Cytokine 73 (2015) 265–269

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.journals.elsevier.com/cytokine

Soluble receptor for advanced glycation end products as a potential biomarker to predict weight loss and improvement of insulin sensitivity by a very low calorie diet of obese human subjects

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ARTICLE INFO

Article history:
Received 28 October 2014
Received in revised form 21 January 2015
Accepted 9 February 2015
Available online 21 March 2015

Keywords:
Soluble receptor for advanced glycation end products
Very low calorie diet
Biomarker
Dietary intervention

ABSTRACT

Introduction: Obesity is associated with low-grade systemic inflammation which is thought to trigger the development of comorbidities such as type 2 diabetes. The soluble receptor for advanced glycation end products (sRAGE) belongs to the innate immune system and has been linked to obesity, recently. The aim of the present study was to examine whether serum sRAGE concentrations are related to the grade of weight loss and improvement of insulin resistance due to a very low calorie diet (VLCD).
Methods: 22 severe obese subjects (Median Body Mass Index (BMI): 44.5 kg/m^2) were included in a dietary intervention study of 6 month, consisting of a very low calorie formula diet phase (VLCD: 800 kcal/d) for 12 weeks and a following 12 week weight maintenance phase. Fasting glucose, fasting insulin, adiponectin, leptin and sRAGE were determined from sera. Insulin sensitivity was estimated by Homeostasis Model Assessment (HOMA) index and leptin-to-adiponectin-ratio (LAR).
Results: Mean body weight reduction by VLCD accounted to 21.7 kg with a significant improvement of insulin resistance. At baseline, sRAGE serum levels were significantly inversely related to BMI ($r_S = -0.642$, $p = 0.001$) and HOMA ($r_S = -0.419$, $p = 0.041$). Of interest, sRAGE serum levels at baseline were significantly lower in study subjects with greater reduction of BMI ($p = 0.017$). In addition, a significantly greater HOMA reduction was observed in subjects with lower sRAGE serum levels at baseline ($p = 0.006$). Finally, correlation analysis revealed, that changes of sRAGE serum levels were significantly correlated to changes of BMI ($r_S = -0.650$, $p = 0.022$) during intervention.
Conclusion: Anti-inflammatory sRAGE might be a potential future biomarker to predict weight loss and improvement of insulin resistance by a VLCD whereby lower baseline sRAGE serum levels indicate a better outcome of the dietary intervention.

1. Introduction

The worldwide increasing prevalence of obesity leads to metabolic comorbidities such as type 2 diabetes, lipid disorders and as a consequence to higher risk for cardiovascular diseases [1]. Nowadays, the link between obesity and its related comorbidities is thought to be driven by low-grade inflammation. With the infiltration of macrophages to the adipose tissue, inflammatory signals in the body are increased and promote the development of metabolic disorders [2]. However, reliable inflammatory biomarkers, predictors and therapy targets in the innate immune system for obesity treatment are still missing.

The receptor for advanced glycation end products (RAGE) belongs to the immunoglobulin superfamily and serves as a receptor for several ligands, such as advanced glycation end products (AGE) or amyloid β-peptide [3]. The receptor can i.a. be found in many cells of the immune system, such as monocytes, macrophages or T-cells [3–6]. Thus, RAGE takes part in the inflammatory

Abbreviations: AGE, advanced glycation end products; BMI, Body Mass Index; esRAGE, endogenous secreted receptor for advanced glycation end products; HOMA, Homeostasis Model Assessment index; JAK/STAT, Januskinase/Signal transducers and activators of transcription; LAR, leptin-to-adiponectin-ratio; NFκB, nuclear factor 'kappa-light-chain-enhancer' of activated B-cells; RAGE, receptor for advanced glycation end products; sRAGE, Soluble receptor for advanced glycation end products; VLCD, Very low calorie diet.

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http://dx.doi.org/10.1016/j.cyto.2015.02.022
1043-4666/

response. With the binding of ligands to RAGE, several downstream signaling pathways are activated, for example nuclear factor 'kappa-light-chain-enhancer' of activated B-cells (NFκB) or Janus kinase/Signal transducers and activators of transcription (JAK/STAT). This leads to the promotion of inflammation and also to an upregulation of RAGE [7,8]. However, distinct isoforms of RAGE exist: the full-length, membrane-bound RAGE with an extracellular, transmembrane and cytosolic domain, a n-truncated RAGE and a C-truncated RAGE with a missing transmembrane and cytosolic domain. The latter can be released into extracellular fluids and is also called soluble RAGE (sRAGE). It can be formed by proteolytic cleavage by metalloproteinases or alternative mRNA splicing which is then also called endogenous secreted RAGE (esRAGE) [9,10].

As it is circulating in the blood, sRAGE is hypothesized to neutralize the action of pro-inflammatory ligands for RAGE and hence to protect against inflammation-associated disorders. This is supported by clinical studies which found an inverse relation between Body Mass Index (BMI) and sRAGE in healthy [11–13] and diabetic subjects [14], but also no relation between BMI and sRAGE has been reported [15]. Moreover, lower levels of sRAGE were present in subjects with higher cardiovascular risk [16–19], while in diabetic patients the opposite relation has been shown [14,20,21]. So far, only studies using exercise [22], bariatric surgery or medical therapy for weight loss [23–25] did examine sRAGE serum levels in response to the intervention, with conflicting results. No study was conducted with a very low calorie diet (VLCD) intervention which is often performed in severe obese patients with or without obesity-related comorbidities.

Therefore, the aim of the present study was to investigate whether sRAGE is modulated by a dietary intervention, consisting of a first phase with a VLCD with formula meals and a second weight maintenance phase in which the formula diet was replaced by hypo-isocaloric diet [26]. In addition, it was of interest to determine the relations between sRAGE and metabolic parameters in the course of this two-phase dietary intervention and to evaluate whether sRAGE is a candidate to serve as a biomarker of success for a VLCD based obesity therapy.

2. Materials and methods

2.1. Dietary intervention study population

The study has been conducted at the University Medical Center in Kiel, Germany and was approved by the local ethics committee. Written informed consent was obtained from each subject before inclusion into the study. A total number of 22 subjects (5 men, 17 women) was included. No dropout occurred during the study. Inclusion criteria were: age between 20 and 65 years, Caucasian descent and Body Mass Index > 30 kg/m^2.

Ten of the 22 subjects suffered from hypertension, 5 had type 2 diabetes mellitus, 3 subjects had a substituted hypothyroidism and 1 each had hyperlipidemia, hyperuricemia, chronic venous insufficiency, psoriasis or colitis ulcerosa. 2 subjects had obstructive sleep apnea, 2 had gonarthrose, and 1 each had coxarthrose, a biliary operation, a lipedema in the lower leg, lactose intolerance, sigma diverticulosis, cholecystolithiasis, uterus myomatosus, endometriosis genitalis externa or allergic diathesis. 1 had an endoscopic resection of a colorectal adenoma with low-grade tubular epithelial dysplasia.

Regarding pharmacotherapy 10 subjects were taking 1 or more blood pressure lowering drugs, 6 subjects were taking angiotensin II receptor subtype 1 antagonist, 5 were taking beta-blockers, 4 were taking angiotensin converting enzyme antagonists, 4 were taking calcium antagonists, 4 were taking diuretics and 2 were taking a diuretic and angiotensin II receptor subtype 1 antagonist combination. 6 subjects had diabetic therapy, 5 were taking metformin, 2 incretin mimetics and 1 insulin therapy. 5 subjects were on any kind of pain killer medication, 3 subjects were taking one or more vitamin or mineral supplements, 3 subjects were taking hypothyroidism therapy. 3 subjects were taking proton pump inhibitors, each 2 subjects were taking cholesterol lowering medication (statins), immune suppressive therapy, glucocorticoid or beta-adrenoceptor-agonist inhalation therapy. Each 1 was taking antibiotics, anti-depressive medication or laxative.

2.2. Dietary intervention program

The study was embedded in a dietary intervention program which consisted of different phases [26]. At the beginning a VLCD was taken by the subjects for 12 weeks. Total caloric intake was approximately 800 kilocalories (kcal) per day divided into 4 to 5 meals of Optifast 800® Mix per day. In a second part, the formula meals were replaced step by general meals (weeks 13–24). In addition, the diet was accompanied by a commercial multimodal obesity program which included nutritional education, behavioral advice and 45 min exercise per week.

2.3. Data collection and biochemical analyses

Blood samples were taken after an overnight fast at baseline ($n = 22$), week 12 ($n = 21$) and week 24 ($n = 11$) in our outpatient clinic. Serum was stored immediately at −80 °C. Fasting glucose and insulin were determined and Homeostasis Model Assessment (HOMA) index was calculated as glucose ∗ insulin/405. leptin, adiponectin, and sRAGE were determined in serum by ELISA (leptin: RE53131 – IBL International; Adiponectin: RD 195023100 – BioVendor; sRAGE: ab100632 – abcam). leptin-to-adiponectin-ratio (LAR) was calculated by the formula: LAR = leptin/adiponectin.

2.4. Statistical analysis

All statistical analyses were calculated with SPSS 22. 1 patient was excluded from analyses due to determined extreme values in sRAGE levels. Data are given as median and range between 25th and 75th percentile according to Tukey. Due to the small sample size a test to determine deviations from normal distribution would have low statistical power. Therefore, exclusively statistical methods for non-parametric data were applied. For overall group comparisons between baseline, week 12 and week 24 Friedman test was applied. In case of significance, comparisons between the single points of measurement were determined using Wilcoxon signed rank test. Spearman's test was used for correlation analyses. Due to small number of cases an adjustment for p-values would have limited strength. Therefore, the explorative description was chosen to emerge the comparisons of strength of associations. For the comparison of the groups with high or low weight loss or change in insulin resistance Mann–Whitney-U-Test was applied. The significance level for all analyses was set at p-value $\leqslant 0.05$, for Wilcoxon signed rank test at $p \leqslant 0.017$ due to Bonferroni adjustment.

3. Results

3.1. Effect of dietary intervention on anthropometric and metabolic parameters

22 obese study subjects were included in a dietary intervention program which consisted of two phases: a first phase of VLCD with