Annals of Biomedical Research
An open access journal
eSciRes
ISSN 2817-2094
Mini Review
ABR-3-120

Why does Adiposity Associate with Hyperuricemia more Strongly in Women than in Men? A Question-oriented Review and Hypothesis

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Introduction

It is well known that uric acid (UA) is associated with hyperlipidemia. Recent studies using Mendelian randomization have strongly supported the causal role of adiposity in increasing serum UA level, without supporting the causal role of UA in the development of dyslipidemia. One notable finding in recent epidemiological studies is that dyslipidemia is more strongly associated with hyperuricemia in women than in men. In this article, we discuss the studies addressing the adiposity-UA relationship with a focus on the gender difference in the association between adiposity traits and serum UA levels. Notably, such a gender difference can partly be ascribed to the difference in metabolism of lipids and sugar. The roles of adipocytokines and glucose-mediated modulation of the activity and expression of UA transporters appear to be of particular importance. In contrast, recent studies on the genotypes of *SLC2A9* (*GLUT9*), a UA transporter that influences serum UA level, suggest that sex hormones can regulate transporters in relatively direct manner(s). Further molecular level analyses including those on 27-hydroxycholesterol and *URAT1* support the view that UA has a compensatory function to counteract inflammation and oxidative stress related to adiposity. This pathway might have come to be utilized in gender-divergent ways during the evolution. These studies are likely to form an important cornerstone in researches aimed at understanding the hormonal effects on UA metabolism.

Serum UA level strongly associates with serum cholesterol and triglyceride levels in women

It is well known that women have lower levels of serum UA relative to age-matched men, but further gender differences in the associations of UA and other biomarkers have been reported. In our assessment of serum UA as a predictive biomarker for metabolic syndrome (MetS), we observed a gender difference in the relationship between serum UA and lipid biomarker levels in a general population of Japan [1]. Specifically, the women with a serum UA<4 mg/dL and those with serum UA ≥ 7 mg/dL showed a wide difference in the Friedewald-estimated LDL-cholesterol level (the average: 118 and 139 mg/dL, respectively). In contrast, this difference was small in men (117 and 122 mg/dL, respectively). The Spearman's correlation coefficient between the LDL-cholesterol was 0.190 for women and 0.045 for men [1]. As the correlation coefficient is largely determined by the covariance of two variables, our data indicate that those subjects with high UA levels have high levels of cholesterol and this association is clearer in women. Overall, our findings corroborated a study by Jeong et al. that used a Korean health check population [2].

Such a gender difference has clinical implications. To name a few studies, the risk of death owing to cardiovascular disease (CVD) was more strongly associated with an increased UA level in women compared to men in Hakoda et al [3]. In a study by a German group using a Cox hazards model analysis, UA levels predicted 1-year mortality with an adjusted hazard ratio (HR) of 1.17 (95% CI: 1.03–1.31) in men and 1.25 (1.06–1.48) in women for 1 SD increase in the natural logarithm [4]. In a meta-analysis by Zuo et al., hyperuricemia increased the risk of coronary heart disease mortality in women (relative risk (RR): 1.47; 95 % CI: 1.21–1.73) compared to men (RR: 1.10; 95 % CI: 1.00–1.19) [5].

Thus, the predictive ability of hyperuricemia to MetS-related conditions is immense in women relative to men. This is somewhat paradoxical given the men > women difference in the absolute level of serum UA. Why is the UA-MetS correlation so strong in women? What is the molecular basis for this gender difference?

Adiposity is causal for UA increase, but the opposite is not supported-- Lyngdoh et al.'s study

Prior to considering the gender difference, let us briefly review the relationship between adiposity and serum UA. It is well known that the serum UA levels are higher in subjects with MetS compared to healthy individuals [6-8], although the biological mechanisms underlying this association have not fully been understood.

Recent studies, particularly those utilizing the Mendelian randomization method, have implicated dyslipidemia as a causative factor in the elevation of serum UA levels [9]. However, the opposite, that is, the causative role for UA in the UA-MetS association was not supported. Let us discuss some details of this study. To address the issue of causality between adiposity and high UA, Lyngdoh et al. performed a bidirectional Mendelian randomization analysis. As instrumental variables, the authors used a SNP of *SLC2A9* (the gene for GLUT9) that is in association with UA, and SNPs of *FTO*, *MC4R*, and *TMEM18* that are amongst the genes strongly associated with obesity traits [10]. Importantly, the elevation of serum UA levels explained by the genotypes of *SLC2A9* did not show association with adiposity traits, providing no support for the causative role of UA in adiposity. Instead, in the two-stage least squares regression (genotype to adiposity traits and adiposity traits to UA), the adiposity traits

explained by genetic variants of the *FTO*, *MC4R* and *TMEM18* genes were positively associated to serum UA levels (regression coefficient: 0.31 [95% confidential interval: 0.01, 0.62]), supporting the causality of adiposity in the increase in UA. Notably, FTO (fatso/fat mass and obesity-associated) is an iron and 2-oxoglutarate-dependent dioxygenase, and has recently been shown to promote lipogenesis via maturation of SREBP1c, a transcription factor that regulates genes required for de novo lipogenesis [11]. The functions of MC4R (melanocortin-4 receptor) and TMEM18 (transmembrane protein 18) have been largely unknown, except for the involvement of MC4R in appetite control.

Although we do not discuss here, that recent Mendelian randomization-based studies utilizing many UA-associated genes generally showed a modest or negligible degree of causative role of UA in adiposity traits [12,13].

Adiposity, insulin resistance, and enhanced renal reabsorption of UA

A number of studies have suggested that deterioration of insulin sensitivity plays an important role in the causative effect of adiposity on UA elevation. Insulin resistance (IR) has been shown to be associated with a decline of urinary UA clearance in Facchini et al. (Pearson correlation coefficient = -0.49; $P < 0.002$) [14]. The antiuricosuric effect of insulin was confirmed by Quinones Galvan et al. [15]. In an analysis of male gout patients, IR (measured as HOMA-IR) was inversely correlated with the clearance of UA [16]. Miao et al. used a spontaneous type 2 diabetes rat model and provided findings suggesting that the IR predisposes the rats to hyperuricemia [17]. Notably, treatment with rosiglitazone (a peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist, insulin sensitizer) significantly reduced the expression level of URAT1 (SLC22A12), a reabsorptive UA transporter on the apical side of the renal proximal tubule, suggesting that IR causes impairment of the capability of the rats to downregulate URAT1 [17]. Conspicuously, UA is subject to both reabsorption and secretion in the renal tubule, and URAT1 is considered important for reabsorption [18].

How about the effect of insulin on the SLC2A9 (GLUT9), the transporter known to be highly influential to the serum UA level? SLC2A9 (GLUT9) mainly mediates the renal reabsorption of UA, and, specifically the interstitial exit of UA into the extracellular fluid [18]. Among its splice variants, SLC2A9a is widely expressed and SLC2A9b is expressed primarily in the kidney and liver of the mouse, and the kidney and placenta of humans [19]. To the best of our knowledge, a direct effect of insulin on SLC2A9 has not been well studied, but hyperglycemic condition leads to upregulation of both splice variants in mouse kidney and liver [19-21]. These effects and the extracellular glucose-induced efflux of UA from the cells [22] may corroborate to increase the serum UA level on hyperglycemia.

These findings are summarized in a diagram (the part with a black font in Figure 1).

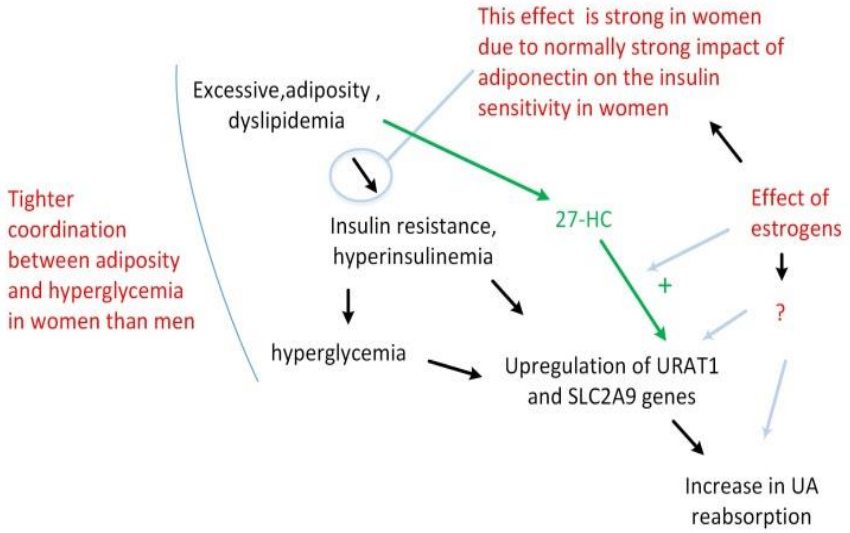

Figure 1: A diagram representing the hypothesized network underlying the gender-divergent effect of adiposity on the UA level. The main pathway linking lipid metabolism to the control of UA level is shown in black. Women-specific features are highlighted in red. The new finding on 27-hydroxycholesterol is shown in green. 27-HC, 27-hydroxycholesterol.

Why, then does the gender difference in the UA−lipids relationship exist? Notably, Choi and Ford have shown that the serum UA levels monotonically increase with the severity of IR [23]. Moreover, they observed that the serum UA level increased sharply with an increase in IR in women. Together with the above arguments, it is likely that the correlation between the decline of fractional excretion of UA (FEUA) and IR is strong in women and is relatively weak in men. Another important finding of the study by Choi and Ford was that the serum UA levels increased with moderately increasing levels of HbA1c (6–6.9%) and then decreased with further increasing levels of HbA1c, forming a bell-shaped curve. This

bell-shaped curve supports the view that, unlike lipids, glucose has more direct effect on the transport machinery of UA. Specifically, with extremely high levels of glucose as in patients with DM, UA is likely to be directly excreted via SLC2A9 in the opposite direction, explaining the uricosuric effect of glycosuria [24]. This feature gives further complexity to the glucose–UA relationship, but it would be reasonable to consider that this effect of glycosuria becomes significant only in populations with blood glucose levels, which are well beyond the renal threshold for glycosuria (~160 mg/dL). We will further discuss the hexose-induced UA transport via SLC2A9.

Gender and age synergy in SLC2A9 genotype effect on BMI

While the above discussion can explain how adiposity exerts causative effects on UA elevation, the cause for the gender differences in the correlation between UA and adiposity traits is not clear. In this regard, another notable line of study are those from Kronenberg et al. [25,26]. Their studies focused on the genetic effects of *SLC2A9*, whose genotypes have been extensively used in Mendelian randomization studies [9]. *SLC2A9* exhibited intriguing gender-specific effects of genotypes in its influence on the serum UA level [26,27]; the association between genotypes of *SLC2A9* and serum UA levels was more pronounced in women relative to men [26,27]. Furthermore, an increase in BMI amplified the effect of genetic variants on UA levels [25]. This means that the effect of the *SLC2A9* genotypes on serum UA becomes more influential in women with obesity than in other populations. This may contribute to the more pronounced association of UA and BMI in women. They further showed that, in women, the effect on serum UA levels explained by the *SLC2A9* genotypes increased linearly with age, whereas, in men, increasing age diminished this effect [26]. In their study, age did not show such modifying effects on the correlations between serum UA and genotypes for *ABCG2* and *SLC17A3*.

Why is the genotype effect of *SLC2A9* on UA levels more pronounced in women relative to men? Can this gender difference be explained by the difference in lipid and glucose metabolism? In our study [1], the BMI values increased with age in women but was largely flat in men. The younger women (≤ 41 years) and those who are ≥ 66 years old had a mean BMI of 20.6 and 22.9 kg/m^2 respectively, but the corresponding values were 23.4 and 23.1 kg/m^2 for men. Moreover, for Chinese population with <25 BMI, the regression coefficient of 2-hr glucose with one SD increase in BMI was greater in women compared to men (0.241 for women and 0.121 for men) [28]. This raises the possibility that the age and gender enhancement of genotype effects may be mainly accounted for by the clear concordance among age, BMI, and fasting glucose level in women. However, it is nonetheless possible that the association of gender with the *SLC2A9* genotypes is mediated by direct effects (not directly related to lipid and sugar metabolism) of estrogens. Notably, Topless et al., showed that the *SLC2A9* genotypes are not only associated with the average level of serum UA but also with variance in the serum UA level in pre-menopausal women, but not in post-menopausal women [29]. This variance in the serum UA level likely reflects the effect from cyclical changes resulting from menstruation. This finding raises the possibility that the female hormones and/or other factors affected by female hormones (such as, iron levels, testosterone) interact with *SLC2A9* in a manner dependent on its genotype.

***SLC2A9* genotypes and UA elevation induced by fructose load**

Transport and metabolism of fructose are linked to the UA level in multiple ways. Fructose is highly lipogenic, and fructose metabolism causes AMP production from ATP, which in turn leads to UA production [30]. Moreover, SLC2A9 transports UA into cells in exchange for intracellular fructose [22,30]. In Dalbeth et al., an analysis with a 64 g oral *fructose* loading (drinking) test showed that the genotype of *SLC2A9* influences acute serum UA response and FEUA in response to a fructose load [31]. Specifically, the subjects without the particular genotype (protective C allele of the rs11942223) exhibited a higher magnitude of increase in serum UA levels (and lower FEUA) after the fructose load compared to those with the allele. Thus, fructose intake exerts a causal effect on increasing serum UA levels (for 0.5 to 2 h after the load). It was also suggested that this increase in serum UA levels in part accounted for by the decrease in FEUA mediated by *SLC2A9* under the influence of the genotypes.

What is the molecular basis for this *SLC2A9* genotype effect on the fructose-induced elevation of serum UA? It is not well understood yet, but Witkowska et al. may have provided a clue. Using the oocyte expression system the authors showed that the presence of extracellular glucose can increase the efflux of urate through SLC2A9a, and intracellular (injected) fructose can increase the cellular uptake of UA through SLC2A9a and SLC2A9b isoforms [22]. SLC2A9a and SLC2A9b are localized in the basolateral and apical membranes of tubular cells respectively. Thus, high fructose and glucose in circulation may facilitate the UA efflux from the tubular epithelial cells to circulation.

It is noteworthy that the *SLC2A9* genotype effects demonstrated by Dalbeth et al. were not related to global alteration of fructose metabolism [31]; indeed, the allele did not affect the serum glucose curve after the fructose tolerance load. Hence, it would be reasonable to assume that the main role for this transporter is via renal tubular transport, although the significance of SLC2A9 in fructose load-induced UA efflux into blood from the liver is not well understood.

The findings by Dalbeth et al. [31] and Witkowska et al. [22] point to a view that the capacity of fructose-facilitated UA transport is influenced by the genotype of *SLC2A9*. Then, one may want to ask, to what extent this plays a causal role in the gender difference. Given the aforementioned observation by Topless et al. [29], it is possible that estrogens regulate SLC2A9 protein or gene in a fairly direct manner. However, further experimental analyses are necessary to examine this idea.

Can sex-dimorphism in adipocytokine regulation explain the lipid-UA strong correlation in women?

It is well known that obesity has a significant association with incident DM and impairment of glucose tolerance. Let us add some discussions regarding the gender difference in some adiposity-related hormones.

A current consensus postulates that adipocytes with excessive or unhealthy fat storage ultimately undergo an inflammatory response, which contributes to the development of IR [32]. Leptin and adiponectin are hormones secreted by adipocytes. Adiponectin improves insulin sensitivity, but the expression of adiponectin decreases with an increase in adiposity. Adiponectin levels have been reported to be significantly higher in women than in men [33,34] and this difference was significant even after adjustment for BMI [35].

In connection to the gender difference in lipid and sugar metabolism, the adiponectin level in plasma had a stronger negative correlation with IR and the glucose level in women than in men with *P* value of 0.011 and 0.051, respectively [35]. This difference may contribute to the higher impact of adiposity on the glucose level in women compared to men. For example, Li et al. showed that, a Chinese population with < 25 BMI, regression coefficient of 2-hr glucose with one SD increase in BMI was 0.121 for men and 0.241 for women [28]. Thus, obesity has stronger associations with impairment in glucose tolerance in women compared to men. This gender difference may be at least partly ascribed to the strong impact of adiponectin on the insulin sensitivity and glucose level in women [35]. Several studies have indicated that adiponectin can multimerize and the generated high-molecular-weight (HMW) form is its most active form. Intriguingly, metabolically healthy women (based on the control of the glucose level, dyslipidemia, and blood pressure) showed substantially higher HMW adiponectin levels compared with metabolically unhealthy women.

Recent notable findings include gender difference in the control of 27-hydroxycholesterol (27-HC), an endogenous selective modulator of estrogen receptors. 27-HC is an intermediate of cholesterol catabolism that increases URAT1 (SLC22A12) expression and upregulates serum UA levels [36]. This is interesting given that estradiol has been shown to suppress the protein levels of URAT1 and SLC2A9 [37]. 27-HC levels in premenopausal women are lower than in men, and increase after menopause [38]. These discussions made us update Figure 1 with findings on the hormones, including adiponectin and estrogen effects on the transporters (Figure 1).

How about the potential role of leptin in the gender difference? Leptin is considered to regulate adiposity by affecting eating behavior (rather than energy expenditure) and enhance fatty acid oxidation, but is also known to decrease glucose level and reduce body fat. Compared with those in men, leptin levels rose 3.4-fold more rapidly as a function of BMI in women [39]. That is, leptin levels increase more rapidly in women with progressive increments in body fat than in men. However, as obese persons are characterized by a state of leptin resistance that becomes more pronounced with progressive degrees of obesity, therefore, the significance of high levels of leptin in the context of UA and adiposity remains ambiguous. Moreover, as DiCarlo et al. discussed, inconsistent results have been reported regarding leptin levels after menopause [40]. It is possible that the increase in body weight and fat mass with a centralization of fat distribution that is known to occur after menopause may mask the effect of leptin [40].

Conclusive remarks and hypothesis

Together, the above findings can be summarized in a diagram (Figure 1). In women, dyslipidemia has strong association with impairment of glucose tolerance, generally causing elevated blood glucose levels after diets. Thus, elevated hexose levels cause UA influx through transporters including SLC2A9- a pathway that contributes to the gender difference. Insulin resistance and/or hyperinsulinemia leads to increased expression of the UA transporters, but the understanding of the molecular mechanisms mediating this effect require further analyses. Another question is about the mechanism for the effects of the *SLC2A9* genotype. This transporter has long been known to show gender-specific genotype effects and estrogens (or factors controlled by estrogens) that may indeed have a direct effect on the efficacy of this transporter. However, it is currently not clear, how this effect is exerted in a genotype-sensitive manner.

It should be noted that the diagram is oversimplified. Although this article did not cover it, a number of studies supported the view that UA is known to exacerbate insulin resistance and plays a role in the development of metabolic syndrome in some settings [41,42]. Such effects may bring about a positive feedback loop in the lipid-UA relationship.

Future studies on the interplay between metabolism, inflammation, and estrogens will provide important insights into UA metabolism. 27-HC is a molecule of importance, in this regard. The plasma concentration of 27-HC has strong positive correlations with that of cholesterol and triglycerides [36]. 27-HC is considered a sensitive modulator of cholesterol metabolism disorder by suppressing cholesterol synthesis. The 27-HC levels in premenopausal women are lower than in men, and are increased after menopause [38,43]. 27-HC increases URAT1 (SLC22A12) expression and upregulates serum UA levels [36]. Probably because of this, the age-dependent change of UA levels resemble that of 27-HC [36]. It is well known that, as an endogenous estrogen receptor (ER) ligand, 27-HC can promote breast tumor growth [44].]. Notably, the promoter of *URAT1* (*SLC22A12*) has nine estrogen response elements [36]. Estrogen, through ER, regulates the expression of its target genes, and intriguingly, 27-HC is a selective estrogen modulator.

Moreover, 27-HC has been shown to have proinflammatory effects on macrophages and endothelial cells through the mediation of ERα, contributing to atherogenesis [45]. Given the tight linkage between adiposity, oxidation, and inflammation [46] that enrolls numerous factors including 27-HC, one possibility is that UA may act as a brake to control the oxidative effects.

Estrogens can also modulate metabolism-related inflammation. In general, metabolic control favored by estrogens avoids the establishment of metabolic inflammation [47]. Obese postmenopausal women have higher serum estrogen concentration than lean postmenopausal women. In postmenopausal women, adipose tissue is a major site of aromatase activity, and estrogens may have a protective role in adipose tissue inflammation [48]. In this context, it would be interesting to envisage that 27-HC-mediated proinflammatory effects may be more ancient in evolution, and that the anti-inflammatory effects of estrogen along with upregulation of UA (an anti-oxidant) evolved later, to counteract the oxidative damage caused by 27-HC.

It is possible that molecules other than 27-HC are also playing important roles, influencing the gender difference in the metabolism. Further characterizations of such molecules may help elucidate the mechanisms for such hormone-mediated control of metabolism, deepening our understanding of the gender difference in metabolism including the UA metabolism.

Conflict of Interest

Authors declare that they have no conflict of interest.

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Received date: May 11, 2020; **Accepted date:** May 13, 2020; **Published date:** May 18, 2020

Citation: Seki R, Nishizawa K (2020) Why does Adiposity Associate with Hyperuricemia more Strongly in Women than in Men? A Question-oriented Review and Hypothesis. *Ann Biomed Res* 3(1): 120.