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Dietary intervention with an Okinawan-based Nordic diet in type 2 diabetes renders decreased interleukin-18 concentrations and increased neurofilament light concentrations in plasma

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ARTICLE INFO

Article history:
Received 5 February 2018
Revised 22 July 2018
Accepted 17 August 2018

Keywords:
Cytokines
Glucose metabolism
IL-18
Inflammation
Neurofilament light
Okinawan-based Nordic diet
Type 2 diabetes

ABSTRACT

Food may induce inflammation and favor development of metabolic diseases, which have been associated with increased inflammation and potential risk of cognitive impairment. It is customary to know whether food or disease promote inflammation. Our hypothesis was that Okinawan-based Nordic (O-BN) diet leads to decreased circulating concentrations of inflammatory and neural biomarkers. The objectives of this study were to examine the effects of the O-BN diet on inflammatory and neural responses. First, 2 different breakfasts; one standard and another O-BN-based, were given in random order to 19 healthy volunteers. Second, a 12-week O-BN-dietary intervention was performed in type 2 diabetes mellitus (T2DM), where the participants were followed for another 16-weeks, with registration of anthropometry and metabolic parameters. Non-diabetic subjects served as controls at baseline. Plasma was analyzed for cytokines by a 10-plex Luminex assay and neurofilament light (NfL) by an ultrasensitive Single molecule assay. Cytokine levels decreased after a single breakfast intake, independent of diet composition. Cytokine levels were higher in T2DM than in controls. Anthropometric and metabolic parameters were improved by the dietary intervention. In parallel, cytokine levels were lowered, although only significantly for IL-18 ($P = .001$), with a tendency of significance for IL-12p70 ($P = .07$). Levels of IL-18 correlated with glucose, HbA1c and lipids, but not with body mass index,

Abbreviations: AD, Alzheimer's disease; CRP, C-reactive protein; E%, energy percent; HRQoL, health-related quality of life; HbA1c, hemoglobin A1c; IFN-γ, interferon gamma; IL, interleukin; NfL, neurofilament light; O-BN, Okinawan-based Nordic diet; TNF-α, tumor necrosis factor alpha; T2DM, type 2 diabetes mellitus.

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https://doi.org/10.1016/j.nutres.2018.08.002

insulin or blood pressure. NfL levels increased during the intervention ($P = .049$). O-BN-based diet does not affect postprandial cytokine levels in health, whereas it renders decreased circulating IL-18 levels along with metabolic biomarkers in T2DM, with no beneficial effect on NfL.

1. Introduction

Obesity and metabolic diseases, such as type 2 diabetes mellitus (T2DM), have previously been shown to be associated with low-grade chronic inflammation in both animal and human interventional trials, as well as epidemiological studies, with increased levels of C-reactive protein (CRP), cytokines and plasminogen activator inhibitor (PAI-1) [1,2]. Whether chronic low-grade inflammation is a precursor to metabolic disease remains undetermined, and longitudinal interventional studies are needed in order to explore causality. Food has been proposed to affect expression of inflammatory parameters, with some diets believed to act pro-inflammatory and others anti-inflammatory, but identification of which dietary components that promote or prevent inflammation is warranted [3]. The typical Western diet with a high carbohydrate intake (50-60 energy percentages (E%) carbohydrates) has been thought to generate low-grade chronic inflammation with increased levels of CRP and cytokines [3]. A diet with lower carbohydrate content but higher E% of fat and protein, e.g. the Okinawan-based Nordic (O-BN) diet with 35 g daily fiber intake [4], would hypothetically decrease systemic inflammation [2]. The Okinawan diet is similar in composition to the Mediterranean diet [5], which has been shown to possess anti-inflammatory properties in many interventional and epidemiological studies in both health and metabolic diseases, with lower levels of inflammatory biomarkers and decreased risk to develop metabolic and cardiovascular diseases [6-8]. The healthy Nordic diet showed improved metabolism and lowered levels of inflammatory biomarkers in the metabolic syndrome [9,10]. However, the anti-inflammatory properties of the Okinawan or O-BN diets have been rudimentarily examined. We have previously shown that a single meal based upon the O-BN diet induced lower postprandial glucose, insulin and triglyceride levels compared to a standard meal in healthy volunteers [11,12]. A 12-week intervention with the O-BN diet in T2DM improved levels of fasting glucose, HbA1c, insulin, haptoglobin, thrombocytes, adipokines and PAI-1, whereas levels of CRP were unaffected and levels of calprotectin and zonulin were increased [13,14]. The observed elevations in calprotectin and zonulin do not necessarily stem from the change in dietary composition, but from liver impact secondary to weight loss [15]. There is no consensus of which inflammatory biomarkers that best reflect presence of chronic low-grade inflammation, but the most studied are CRP, interleukin (IL)-1α, IL-1β, IL-6, IL-8, IL-10, tumor necrosis factor alpha (TNF-α) and PAI-1 [2,3,16,17].

In the T2DM population, diabetes duration, glycated hemoglobin (HbA1c) levels and glycemic fluctuations have been shown to be associated with cognitive decline and dementia [18,19]. There are several proposed pathologic mechanisms linking T2DM to neural damage, such as chronic hyperglycemia and glucose toxicity resulting in osmotic insults and oxidative effects on neurons, ischemia of the microvascular system and insulin metabolic dysfunction promoting amyloid-β accumulation in the brain [18-20]. Indeed, similarities have been observed between Alzheimer's disease (AD) and T2DM neuropathology, including reduced insulin signaling and insulin-like growth factor abnormalities in the AD brain [21]. Neurofilament light (NfL) is a structural protein that is highly expressed in large caliber myelinated axons that extend subcortically [22]. Neurodegeneration results in release of the protein into the brain interstitial fluid, which communicates freely with the cerebrospinal fluid (CSF). Increased CSF NfL concentrations are seen in a broad range of neurodegenerative diseases and may reflect fragmentation of myelinated axons [22]. Recent advances in ultrasensitive measurement technologies have made it possible to measure NfL in blood. Using a Single molecule array (Simoa)-based method, NfL can be measured in blood with robust correlation with CSF levels [23]. AD patients have increased blood NfL concentrations and the levels correlate with the onset and intensity of the neurodegenerative process [24,25].

Our overall hypothesis was that an O-BN diet leads to decreased circulating concentrations of inflammatory and neural biomarkers, along with improved anthropometric and metabolic parameters. To investigate this hypothesis, 2 separate interventional studies with O-BN diet were performed: one study to examine the effect of a single breakfast meal in health and another study to examine the effect of a 12-week complete intervention in T2DM. Blood samples were taken before breakfast meals and during 3 h postprandial. In the 12-week intervention, anthropometric measurements and blood samples were taken before study start, after 12 weeks, and after another 16 weeks with re-introduction of regular food habits. In both studies, metabolic parameters and a Luminex assay of cytokine levels were analyzed in plasma, and in the latter, NfL levels were additionally analyzed by a Single molecule assay. The study population, design and diet of both studies have been thoroughly described in previous publications [4,11-14]. The primary objectives of the present part-study with the O-BN diet were to examine the responses of: 1) circulating cytokines postprandial in healthy individuals before and after a single meal in comparison with a reference breakfast; and 2) circulating cytokines and 3) NfL before and after a 12-week intervention in T2DM patients. The secondary objectives were to correlate the changes of cytokine and NfL levels with anthropometric and metabolic changes.

2. Methods and materials

The studies were performed at the Department of Internal Medicine, Skåne University Hospital, Malmö, Sweden. Blood