Response to a Urate-Lowering Diet According to Polymorphisms in the Apolipoprotein AI-CIII-AIV Cluster

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ABSTRACT. ***Objective.*** The apolipoprotein AI-CIII-AIV cluster has been associated with the response to a urate-lowering diet, and polymorphisms in the apolipoprotein CIII gene have been associated with hyperuricemia and hypertriglyceridemia. We assessed the influence of polymorphisms in the apolipoprotein AI-CIII-AIV cluster on the response to a urate-lowering diet in patients with hyperuricemia.

Methods. A urate-lowering diet was followed for 2 weeks by 64 men with hyperuricemia. Plasma concentrations of triglycerides, cholesterol, glucose, and uric acid, and the uric acid clearance and 24-hour uric acid urinary excretory fraction were measured before and after the diet. The data were analyzed in association with the polymorphisms of the apolipoprotein AI-CIII-AIV gene cluster.

Results. After the urate-lowering diet, the plasma levels of triglycerides, cholesterol, glucose, and uric acid and 24-hour uric acid excretion all fell significantly. Paired sample ANOVA showed that the decrease was mainly due to the diet, except for the plasma triglycerides, which were influenced by allele X2 of the XmnI polymorphism of the apolipoprotein AI gene.

Conclusion. The response of the biological variables to a urate-lowering diet was mainly influenced by diet. Changes in triglycerides were also influenced by the apolipoprotein AI XmnI polymorphism ($p = 0.04$), suggesting a gene-diet interaction ($p = 0.03$). (J Rheumatol 2005;32:903–5)

Key Indexing Terms:
HYPERURICEMIA APOLIPOPROTEIN AI-CIII-AIV GENE CLUSTER DIET

Hyperuricemia, which is associated with obesity, dyslipidemia, and the insulin resistance syndrome, is influenced by dietary factors. The varied response to dietary intervention may have a strong genetic component[1]. The association between polymorphisms of the apolipoprotein AI-CIII-AIV cluster and plasma lipids, cardiovascular disease, and interindividual variations in the response to dietary therapy have all been studied[2].

Apolipoprotein AI polymorphism is involved in the variability of the apolipoprotein AI response to changes in dietary fat. In one polymorphism, a G to A transition 75 bp upstream has recently been shown to have a significant effect on the response to changes in the amount of dietary fat[3].

The frequency of the apolipoprotein CIII mutated allele S2 varies greatly between different racial groups. This allele is associated with decreased plasma concentrations of cholesterol, low density lipoprotein (LDL) cholesterol, and apolipoprotein B after a monounsaturated fatty acid-rich diet[4]. However, few studies have assessed the role of polymorphisms of the whole cluster in hyperuricemia. We evaluated the influence of polymorphisms in the whole apolipoprotein AI-CIII-AIV cluster in the response to a urate-lowering diet in patients with hyperuricemia.

MATERIALS AND METHODS

Subjects. The study was undertaken in 64 men with gout, based on the American College of Rheumatology criteria of Wallace, *et al*[5]. No patient was receiving lipid-lowering or urate-lowering therapy and patients with secondary hyperuricemia (renal failure or use of diuretics), diabetes after an oral glucose tolerance test, and hypothyroidism were excluded, as were patients with alcohol abuse. Biochemical variables were measured before and after a urate-lowering diet[6], which was achieved through dietary advice. The diet includes most sugars, starches, and fats. Protein is supplied chiefly by eggs and cheese, and partly by bread, fruit, and nuts. The usual fluid intake is maintained and no restriction is placed on the amount of food consumed. The following foods are forbidden: meat, poultry, other flesh, fish, seafood, sardines, herrings, kidney, liver, meat extract, alcohol, beans, peas, lentils, spinach, oatmeal, and asparagus.

Procedures. DNA was isolated[7] and amplified by polymerase chain reaction. Primers for the XmnI locus were those described by Shoulders, *et al*[8]; by Jeenah, *et al*[9] for the –75 bp locus of the apolipoprotein AI gene (determined by MspI); and by Dammerman, *et al*[10] for the SstI locus of the apolipoprotein CIII gene.

Statistical analysis. Data are expressed as the mean ± standard deviation (SD). Comparison between groups was by Student t test for independent

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variables and Mann-Whitney U test according to the normality of the variables. Differences in genotype distribution were studied by chi-square test. Analysis of effects of the diet on the biological variables was by paired sample ANOVA. A $p < 0.05$ was considered significant. The power of the study in the Xmnl polymorphism of the apolipoprotein A1 gene is 1.0.

RESULTS

The mean age of the 64 subjects was 50 years, and none showed any significant weight change after the intervention (body mass index 30.2 ± 3.8 kg/m^2). The genotype frequency distribution of the Xmnl polymorphisms of the apolipoprotein AI gene in the patients was not different from the general population[11]. The allelic frequency was G = 0.66, A = 0.34, X1 = 0.83, and X2 = 0.17. The XmnI polymorphism was in Hardy-Weinberg equilibrium. Levels of glucose, cholesterol, triglycerides, and uric acid and uric acid clearance fell significantly in patients after the urate-lowering diet (Table 1). The diet accounted mostly for these changes, except for triglyceride concentrations, which, after adjusting for age, were influenced by genotype X2 ($p = 0.04$; Table 2).

Patients with the G allele of the MspI polymorphism in the apolipoprotein AI gene had significant differences in levels of glucose, triglycerides, and uric acid and uric acid clearance. Patients with the A allele had significant reductions in levels of glucose, cholesterol, and triglycerides and uric acid clearance (Table 2). ANOVA for paired data showed that the diet, not the genotype, accounted for most of the changes (Table 2).

The mutation in exon 4 of the apolipoprotein CIII gene (SstI) had no influence on the clinical variables in the hyperuricemic patients. The changes were mainly due to the diet, not to the genotype (data not shown).

Table 1. Biochemical variables in 64 patients before and after a 2 week urate-lowering diet. Data are means ± SD.

	Baseline	Mean Post-Diet Changes*
Glucose, mg/dl	108.3 ± 19.3	–5.37 ± 12.69**
Cholesterol, mg/dl **	211.7 ± 40.3	–10.6 ± 29.52**
Triglycerides, mg/dl**	246.5 ± 222.9	–66.39 ± 156.29**
Uric acid, mg/dl†	7.7 ± 1.7	–0.57 ± 1.7†
Uric acid clearance, ml/min**	5.4 ± 2.7	–1.3 ± 2.51**
24-hour excretory fraction††	6 ± 2.02	–0.72 ± 2.73††

* Post-diet minus baseline data (before and after a 2 week urate-lowering diet). ** $p < 0.001$, † $p = 0.01$, †† $p = 0.026$.

DISCUSSION

The reduction in the level of triglycerides in patients with the X2 allele was due to both diet and genotype. These patients had greater baseline levels of triglycerides and the greatest reduction in triglycerides after the urate-lowering diet. This finding is in agreement with Kessling, *et al*, who studied hyperlipidemic patients classified according to triglyceride level and found that the frequency of the X2 allele was increased in patients with the highest triglyceride levels[12]. The relation between hypertriglyceridemia and hyperuricemia has also been attributed to alcohol intake or insulin resistance, although lack of this association has also been reported[13]. Indeed, this association was previously related with low renal excretion of urates and high VLDL triglyceride levels[14].

The frequency of the rare allele of the XmnI polymorphism of the apolipoprotein AI gene is higher in patients with combined hyperlipidemia than in persons with normal lipid levels[9]. The A allele of the MspI polymorphism of the apolipoprotein AI gene is associated with higher levels of total cholesterol and LDL cholesterol. Interaction between the XmnI and MspI polymorphisms of the apolipoprotein AI gene has been reported: Dallinga-Thie, *et al* described the existence of a specific combination of high-risk haplotypes associated with increased plasma cholesterol and triglyceride concentrations[15]. Our patients with the X2, A, and S1

Table 2. Change in biochemical variables after a 2 week urate-lowering diet in 64 patients according to polymorphisms XmnI and MspI in the apolipoprotein AI genotypes. Post-diet minus baseline (means ± SD).

	2 Factor Paired ANOVA					2 Factor Paired ANOVA				
	Allele X1, n = 45	Allele X2, n - 19	P Diet†	P Genotype††	P Interaction#	Allele G, n = 33	Allele A, n = 31	P Diet†	P Genotype††	P Interaction#
Glucose, mg/dl	–4.9 ± 13.4	–5.1 ± 9.2	0.004	NS	NS	–5.6 ± 15	–5.4 ± 7.6	0.001	NS	NS
Cholesterol, mg/dl	–6.6 ± 27.4	–20.9 ± 31.6	0.001	NS	NS	–7.5 ± 27.6	–17.4 ± 31.5	0.002	NS	NS
Triglycerides, mg/dl	–38 ± 127	–132.9 ± 206.7*	< 0.001	0.04	0.03	–72.6 ± 183	–59.9 ± 141	0.001	NS	NS
Uric acid, mg/dl	–0.46 ± 1.67	–0.46 ± 1.7	0.05	NS	NS	–0.65 ± 1.5	–0.51 ± 1.9	0.01	NS	NS
Uric acid clearance, ml/min	–1.14 ± 2.2	–0.94 ± 2.5	0.004	NS	NS	–0.77 ± 2	–1.28 ± 2.4	0.002	NS	NS
24-hour excretory fraction	–0.47 ± 2.6	–0.82 ± 2.9	0.12	NS	NS	–0.27 ± 1.39	–0.72 ± 3.3	NS	NS	NS

* Values between X1 vs X2, $p = 0.03$; all others were not significant. Baseline vs diet data: † p diet = mean differences in the total group; †† p genotypes = mean differences between X1 vs X2 alleles; # p interaction = mean differences between genotypes plus diet. Allele X1 = X1X1 and allele X2 = X1X2 and X2X2. Allele G = GG and allele A = AA and GA.

alleles had the most significant reduction in total cholesterol and triglycerides.

The limitations of this study include the lack of a separate control group — the patients served as their own controls before and after the diet, a relatively small sample size for assessing gene-diet interactions, and the short time during which the patients followed the diet — although 2 weeks was sufficient to detect the effects[6].

The response of the biological variables studied after a urate-lowering diet was influenced mainly by diet. Changes in triglycerides were also influenced by the apolipoprotein AI gene XmnI polymorphism, suggesting a gene-diet interaction.

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