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Original Article

Association of interleukin-6 gene -572 C > G polymorphism with dietary intake of n-3 fatty acids on plasma HDL-c level in Chinese male adults

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Objective: Heterogeneity in circulating lipid concentrations in response to different dietary fat intakes may be due, in part, to gene polymorphism of cytokine related to inflammation. The objective was to determine whether dietary n-3 PUFAs intake influenced the effects of IL-6 -572 polymorphism on plasma lipids and apolipoproteins. Study Design: This cross-sectional study included 195 men and 386 women aged 40–65 y. DNA was isolated from white blood cell to determine the IL-6 -572 C-G polymorphisms by the polymerase chain reaction-logation detection reaction (PCR-LDR) method. Dietary fatty acids were assessed by measuring erythrocyte membrane fatty acids, and fasting plasma was collected to determine blood lipids and apoproteins. Results: The frequency of the G allele was 0.214. There were no significant differences in plasma lipids across genotypes (all $p>0.05$). When men and women were grouped into tertiles by the erythrocyte membrane n-3 PUFAs composition; in the lowest group, men with G allele had 18% higher HDL-cholesterol concentrations than did C/C genotype ($p<0.05$). Similar effects were observed for apo A. Adjusting for age, BMI and total PUFA did not alter this association. The interaction was not significant in women. Conclusion: Dietary n-3 PUFA intake influenced the effects of IL-6 -572 genotype on HDL-c concentrations in males.

Key Words: interleukin-6, polymorphism, n-3 polyunsaturated fatty acids, HDL-c, interaction

INTRODUCTION

Cardiovascular disease (CVD) is one of the leading causes of disability and mortality in the world. The critical roles of various inflammatory cytokines in the development of CVD have been extensively described.[1]

Interleukin-6 (IL-6) is a pleiotropic cytokine which is synthesized in response to diverse inflammatory stimuli and, as a key orchestrator of the inflammatory response, may bridge the inflammatory and atherosclerotic processes through its role in endothelial dysfunction, coagulation, insulin resistance and dyslipidemia.[2,3] It has been found that blood IL-6 levels is positively associated with CVD risk,[4,5] which suggests a role of IL-6 in early atherogenesis.

Growing attention has been devoted to the relationship between IL-6 and other cytokines with lipid metabolism.[6,7] Epidemiological studies indicate that high IL-6 levels are associated with high plasma triglyceride (TG)[8] and low high density lipoprotein cholesterol (HDL-c)[9] concentrations. Plasma IL-6 level is influenced, to a large extent, by genetic determinants.[10] The IL-6 gene has a number of common single nucleotide polymorphisms (SNPs) in the promoter region, -572G>C is reported as a predictor of CVD.[11,12] However, few studies have investigated the association between this SNP and blood lipids.

Gene-diet interactions play a major role in the etiology of CVD.[13] It was recently reported that TNF-α genotypes could modify the relationship between dietary PUFAs intake and HDL-c concentration, i.e., PUFAs intake is negatively associated with HDL-c in individuals with the genotype associated with higher TNF-α production, but the association is positive in those with the genotype related to lower production of TNF-α.[14] Such study indicates that the interactions between inflammatory factor genotypes and dietary fat on blood lipids might involve a common mechanism.[15]

The present study was designed to examine whether dietary fat intakes modulates the association between the IL-6 promoter common polymorphisms and blood lipid

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level in a population-based sample from China. Compared with questionnaire-based assessments of fat intake, the composition of erythrocyte fatty acids is more objective and accurate.[16,17] Thus we used this biomarker as a substitution of dietary fatty acids in the present study.

MATERIALS AND METHODS

Subject

Study subjects were recruited during December 2005 and April 2006 via community and clinic advertisements and subject referral. They were required to be Guangzhou residents of Chinese origin aged 40-65 years old. Exclusion criteria included a history of chronic diseases, such as diabetes, hypertension, CVD, dyslipidemia, cancers, which might change their dietary habit or lifestyle, current use or a history of 3-month (or more) use of any drugs known to affect lipid metabolism, and a body mass index (BMI) ≥30 kg/m^2.

After initially screening for their eligibility using a short questionnaire which recorded gender, age and exclusion criteria, 739 potential subjects were then invited to the First or the Second Affiliated Hospital of Sun Yat-sen University, Guangzhou, China. They were further screened for eligibility by staff with relevant knowledge in medical science via face-to-face interview to ensure that they met the inclusion and exclusion criteria. A total of 127 subjects were then excluded for prior diagnosis of the diseases indicated in the above exclusion criteria (29 for diabetes, 12 for CVD, 86 for dyslipidemia), and another 20 subjects were also excluded for uncompleted socioeconomic information. Then, 592 subjects completed the body examination and provided 12-h fasting venous blood, among which, 11 subjects had an inadequate number of cryopreserved erythrocytes for fatty acid measurement, so finally 581 subjects (195 males and 386 females) were analyzed in this study. All participants signed the written informed consent prior to enrollment. The study protocol was approved by the Medical Ethics Committee of Sun Yat-sen University.

Anthropometric data

Height was measured to the nearest 0.5 cm and weight to the nearest 0.1 kg in light clothing and without shoes. BMI was calculated as weight (kg)/height (m)^2. Two consecutive measurements of blood pressure Systolic blood pressure (SBP) and diastolic blood pressures (DBP) were taken from the right arm after each subject had been sitting for at least 10 min by using a mercurial sphygmomanometer to the nearest 2 mmHg. If the difference of two SBP or DBP recorded were ≥4 mmHg, a third measurement would be made. The average of the two blood pressures was used for the subsequent analysis. SBP and DBP were defined as the point of the appearance (Korotkoff I) and disappearance (Korotkoff V) of Korotkoff sounds, respectively.

Blood lipids

12-h fasting venous blood was collected in vacuum tubes containing EDTA for lipid analysis. Plasma was separated after centrifugation at 1500×g for 15min at 4˚C within 2h and then stored at –80˚C until analysis. Blood lipids were measured by Hitachi 7600-010 automatic analyzer. The coefficient of variation for lipid measurements was 2.17% (at 5.03 mmol/L TC), 2.86% (at 1.14 mmol/L TG). 3.47% (at 1.70 mmol/L HDL-c), and 4.67% (at 2.65 mmol/L LDL-c).

Erythrocyte membrane fatty acids

RBC was thawed and ruptured in hypotonic Tris-HCL buffer, membrane were collected by hypothermia ultracentrifugation, lipids were extracted with chloroform/ methanol (2:1, v/v) added with 0.005% BHT, and the extract was dried in N_2. Fatty acids methyl esters (FAMES) were obtained by incubation with 14% boron trifluoride ether/methanol (1:3, v/v) solution at 100℃ for 5 min and analyzed by gas chromatography as described elsewhere.[18]

Genotyping of IL-6 -572 polymorphism

DNA was extracted from 400ul whole blood by using a TIANamp DNA blood extract kit (TIANGEN Biotech China). Genotyping of IL-6 -572 polymorphism was performed using the polymerase chain reaction-logation detection reaction (PCR-LDR) method.

Amplicication of a 208bp product was performed via polymerase chain reaction (PTC-200 Gradient cycler; MJ Research Inc, Watertown, MA) by using a premix PCR system (Takara Bio Inc.), 50ng genomic DNA and 2μmol/L of each oligonucleotide primer (P1, 5' - CTAAGTGGG CTGAAGCAGGT- 3'; P2, 5' – CCAAGC CTGGGA TTATGAAG- 3') in 20μl. Each reaction mixture was heated at 95˚C for 15min, followed by 35 cycles of amplification (94˚C for 30sec, 59˚C for 1.5 min, 72˚C for 1 min) and a final extension step at 72˚C for 10 min. To evaluate the overall amplification efficiency, PCR products were electrophoresed on 3% agarose gels.

LDR was performed in 10 μl solution volumes containing 100 ng PCR product or above, 12.5 μmol/L probe (Table 1) 2 U DNA ligase and 2 μl 10×ligation buffer. The reaction mixtures were initially heated for 2 min at 95˚C, followed by 30 cycles at 94˚C for 30sec and 50˚C for 2 min. The mixture was then analyzed by the ABI Prism 377 DNA Sequencer.[19]

Statistical analysis

All data are expressed as mean ± SD. Genotype frequencies were tested for Hardy-Weinberg equilibrium using chi-square test. Because of the small number of subjects (6 men and 16 women) who were homozygous for the less common allele (i.e., G/G genotype) and because the plasma lipid concentrations for individuals with this genotype and heterozygotes (CG genotype) were not significantly different, individuals with G/G and C/G genotypes were grouped together. Primary analyses were performed by comparing plasma lipids between IL-6 genotypes with or without adjusting for age and BMI using analysis of covariance (ANCOVA). Subjects were categorized into tertiles by the percentage of n-3 fatty acids in erythrocyte membrane. Two-way ANOVA was used to test the associated effects of the IL-6 gene polymorphisms and erythrocyte membrane n-3 fatty acids on lipids with stepwise adjusting for age, BMI and erythrocyte membrane total PUFA. All the analyses were performed

Table 1. IL-6 -572 gene-specific probe

IL-6 -572_modify	p-GGCTGTTGTAGAACTGCCTGGCCAT TTTTTTTTTTTTTTTTTTT-FAM
IL-6 -572_C	TTTTTTTTTTTTTTTTTTTCTGTGTTC TGG CTCTCCCTGTGAGG
IL-6 -572_G	TTTTTTTTTTTTTTTTTTTTTTCTGTG TTCTGGCTCTCCCTGTGAGC

using SPSS for Windows (release 11.5, SPSS Inc., Chicago, IL).

RESULTS

Demographics, anthropometrics and biochemical data, erythrocyte membrane fatty acids composition, and genotype distributions of IL-6 gene -572 locus of 581 subjects are shown by sex in Table 2. There were statistically significant differences between men and women for erythrocyte membrane monounsaturated fatty acid, n-3 fatty acid, total cholesterol, HDL-c and apoA. No deviation from the Hardy-Weinberg equilibrium was observed for genotype distribution. The allele frequencies were 0.786 (95% CI: 0.805, 0.766) for the C allele and 0.214 (95% CI: 0.219, 0.208) for the G allele.

When stratified by gender, no significant differences were found between CC homozygotes and carriers of the G allele in plasma lipid, apolipoprotein concentrations and erythrocyte membrane fatty acids composition (data not shown).

We also analysed whether the erythrocyte membrane fatty acids (n-3 fatty acids, n-6 fatty acids, the ratio of n-6 to n-3 or the ratio of PUFA to SFA) were associated with the IL-6 -572 C-G polymorphism in determining serum lipids and apolipoproteins in a sex-specific manner. No significant interactions were found except that the interaction of sex×IL-6 genotype×n-3 fatty acid on HDL-c was significant (p=0.018). The interaction of IL-6 genotype and n-3 fatty acid on HDL-c in men is significant in the crude model (p for interaction=0.02). Adjusting for age, BMI and PUFAs composition of erythrocyte membrane did not attenuate the interaction (p for interaction=0.04). No similar interactions were found on apolipoprotin A (data not shown).

Mean HDL-c and apo A serum concentration by IL-6 genotypes and sex across the tertiles of erythrocyte membrane n-3 PUFAs compositon are shown in Table 3. IL-6 genotype had a different effect across the categories of n-3 PUFAs composition in men: when erythrocyte membrane n-3 PUFAs composition was low, carriers of the IL-6 G allele had about 18% higher HDL-c concentration and about 17% higher apoA concentration than did CC homozygotes (p <0.05). There is an inverse association, although not significant, between n-3 fatty acids and serum HDL-c concentration in subjects with G allele (p for trend=0.09), but not in CC homozygote (p for trend=0.17). No such associations were observed in female subjects. These findings are also graphically displayed in Figure 1.

DISCUSSION

This observational study conducted in China showed an association of IL-6 gene -572 C > G polymorphism with dietary intake of n-3 fatty acids and plasma HDL-c level in a sex-specific manner. To the best of our knowledge, this is the first report to describe the association of IL-6 gentypes and dietary fat with plasma lipids in Chinese adults.

The mechanisms of the potential gene-diet interactions in the present study have been hypothesized (Figure 2). A study in 108 monozygotic and 60 same-sex dizygotic twin pairs showed that heritability of IL-6 was 0.61, indicating that plasma IL-6 levels are to a major part influenced by genetic determinants.[10] Brull et al.[20] demonstrated that the IL-6 gene promoter -572G > C polymorphisms influence the response of IL-6 to coronary artery bypass graft surgery (CABG) which is a well-characterized

Table 2. Demographic characteristics, plasma lipids, erythrocyte membrane fatty acids and IL-6 -572 genotypes of 581 subjects (gender-grouped)

	Men	Women
n	195	386
Age (y)	54.9±7.62[†]	51.8±6.73
BMI (kg/m^2)	24.0±2.72	23.4±2.93
Systolic blood pressure (mmHg)	122±16.5	121±17.7
Diastolic blood pressure (mmHg)	81.1±10.3	81.0±10.6
Total cholesterol (mmol/L)*	5.21±1.03	5.49±1.12
HDL cholesterol (mmol/L)*	1.52±0.45	1.64±0.38
LDL cholesterol (mmol/L)	3.64±1.08	3.74±1.18
Triacylglycerol (mmol/L)	2.48±2.00	2.18±1.39
Apolipoprotein A (g/L)*	1.42±0.25	1.57±0.30
Apolipoprotein B (g/L)	1.19±0.33	1.20±0.34
Monounsaturated fatty acids of erythrocyte membrane (% of total fatty acid)*	17.4±1.45	16.9±1.44
n-3 polyunsaturated fatty acids of erythrocyte membrane (% of total fatty acid)	10.5±2.64	10.9±2.81
n-6 polyunsaturated fatty acids of erythrocyte membrane (% of total fatty acid)	28.1±2.58	27.9±2.55
polyunsaturated fatty acids of erythrocyte membrane (% of total fatty acid)	38.6±2.63	38.9±2.80
IL-6 genotype (%)		
C/C	56.4	58.3
C/G	39.8	37.0
G/G	3.74	4.70

[†] Data of demographic characteristics, plasma lipids and erythrocyte membrane fatty acid are presented as mean±SD.
*Significantly different by sex (p<0.02)

Table 3. Plasma HDL-cholesterol concentrations in different IL-6 genotypes, erythrocyte membrane n-3 fatty acids and genders

	n-3 PUFA (% of total fatty acids)			p for trend*
	Low (n=128 F, 65 M)	Middle (n=128 F, 65 M)	High (n=130 F, 65 M)	
Men				
HDL-c (mmol/L)				
C/C (110) †	1.41±0.25‡ (42)	1.67±0.48 (34)	1.53±0.35 (34)	0.17
C/G+G/G (85)	1.74±0.40 (23)	1.56±0.38 (31)	1.50±0.31 (31)	0.09
Unadjusted p§	0.02*	0.39	0.66	
Adjusted p¶	0.02*	0.68	0.84	
Adjusted p††	0.01*	0.98	0.88	
ApoA (g/L)				
C/C(110)	1.36±0.18 (42)	1.44±0.27 (34)	1.37±0.26 (34)	0.84
C/G+G/G(85)	1.53±0.29 (23)	1.44±0.27 (31)	1.45±0.25 (31)	0.37
Unadjusted p§	0.02*	0.10	0.24	
Adjusted p¶	0.02*	0.57	0.16	
Adjusted p††	0.01*	0.98	0.88	
Women				
HDL-c (mmol/L)				
C/C(225)	1.68±0.32 (66)	1.67±0.36 (74)	1.72±0.32 (85)	0.55
C/G+G/G(161)	1.67±0.35 (62)	1.71±0.30 (54)	1.65±0.32 (45)	0.69
Unadjusted p§	0.86	0.54	0.23	
Adjusted p¶	0.63	0.85	0.41	
Adjusted p††	0.62	0.10	0.38	
ApoA (g/L)				
C/C(225)	1.62±0.23 (66)	1.61±0.29 (74)	1.56±0.34 (85)	0.30
C/G+G/G(161)	1.63±0.32 (62)	1.58±0.22 (54)	1.53±0.37 (45)	0.13
Unadjusted p§	0.84	0.53	0.59	
Adjusted p¶	0.80	0.69	0.83	
Adjusted p††	0.71	0.81	0.89	

* ANOVA for the global comparison of the 3 erythrocyte membrane n-3 fatty acid categories within genotypes.
† number of subject, all such values.
‡ mean±SD, all such values.
§ Unadjusted comparison between C/C subjects and C/G+G/G subjects combined.
¶ Comparison between C/C subjects and C/G+G/G subjects combined, adjusted for age, BMI.
†† Comparison between C/C subjects and C/G+G/G subjects combined, adjusted for age, BMI and polyunsaturated fatty acids.

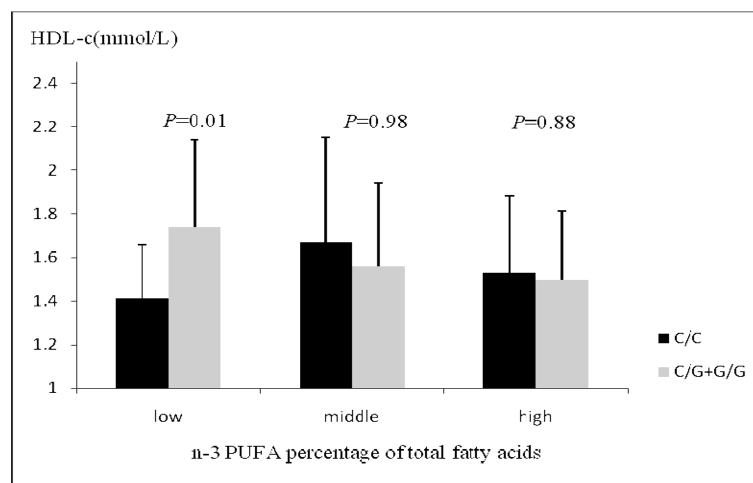

Figure 1. Correlations of HDL-c concentration with IL-6 genotypes C/C and C/G+G/C and erythrocyte membrane n-3 PUFA percentages in men. Means were adjusted for age, BMI and total PUFA percentage.

inflammatory stimulus that causes a substantial rise in circulating IL-6 levels. In their study, baseline IL-6 levels did not significantly differ between 127 patients with different genotypes. However, 6 hours after CABG, the carriers of IL-6 -572 C allele had a 65% higher IL-6 level than GG homozygotes. Ferrari *et al.*[21] also reported the –572 C allele not only shows an increased promoter activity in response to IL-1β (and also TNFα) in *in vitro* HepG2 cells but is also associated with higher levels of C-reactive protein and urinary C-terminal cross-linking of type I collagen, both are served as markers of IL-6 activity in healthy postmenopausal women. Recently, Anders *et al.*[12] confirmed that there is a trend towards association of the -572 G > C polymorphism with plasma concentrations of IL-6 (p=0.07) in a large population (n=2704). This association is statistically significant in

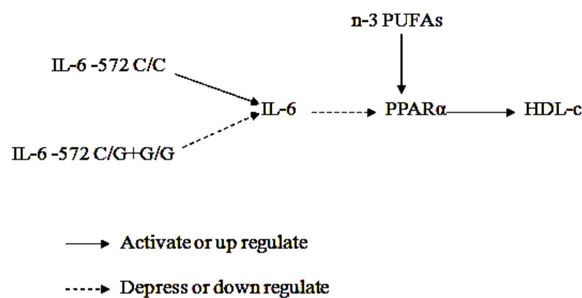

Figure 2. Hypothetic mechanism of the interaction

patients with available high-sensitivity measurements of IL-6 (p=0.01, n=527).

The association of serum IL-6 level with HDL-c has been examined extensively since Mendall *et al.*[8] firstly reported that serum IL-6 levels are negatively associated to HDL-c concentration. Subsequent studies verified that IL-6 is one of the factors which independently contributes to low HDL-c levels. However, the the biological mechanisms involved remain unclear. Peroxisome proliferator-activated receptor-alpha (PPAR-α), a key regulator of lipid metabolism,[22] may be the key crosspoint in the pathway which n-3 fatty acids and IL-6 synergistically affect plasma HDL-c level (Figure 2). PPAR-α can be activated by n-3 PUFAs,[22,23] however be inhibited by IL-6.[24] It is therefore possible that the effect of IL-6 phenotype on PPAR-α, and then on HDL-c becomes more prominent when n-3 intake is low, thus resulting in less influence on PPAR-α activity.

Such theoretical hypothesis might explain the result of present study: the male carrier of -572 G allele with low intake of n-3 fatty acids have highest level of HDL-c, and male CC homozygotes with low dietary n-3 fatty acids have lowest HDL-c level.

The above-discussed interaction was only observed in male subjects. The possible reasons for such gender differences remain unclear. Sex hormones may be involved, for findings suggest that sex hormones act to modify males and females in their ability to synthesise LC n-3 PUFA from ALA and that this disparity is associated with gender differences in the circulating concentrations of LC n-3 PUFA.[25]

Recent studies have consistently shown that serum HDL-c is inversely related to the risk of developing CVD, which is independent of plasma LDL-c and TG concentrations.[26] It has also been reported that the cardiovascular disease event rate is reduced by ≥1% for each 1% increase in HDL.[27] Therefore, raising HDL-c concentrations is a potential strategy for the treatment of CVD.[28] Our present result may indicate that with regard to dyslipidemia prevention, genotype-phenotype personalized dietary recommendations will be more effective.

Some limitations of our study should be noted. First, due to budgetary reason, we did not measure serum IL-6 and PPAR-α levels. Despite literature speculating biological mechanisms contributing to the gene-diet interaction, it has not been directly proven that the gene-diet interaction on HDL-c is via serum IL-6 and PPAR-α. Second, the small sample size limited the power to exclude random error.

In summary, we observed that IL-6 -572 C > G polymorphism associates with n-3 fatty acids intake in determining serum HDL-c concentrations in males. Our results illustrate the complexity of genotype-phenotype associations and also underscored the importance of accounting for gene-diet interactions in individualized dietary guidelines.

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AUTHOR DISCLOSURES

There are no financial relationships or other potential conflict of interest to disclose.

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Original Article

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IL-6 -572位点C>G多态性与膳食n-3脂肪酸对中国成年男性血浆HDL-c水平影响的交互作用

目的：相同膳食状况下，人体循环中脂质水平的差异可能与炎症相关细胞因子基因多态性有关。本研究旨在探讨膳食 n-3 脂肪酸的摄入是否影响 IL-6 -572 位点基因多态性与血浆脂质及载脂蛋白水平的关系。研究设计：一项横断面研究，受试者均为 40-65 岁成人，男性 195 名，女性 386 名。采集空腹 12 小时以上静脉血检测血脂及血载脂蛋白水平，利用血白细胞提取基因组 DNA，并用 LCD-PCR 法检测 IL-6 -572 位点基因多态性。气相色谱检测受试者红细胞膜脂肪酸构成，并用于评价膳食脂肪酸摄入情况。分析受试者 IL-6 -572 位点基因多态性对血浆脂质及载脂蛋白水平的影响及其与膳食 n-3 脂肪酸的交互作用。结果：受试人群 IL-6 -572 位点 G 等位基因出现频率是 0.214，未发现该位点基因多态性与血浆脂质与载脂蛋白水平有关（p>0.05）。按红细胞膜 n-3 脂肪酸构成以三分位分组，发现当红细胞膜 n-3PUFA 成分处于最低水平时，男性 G 等位基因携带者血浆 HDL-c 及 Apo A 水平分别较 C/C 纯合子高 18%和 15%，校正了年龄、BMI 及总脂肪酸后，差异仍然有显著性。未发现女性受试者存在上述交互作用。结论：膳食 n-3 脂肪酸能改变 IL-6 -572 位点基因多态性与男性血浆 HDL-c 水平的相关关系。

關鍵字：白介素-6、基因多态性、n-3 多元不饱和脂肪酸、高密度脂蛋白胆固醇、交互作用