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Research Article

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Influence of Dietary Amino Acid Profile on Serum Lipids in Hypercholesterolemic Chinese Adults

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Abstract

To investigate the significance of Lys:Arg and Met:Gly ratio on serum lipids concentrations and adiponectin in hypercholesterolemic adults, 24 g of soy isolate protein supplement (SIP) or milk protein supplement (CON) were randomly given to 90 subjects (n=45/group) daily for 8 weeks. The correlation between dietary proteins, Lys :Arg and Met:Gly ratio and the percentage changes in lipids and adiponectin in 90 subjects were examined. The percentage changes in total and LDL cholesterol concentrations were significantly positively correlated with the ratio of dietary vegetable protein/animal protein (VP/AP) (rs=-0.595, P<0.001 and rs=-0.606, P<0.001 respectively). The changes of total and LDL cholesterol concentrations were significantly correlated with dietary Lys:Arg ratio (rs=0.574, P<0.001 and rs=0.582, P<0.001 respectively). The change in adiponectin was negatively correlated with dietary Lys:Arg and Met:Gly ratio (rs=-0.668, P<0.001 and rs=-0.309, P=0.003 respectively) and was positively correlated with the ratio of VP/AP (rs=0.566, P<0.001). Vegetable protein diet with low Lys :Arg ratio may have a favorable effect on serum total cholesterol, LDL cholesterol and adiponectin.

Keywords: Dietary amino acid profile; Dietary proteins; Serum lipids

Introduction

The significance of dietary protein in the development of hypercholesterolemia and atherosclerosis has been extensively demonstrated. Findings from early studies suggested that proteins from vegetable sources are less cholesterolemic and atherogenic than from animal sources [1,2]. Many researchers have focused on the effect of protein type and amino acid profiles on blood lipids that cause atherosclerosis, with most comparing the proteins based on their amino acid profiles, especially lysine (Lys) to arginine (Arg) ratio (Lys:Arg). Generally, vegetable proteins have a lower Lys:Arg and Met:Gly ratio than animal proteins. Previous animal studies reported a significant effect of Lys:Arg ratio on lipoprotein concentrations. Rat or rabbit that fed diets with a high Lys:Arg ratio was reported having a higher total, LDL, and HDL cholesterol levels than animals fed a low Lys:Arg ratio [3-8]. Moreover, addition of lysine to diets containing soy or cottonseed protein to match Lys:Arg ratio comparable to that of casein increased whereas the addition of arginine to diet containing casein reduced the atherogenicity [4,5]. Several studies suggested that the sulfur-containing amino acids, i.e., methionine (Met) and cysteine (Cys) were hypercholesterolemic, whereas glycine (Gly) was hypocholesterolemic [9-12]. Similar to the low Lys:Arg ratio, proteins having low Met:Gly ratios were reported to elicit a hypocholesterolemic effect [12]. Notably, these studies were conducted on animals that lack analogies with human cholesterol and lipoprotein metabolism [13,14]. While the favorable effects of Arg or Gly on blood lipids and lipoprotein concentrations in rats appear to be consistent when Arg or Gly is administered using a supplement, the effects of dietary Arg or Gly naturally present in protein rich foods have yet to be determined. The Lys:Arg and Met:Gly ratios are relatively low in soy protein but high in milk protein. When soy protein or milk protein is added to diet, the dietary amino acid profile may change. The aim of this study was to explore the significance of the Lys:Arg and Met:Gly ratios on the responses of serum lipids and lipoprotein concentrations to dietary proteins in hypercholesterolemic adults. We tested the hypothesis that the ratios of Lys:Arg and Met:Gly in the diet would affect serum lipids profile.

Methods

Serum concentrations of adiponectin and lipids and lipoprotein were measured in 90 subjects who participated in a study designed to examine the effects of soy protein on the lipid and lipoprotein profile. Details of this randomized, placebo-controlled design were reported previously [15].

Study population

All subjects were nonsmokers. They had fasting serum total cholesterol concentration ≥ 5.7 mmol/L, LDL cholesterol concentration ≥ 3.61 mmol/L, triglyceride <5.65 mmol/L. All subjects had normal liver, kidney, endocrine and gastrointestinal functions as well as normal fasting glucose concentrations. Subjects who reported having any diseases, such as diabetes, hypertension, CVD, and cancers were excluded. Female subjects were non-pregnancy. Subjects were recruited by distributing advertisement leaflets in each community. The study was conducted in Guangzhou, China from 2008 to 2009, according to the guidelines laid down in the Declaration of Helsinki and was approved by the Medical Research Ethics Committee of Sun Yat-sen University. Written informed consents were obtained from all subjects.

Study design

The trial was performed as a randomized, controlled study. The

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SIP and CON were identically packaged. The supplements were labeled with a sequential subject number and a second three-digit number identifying the product on a randomization code list kept by the study coordinator. The subjects were blinded until all data were entered into a database, validated, and analyzed. Tables 1 and 2 show the composition and amino acids of soy protein and milk protein respectively. SIP and CON both contain 24 g of protein. All subjects were randomly assigned to two groups (n=45/group). Each qualified subject was randomized to receive 30g of SIP (14 men and 31 women) or CON (12 men and 33 women) once-daily for 8 weeks, by an independent clinical dietitian, using numbered envelopes. A block randomization was chosen to equally divide subjects in both groups.

Subjects received their supply in a separate sachet, and were advised to suspend in warm water and ingest with the morning meal. Our dietitian provided dietary instruction the way to substitute the protein supplement into the diet. All subjects were asked to complete a three-day (including 1 weekend day) food recall record at baseline and at week 8 of the study. They recorded the time when the food or supplement was consumed, the amount consumed, and information such as the commercial brand and the method of cooking, and were encouraged to provide as much detail as possible. The study visits occurred every 2 weeks, on day 1, 15, 29, 43, and 57; each visit was preceded by a 12-hour water-only fast. Subjects were instructed to maintain their usual dietary habits and level of physical activity throughout the study. Adherence was evaluated by 3-day dietary records, by personal interviews or telephone calls twice a week and by counting the returned sachets. Blood samples were collected at the beginning and at the end of the study.

Dietary intake assessment and amino acid profile

Dietary intake was assessed twice by means of a consecutive three-day dietary record. Prior to obtaining food records, subjects were instructed on portion size control, and the importance of recording complete data. Each record was evaluated by a dietician for completeness and accuracy afterwards, and subjects were asked to provide additional information about any unclear food item if needed. Energy and other nutrients were analyzed by using CDGSS3.0 software and dietary amino acids including SIP and CON were estimated by the Chinese Food Composition Table [16,17]. Dietary vegetable protein and animal protein were calculated for each subject and the ratios between them were analyzed (VP/AP). All subjects were asked to record in their diaries any signs of feeling or sickness symptom.

Outcome measurements

Serum concentrations of total, low density lipoprotein and high density lipoprotein cholesterol, triacylglycerol, apolipoprotein A1 and B, adiponectin, high-sensitivity C - reactive protein, and tumor necrosis factor-α were determined as previously described [15].

Statistical analysis

All statistical analyses were performed using SPSS software (version 13.0, SPSS Inc., Chicago, IL, USA). Data was tested for normality; variables deviated from normality and were therefore logarithmically transformed for statistical analyses. The results are expressed as mean ± standard deviation (SD). Student's t test was used to compare the differences of independent samples. The percentage change was calculated as follows:(value at week 8 – value at baseline)/value at baseline×100. The two groups merged and spearman's rank correlation coefficients (rs) were calculated to evaluate the relations between the percentage changes in total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, inflammatory markers and the dietary VP/AP, Lys:Arg ratios in 90 subjects. A two-side P-value <0.05 was considered significant for all tests.

Results

There was no significant difference in the consumption of energy; protein; carbohydrate; or fat within or between the groups (Table 3). The ratios of VP/AP, Lys:Arg and Met:Gly at week0 and week8 were shown in Table 4. After 8 weeks, VP/AP increased in SIP group and decreased in CON group. The changing trend of Lys:Arg ratio in the two groups was in reverse. While the average ratio of Met:Gly increased in CON group, no obvious variation was found in SIP group.

At the end of the two diet intervention, there were no significant differences in creatinine, uric acid, albumin, total protein, SGOT, SGPT, LDH, alkaline phosphatase, and GGT and hematology between the two groups (Table 5). Although subjects in the SIP group had significantly higher BUN than the CON group, the values were all within the normal range. As reported previously, there were significant differences in fasting total and LDL cholesterol concentrations for CON group. ApoB decreased and adiponectin increased significantly after 8 weeks in the two groups. However, only serum total cholesterol decreased significantly in the CON group compared with SIP group [15].

In 90 subjects, the percentage changes of total and LDL cholesterol were significantly correlated with the ratio of VP/AP (rs=-0.595, P<0.001 or rs=-0.606, P<0.001 respectively) (Figure 1). Significant correlations were observed between the ratio of Lys:Arg and the percentage changes in serum total or LDL cholesterol (rs=0.574, P<0.001 or rs=0.582, P<0.001 respectively) (FIG.2). The percentage change in adiponectin from baseline to week 8 was significantly correlated with the ratios of dietary Lys:Arg ratio (rs=-0.668, P<0.001), Met:Gly (rs=-0.309, P=0.003) and VP/AP (rs=0.566, P<0.001), respectively (FIG.3). No significant correlations were found between the percentage change in

Per 100g	Soy Protein	Milk Protein
Protein(g)	80.04	80.93
Carbohydrate(g)	11.16	4.96
Ash(g)	5	6.92
Fat(g)	0.874	1.72
Moisture(g)	2.93	5.47
Sodium(mg)	1000	1330
Phosphorus(mg)	98.9	73
Potassium(mg)	231	303

Table 1: Composition of Soy Protein and Milk Protein.

Essential Amino Acids	Soy Protein	Milk Protein	Non-Essential Amino Acids	Soy Protein	Milk Protein
Isoleucine	3.89	5.0	Histidine	2.52	2.8
Leucine	6.96	9.5	Alanine	3.32	3.1
Lysine	5.53	7.8	Arginine	5.7	3.4
Methionine	1.48	2.6	Aspartic Acid	8.82	7.0
Phenylalanine	4.29	4.7	Cysteine	1.1	0.7
Threonine	3.27	4.2	Glutamic Acid	15.67	20.4
Tryptophan	1.04	1.6	Glycine	3.04	1.8
Valine	4.2	6.1	Proline	5.22	9.7
			Serine	4.31	5.0
			Tyrosine	3.34	5.0

Table 2: Amino Acid Typical Amount (g) per 100g of Protein.

	SIP Group		CON Group		P^c
	Week 0	Week 8	Week 0	Week 8	
Energy(kcal/d) b	2165 ± 401	2163 ± 403	2203 ± 371	2190 ± 377	0.298
Fat (% of energy)	36.8 ± 6.3	36.9 ± 6.2	36.6 ± 4.9	36.7 ± 5.0	0.853
SFA(% of energy)	8.8 ± 0.6	8.6 ± 0.4	8.7 ± 0.8	8.5 ± 0.2	0.214
MUFA(% of energy)	12.7 ± 1.2	12.2 ± 1.6	12.6 ± 1.7	12.2 ± 1.1	0.205
PUFA(% of energy)	8.5 ± 0.7	9.1 ± 0.8	8.6 ± 0.5	9.2 ± 0.2	0.317
Carbohydrate (% of energy)	45.6 ± 7.2	45.3 ± 7.1	45.4 ± 5.5	45.3 ± 5.3	0.537
Protein (% of energy)	17.6 ± 1.8	17.7 ± 1.9	18.0 ± 2.2	18.0 ± 2.1	0.56
Soy Products(g/d) d	-	5.5 ± 1.7	-	6.0 ± 1.2	0.197
Milk Products(ml/d) d	-	138.2 ± 13.5	-	134.5 ± 10.7	0.092
Cholesterol(mg/d)	362 ± 230	358 ± 213	360 ± 201	357 ± 197	0.637

Note. Data are shown as mean ± SD. a Assessed by 3-d diet records. b1kcal=4.184kJ. c P value is for comparison between SIP group and CON group after 8 weeks. d The average intake of soy products and milk products excluded soy protein and milk protein supplements

Table 3: Mean Daily Intake a of Nutrients at Week0 and Week8.

	SIP Group		CON Group	
	Week 0	Week 8	Week 0	Week 8
VP/AP	0.63	1	0.78	0.51
Lys: Arg	1.11	1.06	0.87	1.23
Met: Gly	0.45	0.46	0.33	0.54

Table 4: Average ratios of VP/AP, Lys: Arg, Met: Gly in SIP Group and CON Group at Week0 and Week8.

	SIP Group		CON Group		P^a
	Week 0	Week 8	Week 0	Week 8	
Hb (g/L)	134.2 ± 13.0	134.6 ± 12.2	138.2 ± 14.5	137.9 ± 12.9	0.208
Total Protein(g/L)	73.6 ± 3.6	73.8 ± 3.4	74.5 ± 4.4	73.9 ± 4.2	0.831
ALB (g/L)	46.3 ± 2.2	47.4 ± 2.2	46.2 ± 2.3	47.2 ± 2.1	0.55
Cr (mg/dL)	70.6 ± 12.8	63.1 ± 15.9	69.5 ± 11.9	64.3 ± 13.2	0.694
UA (umol/L)	297.4 ± 71.6	273.0 ± 83.9	288.1 ± 74.9	261.7 ± 81.6	0.516
BUN (mmol/L)	4.9 ± 1.1	5.3 ± 1.2	4.6 ± 1.1	4.9 ± 0.9	0.041
ALT (U/L)	21.3 ± 7.5	20.7 ± 7.1	21.2 ± 8.8	21.4 ± 11.9	0.738
AST (U/L)	22.5 ± 5.3	21.6 ± 3.9	21.2 ± 4.4	22.2 ± 5.9	0.701
LDH (U/L)	169.8 ± 31.5	174.9 ± 30.4	165.9 ± 27.3	164.6 ± 31.8	0.118
ALP (U/L)	57.9 ± 16.8	58.6 ± 17.7	61.9 ± 15.9	63.0 ± 16.8	0.232
GGT (U/L)	27.4 ± 11.7	31.2 ± 18.5	27.2 ± 13.1	28.2 ± 16.2	0.408

Note: Data are shown as mean ± SD. ^aP value is for comparison between SIP group and CON group after 8 weeks.

Table 5: Effect of isolate soy protein or milk protein on serum hemoglobin concentration and functional parameters of liver and kidney in hypercholesterolemic adults.

serum triglyceride or HDL cholesterol and the ratio of dietary VP/AP or Lys:Arg, nor between the percentage changes in serum lipids and the ratio of dietary Met:Gly (Data not shown).

Discussion

We demonstrated that dietary amino acid profile can influence serum lipids and adiponectin in hypercholesterolemic adults. The dietary intervention by SIP or CON changed the subjects' dietary protein amino acid profiles. Our results also lend support to previous studies showing favorable effects of lower Lys:Arg ratio on serum lipids and lipoprotein concentration [3,12].

In the present study, TC and LDL-cholesterol levels decreased significantly in the CON group after 8 weeks intervention, while dietary ratios of VP/AP and Lys:Arg increased in CON group. We found that in each group there were more than half of the subjects' dietary ratios of Lys:Arg decreased, and serum TC and LDL cholesterol concentrations were also reduced in SIP group. That lipids reduced in the subjects may have relations to the change of the dietary Lys:Arg ratio. The possible reason might be that the subjects kept their dietary habits during the intervention. The Chinese diet tends to contain more vegetable protein but probably insufficient high-quality protein, such as enough soy protein and milk protein, so it is reasonable to conclude that SIP, CON and the subjects' dietary habits all may contribute to the effects on serum lipids.

Lysine has been reported to be hypercholesterolemic [18]. Previous study has shown that a Lys:Arg ratio of 1.0 significantly lowered serum and aortic cholesterol in rats than diet with Lys:Arg ratio of 2.0 [19]. L-arginine is a precursor of nitric oxide (NO), which can act on vascular endothelial smooth muscle cells and relax blood vessels [20], improving blood flow, oxygen and nutrient supply. Altering the L-Arg-NO pathway has been reported to alter flow mediated dilatation (FMD), a surrogate measure of endothelial function [21]. An acute oral dose of L-Arg was found to increase FMD in patients with hypercholesterolemia [22,23]. Altering administration of L-arginine increased NO production and insulin secretion; these might be responsible for the improvement in lipid metabolism [24]. Giroux et al. [7] reported that addition of arginine but not glycine to lysine plus methionine-enriched diets modulated serum cholesterol and liver phospholipids in rabbits. We were unable to determine the potential effects of endogenous Arg synthesis on the total pool as well as the mechanism through which it might affect the Lys:Arg ratio. Thus further studies are needed.

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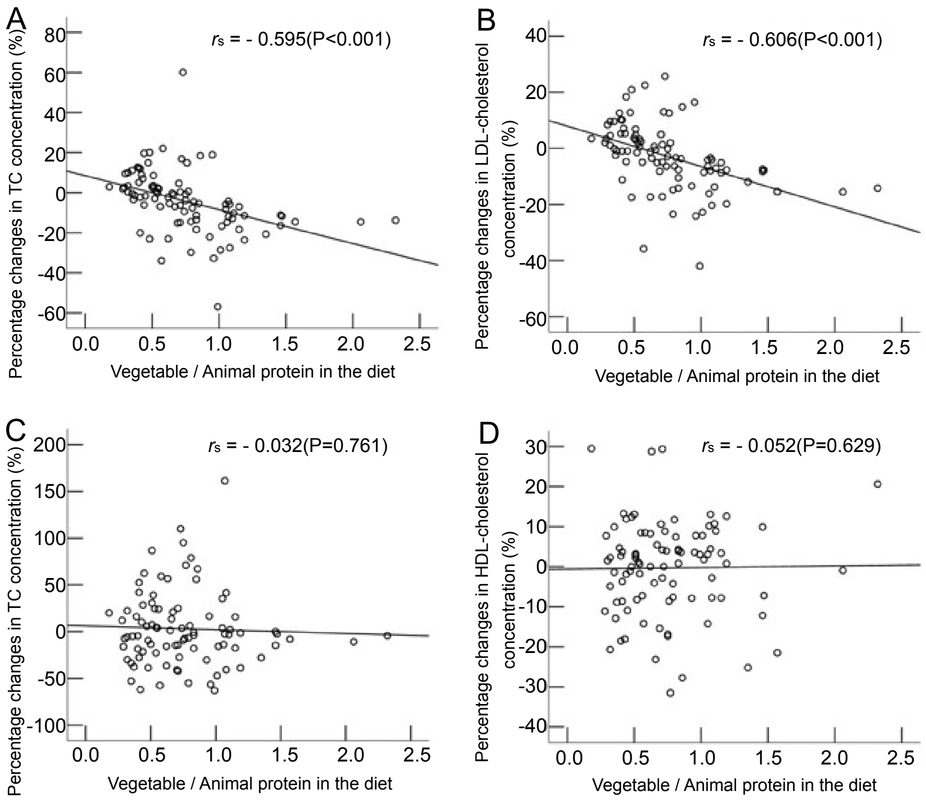

Figure 1: Relations between the dietary vegetable protein/animal protein ratio and the percentage change in serum total cholesterol (TC) (A), LDL-cholesterol (B), TG (C) and HDL-cholesterol (D) concentration in 90 subjects. The values deviated from normality and were expressed as Spearman's rank correlation coefficients (r_s).

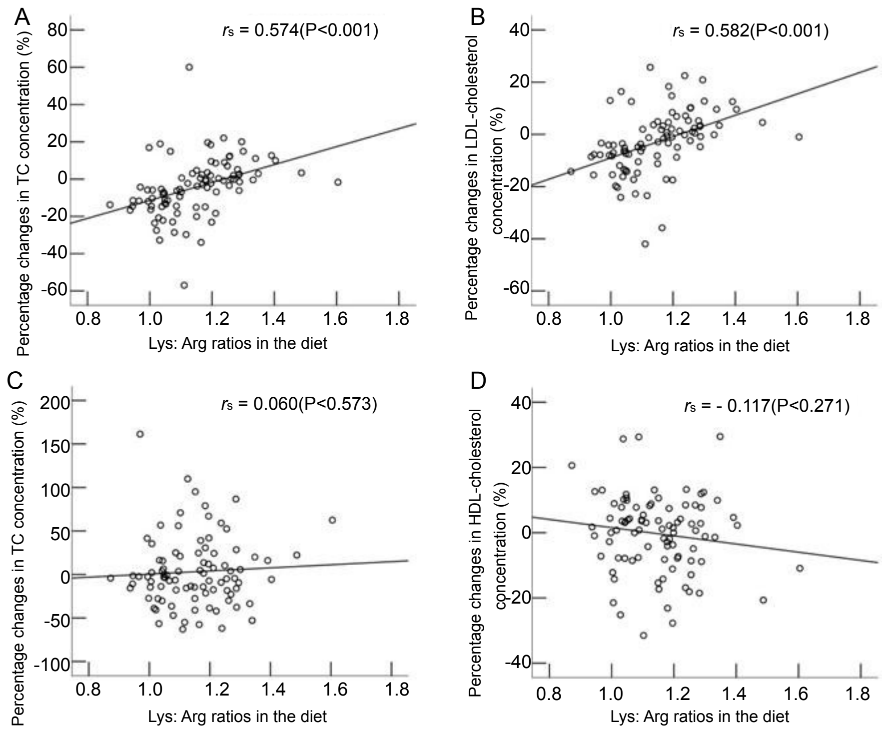

Figure 2: Relations between the dietary Lys: Arg ratio and the percentage change in serum total cholesterol (TC) (A), LDL-cholesterol (B), TG (C) and HDL-cholesterol (D) concentration in 90 subjects. The values deviated from normality and were expressed as Spearman's rank correlation coefficients (r_s).

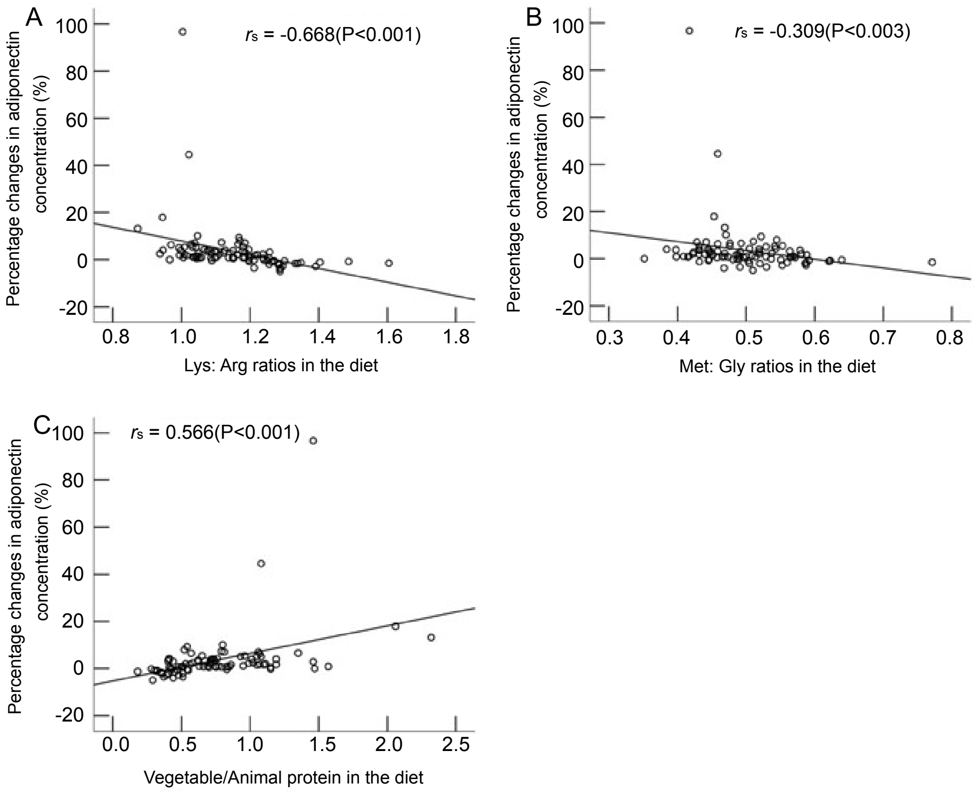

Figure 3: Relations between the percentage changes in adiponectin and the dietary Lys: Arg ratio (A), Met: Gly (B) and the dietary vegetable protein/animal protein ratio (C) in 90 subjects. The values deviated from normality and were expressed as Spearman's rank correlation coefficients (r_s).

Even the ratio of VP/AP or Lys:Arg has changed after the intervention; serum lipid profile did not differ significantly in the two groups. This may due to a relatively low ratio of Lys:Arg. In a 2002 national nutrition survey in Chinese Residents, 42.3% of fat intake came from animal sources and 57.3% came from vegetable sources, indicating the level of saturated fat in the Chinese diet were relatively high [25]. It is possible that substituting any low fat protein source may beneficially impact serum lipids in the Chinese population.

There was a strong correlation between serum cholesterol concentration and Met:Gly ratio [12]. However, correlations between Met:Gly ratio and serum lipid concentrations were not significant in the present study. This may be due to the similar dietary Met:Gly ratio in this population, mostly varying from 0.3~ 0.65 ranges; therefore, it is difficult to evaluate their various effects on the serum cholesterol and lipoprotein cholesterol concentration.

The relationship between dietary protein amino acid profile and the effect on inflammatory markers has not been fully documented. We found that diets with low Lys:Arg and Met:Gly ratios were significantly correlated with the percentage change in adiponectin from baseline to week 8. Our study is in accordance with the result by Park et al. who reported that Korean proso-millet protein (the ratio of Lys:Arg and Met:Gly is 54:123 and 127:1465, respectively) increased plasma adiponectin and decreased TNF, and up-regulated the expression of adiponectin and down-regulated TNF under high-fat feeding conditions [26]. In contrast, high concentration of adiponectin was related to insulin sensitivity and a decreased risk for CVD [27]. Adiponectin was an independent risk marker for metabolic syndrome in patients with type 2 diabetes [28].

The study suggests that the impact of dietary protein on lipid metabolism is source-dependent. In the present study, vegetable protein was found to play an important role on a cardioprotective effect. It improved lipid profile and reduced CVD risks, which appeared to be dependent on the source of protein [26,29]. It is generally agreed that vegetable protein decreases circulating cholesterol concentrations compared to animal protein [1,2]. Almost several vegetable proteins that have been studied, soy protein isolate, wheat gluten, cottonseed protein [5], whole wheat, corn gluten [30], sesame seeds [31], buckwheat protein [32], Korean proso-millet protein [26], potato, and rice [12] have been found to modulate serum lipids profiles. The similar characteristics of these dietary vegetable proteins include a lower Lys:Arg ratio and methionine than animal protein. In addition, dietary proteins with low Met:Gly and Lys:Arg ratios could increase faecal cholesterol, bile acid levels, and the hepatic gene expression of cholesterol 7a hydroxylase in rats. The cholesterol-lowering effect might be related to the enterohepatic circulation [33].

Previous researches have focused on different food compositions. For example, the experimental diet patterns were fed as individual amino acids rather than whole proteins, therefore, the results may not represent the same that occur with whole-protein feeding. The difference in bioavailability between free amino acids and amino acids from whole proteins may offer an explanation for the inconsistent effects. Different amino acids added may behave differently in the digestive tracts from those in peptides, since the mode and the rate of intestinal absorption of two types of amino acids, free or peptide-bound, differ. Thus, the structure of proteins or the amino acid sequence [34] may influence their cholesterolemic effect. The influence of bioactive peptides derived from protein digestion on lipid metabolism leads to an alternative hypothesis. Furthermore, the animals' lipid metabolism in response to diet differs from that of human being.

In conclusion, diets with more vegetable protein and low Lys:Arg ratio improved serum total and LDL cholesterol and adiponectin that are associated with obesity and inflammation in Chinese hypercholesterolemic adults.

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