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Original article

The C-514T polymorphism of hepatic lipase gene modulates the impact of a high carbohydrate diet on lipid profile in healthy Chinese young adults

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Background: Serum lipid concentrations are associated with genetic and environmental factors. Studies of interaction between genetic variations and diets may provide more insight into the mechanisms of lipid metabolism and the development of coronary heart disease.
Objective: We studied the interaction of a common C-to-T substitution at position -514 of the hepatic lipase promoter with high carbohydrate diet in a young and healthy Chinese population lipid profiles.
Methods: Fifty-six young, healthy Chinese subjects were given stabilization diets of 54% carbohydrate to exclude interference from the dietary background of the subjects. This was followed with a high carbohydrate diet of 70%. We analyzed the serum lipid profiles at baseline, after the stabilization diet, and after the high carbohydrate diet. Hepatic lipase gene polymorphisms were also determined.
Results: After the high carbohydrate diet, almost the whole population had significantly lower levels of phospholipids and all the females showed significantly higher levels of triacylglycerol (TAG). Notably, carriers of *C* allele had significantly lower levels of low-density lipoprotein cholesterol (LDL-C). Males with CC, CT genotypes and females with CC genotype had significantly lower levels of total cholesterol. Furthermore, CC genotype males showed significantly increased high-density lipoprotein cholesterol (HDL-C). A significant difference in the hepatic lipase C-514T polymorphism was found in phospholipid of males with TT >CT >CC.
Conclusion: Our results demonstrated that the C-514T polymorphism in the hepatic lipase gene could modulate the impact of a high carbohydrate diet on lipid profiles in this young and healthy Chinese cohort. This influence is gender-specific.

Keywords: Coronary heart disease, hepatic lipase gene, high carbohydrate diet, risk factors, serum lipids

It has been well documented that the risk of coronary heart disease (CHD) can be decreased by a high carbohydrate diet. Serum low-density lipoprotein cholesterol (LDL-C) was reported to be lowered by reducing saturated fat intake, and high-density lipoprotein cholesterol (HDL-C) was elevated due to weight loss [1-4]. The Chinese population has been reported to have a significantly lower prevalence of CHD [5, 6], which is most likely attributed to their diet containing lower fat and higher carbohydrates [7]. However, it is noticeable that the risk of CHD in younger populations has been increasing over the past few decades [8]. Previous studies have shown that high carbohydrate diet can also increase serum triacylglycerol (TAG) concentrations [9, 10], which leads to hypertriacylglycerolemia, an independent risk factor for CHD [11]. Because most cases of CHD were diagnosed after 45 years of age [12], nearly all the previous studies on carbohydrate-induced hypertriacylglycerolemia found in middle-aged or senior subjects. It becomes important to understand the biochemical mechanisms of hypertriacylglycerolemia in these younger populations, as well as the gene-environmental interaction in lipid homeostasis, which may be able to reduce the risk of CHD.

Dietary carbohydrates control the transcription of key enzymes in TAG biosynthesis (lipogenesis) in the mammalian liver [13, 14]. Hepatic lipase is an enzyme that is made primarily by hepatocytes and hydrolyzes triglycerides and phospholipids in all lipoproteins. It

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also plays a role in the clearance of chylomicron remnants by the liver [15, 16]. A common -514 C to T polymorphism in the promoter region of the hepatic lipase gene accounts for 20% to 30% of individual variation of hepatic lipase activity [17]. It has been shown that this polymorphism affects both on hepatic lipase synthesis and activity [18, 19], and was associated with the triglyceride content of LDL, IDL, and HDL, and on the cholesterol content of IDL [20]. Hepatic lipase -514 TT polymorphism, when it interacts with apolipoprotein E2 polymorphism can significantly lower the plasma TAG level among healthy, young, Canadian adults [21]. Furthermore, it has been reported that the presence of the T allele, which shows low hepatic lipase activity, may carry a marginally increased risk of atherosclerosis [22]. However, the subject regarding how the changes in lipid profiles induced by diet are influenced by hepatic lipase C-514T polymorphism remains to be elucidated.

In this study, we investigated the interactions of hepatic lipase C-514T polymorphism with a high carbohydrate diet on serum lipid profiles in a young and healthy Chinese cohort. It was found that C-514T polymorphism in the hepatic lipase gene could modulate the impact of a high carbohydrate diet on the lipid profile in this young and healthy Chinese cohort. This influence is gender-specific.

Materials and methods

Subjects

Two hundred nine students from West China Medical Center College were recruited as volunteers to participate in this research. The recruitment criteria required that participants had no metabolic disease history, understood the study procedures, and signed an informed consent. After ruling out those who were consuming alcohol, taking lipid-lowering medicines, were smoking, or varying widely in sleep time or physical activity, 60 participants were entered into the study. According to the medical questionnaire, the 60 participants had no coronary heart disease, diabetic, renal, or endocrinological diseases. This was further confirmed by physical examination and appropriate laboratory tests. **Table 1** shows their biochemical characteristics. Fifty-six participants (27 males and 29 females) completed the experiment with good compliance but four participants did not complete the experiment due to personal reasons. All participants were asked to maintain their normal daily activities and sleep during the entire study.

Diet and interventions

In order to make the serum lipid levels reach a steady state in all subjects, a 7-day stabilization diet was used [23, 24] which was followed with a 6-day high carbohydrate diet. As shown in **Table 2**, on the stabilization diet, 30% of the energy was derived from fat, 54% from carbohydrates, and 16% from proteins. In the high carbohydrate diet, 14% of the energy was derived from fat, 70% from carbohydrates, and 16% from proteins. The department of nutrition of West China Hospital prepared the meals. Breakfast (7:00-8:00 am), lunch (11:30-12:30 pm), and dinner (5.00 to 6.00 pm) were included. We changed dish of each meal on a daily basis. Subjects were instructed to eat to their satisfaction at each meal and not to eat any other food or drink except water. A daily dietary log was used to assess the compliance of each subject to the experimental procedures. Our protocol was approved by the Human Research Ethics Committee of Sichuan University.

Table 1. Demographic and biochemical characteristics of the study subjects

Variables	Males (n = 27)	Females (n = 29)	Total (n = 56)
Age (year)	22.9±1.9	22.8±1.6	22.8±1.8
phospholipids (mg/dl)	166±24	185±30*	176±28
TAG (mg/dl)	89.1±55.6	65.2±24.2*	76.5±43.4
total cholesterol (mg/dl)	148±21	156±28	152±25
HDL-C (mg/dl)	56.0±14.0	65.8±13.0*	61.2±14.3
LDL-C (mg/dl)	81.5±20.7	79.8±21.5	80.6±21.0
Apo A-I (mg/dl)	193±26	213.7±15.9*	204±23
Apo B-100 (mg/dl)	65.8±22.7	69.3±18.3	67.7±20.3

Data are shown as mean±SD, *p <0.05 for females vs. males (unpaired t-test)

Table 2. Composition of the diets administered to the volunteers of the study as determined by chemical analysis

Ingredients	Stabilization diet (7 days)	High-CHO diet (6 days)
Protein (% of total energy)	15.8±1.8	16.2±1.6
Carbohydrate (% of total energy)	54.1±2.4	70.1±2.8
Fiber (g/day)	11.6±2.3	15.4±3.6
Fatty acids (% of total energy)	30.1±3.6	13.8±1.4
Saturated fatty acids (% of total energy)	7.5±0.9	3.6±0.5
Monounsaturated fatty acids (% of total energy)	16.1±1.4	7.3±0.8
Polyunsaturated fatty acids (% of total energy)	6.4±1.5	2.8±0.3
Fatty acid composition (% of total fatty acids)		
Palmitic fatty acids	15.9±4.4	18.9±5.8
Stearic fatty acids (18:0)	6.9±1.3	7.4±0.9
Palmitoleic fatty acids (16:1)	2.1±0.7	2.0±0.4
Oleic fatty acids (18:1)	30.7±6.5	32.1±3.7
Linoleic fatty acids (18:2)	13.2±3.3	17.0±5.1

Blood collection and serum analysis

After a 12-hour fast, venous blood samples were collected between 7.00 and 8.00 am on the following days: day 1 when the study was started; the day 8, when the stabilization diet was completed and the high carbohydrate diet was first given; and the last day, when the experiment was finished. Serum was prepared by centrifugation at 3,000 g for 15 minutes and was immediately used to measure serum lipids and apolipoproteins. Enzymatic methods were used to measure TAG and total cholesterol. HDL-C concentrations were determined using a biochemical approach involving the precipitation of phosphotungstic-Mg^{2+} with apolipoprotein (Apo) B-containing lipoproteins. Low-density lipoprotein cholesterol (LDL-C) concentrations were calculated using a polyvinyl sulfate precipitation protocol. A semi-automated biochemistry analyzer (BT-224) was used for the above tests. ApoA-I and ApoB-100 concentrations were measured by immunoturbidimetry assays using a Hitachi 7070 analyzer. Less than 6% variation existed among the inter- and intra-assay coefficients. Every parameter of each sample was measured three times, and the averaged value was entered for statistical analysis.

Genetic analysis

A DNA out kit (Tiandz, Mianyang, China) was used to isolate Genomic DNA from peripheral blood leukocytes. Genotyping was performed as described by Guerra et al (25). A 285-bp sequence of the hepatic lipase gene was amplified by PCR by using oligonucleotide primers 52 -TCTAGGATCACCTC TCAATGGGTCA-32 and 52 GGTGGCTTCCACG TGGCTGCCTAAG-32. DNA templates were denatured at 95°C for 3 minutes, and then PCR was subjected to 35 cycles, each consisting of 1 minute of denaturation at 95°C, 0.5 minute of annealing at 63°C, and 0.5 minute of extension at 72°C. The PCR products were digested with 10 U of N*la*III and the fragments separated by electrophoresis on a 1.5% agarose gel. The resulting fragments are 215 and 70 bp for the *T* allele and 285 bp for the uncut *C* allele.

Statistical analyses

Data are expressed as the mean standard deviation (SD) unless otherwise stated. Normality in each group was calculated using the Shapiro-Wilk test. A log power transformation was applied for positively skewed distributions (TAG). Demographic and biochemical characteristics of the females were compared with the males via unpaired *t*-test. Deviation from the distribution of different genotypes was examined using the Hardy-Weinberg equilibrium. The variables before and after the high carbohydrate diet were compared by paired *t*-test, the variables among different genotypes by one-way analysis of variance (ANOVA) and post-hoc analysis, and the variables between the males and the females within the same genotype by unpaired *t*-test. Statistical significance was defined as $p < 0.05$.

Results

Biochemical and molecular characterization of the study population

An unpaired *t*-test was performed to calculate

the differences between male and female subjects. **Table 1** shows that males had higher TAG ($p = 0.040$), while females had higher phospholipids ($p = 0.016$), high-density lipoprotein cholesterol (HDL-C; $p = 0.009$) and ApoA-I ($p = 0.001$).

Distribution of the hepatic lipase polymorphism in the studied population

PCR was conducted to distinguish the distribution of the hepatic lipase C-514T polymorphism in our population. The results are shown in **Table 3**. This distribution agrees with the Hardy-Weinberg equilibrium ($^2 = 0.002$, $p = 0.965$), which states that both allele and genotype frequencies in a population remain constant from generation to generation.

Hepatic lipase C-514T polymorphism and cardiovascular risk factors at baseline

At baseline, no significant difference in cardiovascular risk factors was found by *ANOVA* in subjects with various hepatic lipase C-514T polymorphism backgrounds (**Table 4**). However, when gender was taken into consideration, unpaired *t*-tests indicated that the female CC genotype had higher levels of phospholipids ($p = 0.002$), HDL-C ($p = 0.008$) and ApoA-I ($p = 0.001$) than the corresponding male carriers.

Hepatic lipase C-514T polymorphism and cardiovascular risk factors after the stabilization diet

We used a stabilization diet to correct the imbalance in serum lipids levels due to the indeterminate diet of the subjects before the study. After the stabilization diet, no significant difference in cardiovascular risk factors was found by *ANOVA* in subjects with various hepatic lipase C-514T polymorphism backgrounds as well (**Table 4**). HDL-C ($p = 0.005$) and ApoA-I ($p = 0.002$) still showed significantly higher levels in the female CC genotype comparing to the corresponding male carriers.

Hepatic lipase C-514T polymorphism and cardiovascular risk factors after high carbohydrate diet

We gave all of our participants a high carbohydrate diet for 6 days following the stabilization diet because previous studies have shown that it can make serum lipids reach a new steady state and remain at a constant level (23, 24). After the high carbohydrate diet, phospholipids ($p = 0.001$), total cholesterol ($p = 0.006$), HDL-C ($p = 0.023$), LDL-C ($p = 0.037$) and ApoA-I ($p = 0.004$) showed significantly higher levels in the female CC genotype comparing to the corresponding male carriers. ApoA-I ($p = 0.0022$) also showed significantly higher levels in female TT genotype (**Table 4**). Although not significantly, T allele shows high serum TAG levels which is most likely due to lower hepatic lipase activity as shown in previous research [22]. A significant difference in hepatic lipase C-514T polymorphism was found in phospholipids of males, with TT >CT >CC. Comparing the values obtained after the stabilization diet and after the high carbohydrate diet, paired *t*-tests showed that phospholipids were significantly decreased ($p < 0.05$) in both genders across all genotypes, except for the male TT genotype ($p = 0.074$), which showed a non-significant decrease. LDL-C was significantly decreased in C allele carriers in both genders (male CC $p = 0.002$, male CT $p = 0.005$, female CC $p = 0.001$, female CT $p = 0.028$). Gender-specific differences were found in other studies of risk factors after the high carbohydrate diet. In males, total cholesterol was significantly decreased in C allele

Table 3. Allele and genotype frequencies of *HL -514C/T* polymorphisms

	Males (n = 27) n (%)	**Females (n = 29) n (%)**	**Total (n = 56) n (%)**
Genotype frequencies			
CC	11(40.7%)	9 (31.0%)	20 (35.7%)
CT	12 (44.4%)	15 (51.7%)	27 (48.2%)
TT	4 (14.8%)	5 (17.2%)	9 (16.1%)
Allele frequencies			
C	0.63	0.57	0.60
T	0.37	0.43	0.40

No deviation was found from the Hardy-Weinberg equilibrium in the distribution of genotypes ($^2 = 0.002$, $p = 0.965$).

carriers (CC p = 0.001 and CT p = 0.000). HDL-C was significantly increased in CC genotypes (p = 0.004). In females, TAG showed significantly higher levels in all genotypes (CC p = 0.002, CT p = 0.017 and CT p = 0.032). Total cholesterol was only decreased in the CC genotype (p = 0.016). These results suggest that a high carbohydrate diet can interact with the hepatic lipase C-514T polymorphism to favorably change most cardiovascular risk factors. However, this effect has gender differences, females tend to be at higher risk for carbohydrate-induced hypertriacylglycerolemia due to the significantly rising TAG.

Table 4. Serum lipid profile at baseline, after the stabilization diet and after the high-CHO diet for *HL–514C/T* polymorphism

Variables	Males			Females		
	CC	CT	TT	CC	CT	TT
Number (%)	11 (40.7)	12 (44.4)	4 (14.8)	9 (31.0)	15 (51.7)	5 (17.2)
Age (year)	22.9±2.3	23.2±1.8	22.2±0.9	22.4±1.2	23.0±2.0	22.8±1.0
Phospholipids (mg/dl)						
Baseline	153±17	176±25	172±25	186±22	177±31	207±32
After stabilization diet	190±24	207±20	210±35	215±34	200±24	237±27
After HC/LF diet	134±17***	151±11***	158±36 [a]	168±18***	158±19***	173±14***
TAG (mg/dl)						
Baseline	75.7±49.4	88.4±39.3	124±1	66.4±25.3	62.0±27.3	72.5±11.4
After stabilization diet	76.7±40.7	74.9±16.0	114±63	62.8±17.0	67.3±16.1	65.4±16.4
After HC/LF diet	87.4±44.2	82.3±36.3	103±37	74.4±21.4*	79.6±26.9*	86.3±14.4*
Total cholesterol (mg/dl)						
Baseline	142±22	152±22	146±13	162±24	145±27	179±24
After stabilization diet	128±21	131±18	144±32	144±21	131±22	154±15
After HC/LF diet	111±16***	120±13***	134±23	137±21*	127±16	144±25
HDL-C (mg/dl)						
Baseline	50.2±14.5	59.3±10.3	60.0±20.9	68.8±11.9	61.9±13.1	72.3±13.0
After stabilization diet	45.3±10.0	50.4±9.7	52.9±13.0	62.1±13.1	56.0±9.4	61.9±4.8
After HC/LF diet	50.6±12.0*	55.6±10.6	56.4±9.0	62.9±9.5	56.4±9.7	64.7±5.4
LDL-C (mg/dl)						
Baseline	82.7±25.9	79.2±18.0	85.4±18.5	83.9±16.7	71.6±19.1	96.7±27.4
After stabilization diet	63.7±21.8	67.7±17.4	75.5±29.0	75.3±13.7	64.9±23.7	77.8±17.0
After HC/LF diet	48.8±12.7*	54.4±12.2*	64.8±27.4	62.7±14.7***	55.2±13.4*	66.6±24.5
Apo A-I (mg/dl)						
Baseline	179±28	201±20	212±16	219±9	206±17	224±10
After stabilization diet	157±31	170±19	186±27	200±15	183±25	204±11
After HC/LF diet	162±33	174±18	180±17	202±16	187±23	210±13
Apo B-100 (mg/dl)						
Baseline	65.5±22.6	68.4±24.4	57.6±22.3	72.1±16.9	64.6±18.0	78.6±21.1
After stabilization diet	55.3±19.7	58.9±16.8	62.5±32.8	63.5±15.8	54.3±15.4	65.6±19.3
After HC/LF diet	53.4±19.5	56.6±16.0	68.5±37.9	62.2±14.5	55.5±14.5	65.0±25.7

Data are shown as mean±SD. *p <0.05 for after the high-CHO diet vs. after stabilization diet in males and females (paired t-tests). *** p <0.001for after the high-CHO diet vs. after stabilization diet in males and females (paired t-tests). p<0.05 for comparing within the groups of CC, CT and TT genotypes at baseline, after stabilization diet or after the high-CHO diet (ANOVA). [a]p <0.05 for comparing within the groups of CC, CT, and TT genotypes at baseline, after stabilization diet or after the high-CHO diet (Post Hoc). p <0.05 for females vs. males in the same genotype (unpaired t-tests).

Discussion

A high carbohydrate diet can affect lipid metabolism profoundly. In the liver and other organs, carbohydrates can be converted into fatty acids, TAG, cholesterol, and other lipids. Previous studies have shown that a high carbohydrate diet could increase fasting serum TAG concentrations [4, 9], which leads to hypertriacylglycerolemia, a risk factor of CHD [26]. It has also been documented that the risk of CHD could be decreased by a high carbohydrate diet due to lowering plasma total cholesterol and LDL-C concentrations [4]. Although, in the past decades, the effects of a high carbohydrate diet on the changes of total cholesterol, LDL-C, HDL-C, and TAG have been extensively reported, few reports are available about the effects of a high carbohydrate diet on subjects with different genotypes of the hepatic lipase gene polymorphisms. Since Chinese populations have carbohydrate-enriched diets [7, 27], it becomes interesting to investigate the plasma lipid responses of subjects with a specific genetic background in respect to high carbohydrate diets.

To our knowledge, this is the first study on the effects of a high carbohydrate diet on lipid and glucose metabolism in healthy young Chinese with hepatic lipase C-514T polymorphism. Conceivably, during a short period of 6 days on the high carbohydrate diet, other genetic and environmental factors affecting lipoprotein metabolisms would remain constant for each individual [28, 29]. Therefore, the different changes of lipid profile upon the high carbohydrate diet were most likely attributed to the specific genetic background of the individuals. After the high carbohydrate diet, a significant difference in the hepatic lipase C-514T polymorphism was found in phospholipid of males with TT >CT >CC. Although not significantly, T allele show high serum TAG levels which is most likely due to lower hepatic lipase activity as shown in previous reports, and this increases the risk for atherosclerosis [22]. Total cholesterol was significantly decreased in male C allele carriers and female CC genotypes. HDL-C was significantly increased only in male CC genotype. LDL-C was significantly decreased in C allele carriers in both genders. These results suggest that there is an association between the hepatic lipase C-514T polymorphism and serum lipid profile response to high carbohydrate diet. Gender-specific changes in lipid profile were also noticeable in our study. TAG showed significantly higher levels in all genotypes in females, but not in males. Total cholesterol was significantly decreased in male C allele carriers, while only significantly decreased in the female CC genotype. HDL-C was significantly increased only in male CC genotype. Our explanation for the fact that females were negatively affected by the high carbohydrate diet could be their higher levels of estrogen. The plasma concentrations of TAGs can be adversely increased by high carbohydrate diets [9, 15], which are mainly hydrolyzed by lipoprotein lipase, the key enzyme in the hydrolysis of TAGs in blood. However, the activity of lipoprotein lipase was significantly inhibited by high levels of estrogen in females and, as a result, the process of hydrolysis of TAGs by this enzyme was retarded [30].

Our data also showed that C allele could be more protective against CHD after the high carbohydrate diet. Therefore, the healthy young Chinese with the CC genotype would be good candidates for targeted diet intervention. The male and female responses differ to the diet intervention. A C-to-T substitution in nucleotide -514 in the promoter region of the hepatic lipase gene leads to decreased postheparin plasma hepatic lipase activity [22], and a mutation causing a splice site mutation in intron 1 of the hepatic lipase gene [31, 32]. The biochemical mechanisms related to how this mutation leads to the changes in lipid profile remains to be elucidated.

Conclusion

The response of serum lipid profile changes to a high carbohydrate diet is likely to be under multifactorial control. Our results suggest that there is a gender-specific association between the hepatic lipase C-514T polymorphism and the high carbohydrate diet induced lipid profile changes. The C allele of the hepatic lipase is associated with significantly higher HDL-C levels in males. It is also associated with significantly lower total cholesterol and LDL-C levels in both males and females. Although our conclusions were based on a small sample size and still hypotheses, if our findings could be confirmed in larger studies, they could contribute to formulation of personalized diet-based prevention of CHD.

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