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Dietary management and genetic predisposition of hyperuricaemia

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ABSTRACT

This study aimed to evaluate the effect of food sources, vitamin C rich foods and low-fat dairy foods, versus traditional therapy on uric acid concentrations in serum for hyperuricaemic patients and to study the frequency of SLC22A12 gene mutation (C850G exon5) in hyperuriceamic patients, and its association with demographic and clinical data compared to healthy controls. 60 patients (aged 35 to 60 years, 37 males and 23 females) and 30 control patients of the same age and sex were from outpatient clinics in Assiut University Hospital. Uric acid concentration was measured colorimetrically. DNA was purified from peripheral blood and exon 5 of SLC22A12 gene was sequenced. The patients were randomly selected and equally divided to 3 groups to receive traditional therapy for Gout (anti-inflammatory and uricosuric drugs), vitamin C rich food or low-fat dairy foods diets once daily, in addition to restriction of purine rich foods and increase water intake for 12 weeks. Hematological and lipid profile parameters were also studied. The SLC22A12 gene mutation (C850G exon5) was found in 23 hyperuricaemic patients while the controls were not included, those patients had higher level of triglycerides than others ($P = 0.033$). Serum uric acid decreased significantly in all treated groups ($P < 0.05$). In conclusion, the C850G mutation measuring (exon 5) could be used as a screening and prognostic biomarker for hyperuricaemia; vitamin C rich foods and low-fat dairy intake can replace the traditional therapy of hyperuricaemia with high efficacy and no side effects. However, there may be need to conduct further studies on a larger population.

Keywords: Hyperuricaemia, C850G mutation, vitamin C, low-fat dairy foods.

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INTRODUCTION

Gout is characterized by hyperuricaemia and monosodium urate crystals-induced synovitis. Many patients have a positive familial history, due to an abnormal functioning of the proximal tubule that also reduces the excretion of xanthines, phosphates and other anions (Anzai et al., 2005). Urate reabsoprtion is controlled by urate transporter 1 (URAT1), a 555 amino acid protein that is localized in the proximal renal tubules in humans (Enomoto et al., 2002). SLC22A12 gene (solute carrier family 22, organic anion/urate transporter), member 12 gives instructions for urate transporter 1 (URAT1) protein synthesis that is found in the kidney (PCT) (Kaito et al., 2013; Koepsell and Endou, 2004). The SLC22A12 gene (which is constituted by 2642 base pairs in 10 exons) mutations were reported in Japanese patients with renal hyperuricaemia and healthy population. Approximately two thirds of total body urate is produced endogenously, while the remaining is accounted for by dietary purines. The most common causes of hyperuricemia are diet, excess physical activity, obesity and family history (Miao et al., 2008). Vitamin C has uricosuric properties such as, increasing renal fractional clearance of uric acid, inhibits uric acid synthesis, vitamin C is found naturally in foods such as broccoli, tomatoes, potatoes, green peppers, cantaloupe, citrus fruits, berries and green leafy vegetables (Juraschek et al., 2011).

Low-fat dairy intake has a moderate urate-lowering effect (Dalbeth and Palmano, 2011). Although medical therapy is effective to reduce hyperuricaemia, it carries

significant side-effect profiles (Conaghan and Day, 1994). Therefore, the present work aimed to:

1. To study the frequency of SLC22A12 gene mutation (C850G exon5) in hyperuriceamic patients, its association with demographic and clinical data compared to healthy controls.
2. Evaluate the effect of vitamin C rich foods and low-fat dairy intake versus traditional therapy on reducing serum uric acid concentrations in hyperuricaemic patients.

MATERIALS AND METHODS

For 12 weeks, 60 mild recently diagnosed outpatients (35 to 60 years) from the rheumatology clinic in Assiut University Hospital were equally and randomly assigned to receive either traditional therapy (antinflamatory+ uricosuric drugs) or vitamin C rich foods (100 mg/day in the form of 3 strawberries, pinapples, lemons or orange, each contains about 30 mg vitamin C) or low fat milk (1 cup/day) compared to 30 healthy age and sex matched control subjects. Hyperuricemia was defined as >7 mg/dl in the blood for men, and >6 mg/dl for women. The study protocol was approved by the Ethics Committee of Medicine Faculty, Assuit University. Patients with history of chronic disease such as diabetes and hypertension were excluded from this study. Blood samples were collected after an overnight fast, DNA was purified from peripheral blood, the primer for PCR of exon 5 is F 5´GCC ACA GGC AAT GAC CCC TC-3´, R5´ ACC TTC TTC CCA GGG AGC TG-3′ using PCR purification kit (Qiaex II, Qiagen, Valencia, CA), exon 5 of SLC22A12 gene was sequenced using 310 genetic analyser (Applied Biosystems, Foster City, CA) (Ichida et al., 2004). Uric acid in serum was determined colorimetrically (Roche, cat. no 1661850) before and after the intervention. Enzymatic colorimetric kits were purchased for determination of triglycrides (Quimica Clinica Aplicada, SA, Spain, CAT No TL 20 10), HDL (Egyptian company for biotechnology (SAE) Spectrum ,CAT No 266 001), LDL (Clinica Aplicada, SA, Spain CAT No TL 17 11) and Glucose was estimated by glucose oxidase-peroidase enzymatic colorimetric kit (Spineract, Girona, Spain, No 100 120) and according to the manufacturers' instructions, Erythrocyte sedimentation rate and C-reactive protein were also measured.

Statistical analysis

The data were analyzed by ANOVA using SPSS 11.0 statistical analysis program .The study results are expressed as means ± SDs. The correlations between groups were calculated by Spearman Rank Correlation. P-value was considered to be significant when it is < 0.05.

RESULTS

The results of the current study were summarized in table 1. Comparison between the therapeutic effects of the different treatment modalities is shown in table 2. The SLC22A12 missense gene mutation (C850G exon5) was found in 23 hyperuricaemic patients out of 60 patients (38%) but this gene mutation was not detected in the controls, these patients had higher level of triglycerides than the others (P = 0.033). There were significant positive correlations between serum uric acid and age, sex, BMI, family history, education level, physical activity and smoking (P < 0.05 for all). There were significant increase in Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in patients compared to controls and serum uric acid level was decreased significantly in all treated groups.

DISCUSSION

Urate transporter 1 protein is an integral membrane protein encoded by the SLC22A12 gene located from base pair 64,590,810 to base pair 64,602,353 on the chromosome 11; it acts as urate-anion exchanger which regulates the level of urate in the blood. This protein is primarily found in kidney. Two transcript variants encoding different isoforms have been found for SLC22A12 gene. Single nucleotide polymorphisms of SLC22A12 gene are associated with altered reabsorption of uric acid by the kidneys (Enomoto et al., 2002).

The missense mutation within codon 284 (C850 G) was detected in 38% of patients. The missense mutation led to substitution or arginine amino acid (larg and basic amino acid) instead of glycine amino acid (small and non-polar amino acid), the substitution are associated with both cluster genes (SLC22A12 and apo AI-CIII-AIV) which are localized in the short arm of chromosome 11 (Cardona et al., 2005). This change could modify the interaction between the ligand and the extracellular loop of the Urate transporter 1 protein which affect uric acid transportation and subsequently result in hyperuricaemia. No mutation was detected in healthy patients. A similar glycine to arginine mutation was found to changes a membrane transportation into a calcium channel impairing charged molecules transportation as iron, uric acid forms the dually charged full urate ion (Rouault, 2003) and this mutation may affect the transportation in the same way. Previous studies revealed frameshift mutation in the SLC22A12 gene, which are associated with hyperuricaemia (Vázquez-Mellado et al., 2007) or hypouricaemia (Stiburkova et al., 2013); the activity of URAT1 may depend on alternative splicing or post-translational modifications, which suggested that an adaptation to environmental conditions was happened. Whatever mechanism accounts for this disadvantage, investigating the structural and biochemical properties of this molecular changing will provide a better understanding of this complex disorder.

The serum uric acid level was significantly correlated to age and sex (P < 0.05) as previously reported (Stiburkova et al., 2013), the risk age for hyperuricemia is 30 years for male and 50 years for female (Liu et al., 2011; Vitoon et al., 2008). There were significant correlation between smoking, physical activity and body mass index as previously reported (P < 0.05) (Kumar et al., 2010; Villegas et al., 2010; Choi et al., 2004). All the other clinical and demographic parameters had non-

Table 1. Demographic, clinical and laboratory parameters studied in control and different groups.

Parameter	Control (mean ± SD)	Groups	P value
Age (year)	53.88 ± 4.8	49.12 ± 12.2	N.S
BMI (kg/m^2)	18.5 ± 5.5	29.20 ± 5.3	P < 0.05
Serum uric acid mg/dl			
Male (n = 37)	3.4 ± 1.6	8.16 ± 1.08	P < 0.05
Female (n = 23)	2.4 ± 0.6	6.32 ± 1.97	
The frequency of C850G SLC22A12 gene mutation	-	23/60 (38.3%) (20 male, 3 females)	
Serum uric acid (mg/dl)			
Before treatment	2.9 ± 1.9	8.18 ± 1.27	
Traditional therapy		5.83 ± 0.2	P < 0.05
Vitamin C rich foods		6.13 ± 0.93	
Low fat dairy intake		6.33 ± 0.86	
CRP (mg/L)	0.6 ± 0.2	4.93 ± 1.4	P < 0.05
ESR (mm/hour)	16.2 ± 12.14	23.2 ± 4.09	P < 0.05
Education level			
High	-	10 (16.7%)	
Middle		18 (30%)	P < 0.05
Low		14 (23.30%)	
Illiterate		18 (30%)	
Physical activity			
Active	-	35 (58.33%)	
Moderate		20 (33.33%)	P < 0.05
Low		5 (8.33%)	
Smoking status			
Never	-	30 (50%)	
Former		9 (15%)	P < 0.05
Current		21 (35%)	
No. of effected joints	-	2.2 ± 1.02	N.S
Family history		41 (68.33%)	
Yes		19 (31.67%)	P < 0.01.
No			
Total cholesterol (mg/dl)			
SLC22A12 gene mutation detected	141.23 ± 2.13	142.63 ± 1.26	N.S
SLC22A12 gene mutation not detected		141.13 ± 2.13	
LDL-C (mg/dl)			N.S
SLC22A12 gene mutation detected	120.33 ± 1.21	131.63 ± 19.34	
SLC22A12 gene mutation not detected		123.03 ± 15.22	
HDL-C (mg/dl)			
SLC22A12 gene mutation detected		46.66 ± 7.12	N.S
SLC22A12 gene mutation not detected	45.63 ± 5.13	47.23 ± 4.13	

Table 1. Continues.

Triglycerides (mg/dl)			
SLC22A12 gene mutation detected	133.90 ± 12.13	143.45 ± 6.12	*P* < 0.05
SLC22A12 gene mutation not detected		160.55 ± 4.15	
Serum glucose (mg/dl)			
SLC22A12 gene mutation detected	120 .30 ± 22.13	122 .50 ± 23.1	N.S
SLC22A12 gene mutation not detected		119 .53 ± 25.13	

P values < 0.05 were considered significant.
BMI = body mass index.

Table 2. Clinical and laboratory parameters studied in different treated groups.

Parameter		Traditional therapy	Vitamin C rich foods	Low fat dairy intake
Serum uric acid (mg/dl)	Before treatment	8.18 ± 1.27	7.96 ± 0.8	8.35 ± 1.16
	After treatment	6.84 ± 0.79*	6.75 ± 0.96*	7.36 ± 0.86*
ESR (mg/dl)	Before treatment	20 ± 5.83	24.1 ± 0.8	25.5 ± 5.63
	After treatment	8.2 ± 1.54**	9.2 ± 1.11**	9.05 ± 1.63**
CRP (mg/dl)	Before treatment	5.3 ± 1.03	6.1 ± 1.52	6.5 ± 1.47
	After treatment	3.5 ± 1.50**	2.55 ± 1.8**	1.79 ± 1.47**
BMI (kg/m^2)	Before treatment	27.14 ± 4.07	29.12 ± 3.63	29.87 ± 4.2
	After treatment	26.16 ± 3.36	29.01 ± 3.68	28.90 ± 3.86
No. of affected joints	Before treatment	2.2 ± 1.23	2.6 ± 0.87	2.6 ± 1.1
	After treatment	0.43 ± 0.047*	0.25 ± 0.08*	0. 44 ± 0.035*

*p < 0.05, **p < 0.01.

significant differences between treated patients and controls.

Vitamin C rich foods tend to lower serum uric acid as reported in the current study, this finding agrees with previous studies because vitamin C exerts an uricosuric effect (Choi et al., 2005; Tauler et al., 2003). Low-fat dairy products was found to reduce uric acid levels (Stamp et al., 2013; Fulgoni et al., 2011) may be due to mild uricosuric effects of dairy protein (casein and lactalbumin) consumption (Dalbeth and Palmano, 2011). In addition, certain dairy fractions, particularly glyco-macropeptide and milk fat extract, have anti-inflammatory properties (Bieber and Terkeltaub, 2004) as detected in the current study.

Conclusion

The current results revealed that of SLC22A12 gene mutation (C850G exon5) was detected in 38% of hyperuricaemic patients except control, the role of this mutation in Urate transporter 1 protein activity need further studies, both vitamin C and low-fat dairy foods tend to decrease serum uric acid concentrations to the same extent as uricosuric drugs without any side effects. While the role of the SLC22A12 gene mutation may be unclear, the combination of lifestyle, genetic, and environmental factors play a role in determining the risk of this complex disorder.

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