywords that we have used were: circulating levels of IL-6; circulating levels of TNF alpha; oral glucose tolerance test; high-fat meal; oral lipid tolerance test; postprandial inflammation; postprandial low-grade inflammation; metabolic disorders; type 2 diabetes. The present review summarizes publications from the 2001 – 2016 period.

OGTT and OLTT Effects Are Measured by Clinical Biochemical Biomarkers

The oral glucose tolerance test (OGTT) is widely used and has been applied to diagnose diabetes for decades. It is based on the fact that patients with diabetes mellitus have significantly lower ability to metabolize the blood sugar after glucose loading compared to healthy people. OGTT is a tool in the diagnostics of diabetes providing accurate assessment of the ability of the organism to metabolize glucose, much more precise than the measurement of fasting blood sugar levels. It determines the ability of the pancreas to secrete insulin and enables the detection of such metabolic disturbances (4). The postprandial state is characterized usually by the changes in lipid and carbohydrate metabolism, including hypertriglyceridemia, hyperglycemia and reduced concentration of HDL-cholesterol (30). These fluctuations are physiological processes which occur many times a day in a lipid-enriched diet. Different metabolic disturbances, type 2 diabetes (T2D), cardiovascular diseases are accompanied by hyperglycemia and impaired glucose tolerance and/or dyslipidemia. In such conditions increased ratio of LDL/HDL-cholesterol, increased levels of LDL-cholesterol and increased levels of plasma triglycerides are determined (15).

The oral lipid tolerance test (OLTT) has been widely used to evaluate the postprandial fat load effect on single markers of inflammation. Postprandial dietary lipids are absorbed in the intestine and secreted into the lymph as chylomicrons, rich in triglycerides. After a fatty meal, exogenous fatty acids are delivered to the liver by chylomicron remnants and may then be reassembled and returned to the blood in very low-density lipoproteins (VLDL) (24). The hypertriglyceridemia, observed postprandially, is due to elevated levels of chylomicrons, VLDL, and their respective remnants. In the postprandial phase, capillary lipoprotein lipase is highly active and the triglyceride-rich lipoproteins are in a competition for this enzyme, which is not able to metabolize all of them. The non-metabolized lipoprotein complexes accumulate and lead to hypertriglyceridemia. The increased levels of free fatty acids as a result of a hypercaloric diet were regarded as one of the key etiologic components of obesity and related disorders such as metabolic syndrome, T2D and low-grade inflammation (11).

OGTT Affects the Cytokine Levels

The oral glucose challenge has been associated with a significant increase in the expression of pro-inflammatory cytokines, including interleukin IL-1α/β, IL-6, and IL-8 which may result from endoplasmic reticulum stress (29).

In the study of Manning et al. (2008), the IL-6 levels changed acutely in the postprandial state with an initial significant decline of IL-6 levels followed by a later rise at the end of OGTT. Similarly, initial reduction in plasma IL-6 was observed after an oral glucose load and a fatty meal (17). Furthermore, such observation was established in lean and obese individuals (20) as well as in an investigation on overweight women (12).

In a later investigation, Manning et al. (2013) revealed that plasma IL-6 concentrations were acutely and temporarily decreased at the 30th, 60th and 90th minute after an oral glucose load. On the other hand, intravenous glucose administration did not noticeably affect plasma IL-6 concentrations.

The early decrease of plasma levels of IL-6 after oral glucose load could be attributed to elevated insulin levels at this time (21). Insulin is considered to have anti-inflammatory properties, hence it could attenuate the pro-inflammatory effect of hyperglycemia (3,9). Beisswenger et al. (2011) also speculated that an acute increase in the circulating insulin lev-

els during a meal was the cause of decreased plasma IL-6 concentrations in patients with T2D.

OLTT, HFM and Mixed-Meal Challenge Tests Affect the Cytokine Levels

A study of Phillips et al. (2013) suggests that administration of a standardized high-fat meal leads to a postprandial decrease of IL-6 in subjects with T2D and the complete opposite - an increase - in lean subjects (26).

In a study involving forty-eight people with T2D and 32 individuals with normoglycemia the application of a mixed-meal challenge test (carbohydrates, proteins and fat content 79.1%, 7.7% and 13.2%, respectively) resulted in a postprandial decrease of the levels of IL-6 in both groups. Thus, the consumption of a carbohydrate-rich meal was associated with a decrease in IL-6 among healthy individuals and people with T2D (22). In contrast, in overweight individuals noticeably increased levels of IL-6 and less pronounced rise of TNF alpha after HFM were observed (14,19,25).

Moher et al. (2014) measured the postprandial levels of IL-6 and TNF alpha among normal individuals and people with T2D in an Indian population. Their observation was that 4 h after a mixed-meal intake the levels of proinflammatory cytokines IL-6 and TNF alpha were elevated. Hence, the postprandial increase in plasma IL-6 levels was expected and was consistent with the general proinflammatory and prothrombotic effects of hypertriglyceridemia. In a study including OLTT combined with physical activity, the levels of plasma IL-6 increased significantly throughout the postprandial period in both of the examined groups (exercise trial and rest trial). However, exercise did not significantly affect beneficially the postprandial IL-6 response in plasma. At the same time, exercise significantly lowered the IL-6 expression in subcutaneous adipose tissue (10).

Study with rodents established that plasma IL-6 levels were significantly elevated in the postprandial state and two hours after a meal high in saturated fat they reached their maximum (18). IL-6 gene expression in adipose tissue was higher 2 h after the HFM compared to the group of control animals receiving water ad libitum. At the same time, TNF alpha gene expression levels in adipose tissue remained very similar, 2 and 6 h after the HFM, both compared to control water load. On the other hand, the increase in circulating markers of low-grade inflammation was transient and occurred very early (2 h after the HFM) when compared to the gradual increase in plasma triglycerides (18).

Poppit et al. (2008) observed that IL-6 levels increased postprandially in response to HFM in lean healthy males. Earlier studies revealed an increase of both IL-6 and TNF alpha levels in healthy individuals and in patients with T2D. TNF alpha levels increased in patients with metabolic syndrome as well.

In another investigation, there was no associated rise of postprandial TNF alpha levels in obese subjects. Blackburn et al. observed a significant decrease of TNF alpha levels in a subgroup of insulin-sensitive obese men 4 hours after HFM administration. In contrast, there was no significant response in a group of subjects with high HOMA-IR in the same study (14).

Mechanism of Postprandial Inflammatory Signaling

To examine the mechanisms underlying postprandial inflammatory signaling, in vitro studies have suggested that triglyceride-rich lipoproteins isolated from human plasma after a HFM may directly induce inflammatory changes affecting both endothelial cells and leukocytes (2). Concomitant with postprandial endothelial activation, Suganami et al. (2007) established that saturated fat could activate the Toll-like receptor 4/NFκB pathway in a co-culture of adipocytes and macrophages, suggesting a contribution of adipose tissue to postprandial inflammation. According to Carpentier et al. (2008), saturated fatty acids may activate Toll-like receptors, which in turn activate the NFkB pathways including in the expression of various proinflammatory cytokines as IL-6 and TNF alpha.

The study of Magne et al. (2010) of healthy rats suggested that an HFM could provoke an early transient activation of the transcription factor NFκB in visceral adipose tissue, which is supported by an acute increase in IL-6 gene expression (an NFκB target gene) in visceral adipose tissue. The postprandial activation of NFκB and IL-6 upregulation in adipose tissue is consistent with the marked increase of IL-6 in plasma. Nowadays, it is considered that the visceral adipose tissue, not only a fat mass depot, but an

endocrine organ as well is the source of a significant part of IL-6 recovered in the circulation.

CONCLUSION

Some studies report that the levels of IL-6 significantly increased during and soon after OGGT. On the other hand, there are evidences about an initial decline of IL-6 circulating levels due to a simultaneous increase of insulin after a glucose load in healthy subjects, later this response being followed by a rise in IL-6 levels. High fat load could contribute to postprandial increase of certain early proinflammatory cytokines (IL-6 and TNF alpha) in plasma consistent with the general proinflammatory effect of hypertriglyceridemia.

In addition, there are some considerations to follow in such studies. In particular, circulating levels of IL-6 and TNF alpha cytokines are in concentrations as low as picograms per milliliter and therefore it is quite challenging to measure them accurately. In addition, researchers should keep in mind that these molecules display marked daily and postprandial variations. Challenge tests still remain quite of a challenge to the research community with much more to reveal ahead.

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