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Serum uric acid and the risk of ventricular arrhythmias: a systematic review

Uric acid (UA) is the end product of purine degradation in humans. It promotes inflammation via activation of pro-inflammatory cytokines and increases oxidative stress. The serum uric acid level has emerged as an independent risk factor of cardiovascular disease such as ventricular arrhythmias (VA). Here we had done a systematic review to assess the association between serum UA levels and the occurrence of VA. This systematic review included a total of four clinical studies with 99.383 patients for analysis. The scientific quality of all four studies was good. Three studies showed that serum uric acid levels were associated with VA in many populations. In contrast, one study with a large sample size evaluated that serum uric acid increases premature ventricle contraction prevalence. A significant association between serum uric acid level and VA was found in four studies ($p<0.01$; $p<0.101$; $p=0.002$; $p=0.008$). In conclusion, this systematic review shows an association between serum UA levels and VA.

Keywords Uric acid; hyperuricemia; ventricular arrhythmia; risk factor

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Introduction

Uric acid (UA) is the end product of purine degradation in humans. DNA and RNA are degraded into purine nucleotides and bases that are then metabolized via xanthine oxidase (XO) to xanthine and uric acid, forming reactive oxygen species (ROS). UA is synthesized endogenously, especially in the liver, intestines, muscles, and vascular endothelium. UA increases with the intake of red meat, seafood, fatty foods, alcohol, and sweet drinks containing sucrose or fructose.

The role of UA in cardiovascular disease (CVD) or cardiometabolic disease is still controversial. Several clinical and epidemiological studies show an association between UA and various disorders, including CVD, metabolic syndrome, and kidney disease [1]. Overproduction of UA, generated from purine metabolism, leads to hyperuricemia which has been proven to play an emerging role in the morbidity and mortality of various CVDs. Serum UA has also emerged as an independent risk factor for ventricular arrhythmias (VAs). UA can promote inflammation via activation of pro-inflammatory cytokines and increased ROS. The generation of ROS in these disorders can contribute to the induction of arrhythmias via multiple mechanisms, including altering cardiac ionic channels and cardiac cell death-associated ventricular dysfunction [2]. Oxidative-stress mediated tissue injury during ischemia and reperfusion may be related to both ischemia and to reperfusion-induced arrhythmias. However, little is known about the association between serum UA and the occurrence of VAs. The purpose of this literature review was to determine whether UA is associated with risk of VAs.

Material and methods

Search strategy

This study was conducted in a series of steps following the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guidelines. These steps included searching for articles and assessing each article's quality, extracting and analyzing data, as well as summarizing and interpreting findings.

We searched for observational studies or trials that assessed UA as a predictor in VA. Major medical databases (PubMed, MEDLINE, Clinical Key, Cochrane Library, EMBASE) were systematically searched using keywords: uric acid, hyperuricemia, or ventricular arrhythmias and risk in the title, abstract, and medical subject heading (MeSH). The search was limited to clinical trials published within the last 10 yrs, written in English, and with full-text availability. Lists of references from the literature matching the inclusion requirements were also screened manually to find additional, relevant studies.

Article selection

Narrative review, editorials, commentaries, and consensus documents that did not include patient results or outcomes

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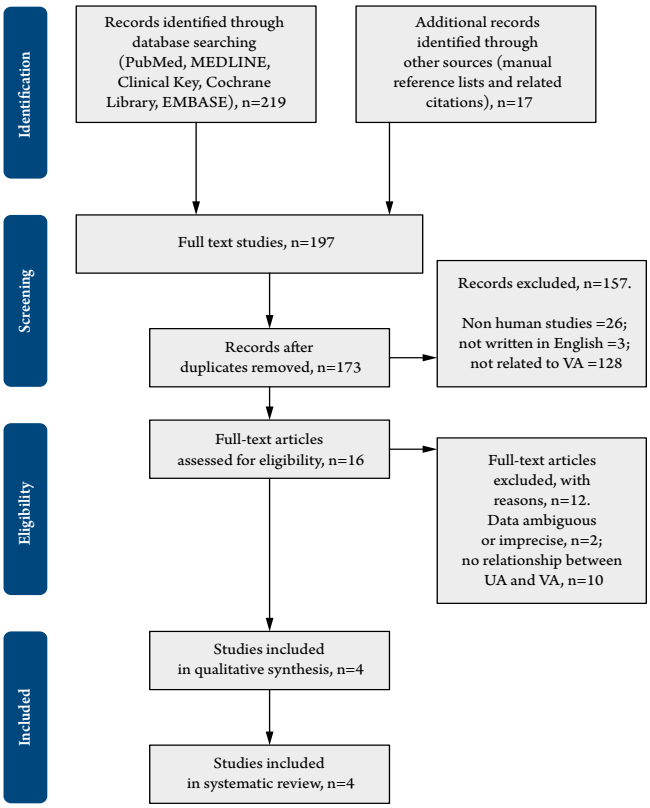
Figure 1. PRISMA flowchart of literature search



were excluded. Studies were included if they contained primary details on patients' serum UA and VA incidence. Three investigators evaluated titles and abstracts prior to full text retrieval. The authors, publication year, location, research design, subject, study result, and VA incidence were all collected by two investigators from full-text publications. Details of the of literature search and selection of articles for inclusion in the review are shown in Figure1.

Quality Assessment

The Newcastle Ottawa Scale (NOS) was used to measure the quality of the four included articles. Base on this quality score, none of these articles were excluded.

Data extraction

Data extracted from the included articles were tabulated, and then a narrative synthesis was undertaken to identify key themes in that literature.

Results

Four observational studies, one case-control study, and three cohort studies met our inclusion criteria with a total of 99,383 patients for analysis. These studies were conducted in Japan, China, and Turkey. The VA incidence varied in each study from a few (1.1%) to quite frequent (20.87%). The baseline characteristics of the included articles are presented in Table 1. The scientific quality of all four studies was good (Table 2). Three studies showed that UA concentrations were associated with VAs in many types of patients. One study with a large sample size (n=98,965) found that UA increased prevalence of premature ventricle contractions (PVCs). A significant association between serum UA and VA occurrence was found in all four studies (p<0.01; p<0.101; p=0.002; p=0.008) (Table 3). Several limitations were present, including non-random trial assignment, small sample size, and insufficient follow-up duration.

Discussion

UA is commonly measured in clinical laboratories. Elevated serum UA concentration is thought to be associated with cardiac events, such as heart failure, myocardial infarction, angina pectoris, and atrial fibrillation (AF), and with total mortality [7]. Evidence of a relationship between increased serum UA concentration and VA is still sparse. In 1985, while investigating a potential arrhythmogenic effect of diuretic usage, McDonald et al. noticed a relationship

Table 1. Description of the studies included in this review

Authors	Year	Country	Method	Subjects	% VAs
Yamada et al. [3]	2012	Japan	Case control	167	16.2
Chen et al. [4]	2018	China	Cohort	98,965	1.1
Nodera et al. [5]	2018	Japan	Cohort	56	39
Ozylmaz et al. [6]	2018	Turkey	Cohort	115	20.9

Table 2. Newcastle Ottawa Scale

Authors	Selec – tion	Compa – rability	Expo- sure	Total score	Overall grade
Yamada et al. [3]		**	**	8	Good
Chen et al. [4]	***	*	****	8	Good
Nodera et al. [5]	****	**	*	7	Good
Ozylmaz et al. [6]	****	**	**	8	Good

Table 3. Summary of results of the included reports

Authors	(OR*, HR**) 95% CI; p	Results
Yamada et al. [3]	OR 1.61; 95% CI 1.18–2.2; p<0.01	Uric acid concentration was an independent predictive factor for the occurrence of VT in LVH patient
Chen et al. [4]	OR 1.13; 95% CI 1.06–1.21; p<0.001	Serum uric acid was associated with the prevalence of PVCs
Nodera et al. [5]	HR 1.826; 95% CI 1.248–2.671; p=0.002	Uric acid might be a predictor of VT, providing a new aspect ICD implantation decision
Ozylmaz et al. [6]	p=0.008	Higher uric acid concentration was associated with higher VT incidence

*OR: Odds Ratio; **HR: Hazard Ratio.

between serum UA and ventricular ectopy [8]. The authors speculated that this might be attributed either to the diuretics, the studied population's comorbidities, or direct effects of UA on the ventricular myocardium.

It has been shown that an increase in serum UA is associated with the development of cardiovascular disease. Two main factors increase the concentration of serum UA, namely excretion impairment due to renal dysfunction and an increase in UA production by activation of the XO system. One study showed that UA and renal dysfunction markers, such as BUN and eGFR, were associated with VT occurrence [9]. In general, renal dysfunction increases serum UA. Many epidemiological studies have suggested that increasing serum UA through activation of the XO system is associated with the formation of oxidative stress and inflammatory mediators. UA inhibits NO formation and activates inflammatory mediators such as TNF-α and mitogen-activated protein kinase (MAPK), which further impairs endothelial function and smooth muscle cell proliferation [10]. UA is also involved in angiotensin II-mediated hypertrophy and hyperplasia of myocytes and vascular smooth muscle cells. Greater production of angiotensin II will affect fibrogenic cytokine expression and increase perivascular and interstitial fibrosis, resulting in increased myocardial fibrosis. UA is also known to be involved in myocardial pathogenesis, where oxidative stress and inflammatory mediators induce electrophysiology and structural remodeling of the atrial and ventricular myocardium [4].

Hyperuricemia is common in hypertensive patients. Several large studies have shown that increased UA is associated with the emergence of left ventricular hypertrophy (LVH) in essential hypertension [11]. On the other hand, LVH is an important predictor of ventricular tachyarrhythmias (VT) and sudden cardiac death. One study showed that an increase in serum UA had the strongest association with the occurrence of VT in patients with LVH [12]. Radovanovic, et al. recently reported that UA was associated with the left ventricular remodeling in patients with chronic ischemic heart failure [13]. Chen, et al. also revealed a similar correlation between UA and ventricular remodeling in mice with myocardial infarction subjected to experimental hyperuricemia [14]. These results suggest that serum UA level is a helpful marker for predicting ventricular arrhythmias in patients with LVH. However, the exact mechanism has not been fully elucidated.

It has been shown that cardiomyopathy is associated with oxidative stress, i.e., an imbalance between the production and neutralization of ROS. Several experimental studies have shown that oxidative stress can induce focal activity and reentry processes and cause VT [15]. Serum UA is a metabolic product in the final stage of purine metabolism, and it is produced through the action of XO, an enzyme involved in oxidative processes [16]. Thus, a high serum UA concentration is a marker of oxidative stress and inflammation. Although impaired excretion due to renal dysfunction increases serum UA concentrations, renal parameters such as BUN and eGFR do not impact implantable cardioverter-defibrillator (ICD) therapy appropriate for VT [5].

Some argue that abnormal fibrosis associated with hypertrophic cardiomyopathy (HCM) that triggers ventricular arrhythmias. Methods for evaluating cardiac fibrosis include measuring galectin-3 and fragmented QRS (fQRS). Galectin-3 is a beta-galactoside-binding lectin that is expressed by macrophages. Recent studies have shown that galectin-3 concentration is elevated in diseases associated with heart inflammation and fibrosis [17]. The fQRS complex seen on a 12-lead EKG is related to myocardial fibrosis and to a high risk of sudden cardiac death (SCD) in HCM patients. Özyılmaz, et al. showed that UA values correlate positively with the risk of HCM and SCD [18]. Serum UA concentrations correlate with serum galectin-3 concentrations, and high UA concentrations seem to be associated with increased frequency of fQRS, VT, and the need for CPR and an implantable cardioverter-defibrillator (ICD) [18].

One study found a correlation between serum UA and PVCs in patients without myocardial infarction or stroke [19]. A gender-specific analysis found a significant correlation between elevated serum UA concentrations and PVC prevalence in men but not in women [4]. This is consistent with the report by Nakanishi et al. that showed a positive correlation of serum UA with cardiovascular morbidity and mortality in a large male population, but not in women [20]. Also, Sun, et al. found that an independent association between serum UA and AF was significant in males [21]. In contrast, two previous studies, namely by Freedman, et al. [22] and Levine, et al. [23], showed that hyperuricemia is a risk factor for cardiovascular events in women, but not in men. Thus, it is likely that a sex-specific mechanism may underlie the association between serum UA and cardiovascular disease. The difference between the findings from various studies can be related to ethnic and territorial specificity [4]. In addition, it is likely that the incidence of PVC may be associated with adverse ventricular remodeling associated with UA. However, the exact mechanism underlying the UA association remains to be investigated.

In addition, a study demonstrated that treatment with allopurinol was a predictor of improved survival. However, this association does not prove causality. Recently, Singh and Cleveland investigated whether use of allopurinol was associated with a reduction in the risk of VA [24]. Their study of 28,775 cases of new allopurinol use showed that allopurinol was associated with a hazard ratio of VA of 0.82 (95% CI 0.76–0.90). More prolonged use was significantly associated with a lower multivariate-adjusted hazard ratio: 1–180 d, 0.96 (95% CI 0.85–1.08); 181 d to 2 yrs, 0.76 (95% CI 0.68–0.85); > 2 yrs, 0.72 (95% CI 0.60–0.87). A longer duration of allopurinol treatment was associated with greater VA hazard reduction.

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Conclusion

This literature review found evidence of an association between uric acid concentration and ventricular arrhythmias. However, further studies with improved research methodology are required to prove causality rather that only association. Additional studies are required to determine the ability of uric acid-lowering therapy to reduce ventricle arrhythmias.

Author contribution

IPD and KPD conceived the idea and designed the report. IPD and KNSP were major contributors in writing the manuscript. IPD and LFKW edited the manuscript for publication. RJ and BBD supervised the article content. All authors read and approved the final manuscript.

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