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HYPERURICEMIA AS A RISK FACTOR OF CARDIOVASCULAR DISEASES

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SUMMARY. **Introduction.** The increasing frequency of hyperuricemia is likely to be caused by westernized lifestyle and environment. At organ level, regulation of uric acid is controlled by the excretion form the kidney and the digestive tract. Higher serum uric acid levels thus suggest towards or are the markers of systematic circulatory failure or digestive tract anomalies. **The aim.** Analysis of current experimental and clinical scientific research on the levels of uric acid as a risk factor for cardiovascular diseases. **Material and methods.** Hyperuricemia is defined as serum urate levels exceeds above 7 mg/dl. Physiological solubility of uric acid occurs at 6.4 mg/dl which is further increased by the presence of uric acid-binding proteins up to 7mg/dl, at which stage further increase in uric acid leads to its crystallizations in the body. Uric acid is produced by the during the ATP metabolism. **Results and Discussion.** The first modern realization of urate induced malignancy (i.e., gout) to cardiovascular event (i.e., unstable angina) came from the Framingham heart study [Abbott R.D. et al. 1988; Bhole V. and Krishnan E. 2014]. However, Framingham Heart Study and NIPPON DATA 80 [Sakata K. et al. 2001] indicated that hyperuricemia (alone) is not an independent risk factor for cardiovascular disease or death, but is only a marker of pathological conditions. In contrast to that, the Rotterdam [Bos et al., 2006] and NHANES I studies [Fang J. and Alderman M.H., 2000] that targeted the general population, the association between high levels of uric acid and myocardial and cerebral infarctions, and cardiovascular death persisted even after adjustment for related factors. In light of these studies, recent observation shifted the

focus on the hyperuricemia and CVD in the absence of gout [Bhole V. and Krishnan E., 2014], and to understand the CVS morbidity and mortality in the absence of uric acid induced gout.

Conclusions. The issue of hyperuricemia as a risk factor for cardiovascular disease remains controversial and requires study.

Key words: hyperuricemia, clinical scientific research, cardiovascular diseases.

Introduction. The increasing frequency of hyperuricemia is likely to be caused by westernized lifestyle and environment. At organ level, regulation of uric acid is controlled by the excretion form the kidney and the digestive tract. Higher serum uric acid levels thus suggest towards or be the markers of systematic circulatory failure or digestive tract anomalies.

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Results and Discussion. Hyperuricemia is defined as serum urate levels exceeds above 7 mg/dl. Physiological solubility of uric acid occurs at 6.4 mg/dl which is further increased by the presence of uric acid-binding proteins upto 7mg/dl, at which stage further increase in uric acid leads to its crystalization in the body. Uric acid is produced by the during the ATP metabolism. Adenine nucleotide, part of ATP structure, is converted into hypoxanthine, xanthine, and eventually uric acid during, and is subsequently into the blood. Uric acid production, by xanthine oxygenase (XO) enzyme, also led to the production of reactive oxygen species (ROS) during metabolism. ROS binds to nitric oxide (NO), a

vasodilator substance, and inhibits its function, which is supposedly one of the factors involved in the development of arteriosclerosis. In pathologies compromising oxygenation, such as congenital heart failure and serious heart failure, aggravated anaerobic metabolism in tissues due to oxygen shortage increases the levels of serum lactic acid. This increased levels of lactic acid in turn accelerates the reabsorption of uric acid in the kidney, which then in turn leads to increased serum uric acid levels [30]. Further, environmental and lifestyle factors, such as exercise, diet etc. also influences the uric acid levels in the body. At organ level, regulation of uric acid is controlled by the excretion form the kidney and the digestive tract. Higher serum uric acid levels thus suggest towards or be the markers of systematic circulatory failure or digestive tract anomalies. Casual association of hyperuricemia with hypertension was reported back in 1870, and continues to be reported thereafter. Association of hyperuricemia to hypertension arose from two angels; first epidemiological studies reported hyperuricemia as an independent indicator of hypertension, secondly the animal studies have mechanistically linked hyperuricemia to hypertension [16]. Number of studies have shown that serum uric acid (SUA) levels are potential risk factor for developing insulin resistance, hypertension, dyslipidemia and cardiovascular diseases which are characterized as the so-called metabolic syndrome [33]. Risk of developing metabolic syndrome is enhanced by increasing SUA level, which in turn shows gender and age dependency.

The first modern realization of urate induced malignancy (i.e., gout) to cardiovascular event (i.e., unstable angina) came from the Framingham heart study [1, 4]. However, Framingham Heart Study and NIPPON DATA 80 [31] indicated that hyperuricemia (alone) is not an independent risk factor for cardiovascular disease or death, but is only a marker of pathological conditions. In contrast to that, the Rotterdam [5] and NHANES I studies [6] that targeted the general population, the association between high levels of uric acid and myocardial and cerebral infarctions, and cardiovascular death persisted even after adjustment for

related factors. In light of these studies, recent observation shifted the focus on the hyperuricemia and CVD in the absence of gout [4], and to understand the CVS morbidity and mortality in the absence of uric acid induced gout.

Number of cross-sectional studies have been reported linking progressive increase in serum uric acid with greater coronary artery calcifications. Also, studies have reported strong associations between serum urate concentrations and incidence of hypertension and incidence of heart failure [4, 15]. Clinical trials revealed the effects of lowering uric acid on the carotid intimal thickness [13], alleviating left ventricular hypertrophy [20], angina [27], and cardiovascular events in subjects with and without chronic kidney disease [10-12]. Worksite study of hypertensive patients reported the significant increase in cardiovascular disease when he serum uric acid level exceeds 7.5 and 6.2 mg/dl in male and female patients, respectively [3]. Further towards the cardiovascular complications of hyperuricemia, substudy reported an increase in the serum uric acid level by 1 mg/dl resulted in an equivalent risk of 20 mg/dl increase in serum cholesterol as well as 10 mm Hg elevation of systolic blood pressure [2]. In line with these studies, PIUMA study, where a significant increase in the onset of cardiovascular disease was seen when the serum uric acid level exceeded 6.2 and 4.6 mg/dl in male and female patients, respectively [32]. NHANES III study also highlighted the onset of cerebral and cardiovascular disease significantly increased when the serum uric acid level exceeded 6.0 mg/dl in both male and female patients [35]. The LIFE study, also reported the better prognosis of cardiovascular patients with management of hyperuricemia pharmacologically. They reported compared the serum uric acid levels with the onset of cardiovascular disease among patients receiving losartan and atenolol, and reported that the lowering effect of losartan on serum uric acid levels contributed to 29% of the improvement in prognosis in females [14]. Similar results were also reported in SHEP study, where they targeted senior patients with hypertension, the serum uric acid levels after the blood pressure control were 6.7 and 5.7 mg/dl or

higher in male and female patients, respectively, indicating a significant increase in the risk for cardiovascular disease [7]. Syst-China study also reported an increase in serum uric acid levels by 0.86 mg/dl increased the occurrence of death from cerebral or cardiovascular disease significantly [34]. Apart from hypertension, similar results are also reported for other malignancies. As such, J-CAD study, reported a significant increase in the onset of cerebral and cardiovascular events including total death in a group with serum uric acid levels of 6.8 mg/dl or above. Patients cohort in J-CAD, a 3-year tracking cohort, consisted of Japanese patients with coronary artery disease with high uric acid levels, and confirmed the hyperuricemia and cardiovascular related pathologies [28].

In agreement to above-discussed observational studies, prospective interventional studies also corroborated those observational studies. Although prospective interventional studies have been limited and small in scale, they are considered very important in linking hyperuricemia with cardiovascular events. Goicoechea et al conducted an interventional study using antihyperuricemic drugs reported on their preventive effects on cardiovascular disease. They compared cardiovascular patients groups with and without the receiving allopurinol, a uric acid production inhibitor. In the absence of the oral administration of allopurinol, a uric acid production inhibitor, patients with serum uric acid levels of 6 mg/dl (n = 57) was compared to a group with levels at ≥7 mg/dl (n = 56). Follow-up (mean, 23.4 months) of these groups showed that the onset of cardiovascular disease was significantly lower in the group receiving allopurinol [10]. Lower uric acid level is also reported to be beneficial in settings of angina. High doses of allopurinol (600mg/day) results in significant extension of time to the onset of angina episode, as well as the time required for the ST segment decrease and total time for exercise by treadmill load test [27]. Based on these small and limited prospective interventional studies, it is however difficult to establish if the interventions for hyperuricemia directly prevent cardiovascular disease remains controversial. Research on hyperuricemia is often confounded with range of pre-symptomatic and overlapping syndromes such as

diabetes, obesity, as well as environmental and genetic factors which makes the results difficult to interpret and establish causality with cardiovascular endpoints. However, with well-planned studies controlling for the potential confiding factors and consisting more than 90, 000 subjects revealed that an increase in serum uric levels by 1 mg/dl increased the prevalence of hypertension by 1.2-fold. Further, quartile prospective examination of individuals with high serum levels also showed that they have 1.7- and 3.4-fold prevalence of hypertension in male and female patients, respectively, compared to the group with the lowest serum uric acid levels [21, 22].

It is well known that two major complication of hypertension is stroke and heart failure. With studies, it has been shown that hyperuricemia is risk factor for hypertension, thus already indirectly linking hyperuricemia as risk factor of stroke and heart failure. Collective understanding from studies using thiazide diuretics, chlorthalidone and similar approaches have shown the effect of antihypertensive agents on cardiovascular outcomes is worsened if the treatment raises uric acid levels (such as with diuretics) [16]. Elevated serum uric acid levels in subjects with congestive heart failure is associated with reduced exercise capacity, inflammation markers, endothelial dysfunction, oxidative stress and diastolic dysfunction, and is predictive both of symptom status (ie, morbidity) and prognosis (ie, mortality) [23, 26]. In spite of these observations, the association of hyperuricemia with respect to heart failure has been difficult to establish, else otherwise no concrete association has been reported to establish the role of hyperuricemia in heart failure. The EXACT-HF study, 253 patients were included with advanced heart failure and with serum uric acid levels of ≥9.5 mg/dl. These patients were compared the oral administration of allopurinol with a placebo control group. At 24 weeks, no changes in the clinical status, exercise capacity, quality of life, or left ventricular ejection fraction were reported for the respective groups [9]. Further, the efficacy of xanthine oxygenase inhibitor on heart failure complicated by hyperuricemia remains uncertain [21].

As mentioned earlier, epidemiological studies have shown the link of hyperuricemia with hypertension and cardiovascular disorders. The mechanistic understandings came from the animal studies. Johnson and colleagues establish the tat model of pharmacologically induced hyperuricemia. In rat model of pharmacological induced hyperuricemia, hypertension could be induced as soon as 2 weeks of elevated blood uric acid level. Hyperuricemia increased the systolic as well as diastolic blood pressure, and these indicators were increased proportional to the increase in uric acid level [25], and the effects were reversible with administrating the uric acid-lowering drugs such as allopurinol or benziodarone [25]. In this mode, the early hypertension was mediated by elevated renal renin active and the reduced circulating plasma nitrates [8, 24]. This mimic the phenotype of excessive vasoconstriction which could alleviated by reducing the uric acid levels or administrating the renin–angiotensin system blockade pharmacologically. However, at the later stages, hypertension in these models were irreversible mediated by altered intrarenal vascular. Uric acid enters the vascular smooth muscle cells via uric acid anion transporter-1 channel [29]. Intracellular uric-acid activates kinases, transcription factors, and many cellular mediators resulting altered vasculatures and hypertension [17-19]. These mechanistic studies along with epidemiological data strongly suggest the role of hyperuricemia in the etiology of hypertension and cardiovascular disorders.

Conclusions. The issue of hyperuricemia as a risk factor for cardiovascular disease remains controversial and requires study.

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РЕЗЮМЕ

ГІПЕРУРИКЕМІЯ ЯК ФАКТОР РИЗИКУ СЕРЦЕВО-СУДИННИХ ЗАХВОРЮВАНЬ

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Вступ. Подальше збільшення частоти гіперурикемій, ймовірно, буде викликано стрімким способом життя і навколишнім середовищем. На органному рівні вміст сечової кислоти контролюються здатністю нирок до екскреції і роботою шлунково-кишкового тракту. Збільшення рівня сечової кислоти в сироватці крові може бути маркером недостатності кровообігу або порушенням роботи травного тракту. **Мета** – аналіз сучасних експериментальних і клінічних досліджень про роль гіперурикемії як фактора ризику серцево-судинних ускладнень. **Матеріали та методи.** Рівень сечової кислоти визначали у сироватці крові. Гіперурикемія визначається як рівень уратів в сироватці, який перевищує 7 мг/дл. Фізіологічна розчинність сечової кислоти становить 6,4 мг/дл, подальше збільшення рівня сечової кислоти

призводить до її кристалізації в організмі. Сечова кислота продукується під час метаболізму АТФ. **Результати та обговорення.** Вперше на зв`язок гіперкристалурії з ураженням серця вказано у дослідженні Framingham [Abbott R.D. et al. 1988; Bhole V. і Krishnan E., 2014]. Проте, Framingham Heart Study і NIPPON DATA 80 [Sakata K. et al. 2001] вказали, що гіперурикемія (самостійно) не є незалежним чинником ризику серцево-судинних захворювань або смерті, а є лише маркером патологічних станів. На відміну від цього в дослідженнях Rotterdam [Bos M.J. et al., 2006] і NHANES_I [Fang J. and Alderman M.H., 2000], що призначалися для населення в цілому, зв'язок між високим рівнем сечової кислоти і інфарктів міокарда і церебральних артерій і серцево-судинної смертю зберігалася навіть після коригування пов'язаних факторів. У світлі цих досліджень недавнє спостереження змістило акцент на гіперурикемії і серцево-судинні захворювання за відсутності подагри [Bhole V. and Krishnan E., 2014], а також для розуміння захворюваності і смертності внаслідок серцево-судинних хвороб при відсутності подагри, викликаної сечовою кислотою. **Висновки.** Проблема гіперурикемії як фактора ризику серцево-судинних захворювань залишається дискусійною і потребує подальшого вивчення.

Ключові слова: гіперурикемія, клінічні наукові дослідження, серцево-судинні захворювання.

РЕЗЮМЕ

ГИПЕРУРИКЕМИЯ КАК ФАКТОР РИСКА СЕРДЕЧНО-СОСУДИСТЫХ ЗАБОЛЕВАНИЙ

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Вступление. Увеличение частоты гиперурикемии, вероятно, будет вызвано изменением образа жизни и окружающей средой. На

органном уровне регулирование уровня мочевой кислоты контролируется экскрецией почек и пищеварительным трактом. Более высокие уровни мочевой кислоты в сыворотке являются маркерами недостаточности кровообращения или нарушением работы пищеварительного тракта. **Цель работы** - анализ текущих экспериментальных и клинических научных исследований о роли гиперурикемии как фактора риска сердечно-сосудистых заболеваний. **Материалы и методы.** Уровень мочевой кислоты определяли в сыворотке крови. Гиперурикемия определяется как уровень уратов в сыворотке крови, превышающее 7 мг/дл. Физиологическая растворимость мочевой кислоты составляет 6,4 мг/дл, что еще больше повышается за счет присутствия связывающих мочевую кислоту белков, при повышении до 7 мг/дл и выше увеличение уровня мочевой кислоты приводит к ее кристаллизации в организме. Мочевая кислота продуцируется во время метаболизма АТФ. **Результаты и обсуждение.** Впервые на связь гиперкристалурии с поражением сердца указано в исследовании Framingham [Abbott R.D. et al. 1988; Bhole V. i Krishnan E., 2014]. Однако, Framingham Heart Study и NIPPON DATA 80 [Sakata K. et al. 2001] указали, что гиперурикемия (самостоятельно) не является независимым фактором риска сердечно-сосудистых заболеваний или смерти, а является лишь маркером патологических состояний. В отличие от этого в исследованиях Rotterdam [Bos M.J. et al., 2006] и NHANES_I [Fang J. and Alderman M.H., 2000], предназначавшихся для населения в целом, связь между высоким уровнем мочевой кислоты и инфарктов миокарда и церебральных артерий и сердечно-сосудистой смертью сохранялась даже после корректировки связанных факторов. В свете этих исследований недавнее наблюдение сместило акцент на гиперурикемии и сердечно-сосудистые заболевания при отсутствии подагры [Bhole V. and Krishnan E., 2014], а также для понимания заболеваемости и смертности от сердечно-сосудистых заболеваний при отсутствии подагры, вызванной мочевой кислотой. **Выводы.**

Проблема гиперурикемии как фактора риска сердечно-сосудистых заболеваний остается спорной и требует дальнейшего изучения.

Ключевые слова: гиперурикемия, клинические научные исследования, сердечно-сосудистые заболевания.