Review Article:
URIC ACID HOMEOSTASIS AND DISTURBANCES

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ABSTRAK

Review ini mengkaji mengenai homeostasis asam urat di dalam tubuh manusia dan menganalisis studi terbaru mengenai variabel-variabel utama yang memengaruhinya. Konsentrasi asam urat subjek normal pria adalah 3,5-7,2 mg/dL dan wanita adalah 2,6-6 mg/dL. Turnover harian asam urat tubuh normal berkisar 498-1392 mg/hari, miscible pool 767–1650 mg, reabsorbsi 8064 mg/hari, ekskresi melalui ginjal 262–620 mg/hari dan usus 186–313 mg/hari. Dinamika asam urat dipengaruhi oleh faktor makanan, minuman, usia, riwayat penyakit, dan genetik. Konsumsi makanan purin tinggi meningkatkan asam urat darah sebesar 1–2 mg/dL, minuman berfruktosa 213–290 g/hari meningkatkan 0.52–1.7 mg/dL, sukrosa 1.5 g/kgBB meningkatkan 0.61 mg/dL, dan bir 10–20 ml/kgBB meningkatkan 0.50–0.92 mg/dL. Gen ABCG2 berperan untuk membawa asam urat keluar dari tubuh sebesar 114.31–162.73 mg/dL, SLC2A9 sebesar 5.43–20.17 mg/dL, dan SLC22A12 sebesar 5.77–6.71 mg/dL. Data tersebut menggambarkan homeostasis asam urat tubuh dan besarnya dampak faktor lingkungan (konsumsi makanan, minuman, dan lifestyle) maupun genetik. Pemahaman homeostasis asam urat dan gangguannya penting dalam pengelolaan penyakit, apakah itu hiperurisemia ataupun sebaliknya hipourisemia. ***(FMI 2017;53:292-298)***

Kata kunci*: Homeostasis; asam urat; gangguan*

ABSTRACT

This review examined the homeostasis of uric acid in human body and analyzed recent studies of the affecting major variables. Normal uric acid concentration in male is 3.5-7.2 mg/dL and in female is 2.6-6 mg/dL. Daily turnover of normal uric acid ranges from 498-1392 mg/day, miscible pool is 767-1650 mg, reabsorption is 8064 mg/day, renal excretion is 262-620 mg/day and intestine 186-313 mg/day. The dynamics of uric acid is influenced by factors of food, drink, age, history of disease, and genetic. High purine dietary consumption increases blood uric acid by 1-2 mg/dL, 213-290 g/day fructose drinks increases 0.52-1.7 mg/dL, 1.5 g/kgBW sucrose increases 0.61 mg/dL, and 10-20 ml/kgBW beer increases 0.50-0.92 mg/dL. The ABCG2 gene plays a role in bringing uric acid out of the body by 114.31-162.73 mg/dL, SLC2A9 of 5.43-20.17 mg/dL, and SLC22A12 of 5.77-6.71 mg/dL. The data described the homeostasis of uric acid and the magnitude of the impact of environmental (consumption of food, beverages, and lifestyle) and genetic factors. Understanding uric acid homeostasis and its disturbances is important in managing diseases as a consequence of hyperuricemia and hypouryscemia ***(FMI 2017;53:292-298)***

Keywords*: Homeostasis; uric acid; disturbances*

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INTRODUCTION

Uric acid (C5H4N4O3) (IUPAC: 7,9-dihydro-3H-purine-2,6,8-trione) is a heterocyclic compound found in many organisms. In birds, reptiles, and insects, uric acid is almost insoluble and is a nitrogenous waste product. In certain mammals, uric acid is found in blood and urine, and is the final form of purine metabolism. In primates, uric acid is the result of the catabolism of nucleic acids and proteins, then is discarded with urine. Plants also produce uric acid. Hauck et al (2014) found that uric acid accumulates throughout the Arabidopsis tissues when urate oxidase (UOX) genes mutate. Algae in symbiosis with marine anemones were initially suspected to accumulate a lot of potassium oxalate, but after being identified, it turned out to be uric acid (Clode et al 2009). In addition, microorga-nisms such as fungi and some bacteria (Enterobacteria and *Bacillus spp*.) produce uric acid as an intermediate, then it is converted into ammonia as the final product for excretion (Vogels & van der drift 1976, Lee et al 2013).

In humans, uric acid is maintained at homeostasis condition to be beneficial to the body. However, uric acid homeostasis can exceed their minimum and maximum limits which is largely influenced by a number of factors, including exogenous factors, processes in the body, and uric acid excretion. Exogenous factors can be foods and beve-rages that contribute to increased production of uric acid in addition to cellular catabolism in the body. The ex-cretion of uric acid becomes the key factor to maintaining balance. Important questions arise.

What is the basal concentration of uric acid in the body? And what is the contribution of uric acid removal to homeostasis, and what is involved in the regulation? A study is needed to explain quantitatively the homeostasis and dynamics of uric acid, and this review examined the homeostasis of uric acid in human body and analyzed recent studies of the affecting major variables.

LITERATURE REVIEW

Uric acid homeostasis

In this section, the reversion of uric acid to the blood and its excretion from the body will be assessed quantitatively to form a model of uric acid homeostasis.

Exogenous and endogenous factors

Several studies have shown that exogenous and endogenous factors affect the amount of soluble acid (miscible pool) and the rate of urinary turnover in both normal and gout subjects (Table 1), as proven by some experiments using isotope uric acid. Studies using diet with low protein or purine content showed basal miscible pool of 767-1650 mg and turnover rate of 498-1392 mg/day in normal subjects, and very high miscible pool in gout patients.

Sexual identity and uric acid

Men and women have different ranges of concentrations of uric acid in the blood. The difference is due to physiological factors that affect uric acid metabolism in the body. The average level of uric acid in the blood of normal men ranges from 3.74-6.2 mg/dL, while that in women ranges from 4-5.3 mg/dL (Table 2).

Reabsorption and uric acid extraction

Two-third of the uric acid is excreted through the kidney and the rest is through the intestine. Several studies have shown quantitative data on uric acid excretion. Data in Table 3 show that uric acid excretion in urine in normal subjects ranges from 262-620 mg/day. Whereas, in the intestine, uric acid excretion in urine in normal subjects ranges from 186-313 mg/day.

Table 1. Summary of miscible pool and uric acid turnover rate observation

Diet	Miscible pool (mg)		Turnover rate (mg/day)		References
	Normal	Gout	Normal	Gout	
Equivalent to 2.4-3.1 mg/day AU in urine	1100–1300	4742–18450	690–870	2485–8530	Benedict et al (1949)
70 g protein, 350 g carbohydrate, 100 g fat	946–1290	1053–3078	593–729	535–1693	Seegmiller et al (1961)
Equivalent to 200 mg purin	992–1650	1248–3199	602–838	506–1542	Scott et al (1969)
(a) 13 g and (b) 62 g protein	(a) 767–1485 (b) 975–1469	-	(a)498–772 (b)1179–1392	-	Bowering et al (1970)

Note: AU (uric acid), (-) no data, (a). Subjects treated with 13 g dietary protein, (b). Subjects treated with 62 g dietary protein

Table 2. Mean concentrations of uric acid in the blood of men and women

Sex	Population Origin	Mean Uric Acid (mg/dL)	Range (mg/dL)	References
Male	-	3.74–4.90	2–7	Rehman & Naqvi (1980)
	India	5.8–6.2	3.5–8.7	Das et al (2014)
	America	6.07	-	Choi & Curhan (2007)
	Java, Indonesia	6.2	-	Darmawan (1988)
Female	-	4–4.40	2–6.4	Rehman & Naqvi (1980)
	India	4.3–5	2.5–6.9	Das et al (2014)
	America	4.65	-	Choi & Curhan (2007)
	Java, Indonesia	5.3	-	Darmawan (1988)

Note: (-) no data

Table 3. Concentrations of uric acid released in urine and feces

Samples	Reabsorption (mg/day)	Urine (mg/day)	Feces (mg/day)	References
Normal	-	560–620	-	Benedict et al (1949)
Gout	-	408–424	-	
Normal	8064	436–618	-	Nugent & Tyler (1959)
Normal	-	465–539	-	Puig et al (2012)
Normal	-	-	186–200	Sorensen (1962, 1965)
Normal	-	262–321	186–313	Löffler et al (1981)
Normal*	-	526–784	478–631	

Note: (-) no data, (*) normal subject given diet 4 g of RNA/day

Table 4. Effect of foods on increased uric acid concentration

Food Types	Amount of Consumption	Increase (mg/dL)	References
Meat, seafood, eggs, spinach	-	1–2	Emmerson (1996), Fam (2002)
Meat	>1.53 times/day	0.48	Choi et al (2005)
Seafood	-	0.16	Choi et al (2005)

Note: (-) no data

Table 5. Effects of alcohol, fructose and sucrose consumption on uric acid

Beverage Types	Total	Increase (mg/dL)	References
Beer	10 ml/kg BW	0.50–0.59	Yamamoto et al (2004)
Beer*	20 ml/kg BW	0.91–0.92	Moriwaki et al (2006)
Fructose	213–219 g/day	0.52	Wang et al (2012)
Fructose	250–290 g/day	1–1.7	Emmerson (1974)
Sucrose	1.5 g/kg BW	0.61	Kobayashi et al (2007)
Other (green tea)	1 cup/day	0.42	Teng et al (2013)

Note: (*) containing 5% ethanol and 56 mg/L purine

Uric acid homeostasis and disturbances

This section examines the effect of food and beverage consumption as well as the function of genetic component to uric acid homeostasis and its disturbances based on quantitative data.

High purine-containing food

It has long been established that consumption of high purine-containing food contributes to increased uric acid production (Emmerson 1974, Choi et al 2005). Types of food containing high purines such as meat, seafood, eggs, and spinach contribute to uric acid increase of about 1-2 mg/dL (Table 4) (Emmerson 1996, Fam 2002). However, the type, frequency, pattern, and amount of food consumed have major contribution to uric acid in the body.

Effects of alcohol, fructose and sucrose

Consuming alcohol, fructose and sucrose may increase the concentration of uric acid in the blood. Consuming beer as much as 10-20 ml/kgBW may increase uric acid as much as 0.50-0.92 mg/dL. In contrast, alcoholic beverages, such as wine, are known not to contribute to increasing uric acid concentration in the body (Choi & Curhan 2004). Consumption of fructose around 213-290 g/day may increase uric acid around 0.52-1.7 mg/dL. Whereas, consuming sucrose of 1.5 g/kgBW may increase uric acid of 0.61 mg/dL (Table 5).

Effects of food and beverage variation on uric acid

Certain types of food and beverage consumption have no significant effect on the increase of uric acid concentration, and some even decrease. Epidemiological studies have shown that consumption of vegetables, milk, cheese, yogurt, black tea, coffee and vitamin supplements do not affect the increase of uric acid in blood (Choi et al 2005, Teng et al 2013, Ryu et al 2014).

Table 6. Capacity of key genes in transporting uric acid in the kidneys

Gen	Capacity (mg/dL)	References
ABCG2	114.31–162.73	Nakayama et al (2011)
SLC2A9	5.43–20.17	Caulfield et al (2008), Anzai et al (2008), Vitart et al (2008), Bibert et al (2009), Witkowska et al (2012)
SLC22A12	5.77–6.71	Enomoto et al (2002)

Influence of genetic background

Recently, research on the human genome have grown rapidly. Genome-wide Association Studies (GWAS) has helped to analyze the genetic components associated with uric acid in population. The GWAS study has identified several gene loci associated with uric acid, including: ABCG2 (coded BCRP), SLC2A9 (GLUT9), SLC22A11 (OAT4), SLC22A12 (URAT1), SLC16A9, SLC17A1, LRCC16A, PDZK1, GCKR, MYL2-CUX2, and CNIH-2 (Kolz et al 2009, Reginato et al 2012, Yang et al 2014, Matsuo et al 2015).

Uric acid transporter genes were found to have pivotal roles in maintaining uric acid homeostasis and their polymorphisms imply disturbances leading to some serious diseases. Through functional studies using gene expression systems in model cells, several genes are known to have different capacity in trans-porting uric acid as indicated by Michaelis-Menten (Km) parameters (Table 6).

DISCUSSION

An interesting study from Gosling et al (2013) discussed the phenomenon of different uric acid levels in Pacific countries. Based on population studies, the data shown in most Pacific populations had a range of uric acid levels between 4-6 mg/dL. If the normal range is 3-7 mg/dL, then the population in Pacific countries has a range of uric acid levels close to hyperuricemia. Possibly, some populations in the Pacific have shown different homeostatic changes as a result of adaptation to long term exposure to environment such as food or diseases. Unfortunately, these data were not supplemented by the development of uric acid over a period of time, making it difficult to answer whether at any given period the uric acid level is below the 4-6 mg/dL range. Then, what causes these levels to be close to hyperuricemia? Is it caused by environmental or genetic factors? Specifically in Indonesia, Gosling et al (2013) used population data in Java with a mean of 6.2 ± 1.3 mg/dL of uric acid. The data were less represent-ative of the population in Indonesia due to different ethnic and geographical diversity (Karwur & Triandhini 2016). It could be possible that the average uric acid in Indonesia is above or below the world population ave-rage. In essence, Gosling gave an idea that uric acid homeostasis in a population may change according to adaptation and tolerance of human survival.

According to some studies, certain food, such as red meat, seafood, and innards, contribute high uric acid in plasma. Not only foods, alcoholic and high fructose-containing beverages that reflect a change in lifestyle also spur increased uric acid. However, studies of exogenous effects (food and beverages) still need to be studied in more detail to identify how much they increase uric acid in the body. Based on the cultural factors in the society, variations of food and beverages (including the number and frequency), and lifestyle vary in each country or region. For example, how much is the influence of alcoholic beverages of tuak, commonly consumed by some Indonesians, on the increase of uric acid in plasma? Can it be compared to wine or beer? Thus, the relationship between culture and local food types with increased uric acid should be studied in more detail.

Age, sex, history of disease and genetic factors are also known to affect the concentration of uric acid in plasma. Along with the increase of age, diet, lifestyle, and disease, uric acid can be potentially stable, decreased or increased. It should also be taken into consideration that ethnic factors influence tolerance to uric acid regulation. Based on sex, the factors of male and female are different because of physiological conditions of the body. Normal (healthy) premenopausal women have lower uric acid concentrations than men. It is predicted that the causes are estrogen and progesterone hormones which are diuretic or uricosuric. At postmenopause phase, the concentration will increase compared to that in premenopause phase (Rights & Choi 2008). Disease factors also affect the concentration of uric acid. For example, disorders of the kidneys tend to affect increased uric acid in plasma.

Recent study has shown that genetic factors in the excretory system affects the homeostasis of uric acid in the body. The ABCG2 gene has the capacity to transport more than any other gene. This gene plays a major role in the excretion of uric acid to get out of the kidney and to remove it with urine. Furthermore, any interference or dysfunction may impact on the increase of uric acid in the plasma due to accumulation in the kidney.

Another transporter gene is SLC2A9 (GLUT9) which acts as a uric acid reabsorption in the kidney. If the gene is impaired or dysfunctional (due to mutation), then there will potentially be hypouricemia or hyperuricemia. It has not been well known how SLC2A9 dysfunction mechanism can affect hypouricemia or hyperuricemia in the body. Transporter genes with dysfunction due to mutations are difficult to treat. If the gene function information can be utilized, then appropriate treatment settings and management of consumption and lifestyle will be better arranged.

The presence of uric acid in the blood can have implications for health and disease. Uric acid protects erythrocytes from lipid peroxides and lysis damage (Ames et al 1981). Other roles include protect-ing DNA damage from free radicals, activating the immune system by promoting T-cell directly, and maintaining blood pressure in salt-deprived environ-ment (Cohen et al 1984, Webb et al 2009).

CONCLUSION

Human body needs uric acid as it may have implications to health and disease. Basal normal uric acid homeostasis is as follows: turnover ranges from 498-1392 mg/ day, miscible pool is 767-1650 mg, reabsorption is 8064 mg/day, kidney excretion is 262-620 mg/ day and intestine is 186-313 mg/day. The dynamics of uric acid is influenced by the factors of food, drink, age, history of disease, and genetic. The consumption of high purine foods increases uric acid of 1-2 mg/dL, 213-290 g/day fructose drinks increase 0.52-1.7 mg/dL, 1.5 g/kgBW sucrose increases 0.61 mg/dL, and 10-20 ml/kgBW beer increases 0.50-0.92 mg/dL. Along with age, the accumulation of uric acid increases with decreasing organ function. ABCG2 gene expression plays a role in transporting uric acid out of the body of 114.31-162.73 mg/dL, SLC2A9 of 5.43-20.17 mg/dL, and SLC22A12 of 5.77-6.71 mg/dL. Less functional excretory system has a significant effect on uric acid accumulation in the body. In the management of hyperuricemic, hypouricemia and gout diseases, quantitative data play a significant role in determining the appropriate clinical treatment according to the physiological and genetic conditions of the patient.

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