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Relationship between Hyperuricemia, Hyperglycemia and Elevated Triglyceride Levels in Cardiometabolic Disorder

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Abstract

Introduction: *High levels of triglycerides and uric acid have each been reported to be independently associated with an elevated risk for coronary heart disease.[1,2]*
However, it is less well established whether high levels or triglycerides or uric acid, per se, represent independent cardiovascular risk factors. Rather, both hypertriglyceridemia and hyperuricemia serve as biomarkers for increased coronary heart disease risk.

Materials and methods: *We retrospectively analyzed results of serum uric acid, fasting plasma glucose (FPG) and triglyceride tests performed on the whole cohort of outpatient adults consecutively referred to our laboratory for routine blood testing for one year. This study included 150 cardiometabolic subjects aged 25 to 80 years. The body mass index (BMI), waist circumference, total and HDL cholesterol, serum triglycerides and serum uric acid were measured.*

Results: *Data were analyzed using student t-test, pearson's coefficient and linear regression model. The prevalence of a serum uric acid level >0.42 mmol/L in men was 18.32% and the prevalence of a serum uric acid level >0.36 mmol/L was 15.9% in women. Serum uric acid was strongly related to serum triglycerides in men as well as in women (r = 0.255 in men and r = 0.254 in women, p < 0.001). Uric acid levels were also significantly associated but to a lesser degree with age, BMI and waist circumference. This study shows that serum uric acid is markedly associated with parameters of the metabolic syndrome, in particular serum triglycerides.*

Conclusion: *The mutual biological interrelationship observed between serum uric acid, hypertriglyceridemia and hyperglycemia raises the possibility of a potential pathogenetic overlap between these conditions.*

Keywords: *Cardiometabolic disease, Hyperuricemia, Hypertriglyceridemia, Hyperglycemia, Metabolic syndrome.*

Introduction

Cardiometabolic disease includes a wide range of indications leading to heart and coronary disease. Today, it affects more than 100 million people in the developed world and represents the leading cause of death in the world, before cancer and accidents. Even if patient care is improving, the disease continues to grow to epidemic proportions, with the continued prevalence of a variety of risk factors including dyslipidemia, obesity and diabetes. It is defined as an array of metabolic, hemodynamic and renal abnormalities.

The syndrome is also associated with essential hypertension, abnormalities in the circadian rhythm of blood pressure and heart rate, the diabetic dyslipidemic syndrome, hypercoagulability and increased cardiovascular inflammation, all of which contribute to an increased risk of cardiovascular disease, morbidity and mortality. Hypertriglyceridemia is almost certainly an independent risk factor for CVD though the complex mechanism underlying the association between triglycerides and atherosclerosis obscures detection of their direct causal relationship. In a previous study hypertriglyceridemia was reported to be frequently found in patients with hyperuricemia. Epidemiological studies have shown significant associations between increased serum uric acid concentrations and several components of the metabolic syndrome, such as obesity, type 2 diabetes and hypertriglyceridemia [3,4]. Notably, these associations were already present in children and young adolescents [5,6]. It was also recently emphasized that elevated serum uric acid levels are strongly associated with the metabolic syndrome, yet are not an independent risk factor for vascular disease in patients with this syndrome[7]. Additionally, Liou et al. reported that the presence of metabolic syndrome was not associated with increased circulating uric acid levels [8], whereas Lin et al. did not observe any association between serum uric acid, hyperglycemia and other components of the metabolic syndrome[9]. Thus, this study was designed to unveil potential biological relationships between uric acid, fasting plasma glucose (FPG) and triglycerides in the general population.

Methods

Cases were divided into four groups namely, Group 1: normal, healthy adults as control group, Group 2: patients with type 2 diabetes mellitus, Group 3: patients with known history of CHD, and Group 4: patients with metabolic syndrome (diagnosed as per NCEP-ATP III criteria) (10). A total of 150 cases were selected which included 69

metabolic syndrome cases, 51 cases of diabetes mellitus type 2 and 30 cases with cardiovascular disease.

Renal function was assessed by doing creatinine clearance and blood urea measurements and only cases with normal renal function were included for further study. All participants were subjected to a detailed questionnaire and a medical examination at the study centre was performed.

Anthropometric data

Height and body weight were measured with participants standing without shoes and heavy outer garments. Body mass index (BMI) was calculated as weight divided by height (Kg/m^2). Waist circumference was measured to the nearest 1cm. Patients were queried about for the existence of hypertension. Hypertension was defined as diastolic BP $\geq$ 95 and/or current intake of antihypertensive medication. Smoking habits were classified as persons who never smoked, ex-smokers designated as persons who reported no current smoking but regular smoking in the past, occasional smokers referred to persons reporting non-daily consumption of cigarettes and regular smokers currently smoking at least one cigarette per day. Alcohol consumption was assessed according to the frequency of alcohol drinking as never, occasionally and regular. The participants were classified as vegetarians and non-vegetarians according to the type of regular diet. The diagnosis of diabetes mellitus was considered when individuals reported to have been told by a doctor or tested positive for glycosuria. All the patients were tested for serum glucose level after an overnight fast and also 2hrs after taking regular meal.

Biochemical Analysis

Only blood samples collected in the Clinical Biochemistry laboratory were used for in vitro biochemical analysis. The samples were collected by standard procedures under aseptic conditions. Standard procedures were followed for the preservation and storage of samples before

analysis. Triglyceride (GPO/PAP method) [11] and uric acid (Uricase/POD method) [12] levels were measured using standard autoanalyser. Internal quality control for the laboratory determinations was regularly performed.

Statistical Analysis

All statistical analyses were carried out separately by sex using the unpaired student t-test. P-value <0.05 was considered as significant. Linear regression technique was used to determine the independent predictors of serum uric acid. The various components (CVD, Diabetes mellitus type 2 and metabolic syndrome) of the cardiometabolic disease, as well as the other established risk factors of uric acid, were considered as potential explanatory variables in this model. Values of uric acid above the sex-specific percentile 75 (i.e. >0.383 mmol/L for men and >0.354 mmol/L for women) were defined as high.
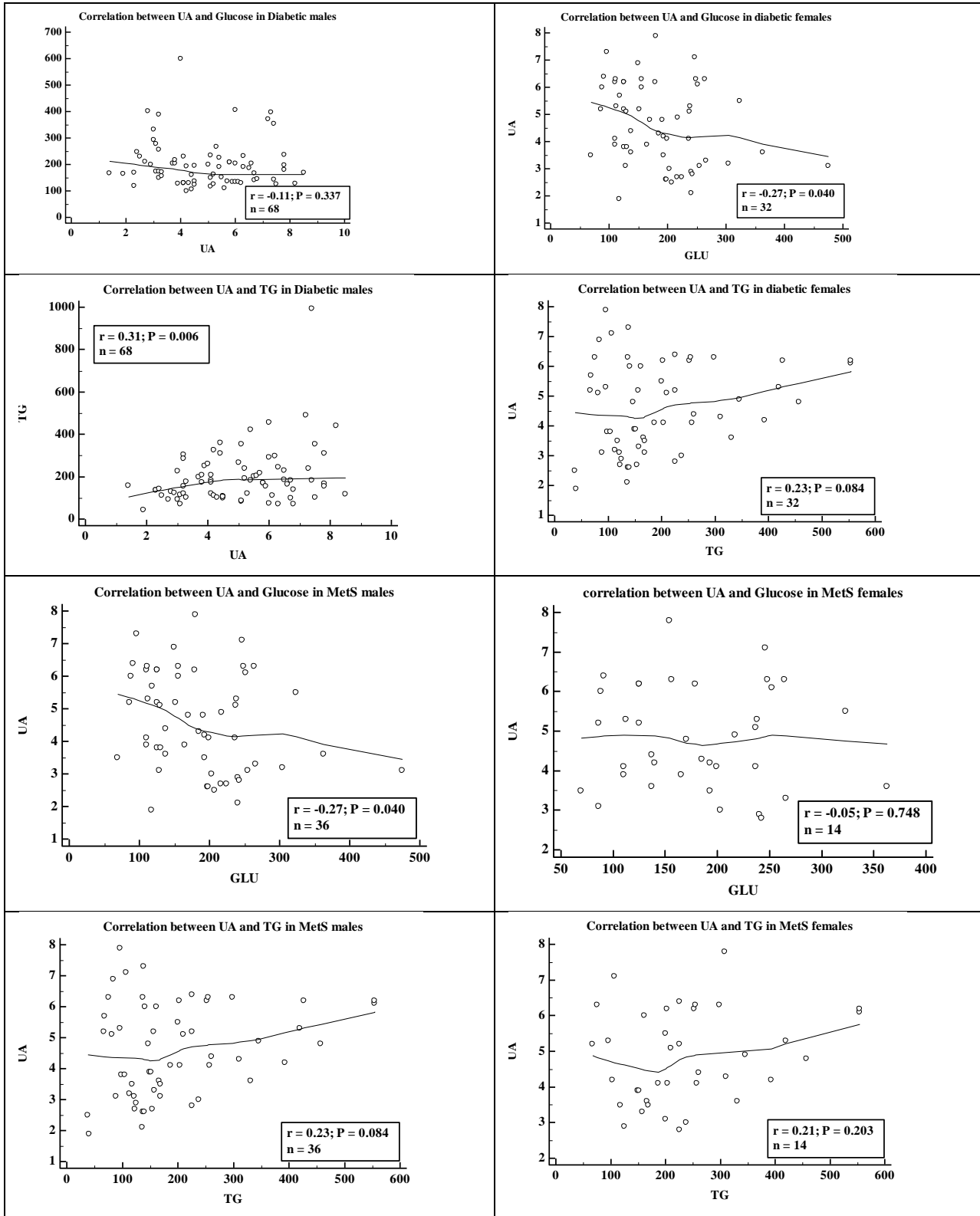
Results

The characteristics of the participants are presented in Table 1. BMI, triglycerides and uric acid levels were significantly higher in morbid group than in control group (p<0.001). Smoking, alcohol consumption and high triglyceride levels were more common in men than in women (Table 1). Serum uric acid levels were significantly higher in men than in women ($p < 0.05$). When using the commonly accepted cut-off values for serum uric acid levels, i.e. a serum uric acid >0.42 mmol/L in men and >0.36 mmol/L in women [15], the prevalence of hyperuricemia would be 18.32% in men and 15.9% in women ($p < 0.05$). In this analysis, however, we have used the sex-specific 75th percentile which gives a cut-off at 0.383 mmol/L for men and 0.354 mmol/L for women. Accordingly, the frequency of abnormal values of uric acid was higher among subjects with high triglyceride and high glucose values, suggestive for diagnosing the metabolic syndrome, than among those with normal triglyceride and glucose values. In both sexes, serum triglycerides and serum uric acid levels were strongly correlated ($p < 0.001$). (Figure 1)

Table 1: Mean levels, standard deviations and correlations with uric acid for selected cardiometabolic risk factors by sex. SD: standard-deviation, Corr: correlation coefficient with serum uric acid

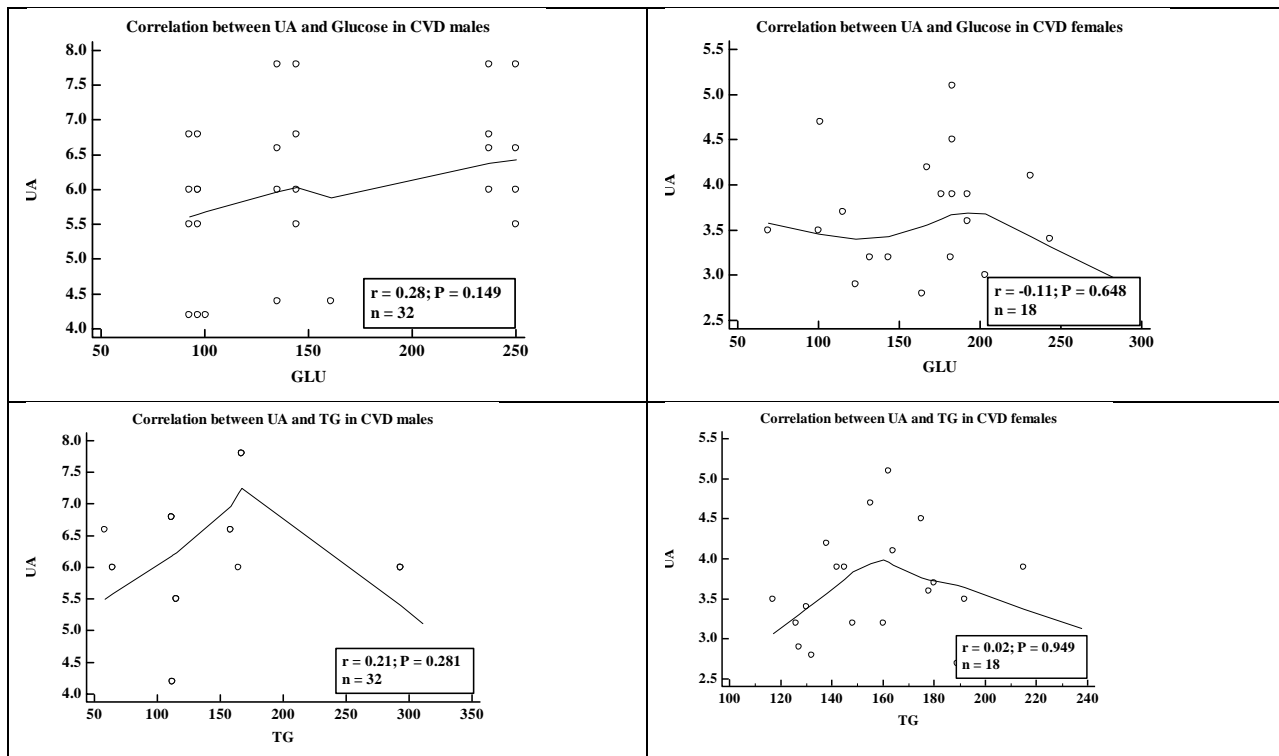| Risk Factor	unit	Men (n=90)		Women (n=60)	
		Mean ± SD	Corr.	Mean ± SD	Corr.
URIC ACID	mmol/L	0.30±0.10	1	0.27±0.09	1
GLUCOSE	mmol/L	195.64±89.80	-0.2	184.8±75.6	-0.17
TRIGLYCERIDES	mmol/L	2.23±1.46	0.255	2.20±1.32	0.26
SMOKING	%	20	-	-	-
HYPERTENSION	%	46.6	-	38.3	-
HISTORY OF DIABETES	%	54.4	-	55	-
ALCOHOLIC	%	7.7	-	-	-

Figure 1: Correlation of Uric Acid with Glucose and Triglycerides in cardiometabolic subgroups

Discussion

There is debate whether uric acid is simply a marker of cardiovascular disease or it may exert an atherogenic effect independently of other known cardiovascular risk factors. Elevated levels of uric acid correlate with older age, male gender, hyperlipidemia, obesity, insulin resistance and type 2 diabetes [13,14] and accelerate the progression of hypertension-induced end-organ injury [15]. Uric acid also activates the complement system inducing the development of oxidative stress and LDL oxidation [16], and exerts proinflammatory effects stimulating human mononuclear cells to produce inflammatory cytokines. Finally, uric acid induces systemic endothelial dysfunction, a pathogenetic mechanism in mediating hypertension [17,18].

The major finding of this study is that hypertriglyceridemic and hyperglycemic adults have increased prevalence rate of elevated serum uric acid levels, and that hypertriglyceridemia and hyperglycemia are the strongest predictors of hyperuricemia in a large sample of the general population. At first glance, these findings could appear unsurprising, given the strong association between serum uric acid levels and insulin resistance and the previous observations of a positive association of serum uric acid levels with hyperglycemia and dyslipidemia. However, the underlying pathophysiological mechanisms linking hyperglycemia, hypertriglyceridemia and hyperuricemia are currently unknown. Both the factors that increase serum uric acid synthesis (e.g., an increased activity of the hexose monophosphate shunt and thereby purine biosynthesis) or those that decrease urinary uric acid excretion rate (e.g., an increased tubular reasorption and/or diminished tubular secretion) might be involved. Indeed, it has been shown that patients with insulin resistance or impaired glucose tolerance have reduced values of urinary uric acid clearance [19] and chronically increased extracellular adenosine concentrations, thereby contributing to increasing uric acid synthesis [20]. The strengths and limitations of the present study deserve comment. The biochemical variables (hyperglycemia, hypertriglyceridemia) that typically cluster in the metabolic syndrome were retrieved from a large database of outpatient test results and confirm the previous observation that fasting plasma glucose was significantly and

positively associated with the uric acid level. However, the cross-sectional design of the study precludes the establishment of causal or temporal relations among these variables, and prospective studies will be required to sort out the time sequence of events. Further, the study population of outpatient adults from laboratory may not be a representative sample of general population and, unfortunately, neither additional clinical information is available on this large cohort of outpatients, nor the effective prevalence of metabolic syndrome as defined by the complete ATP III criteria. Nevertheless, the biological interrelationships observed in this study population raise the possibility of a potential pathogenetic overlap (or a vicious circle) between hyperuricemia, hypertriglyceridemia and hyperglycemia.

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