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Association between serum cytokine concentrations and the presence of hypertriglyceridemia

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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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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

Table 1
Clinical characteristics of population.

Characteristics		Normal triglycerides (n = 260)	Borderline triglycerides (n = 87)	HT (n = 95)	P1	P2	P3
Age (year) (Mean ± SD)		47.9 ± 11.9	50.4 ± 11.4	50.5 ± 10.9		0.078	
Sex (No. (%))	Male	98 (37.7)	33 (37.9)	45 (47.4)		0.237	
	Female	162 (62.3)	54 (62.1)	50 (52.6)			
Smoking (No. (%))	No	145 (73.2)	48 (67.6)	51 (63)		0.217	
	Yes	53 (26.8)	23 (32.4)	30 (37)			
BMI (kg/m^2) (Mean ± SD)		28.8 ± 5.6	30.5 ± 4.2	30.7 ± 4.8	0.029	0.008	0.993
WC (m) (Mean ± SD)		0.97 ± 0.13	1.02 ± 0.10	1.02 ± 0.12	0.006	0.003	0.968
HC (m) (Mean ± SD)		1.07 ± 0.11	1.08 ± 0.10	1.08 ± 0.08		0.185	
FBG (mmol/L) (Mean ± SD)		5.48 ± 1.67	6.30 ± 2.4	6.23 ± 4.15	0.014	0.247	0.999
TC (mmol/L) (Mean ± SD)		4.82 ± 0.91	5.31 ± 0.93	5.44 ± 1.09	<0.001	<0.001	0.790
TG (mmol/L) (Median(IQR))		1.17 (0.90–1.42)	1.91(1.81–2.05)	2.77(2.50–3.25)	<0.001	<0.001	<0.001
HDL–C (mmol/L) (Mean ± SD)		1.14 ± 0.24	1.08 ± 0.20	1.00 ± 0.16	0.105	<0.001	0.013
LDL–C (mmol/L) (Mean ± SD)		3.04 ± 0.85	3.34 ± 0.80	3.23 ± 0.95	0.017	0.187	0.656
SBP (kPa) (Mean ± SD)		15.81 ± 3.59	17.16 ± 3.27	16.55 ± 3.06	0.005	0.190	0.434
DBP (kPa) (Mean ± SD)		10.56 ± 2.30	11.25 ± 1.94	10.96 ± 2.09	0.030	0.286	0.638

Comparisons were performed by one–way ANOVA and Kruskal–Wallis test. Also the post hoc test and Mann–Whitney Utest were used for comparison between groups. X^2 of test results for categorical data.
Values are expressed as mean ± SD, median and interquartile range for normally and non–normally distributed variables, respectively.
P1: comparison between groups of control and borderline, P2: comparison between groups of control and hypertriglyceridemia and control, P3: comparison between groups of borderline and hypertriglyceridemia.
Borderline: 1.69 ≤ TG < 2.25 mmol/L, HT: hypertriglyceridemia, TG ≥ 2.25 mmol/L, BMI: body mass index; WC: waistcircumference, TC: total cholesterol; TG: triglycerides; HDL–C: high–density lipoprotein cholesterol; LDL–C: low–density lipoprotein cholesterol; FBG: fasting blood glucose; HC: hip circumference, SBP: systolic blood pressure; DBP: diastolic blood pressure.

including age, sex, smoking, BMI, FBG and HTN(Table 3). The serum TNF-α concentration was inversely related to serum HDL-C concentrations. This association remained statistically significant following the multivariate analysis after correction for the confounding factors ($P < 0.05$) (Table 3).

4. Discussion

To the best of our knowledge this is the first study demonstrating an association between serum concentrations of IL-8 and MCP-1 with hypertriglyceridemia, and TNF-α levels in individuals with low HDL-C (<1.03, 1.29 mmol/L). These findings are consistent with our previous findings in patients with cardiovascular disease or metabolic syndrome [18,24]. Our data show that IL-8 and IL-10 concentrations were higher in patients with hypertriglyceridemia; however IL-8 and IL-10 levels were statistically different between groups of individuals with normal triglycerides and those with hypertriglyceridemia. We did not find any significant difference in serum IL-10 level in relationship to lipid profile which is in line with the results of Ferreira-Hermosillo and colleagues [25].Hypertriglyceridemia is associated with altered levels of pro-/anti- inflammatory cytokines, which might suggest the involvement of inflammatory process with progression of this condition and increased the risk of developing CAD.

Serum cytokines are associated with the risk of CVD and altered lipid metabolism [26]. TNF-α is a key player in the inflammatory process, which also modulates the synthesis of fatty acids. Feingold and colleagues showed that TNF-α stimulated hepatic lipogenesis and administration of TNF-α increased the plasma level of triglycerides and cholesterol in animal mode [12].Hence, TNF-α appears to have a role in lipid metabolism via the modulation of lipoprotein lipase activity, adipose tissue and hepatic fatty acid synthesis and lipolysis. We have previously reported an association between TNF-α with CVD risk and

Table 2
Cytokines and growth factor levels in population.

Cytokines & GF	Normal triglycerides (n = 260)	Borderline triglycerides (n = 87)	HT (n = 95)	P1	P2	P3
Interleukin 2 (ng/L)	2.7 (2.5–3.4)	2.7 (2.5–3.1)	2.8 (2.5–3.2)		0.767	
Interleukin 4 (ng/L)	1.9 (1.6–2.4)	2.2 (1.6–2.7)	1.9 (1.7–2.7)		0.290	
Interleukin 6 (ng/L)	1.0 (0.6–1.5)	0.8 (0.6–1.3)	1.2 (0.8–1.8)	0.125	0.037	0.006
Interleukin 8 (ng/L)	5.7 (3.6–11.9)	6.0 (3.2–14.6)	7.8 (4.6–18.9)	0.889	0.010	0.103
Interleukin 10 (ng/L)	0.8 (0.6–1.0)	0.8 (0.7–1.1)	0.9 (0.7–1.5)	0.955	0.001	0.007
VEGF (ng/L)	81.1 (32.3–120.2)	87.9 (24.6–149.3)	85.5 (35.4–170.3)		0.617	
Interferon γ (ng/L)	0.5 (0.4–0.7)	0.5 (0.4–0.8)	0.7 (0.5–1.6)	0.098	<0.001	0.054
TNFα (ng/L)	1.6 (1.2–2.0)	1.7 (1.2–2.2)	2.0 (1.6–2.8)	0.211	<0.001	0.010
Interleukin 1α (ng/L)	0.5 (0.5–0.6)	0.5 (0.4–0.6)	0.6 (0.5–0.7)	0.605	0.059	0.050
Interleukin 1β (ng/L)	0.5 (0.4–0.7)	0.6 (0.4–0.8)	0.6 (0.4–0.8)		0.376	
MCP-1 (ng/L)	118.8 (59.1–182.3)	84.4 (43.1–171.0)	134.5 (57.2–219.2)	0.058	0.161	0.024
EGF (ng/L)	32.6 (7.9–126.8)	36.4 (12.8–98.1)	29.7 (7.3–99.3)		0.850	
hs-CRP(mg/L)	3.7 (1.5–6.6)	2.9 (1.8–6.9)	3.0 (1.3–7.8)		0.915	

HT: hypertriglyceridemia, GF: growth factors, EGF: epidermal growth factor, INF γ: Interferon γ, IL1α: Interleukin-1α, IL1β: Interleukin-1β, IL2: Interleukin-2, IL4: Interleukin-4, IL6: Interleukin-6, IL8: Interleukin-8, IL10: Interleukin-10, MCP1: Monocyte chemoattractant protein-1, TNF-α: tumor necrosis factor, VEGF: vascular endothelial growth factor.
Values were expressed as median (interquartile range).
Serum cytokines levels expressed as ng/L.
P1: comparison between groups of those with normal triglycerides and borderline triglycerides, P2: comparison between groups of with normal triglycerides and hypertriglyceridemia, P3: comparison between groups of borderline triglycerides and hypertriglyceridemia.

Table 3
Association of lipid profile and cytokines levels.

			Univariate					Univariate	
			β	P				β	P
IL–2	HT	Hyper T (n = 95)	–0.25	0.549	IL–4	HT	Hyper T	–.023	0.890
		Borderline (n = 87)	–0.27	0.605			Borderline	0.04	0.785
		Normal[a] (n = 260)	–				Normal[a]	–	
	TC	≥5.172 (n = 177)	–0.49	0.154		TC	≥5.172	–0.09	0.478
		Normal[a] (n = 243)	–				Normal[a]	–	
	HDL–C	<1.03, 1.29 (n = 286)	–0.36	0.314		HDL-C	<1.03, 1.29	0.22	0.110
		Normal[a] (n = 134)	–				Normal[a]	–	
	LDL–C	≥3.36 (n = 260)	–0.25	0.484		LDL-C	≥3.36	0.10	0.147
		Normal[a] (n = 164)	–				Normal[a]	–	
IL–6	HT	Hyper T	–0.04	0.898	IL–8	HT	Hyper T	9.70	0.010
		Borderline	–0.14	0.745			Borderline	10.58	0.007
		Normal[a]	–				Normal[a]	–	
	TC	≥5.172	–0.20	0.468		TC	≥5.172	3.18	0.242
		Normal[a]	–				Normal[a]	–	
	HDL–C	<1.03, 1.29	0.60	0.041		HDL-C	<1.03, 1.29	5.97	0.065
		Normal[a]	–				Normal[a]	–	
	LDL–C	≥3.36	0.23	0.111		LDL-C	≥3.36	5.11	0.115
		Normal[a]	–				Normal[a]	–	
			Multivariate*					Multivariate*	
	HDL–C	<1.03, 1.29	0.65	0.076		HT	Hyper T	8.05	0.077
		Normal[a]	–				Borderline	11.92	0.014
							Normal[a]	–	
IL–10	HT	Hyper T	0.13	0.382	VEGF	HT	Hyper T	18.16	0.108
		Borderline	–0.22	0.183			Borderline	11.08	0.343
		Normal[a]	–				Normal[a]	–	
	TC	≥5.172	–0.14	0.275		TC	≥5.172	10.20	0.261
		Normal[a]	–				Normal[a]	–	
	HDL–C	<1.03, 1.29	0.01	0.925		HDL-C	<1.03, 1.29	–6.93	0.473
		Normal[a]	–				Normal[a]	–	
	LDL–C	≥3.36	–0.09	0.486		LDL-C	≥3.36	–1.65	0.863
		Normal[a]	–				Normal[a]	–	
IFNγ	HT	Hyper T	0.64	0.024	TNFα	HT	Hyper T	0.56	0.002
		Borderline	–0.06	0.838			Borderline	0.29	0.147
		Normal[a]	–				Normal[a]	–	
	TC	≥5.172	0.07	0.751		TC	≥5.172	–0.25	0.099
		Normal[a]	–				Normal[a]	–	
	HDL–C	<1.03, 1.29	–0.18	0.450		HDL-C	<1.03, 1.29	0.39	0.014
		Normal[a]	–				Normal[a]	–	
	LDL–C	≥3.36	–0.06	0.795		LDL-C	≥3.36	0.12	0.620
		Normal[a]	–				Normal[a]	–	
			Multivariate*					Multivariate*	
	HT	Hyper T	.613	0.075		HT	Hyper T	0.39	0.078
		Borderline	–.182	0.620			Borderline	0.19	0.438
		Normal[a]	–				Normal[a]	–	
						HDL-C	<1.03, 1.29	0.52	0.005
							Normal[a]	–	
IL–1α	HT	Hyper T	–.021	0.710	IL–1β	HT	Hyper T	–0.18	0.472
		Borderline	–.087	0.132			Borderline	–0.18	0.506
		Normal[a]	–				Normal[a]	–	
	TC	≥5.172	–.057	0.345		TC	≥5.172	0.19	0.236
		Normal[a]	–				Normal[a]	–	
	HDL–C	<1.03, 1.29	.01	0.786		HDL-C	<1.03, 1.29	–0.23	0.345
		Normal[a]	–				Normal[a]	–	
	LDL–C	≥3.36	.01	0.895		LDL-C	≥3.36	0.35	0.113
		Normal[a]	–				Normal[a]	–	
MCP–1	HT	Hyper T	30.93	0.008	EGF	HT	Hyper T	4.34	0.745
		Borderline	–10.85	0.361			Borderline	4.67	0.736
		Normal[a]	–				Normal[a]	–	
	TC	≥5.172	–4.24	0.651		TC	≥5.172	–2.83	0.793
		Normal[a]	–				Normal[a]	–	
	HDL–C	<1.03, 1.29	3.79	0.703		HDL-C	<1.03, 1.29	7.97	0.458
		Normal[a]	–				Normal[a]	–	
	LDL–C	≥3.36	–4.48	0.656		LDL-C	≥3.36	20.43	0.072
		Normal[a]	–				Normal[a]	–	
			Multivariate*						
	HT	Hyper T	25.93	0.039					
		Borderline	11.48	0.381					
		Normal[a]	–						

Table 3 (*Continued*)

hsCRP	HT	Hyper T	1.35	0.242
		Borderline	2.01	0.091
		Normal[a]	–	
	TC	≥5.172	0.41	0.656
		Normal[a]	–	
	HDL–C	<1.03, 1.29	0.68	0.510
		Normal[a]	–	
	LDL–C	≥3.36	–0.38	0.659
		Normal[a]	–	

*In present of age, sex, smoking, BMI, FBG and HTN.
Serum cytokines and hsCRP levels were expressed as ng/L and mg/L respectively.
[a]: category reference, Hyper T: triglyceridemia, TC: total cholesterol, HDL–C: high–density lipoprotein cholesterol; LDL–C: low–density lipoprotein cholesterol; HT: Hypertriglyceridemia

the development of MetS [27]. In the current study we have shown that the serum TNFα was significantly ($P < 0.05$) increased in subjects with hypertriglyceridemia, which was also associated with lower concentrations of HDL-C. Consistent with this observation, several other studies have showed the association of IL-6 and TNF-α with hyperglycemia in diabetes [28] and CAD [18]. IL-4 has been reported to inhibit liver lipogenesis, induced by TNFα, IL-1 and IL-6. IL-4 inhibits liver lipogenesis by affecting the rate of liver citrate production [29]. However, we did not find a significant difference in the level of this cytokine between our subject groups. IL-1 is involved in inflammatory bowel disease, as detected in overweight and obese individuals as well as it is involved in diabetes, atherosclerosis [30,31], diabetic patients [17] and CAD [18].We did not find a significant association between serum IL-1 and hypertriglyceridemia in our study. Although the serum levels of some of them were changed in hypertriglyceridemia group, compared to the non-hypertriglyceridemic group. We have previously reported that patients with the MetS have an altered blood cytokine and growth factor profile that may partially account for its adverse clinical outcomes [24].

Adiposity is related with abnormal lipoprotein metabolism and increased cytokine production. Also, glycemic control is reported to be affected by adiposity and cytokine concentrations. It has been shown that serum cytokine levels are increased in diabetic patients [17,32]. Among the pro-inflammatory cytokines, TNF-α may play an essential role in the initiation and maintenance of chronic inflammation, and atherosclerotic plaque. In our current study we showed the important role of this cytokines in subjects with hypertriglyceridemia, and reducing the level of HDL-C, which are the main risk factors of CAD.

Our study was conducted in a large and well-characterized cohort of individuals together with profiling of 12 cytokines and growth factors in the subjects. However the main limitations of this study were the cross-sectional study design and lack of complete information on lifestyle characteristics of the population and possible influence of infection and other diseases such as influenza, infectious diseases, asthma and allergy, which might have an influence on cytokine levels. Further prospective investigations are needed to unravel the functional role of emerging markers with hypertriglyceridemia and cardiovascular outcomes.

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Conflict of interest

The authors have no conflict of interest to disclose

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