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Serum Urea Nitrogen Level Shows Stronger Correlations with Metabolic Syndrome Risk Factors in Women Than in Men in a Japanese General Population

Reiko Seki and Kazuhisa Nishizawa*
School of Medical Technology, Teikyo University, Japan

Abstract

Urea nitrogen (UN) is widely used as a clinical marker for renal dysfunction. In an analysis of a health check data of Japanese adults, we incidentally observed that the serum UN level correlated with many metabolic syndrome (MetS)-related parameters in women but not in men. Similar gender differences were observed in the associations between the UN/creatinine ratio and MetS-related parameters, highlighting the link between lipid metabolism and urea metabolism, which is unrelated to changes in renal functions. The implications of this finding for a recent understanding of the effects of dietary fibers and hormones on lipids and nitrogen metabolism are discussed.

Introduction

In a population-based study conducted by one of us (R.S.), the serum level of uric acid (UA) correlated with metabolic syndrome (MetS) components, and the correlations were stronger in women than in men [1]. Incidentally, the UA level was found to be associated with the urea nitrogen (UN) level in women but not in men. As it has been well documented that the serum UA level is associated with obesity/adiposity [2,3], we were motivated to examine the possible association of UN with the MetS risk factors (i.e., MetS components and MetS-related parameters). In this study, we examined whether the serum UN level correlates with the MetS risk factors in a health check population in Japan, and whether such correlations, if any, show gender differences.

Methods

This study used the same dataset as the one described recently, which was derived from the health screening program for middle-aged and older individuals, performed by the Yuport Medical Check Center in Tokyo, Japan, between April 1998 and March 2002 [4,5]. The dataset of 16 389 men and 16 654 women that had complete data for the parameters listed in Table 1 was used, without any specific exclusion procedure. The basic characteristics of this population were similar to those described previously [5]. To measure fasting triglycerides (TG), enzymatic methods utilizing glycerol kinase (Daiichi Pure Chemicals Co., LTD, Tokyo) were used. Total cholesterol was measured using the cholesterol oxidase method (Daiichi Pure Chemicals). Low-density lipoprotein (LDL)-cholesterol was estimated using the Friedewald formula (LDL-cholesterol = total cholesterol – high-density lipoprotein (HDL)-cholesterol – (1/5) TG). For estimated glomerular filtration rate (eGFR), the equation used was $194 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287}$, and the result was further multiplied by 0.739 for women [6]. For UN measurement, the urease-glutamic acid dehydrogenase method was used.

All statistical analyses were performed using SPSS for windows 15.0 (SPSS Inc., Tokyo, Japan). $p<0.05$ was considered significant in this study. This study was approved by the Ethics Committee of Teikyo University School of Medicine, Japan (No.15-205-2).

Results

Association between serum UN level and MetS-related biomarkers in women

We used the health check data previously described [5], with a general population of 16 389 men (mean age 51.2 [SD = 13.2]) and 16 654 women (52.4 [13.0]). The mean value of each biomarker will be published in our sister paper [1]. The Spearman's correlation coefficients between the serum levels of UN and various clinical markers are shown in Table 1. As expected, the UN level correlated with creatinine, but the correlation coefficient was not high (0.225 and 0.188 for men and women, respectively), possibly because we used a general population. In fact, the proportion of the subjects with creatinine levels higher than 1.5 mg/dL was small (0.2 and 0.1% for men and women, respectively).

Notably, the UN level showed more significant correlations with most of the MetS risk factors in women than in men. For example, the correlation coefficients had "women > men" differences greater than 0.1 for the parameters including fasting plasma glucose (FPG), HbA1c, LDL-cholesterol, and total cholesterol. Such gender differences were also seen for TG and C-reactive protein (CRP). Additionally, these same gender differences in correlations were also seen for liver biomarkers, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST),

alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γGT), bilirubin, and albumin. Of note, although the unsigned values of the correlation coefficients were relatively small (< 0.3), these showed significant gender differences as indicated by asterisks in Table 1. Strikingly, UN/creatinine also showed similar correlations with MetS risk factors in women and similar gender differences. In contrast, the gender difference was little for the correlations between creatinine and other clinical biomarkers. Thus, the associations between UN and MetS risk factors in women cannot be attributed to renal functions; instead, these highlight the distinct features of UN independent of renal functions.

Thus, the serum UN level in a Japanese general population is associated with MetS components and MetS-related markers in women, but such associations are absent or weak in men.

	Correlation coefficient with					
	Urea nitrogen		**Urea nitrogen/creatinine**		**Creatinine**	
	men	**women**	**men**	**women**	**men**	**women**
Age	0.25	**0.398****	0.177	**0.320****	0.078	0.070
Urea nitrogen	1	**1**	0.78	0.799	0.225	0.188
Body Mass Index	-0.007	**0.095****	-0.067	**0.079****	0.101	0.014**
Systolic blood pressure	0.012	**0.130****	-0.003	**0.128****	0.016	-0.021
Diastolic blood pressure	-0.003	0.094*	-0.013	**0.095****	0.009	-0.019
White blood cells	-0.062	-0.033	-0.048	-0.021	-0.02	-0.021
Platelet	-0.126	-0.109	-0.071	-0.045	-0.071	-0.093
Fasting plasma glucose	0.074	0.144**	0.088	0.145**	-0.025	-0.026
HbA1c	0.116	**0.247****	0.108	**0.228****	0.003	0.002
Estimated glomerular filtration rate (eGFR)	-0.297	-0.327	0.251	0.206	-0.889	-0.895
Creatinine	0.225	0.188	-0.38	-0.394	1	1
Triglyceride	-0.107	**0.064****	-0.141	**0.029****	0.063	0.045
Low Density Lipoprotein (LDL) cholesterol	0.109	**0.224****	0.049	**0.168****	0.09	0.067
High Density Lipoprotein (HDL) cholesterol	0.059	0.041	0.098	0.029	-0.07	0.021
Total cholesterol	0.075	**0.229****	0.025	**0.166****	0.074	0.079
Uric acid	0.041	**0.191****	-0.129	**0.016****	0.272	0.276
Lactate dehydrogenase	0.095	**0.238****	0.095	**0.205****	-0.017	0.022
gamma-glutamyl transpeptidase	-0.127	**-0.011****	-0.058	0.025**	-0.098	-0.055
Alkaline phosphatase	-0.103	**0.105****	-0.041	**0.136****	-0.09	-0.066
Alanine aminotransferase	-0.059	**0.142****	-0.041	**0.161****	-0.021	-0.046
Aspartate aminotransferase	0.005	**0.201****	0.003	**0.162****	0.004	0.045
Total bilirubin	-0.008	-0.042	-0.029	-0.047	0.038	0.021
Albumin	0.011	0.078*	0	0.066*	0.023	0.013
Total protein	0.049	0.084*	0.011	0.063*	0.06	0.026
C-reactive protein	-0.019	0.065*	-0.009	0.065*	-0.02	-0.007

Table 1: Spearman's correlation coefficients between UN (UN/creatinine and creatinine) and several clinical biomarkers. The correlation coefficients that showed a "women > men" difference greater than 0.1 are highlighted in bold. All correlations with r>0.02 or < -0.02 showed significance (p<0.01) and the asterisks denote the significance in gender differences (**, p<0.001; *, p<0.05).

Discussion

Implications for hormonal and dietary effects on metabolism

Although the absolute values of the correlation coefficients in Table 1 are generally small, to our knowledge, the gender differences have not been reported. Why are the UN level and MetS risk factors correlated in women but not in men?

One possible reason is that estrogen modifies or enhances the coordination of the sugar, lipids, and nitrogen metabolisms. In Table 1, creatinine weakly correlated with age, which was not surprising, as the number of subjects with impaired renal functions increases with age. Of note, UN/creatinine showed an even higher correlation with age, especially in women, suggesting potential effects of menopause on the UN increase. It has been shown that estrogen decreases dependence on amino acids as a fuel source, thereby increasing lipid oxidation [7]. Therefore, it may be conceived that, in postmenopausal women, the lack of estrogen tends to promote the catabolism of amino acids, thereby increasing UN and decreasing lipid oxidation and subsequently increasing the levels of plasma lipids [7].

However, such hypothesis requires substantiation through further analyses, as the number of studies on hormonal effects on metabolic pathways involving UN is limited.

In general, gender differences in the coordination of lipids and sugar metabolism are also known. For example, the plasma level of adiponectin, an insulin-sensitizing hormone, has been shown to be higher and to have a stronger negative correlation with insulin resistance in women than in men [8], likely contributing to the high association of obesity with impaired glucose tolerance in women relative to men [9]. In general, adiposity and hyperglycemia are more tightly coordinated (correlated) in women than in men. Therefore, it is possible that the effects of diet and, in particular, postprandial changes of parameters are coordinated tightly in women, and this may partly account for the wide correlations across many biomarkers previously observed. However, further analyses are necessary to discuss the roles of sex hormones in the association between lipids and nitrogen metabolism.

As such, gender differences were seen in a wide range of parameters including ALP, ALT, and AST; lipids metabolism including bile acid synthesis/excretion and enterohepatic circulation may be linked with the UN metabolism, especially in women. As dietary fibers are known to exert profound influences on lipid and nitrogen metabolisms, we considered whether dietary habits contribute to the associations seen above. The cholesterol-lowering effect of soluble dietary fibers (SDFs), such as β-glucan, pectin, guar gum, and psyllium, has been established [10,11]. Three mechanisms are considered important for this effect [11]. First, SDFs have been shown to increase bile acids/bile salts excretion [12]. Second, SDFs lower postprandial glycemia; in the case of fibers with high viscosity, this effect is likely due to the increased insulin sensitivity caused by fibers through the delayed absorption of macronutrients. Third, SDFs can cause an increase in short chain fatty acids, which are fermentation products of SDFs that downregulate cholesterol synthesis [11]. The effects of dietary fiber on lower blood pressure have also been reported [13,14]. Moreover, the intake of SDFs has been shown to be inversely related to TG concentrations [15].

Indigestible carbohydrates (such as nonfermentable fiber, fermentable fiber, and fermentable oligosaccharides) can modulate the nitrogen metabolism as well. In men, plasma urea is mainly excreted through the urine (70 to 80%), and the remaining 20-30% is hydrolyzed in the intestine [16,17]; however, this balance can be modified by such carbohydrates [18]. Such effects of fermentable carbohydrates are considered to be mediated by the increase in nitrogen requirements in the intestine due to bacterial growth caused by fermentation as well as by the facilitated intestinal uptake of blood urea due to the enlargement of the cecal mucosa induced by fermentation [17]. A similar observation has been reported for patients with cirrhosis [19]. Furthermore, in an analysis of patients with chronic renal failure, fermentable carbohydrate 40 g/day caused a shift in nitrogen excretion from the urinary route toward the digestive route, lowering plasma urea [20].

Segawa et al. showed that psyllium seed treatment lowered serum cholesterol and TG in patients with hypercholesterolemia and that those who showed better response (greater decrease in cholesterol) showed greater degrees of reduction of UN with a correlation coefficient of 0.51 [21]. Thus, some dietary fibers are likely to simultaneously modify nitrogen and lipids metabolism though mechanisms mediated by intestinal bacteria flora.

In Japan, a gender difference in the daily intake of fibers has been reported. The national health and nutrition examination survey conducted in Japan in 2002 reported that the daily vegetable intake /kg body weight was greater in women than in men: 305.5 g (4.64 g/kg) and 303.2 g (5.58 g/kg) for men and women, respectively, among those aged 50-59 years [22]. Accordingly, the daily fiber intake was greater in women (detail not shown). The protein intake was also similar (1.28 g/kg and 1.32 g/kg for men and women, respectively), arguing against the idea that a higher protein intake in men obscured the urea flux from blood to the intestine. However, it is unlikely that such a "between-gender" difference in dietary habits alone can explain the aforementioned lack of correlation in men.

The gender difference may be ascribed to a gender-divergent response to dietary fibers. Ulmius et al. has shown that the incremental glucose concentration was lower in women than in men for the groups that consumed rye bran, oat fiber, and the mixed meal [23]. However, studies that focus on gender difference in this regard are still limited.

Conclusion

The serum UN levels had stronger correlations with MetS risk factors such as glucose, blood pressure, and LDL-cholesterol in women than in men in this Japanese general population. This could be partly caused by the dietary habits of Japanese women, which favor fiber-rich diets; yet, it is possible that gender-differences in the associations between lipid and sugar metabolism and in the response to dietary fibers play roles in this. Our study does not provide any information concerning the molecular basis for gender differences in the correlations between UN and other MetS-related parameters. Hence, further analyses are necessary in order to elucidate the mechanisms for the gender-difference in UN and lipids metabolism correlations.

Conflict of Interest

Authors declare that they have no conflict of interest.

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***Corresponding author:** Kazuhisa Nishizawa, Teikyo University School of Medical Technology, Kaga, Itabashi, Tokyo, 173-8605 Japan, Tel: +81-3-3964-1211, Fax: +81-3-5944-3354; Email: kazunet@med.teikyo-u.ac.jp

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