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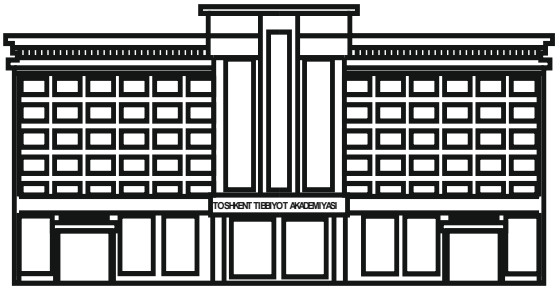

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GENDER DIFFERENCES AND HYPERURICEMIA IN ETIOPATHOGENESIS OF GOUT

Nabieva D.A., Tashpulatova M.M.

ПОЛОВЫЕ РАЗЛИЧИЯ И ГИПЕРУРИКЕМИЯ В ЭТИОПАТОГЕНЕЗЕ ПОДАГРЫ

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PODAGRA ETIOPATOGENEZIDA JINSIY TAFOVUTLAR VA GIPERURIKEMIYA

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В обзоре суммированы современные представления об уратах как о факторе риска заболеваний и о том, как может защитить принадлежность к женскому полу. Использование половых различий при обращении с уратами послужит в качестве мощного инструмента для дальнейшего понимания физиологической регуляции гомеостаза уратов и для открытия новых возможностей лечения совокупности патологий, связанных с уратами.

Ключевые слова: *половые различия, эстрогены, подагра, мочевая кислота, сывороточные ураты.*

Ushbu sharh urat kislotasining podagra kelib chiqishidagi xavf omil sifatidagi tushunchamizni va ayol jinsi qanday himoya omillariga ega ekanligini umumlashtiradi. Shuningdek, biz jinsiy gormonlarning giperurikemiyadagi roli haqida ma'lumot beramiz. Urat gomeostazini fiziologik tartibga solishni anglash va urat bilan bog'liq patologiyalar turkumini davolashning yangi usullarini o'rganishda jinsiy tafovutlardan foydalanish maqsadga muvofiq bo'ladi.

Kalit so'zlar: *jinsiy tafovutlar, estrogenlar, podagra, siydik kislotasi.*

Understanding the mechanisms of common heritable diseases has long proven to be challenging [4]. One such common human disease is gout, the most common inflammatory arthritis [2]. Gout is caused by the deposition of sodium urate (UA) crystals in the synovial fluid of joints, a process that leads to a cascade of inflammatory responses and extreme discomfort [5]. Precipitation of the weakly soluble UA occurs as the UA levels in the blood and other body fluids rise, termed hyperuricemia. Gout is one of the most well documented human diseases, recognized as early as 2460 BCE by the ancient Egyptians [12]. A staple throughout the development of the civilized world, cases were also noted by Hippocrates and Galen in ancient Greece, with a surge in cases in the 17th and 18th centuries during the industrial revolution, commiserate with rising wealth across the western world. Today, the prevalence of gout is roughly 4% of the population of the United States, Europe, and Southeast Asia [3]. Interestingly, recent research has found that gout is only one of many potential diseases caused or contributed to by hyperuricemia (HUA); HUA is also an independent risk factor for additional pathologies including renal diseases, cardiovascular disease, hypertension, and metabolic syndrome [14,22] (Figure). As this list of diseases continues to grow, so does the critical need for a deeper understanding of not only how we regulate UA homeostasis, but also the causes of disruptions of these processes.

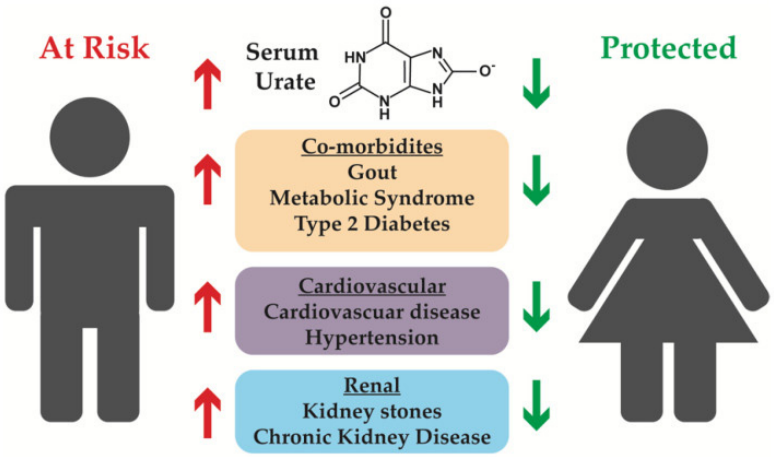

Figure. Co-morbidities associated with hyperuricemia, with an emphasis on conditions that can affect the kidneys. Males tend to have higher serum urate levels, and therefore have an increased risk of associated co-morbidities, while females have lower serum urate levels and are protected from developing associated co-morbidities.

A mechanistic picture of the effectors of UA homeostasis has emerged, yet we lack an understanding of how these proteins are regulated. New tools are needed to examine this problem to provide relief for the large and growing population of hyperuricemic individuals. Additionally, new work has reinforced the importance of an ancient observation, the male sex is a significant risk factor for hyperuricemia and gout [8], where men are up

to four times more likely to be affected than women. This observation has now been coupled to investigations of differences in UA handling in the kidney, as well as differential effects of pathogenic variants in UA transporter genes, presenting the potential to use sex differences in UA handling as a powerful comparative analysis revealing how these systems are regulated. Here, we review sex differences in UA handling to explore how the female sex may be protective against the development of UA related diseases and to illustrate the power of using sex differences as a tool HUA is clinically defined as elevated serum UA (SUA, >6 mg/dl), which increases the risk of the precipitation of weakly soluble UA. Increased UA leads to precipitation of monosodium UA crystals, which can cause UA kidney stones and gout. The number of affected individuals continues to climb with current estimates being approximately 47.2 million HUA individuals in the United States; roughly 27.9 million individuals have severe HUA (>7 mg/dl), with men being affected five times more often than women [22]. Similar results have been observed in China, with an overall HUA prevalence of 13.3%, with striking differences in prevalence by sex, with 19.4% in men and only 7.9% in women [17]. However, the risk of the development of HUA increases roughly four-fold for women after menopause, and postmenopausal hormone replacement therapy reduces this risk [8], providing evidence that female hormones may contribute to the protection from HUA. HUA is just one of many conditions that have observable sex differences, as differing pathologies based on sex have been observed in a variety of fields [9] including cardiovascular [13], neurological, immunological, and renal diseases [1]. The architecture of the female kidney is likely distinct from that of the male kidney, given women have a lower blood pressure than men, women are less likely to develop acute kidney injury than men, women demonstrate improved tolerance to renal ischemia and women are protected from renal and cardiovascular disease before menopause as compared to men. A recent study determined that females with chronic kidney disease (CKD) had a slower decline in glomerular filtration rate (GFR), lower risk of progression to end-stage renal disease (ERSD), and a lower risk of death compared to age-matched men with similar mild-to-moderate CKD [10]. In diabetic kidney disease, men tended to demonstrate renal complications roughly 10 years earlier than women [12], while sex differences in obesity-related kidney disease demonstrated that female sex hormones may safeguard against worsening pathology [9]. Thus, being female may have a protective effect on the kidney, preventing women from developing the more severe phenotypes observed in men. All these studies illustrate the need for greater emphasis on the idea of sex as a biological variable [19], going beyond merely looking at sex differences, and instead examining the influence of sex on various physiological and pathophysiological pathways [1] to help elucidate underlying mechanisms. HUA increases the risk of developing CKD for both men and women and increases the likelihood of progression to ESRD in both sexes, yet this risk is much higher in HUA females than HUA males [6]. Similarly, the incidence of CKD increases two-fold to six-fold higher in HUA females than HUA males [17], demonstrating that once females have lost the benefit of low SUA, renal health is more likely to decline. Males and females with both HUA and CKD had a higher incidence of left ventricular hypertrophy and hypertension, however, this association was only significant in females [13]. HUA also increases the overall risk for hypertension for both sexes, but once again females with HUA are more likely to develop hypertension than HUA males compared to non-HUA controls [4]. Finally, females have a higher incidence of type 2 diabetes mellitus than males, yet HUA females are even more likely to develop diabetes than HUA males, further emphasizing that an increase in SUA can be more detrimental to females than males. However, since HUA is only one of several pathologies to affect people later in life, the role of UA in the biogenesis of the underlying pathology is difficult to tease out, demonstrating the critical need for additional studies.

UA is the protonated form of uric acid and enters the circulation as the terminal metabolite of purine metabolism in humans and the other great apes. It is produced from the degradation of purine nucleotides and amino acids, mediated by xanthine oxidase. Higher-order primates have lost the activity of the enzyme uricase, which further metabolizes UA to the much more soluble allantoin [8]. Loss of uricase gene function in the ape lineage supports the idea of a possible selective advantage of increased SUA [22]. Contributing to this complicated process is the fact that the physiological concentrations of UA occupy a wide range, which is higher in men (3.5 to 7.2 mg/dL) than in pre-menopausal women (2.6 to 6.0 mg/dL) [4]. Interestingly, concentrations in post-menopausal women increase to levels observed in men [2]. Since UA is weakly soluble, high concentrations (>6 mg/dl) can lead to precipitation and crystal formation resulting in UA kidney stones. These crystals can also precipitate in joints and synovial fluid causing gout [22]. Of the UA excretion, 70% is mediated by the kidney and 30% by extrarenal pathways including the gut and the liver [12]. A delicate balance between secretion and reabsorption exists in the kidney to maintain UA homeostasis. UA is freely filtered at the renal glomerulus, then reabsorbed, actively secreted, and reabsorbed again in the proximal tubule [23]. Several proteins have been identified as UA transporters based primarily on in vitro studies demonstrating UA affinity. Based on in vivo renal tubule expression, the initial reabsorption of 95% of the initial filtered UA load may occur via organic anion transporter (OAT) family proteins, including OAT1 (encoded by SLC22A6), OAT3 (encoded by SLC22A8), OAT4 (encoded by SLC22A11), and OAT10 (encoded by SLC22A13), as well as SLC2A9 (also called GLUT9) [1]. Approximately 50% of the initial filtered load is then actively secreted back into the tubular lumen, primarily where ABCG2, NPT1 (encoded by SLC17A1), and NPT4 (encoded by SLC17A3) are expressed [12]. Reabsorption of another 40% of the filtered UA occurs downstream of the secretion in the S3 segment of the proximal tubule, where expression of URAT1 (encoded by SLC22A12) and SLC2A9 have been reported [14], resulting in a frac-

tional excretion (FEUA) of 4-8% of the initial filtered load. This somewhat controversial [23] and complicated mechanism of filtration, reabsorption, secretion, and a second round of reabsorption demonstrates that the kidney spends an exorbitant amount of energy fueling these transporters in an effort to carefully regulate UA excretion from the kidney for reasons yet to be fully understood. Functional data of these and other [22] transporters demonstrate that these proteins can transport UA. However, whether or not transport of UA occurs in the renal tubules by these particular transporters remains unclear. The next logical step would be to explore genetic perturbations in these transporters to determine if those alterations affect SUA levels. Thus, exploring human genetics and genetic variations in the form of genome-wide association studies (GWAS) can be a powerful tool for understanding which genes are most important to UA handling. GWAS use common single nucleotide polymorphisms (SNPs) that exist in a given population as signposts for genomic space that correlate with a given condition [16], including SUA levels. The larger the study population, the higher the genomic resolution to identify regions of interest that associate with altered SUA. Once these genomic regions have been identified, additional analyses can then be performed to identify those genes most likely to underlie the associated SNP, in some cases identifying novel causal variants that contribute to the development of HUA.

To explore the possible role of sex hormones in regulating UA transporters and more generally UA levels, an early study examined the effects of oral administration of synthetic sex hormones on both women and men [6]. The study demonstrated an inverse relationship between SUA and administered exogenous estrogen, as well as an increase in urinary UA. Similar effects were observed when post-menopausal women received progesterone. Additional studies demonstrated changes in SUA during ovulation in pre-menopausal women [9], with peak SUA levels occurring during the follicular phase [11] when estrogen levels are lowest. Furthermore, SUA was positively correlated with follicle stimulating hormone and inversely associated with estradiol and progesterone [7]. Another study examined the effects of hormone therapy on transsexual participants, demonstrating a decrease in SUA in male-to-female (MTF) participants, and an increase in SUA in female-to-male (FTM) participants after one year of cross-sex hormone administration. Furthermore, baseline FEUA was higher in FTM subjects and significantly decreased after the loss of estrogen, while MTF subjects demonstrated an increase in FEUA with the addition of estrogen [21]. These studies provide strong evidence for the role of female sex hormones in regulating FEUA, which can strongly contribute to SUA. Finally, as female sex hormone levels decrease after menopause, SUA increases, but this increase in SUA can be mitigated by hormone replacement therapy [20]. This evidence further reinforces that the female sex hormones may be regulating UA handling machinery, at either the transcriptional or post-transcriptional levels. Estrogen could explain the observed sex differences in UA associated UA transporters. Therefore, understanding the role of estrogen in regulating UA transporters is critical in unraveling the complex mechanisms of UA handling. Estrogen has been reported to have direct effects on sex-associated UA transporters. For example, ER binding sites have been identified in the promoter region of ABCG2 [19], implying ABCG2 can be transcriptionally regulated by estrogen. Additional reports have demonstrated that ABCG2 protein expression is down-regulated by estrogen [11], possibly through proteasome activation via ER-β induced PTEN/PI3K/AKT signaling [24]. Based on these studies, increased estrogen could decrease ABCG2 expression, which would decrease secretion, leading to an increase in SUA. This seems to be in conflict with the fact that females have lower SUA levels, demonstrating that in vitro models may have limited utility regarding ABCG2 regulation. Combinatorial signaling through ER-α and ER-β may also induce internalization of ABCG2 protein at the plasma membrane, decreasing ABCG2 activity, as observed in the blood-brain-barrier of mice [18]. This study provides some evidence of estrogen-mediated post-transcriptional regulation of ABCG2, yet further studies are required to elucidate the role of estrogen regulation of ABCG2 in the kidney. Similarly, estrogen has also been shown to down-regulate SLC2A9 at the post-transcriptional level through ER-β induced proteasomal activation [15]. Decreased SUA levels in females could be explained as ER-β signaling causing a greater decrease in SLC2A9 than ABCG2, resulting in a greater decrease in the reabsorption of UA, leading to a higher FEUA, as seen in females, however, this requires additional study.

Conclusions

Female sex hormones, specifically estrogen, may play a role in the regulation of expression or activity of UA transporters, specifically ABCG2 and SLC2A9. This is emphasized by the fact that females may have differences in renal UA transporter expression, localization, or activity. Estrogen could mediate either direct transcriptional regulation of the transporter genes, or activate transporter specific transcription factors, including HNF4α. Observable differences in how transporter transcription and post-translational modification are regulated between the sexes may reveal significant information about these regulatory pathways and provide targets for therapy. Thus, using sex as a biological variable may provide key insights into understanding UA handling, elucidating underlying physiological regulatory mechanisms, and underscoring a critical need for future studies.

The list of references can be found in the editorial office

GENDER DIFFERENCES AND HYPERURICEMIA IN ETIOPATHOGENESIS OF GOUT

Nabieva D.A., Tashpulatova M.M.

This review summarizes our current understanding of urate as a disease risk factor and how being of the female sex appears protective. Finally, we advocate the use of sex differences in urate handling as a potent tool in gaining a further understanding of physiological regulation of urate homeostasis and for presenting new avenues for treating the constellation of urate related pathologies.

Key words: *sex differences, estrogens, gout, uric acid, serum urate.*