Clinical Biochemistry 49 (2016) 750–755

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Association between serum cytokine concentrations and the presence of hypertriglyceridemia

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ARTICLE INFO

Article history:
Received 26 October 2015
Received in revised form 26 March 2016
Accepted 30 March 2016
Available online 2 April 2016

Keyword:
Cytokines
Hypertriglyceridemia
Dyslipidemia
Triglyceride

ABSTRACT

Objective: Hypertriglyceridemia is an established risk factor for coronary-heart-disease. Inflammatory cytokines are known to be important mediators of atherogenesis; however, the relationship between the concentrations of specific inflammatory cytokines and the presence of hypertriglyceridemia has not been well established. The purpose of this study was to investigate the relationship between the serum levels of several pro- and anti-inflammatory cytokines and the presence of hypertriglyceridemia.

Design and methods: Four hundred and eighty-four subjects with/without established hypertriglyceridemia were recruited. Anthropometric parameters and biochemical analysis (including a full fasting lipid profile) were determined. The serum levels of several cytokines and growth factors including IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, MCP-1, IFN-γ, EGF, and VEGF were measured followed by univariate and multivariate analyses.

Results: Individuals with hypertriglyceridemia had a significantly higher body mass index, total-cholesterol and triglyceride, compared to the group without hypertriglyceridemia. Serum levels of MCP-1, TNF-α and IL-8 were significantly higher in subjects with hypertriglyceridemia [e.g., IL-8 from 7.8 ng/L (95% CI: 4.6–18.9) versus 5.7 ng/L (95% CI: 3.6–11.9), $P < 0.05$]. The multivariate analysis showed that the increased serum concentration of TNF-α was independently associated with high-density lipoprotein cholesterol (HDL-C), while the serum levels of IL-8 and MCP-1 were associated with hypertriglyceridemia.

Conclusion: Subjects with serum triglycerides of ≥2.25 mmol/L had an altered cytokine-profile, particularly with respect to serum IL-8, MCP-1 and TNF-α, which might partially account for its adverse clinical-consequences. Further-investigations in a large multi-center setting are warranted to unravel the potential functional-importance of these cytokines in individuals with hypertriglyceridemia.

1. Introduction

Hypertriglyceridemia is defined by triglyceride (TG) concentrations of >1.69 mmol/L, which has been shown to be associated with an increased risk factor for coronary heart disease (CHD) [1]. It has been

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http://dx.doi.org/10.1016/j.clinbiochem.2016.03.009
0009-9120/

reported that approximately 53% of American adults have lipid abnormalities [2], including a raised level of serum triglycerides (TG) [3]. The prevalence of hypertriglyceridemia in adults in the USA is approximately 32.6% [4]; the prevalence of hypertriglyceridemia in Iran is reported to be of a similar magnitude (29.0–49.3%) [5].

Previous studies have shown that hypertriglyceridemia is associated with systemic inflammation and atherogenic factors [6,7]. Inflammatory processes are involved at various stages during the atherosclerotic process, from lesion initiation to plaque rupture [8]. The atherosclerotic plaque contains cells that elaborate several cytokines, and the balance between pro- and anti-inflammatory cytokines may contribute to the severity and stability of atherosclerotic plaques [9]. Cells within the adipose tissue also produce pro-inflammatory factors such as tumor necrosis factor-α(TNF-α), interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1) [10] and hence there is a potential link between adiposity and a pro-inflammatory milieu.

It has been shown that IL-1 and the TNF stimulate hepatic synthesis of fatty acids [11], which is closely paralleled by an increased level of serum triglyceride levels [12]. An increase in the level of hepatic fatty acid synthesis is observed following the initiation of a variety of diets that include a high-sucrose diet to a high-fat diet [13]. Moreover, recent data have shown that some cytokines enhance the synthesis of fatty acids in the liver [14], although the molecular mechanism is not known [15]. Additionally, it has been shown that hypertriglyceridemic patients have a higher level of blood TNF-α, IL-6, C-reactive protein and fibrinogen [16]. TNF can affect lipid metabolism via adipose tissue lipoprotein lipase, hepatic fatty acid synthesis, and lipolysis [17]. In our previous studies, we have investigated the role of 12 cytokines in patients with metabolic syndrome and coronary artery diseases and suggested that these patients had an altered blood cytokine and growth factor profile that may partially account for its adverse clinical outcomes [18]. In the present study we have further investigated the association between the presence of hypertriglyceridemia and the serum concentrations of 12 cytokines and growth factors in 484 subjects with, or without hypertriglyceridemia.

2. Materials and methods

2.1. Phenotypic definition of hypertriglyceridemia

A fasting serum TG was used to define individuals with hypertriglyceridemia (≥2.25 mmol/L), borderline hypertriglyceridemia (1.69 ≤ TG < 2.25 mmol/L) and normal serum triglycerides (TG < 1.69 mmol/L) according to the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) guidelines [19].

2.2. Population

A total of 484 subjects, including 265 individuals with hypertriglyceridemia, were recruited from Mashhad stroke and heart atherosclerotic disorder (MASHAD) study [20]. Subjects who had no history of endocrine abnormalities, chronic liver and/or renal diseases, and cardiac diseases, subjects being treated with hypoglycemic or other medications, or those consuming alcohol were excluded. Informed consent was obtained from all participants using protocols approved by the Ethics Committee of the Mashhad University of Medical Sciences.

2.3. Anthropometric assessments

Height, weight, body mass index (BMI), waist circumference (WC), hip circumference (HC), and blood pressure were measured in all the subjects as described previously [20,21].

2.4. Biochemical measurements

Total serum cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and TG, serum C-reactive protein (CRP) and fasting blood glucose (FBG) concentrations were determined in all the subjects, as described previously [20,21].

2.5. Measurement of cytokines

The level of serum cytokines and growth factors including IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, IFN-γ, MCP-1, EGF and VEGF were measured using an EV 3513 cytokine biochip array (Randox Laboratories, Crumlin, UK) and competitive chemiluminescence immunoassays (Randox Laboratories, Crumlin, UK), according to the manufacturers' instruction, using the RANDOX Evidence Investigator [22,23].

2.6. Statistical analysis

Data was analyzed using SPSS-16 software (SPSS Inc., IL, USA). The normality of distribution was assessed using the Kolmogorov–Smirnov test. Descriptive statistics (mean ± standard deviation (SD) or median ± interquartile range (IQR)) were determined for normally or not normally distributed variables, respectively. Baseline demographics and clinical characteristics were compared by one-way ANOVA and Kruskal–Wallis test. Also the post hoc test and Mann–Whitney U test were used for comparison between groups. The chi-square test, and/or Fisher exact test was used for comparing categorical variables. Bonferroni correction was used for multiple comparisons.

Linear regression analysis was utilized to calculate relationship between serum cytokines level and hypertriglyceridemia in present of confounder factors (such as age, gender, BMI, FBG and HTN). A P value < 0.05 was considered as statistically significant.

3. Results

3.1. Clinical characteristics of the population

The clinical and baseline characteristics of subjects are shown in Table 1. Individuals with hypertriglyceridemia had a significantly higher BMI, WC, and TC compared to the group with normal serum triglycerides, while the group with borderline triglycerides (1.69 ≤ TG <2.25 mmol/L) had a significantly higher WC, BMI, FBG, TC, TG, SBP and DBP compared to the group with normal triglycerides (Table 1).

3.2. Serum cytokine concentrations in individuals with hypertriglyceridemia

As shown in Table 2, subjects with hypertriglyceridemia had significantly higher serum concentrations of IL-6, IL-8, IL-10, IFN-γ and TNF-α, compared to the group with normal triglycerides. A significant difference was found for serum IL-6, IL-10, and MCP-1 between the hypertriglyceridemia and borderline groups (Table 2).

3.3. Association of cytokines and growth factors with lipid profile

In order to determine the association between serum cytokine and growth factor concentrations with hypertriglyceridemia, univariate and multivariate analyses were undertaken (Table 3). The serum IL-6 level in subjects with low HDL-C was significantly (P < 0.05) higher than the group with normal HDL-C. However, following the adjusted multivariate analyses, no significant relationship was observed. The serum IL-8 level was higher in the borderline and hypertriglyceridemia groups compared to the subjects with normal triglycerides. This remained significant following adjustment for the confounding variables