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# Is Serum Uric Acid Level a Prognostic Value for Tinnitus Severity?

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## ABSTRACT

**Objective:** Tinnitus is a disease that concerns a large part of society and its pathophysiology and etiology have not been exactly clarified. This study will investigate the association between serum uric acid (SUA) levels and idiopathic subjective tinnitus.
**Material and Methods:** Ninety-one tinnitus patients and 45 age- and sex-matched healthy volunteers were included in the study. Patients were divided into two groups as mild tinnitus and severe tinnitus according to the Tinnitus Handicap Inventory questionnaire. They underwent otolaryngologic examination, routine hematological and biochemical analyses, pure tone audiometry, doppler ultrasound, and magnetic resonance imaging to exclude possible causes of tinnitus. Patients with abnormalities in any test result were excluded from the study. The blood test results were statistically compared between the groups.
**Results:** Except for SUA levels, no significant difference was found between groups in any blood test results ($p>0.05$). Significant differences among the groups were determined in SUA levels ($p=0.001$). SUA levels were found to be significantly higher in the severe tinnitus group than in the mild tinnitus or control group ($p=0.002$, $p=0.001$). However, there is no statistically significant difference between the mild tinnitus group and the control group ($p=0.617$).
**Conclusion:** In this study, it was observed that there was a clear correlation between higher SUA levels and severe tinnitus. But this association did not reveal SUA levels as an accurate biological marker for tinnitus. It could only be utilized as a marker of disease severity. Further studies will help to reveal the exact relation.

**Keywords:** Biologic marker, blood tests, subjective tinnitus, tinnitus, uric acid

## INTRODUCTION

Tinnitus is the perception of sound heard spontaneously in one or both ears, in the absence of any external audio stimulus. It is divided into two categories: objective and subjective (1). Objective tinnitus is described as tinnitus perceptible to the clinician as a sound coming out from the external auditory meatus, whereas subjective tinnitus is perceptible solely to the patient and has prevalence ranging from 2-32% (1-3). Although the most common cause of subjective tinnitus is acoustic trauma, conditions such as arterial hypertension, diabetes, cardiovascular diseases (CVD) and hyperlipidemia are also associated with tinnitus (1-4).

Uric acid (UA) is the product of purine metabolism and consists of xanthine through the reaction of xanthine oxidase (5, 6). Serum uric acid (SUA) levels frequently increase when renal excretion is reduced, such as when there is impaired renal function or decreased renal blood flow (6). In addition, some epidemiological studies have implicated a relationship between elevated SUA levels and hypertension, hyperlipidemia, cardiovascular disease, pre-eclampsia, renal failure, cerebrovascular events, and vascular dementia. Many authors have suggested that SUA might be an independent risk factor for all these conditions (1, 7, 8). However, there is no study showing whether SUA levels, which are known to be associated with cardiovascular diseases, can be used as a marker for tinnitus. The aim of the current study was to evaluate the possible relationship between SUA levels and subjective idiopathic tinnitus.

## MATERIALS AND METHODS

Erzincan Binali Yıldırım University Clinical Research Local Ethics Committee's approval was obtained on 20.03.2020 with the

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decision numbered 03/24 prior to this prospective clinical trial. The study included patients from the ENT outpatient clinic with the complaint of tinnitus which had been ongoing for at least two weeks. All the patients underwent a detailed otorhinolaryngological examination, pure tone audiometry (PTO), carotid and vertebral artery Doppler ultrasound (US), and magnetic resonance imaging (MRI) of the inner ear to exclude possible causes of tinnitus. Auscultation of the neck was performed on all patients to eliminate objective tinnitus. According to evaluations, patients who were diagnosed with idiopathic subjective tinnitus (IST) were included in the study.

The Tinnitus Handicap Inventory (THI) was used to assess the intensity of the tinnitus. Turkish validity and reliability tests of the THI were conducted by Aksoy et al. (9). The THI consists of 25 questions with each item scored from 0-4 (0=no, 2=sometimes, 4=yes) and the total score ranges from 0 to 100 points. The patients were classified into five intensity grades in respect of the THI scores as slight (0–16 points), mild (18–36 points), moderate (38–56 points), severe (57–76 points), and catastrophic (77–100 points). For analysis in this study, two groups were formed according to the THI scores. Patients with a grade of 1 or 2 were included in the "mild tinnitus group", and those with grade 3, 4, or 5 in the "severe tinnitus group".

The study exclusion criteria was defined as the presence of neuro-otological problems that are known to cause tinnitus (Meniere's disease, asymmetric sensorineural hearing loss, vertigo, chronic otitis media, otosclerosis), chronic disease (diabetes, hyperlipidemia, hypertension, cardiovascular disease, liver, or kidney failure etc.) or medication use for any reason. Complete blood count and full biochemical analysis (glucose and UA levels, liver, renal and thyroid function tests) were performed from venous blood samples taken after 8 hours fasting. Patients with abnormalities in any test result (physical examination, blood tests, PTO, Doppler US, and MRI) were excluded from the study.

The study control group was formed of 45 age and sex-matched volunteers who attended the Outpatient Clinic for a check-up with no complaints. The control group subjects underwent the same physical examination, audiometric and blood tests as the tinnitus patients, but not Doppler US and MRI. Glucose and uric acid levels, liver, renal, and thyroid function tests of the patients and control group were recorded. All the test results were statistically compared between the three groups (mild tinnitus, severe tinnitus, and control).

Informed consent forms were obtained from all the patients and control subjects.

**Statistical Analysis**

Data obtained in the study was analyzed statistically using SPSS version 22 software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA). Conformity of the data to normal distribution was checked with the Shapiro Wilk test, histograms, and q-q plots (Figure 1). Homogeneity of variance was assessed using the Levene test. Pearson Chi-Square analysis was used to compare the difference between categorical variables (groups and gender). The Kruskal–Wallis test was used to evaluate statistical significance between the groups for non-normal distributed parameters (WBC, hemoglobin, glucose, creatinine, AST, ALT, TSH, FT4). Parameters with normal distribution (age, BUN, platelet, and UA levels) were examined with One-Way ANOVA. The LSD post-hoc test was applied to multiple comparisons of SUA levels between the groups. A value of $p<0.05$ was accepted as statistically significant.

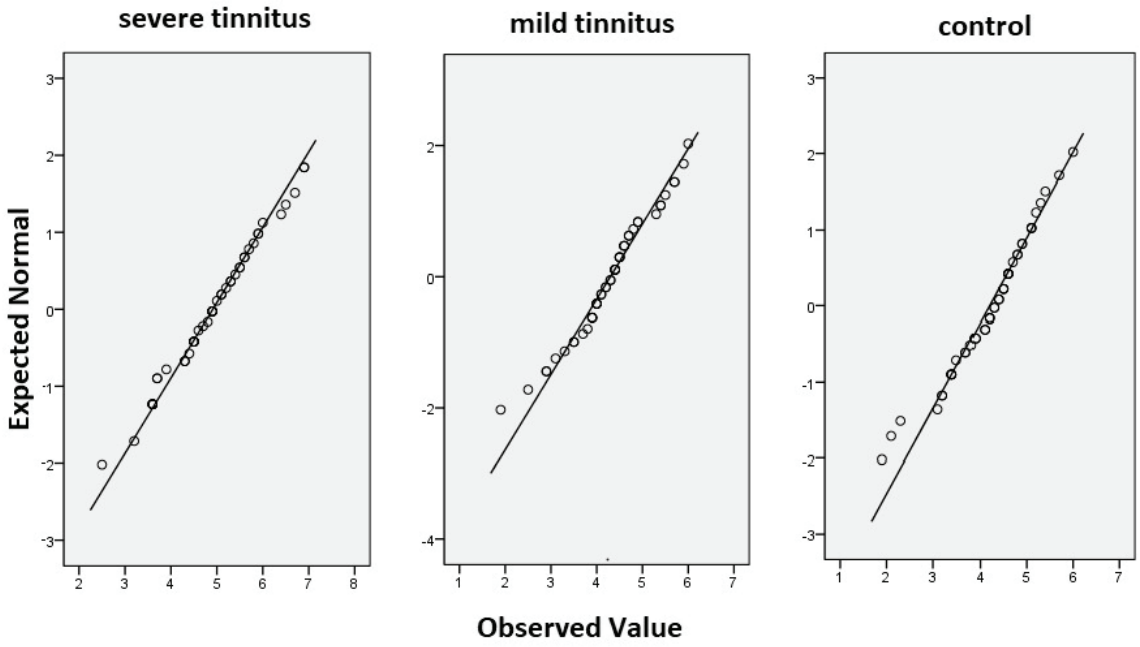


**Figure 1. Normal Q-Q plot of serum uric acid levels.**

**Table 1: Demographic data and laboratory test results according to groups.**

| Variables | Control | Mild tinnitus | Severe tinnitus | P value |
|---|---|---|---|---|
| Age (years) | 37.2±11.33 | 36.6±11.72 | 37.5±12.35 | 0.937 |
| Gender (female/male) | 23 (51.1)/22 (49.9) | 24 (52.2)/22 (47.8) | 24 (53.3)/21 (46.7) | 0.978 |
| WBC ($10^3$/$mm^3$) | 6.9 (5.77-8.1) | 6.7 (5.57-8.15) | 6.9 (5.8-8.1) | 0.833 |
| Haemoglobin (g/dl) | 14 (13.05-14.55) | 13.8 (13.2-15.3) | 13.8 (13.4-15.65) | 0.341 |
| Platelet ($10^3$/$mm^3$) | 261.6±46.6 | 255.9±54.2 | 262.8±46.4 | 0.772 |
| FG (mg/dl) | 92 (87-955) | 92 (90-96) | 93 (89-97) | 0.18 |
| BUN (mg/dl) | 14.06±3.58 | 14.06±3.22 | 14.15±3.26 | 0.989 |
| Creatinine (mg/dl) | 0.8 (0.7-0.91) | 0.81 (0.71-0.92) | 0.88 (0.76-0.98) | 0.089 |
| AST (IU/l) | 22 (18-26) | 21 (17-24) | 22 (17-25) | 0.884 |
| ALT (IU/l) | 20 (14-27) | 18 (13-28) | 21 (16-27) | 0.716 |
| TSH (mIU/l) | 1.83 (1.42-2.58) | 1.74 (1.43-2.73) | 2.15 (1.56-2.61) | 0.56 |
| FT4 (ng/dl) | 1.21 (1.09-1.45) | 1.16 (1.04-1.3) | 1.17 (1.08-1.3) | 0.151 |
| Uric acid (mg/dl) | 4.2±0.89 | 4.29±0.87 | 4.91±1.02 | **0.001** |

Values are stated as *n* (%), mean±SD or median ($25^{th}$-$75^{th}$ percentiles). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; FG, fasting blood glucose; FT4, free thyroxine; TSH, thyroid-stimulating hormone; WBC, white blood cells. Bold value indicates statistically significance (p<.05).

## RESULTS

A total of 134 patients were screened in the study, abnormal complete blood count and biochemical analysis were found in 36 patients, chronic diseases, and regular drug use in 18 patients, abnormal Doppler USG in 7 patients, Meniere's disease in one, and asymmetric hearing loss in two patients. Some of the patients had more than one exclusion criteria at the same time. Forty-three patients were excluded because they did not meet the criteria, and 91 patients were included in the study (48 females, 43 males; mean age, 37.1±12.05 years). According to THI, 46 patients were included in the mild tinnitus group and 45 patients in the severe tinnitus group. The demographic data and blood test results of the patients and control group are listed in Table 1. Age and sex were compared between the groups and no statistically significant difference was observed (p>0.05). Apart from SUA levels, no significant difference was found between the groups in any blood test results (p>0.05). A significant difference was determined between the SUA levels of the groups (p=0.001). According to the paired comparisons of the groups, the SUA levels were found to be significantly higher in the severe tinnitus group than in the mild tinnitus group and the control group (p=0.002, p=0.001). No statistically significant difference was determined between the mild tinnitus group and the control group (p=0.617). A scatter plot graph of the SUA levels of the three groups is shown in Figure 2. Multiple comparisons of serum uric acid levels between the groups are presented in Table 2.

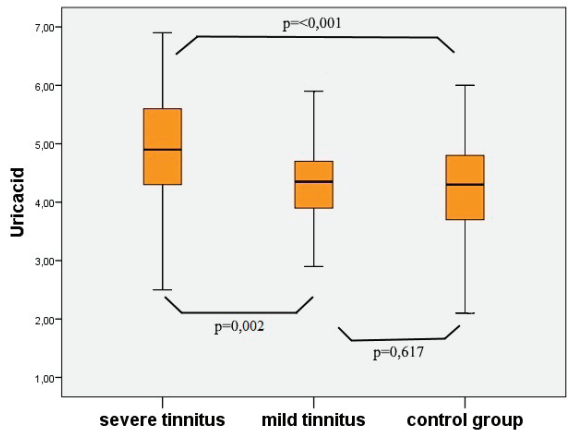


**Figure 2. Scatter plot graph of serum uric acid levels**

**Table 2. Multiple comparisons of serum uric acid levels between the groups (LSD post-hoc test).**

| Groups | Mean difference | Std. Error | p value |
|---|---|---|---|
| Severe tinnitus - Mild tinnitus | 0.613 | 0.195 | **0.002** |
| Severe tinnitus - Control | 0.711 | 0.196 | **<0.001** |
| Mild tinnitus - Control | 0.097 | 0.195 | 0.617 |

Bold values indicate statistically significance (p<.05)

## DISCUSSION

Tinnitus is the perception of sound in the absence of any environmental acoustic stimulation. If this sound can be heard by the physician or another person, it is categorized as objective tinnitus, and if heard only by the patient, as subjective tinnitus (1). Causes of subjective tinnitus include presbycusis, noise-induced hearing loss, chronic otitis media, ototoxicity, labyrinthitis, Meniere's disease, otosclerosis, acoustic neuroma, metabolic dysfunction, and neurological diseases such as multiple sclerosis (1, 10). When no cause can be found in patients with subjective tinnitus, it is known as IST (11). It is thought that approximately one third of the population suffers

from tinnitus at least once per lifetime, and approximately 1–5% experience severe psychosocial complications (12).

The pathophysiology of the disease, which is common and impairs quality of life, has not yet been fully clarified. According to one theory, the pathogenesis of tinnitus is the perception of stimulation of the nerve endings with repeated spontaneous discharges as a real sound due to cochlear hair cell damage caused by noise or head trauma (10). Another theory has claimed that tinnitus occurs due to synchronization of the auditory nerve fibers that develops as a result of damage or metabolic abnormality in the central nervous system and auditory pathways (10).

The most common clinical conditions associated with tinnitus are chronic noise exposure, head trauma, and infections (13). In addition, many recent studies have shown a relationship between tinnitus and cardiovascular diseases (14). In a study by Figueiredo et al., a strong relationship was shown between tinnitus and hypertension, especially in elderly patients (15). Huang et al. reported a strong association between ischemic CVD and tinnitus in adults aged <40 years (14). Strikingly, there are also some studies indicating that SUA levels are a strong marker for CVD (6, 16). Therefore, the aim of this study was to reveal the possible association between tinnitus and SUA levels.

SUA level is a rapid and inexpensive test that is obtained from venous blood. In general, the SUA level is increased in kidney-related diseases. However, according to recent research, SUA levels have become a widely used biological marker for many clinical health issues such as systemic inflammatory diseases, hypertension, metabolic syndrome, and CVD (17-20). In addition to systemic diseases, it has been also investigated as a marker for some otological diseases. Ilancioglu et al. researched whether SUA levels are a cue for sudden sensorineural hearing loss (SNHL) and reported no significant difference in SUA levels between SNHL patients and the control group (21). Celikbilek et al. reported a strong positive correlation between SUA levels and benign paroxysmal positional vertigo (BPPV) (5). Yang et al. published a systematic review and meta-analysis, in which it was stated that BPPV is associated with elevated SUA levels but may not be an independent risk factor for the disease (22). To the best of our knowledge, this is the first study to have investigated the relationship between tinnitus and SUA levels.

The tinnitus patients in this study were separated into two groups according to the THI score. The reason for this division was to reveal whether SUA is also a prognostic factor for tinnitus in terms of severity. The statistical analysis results showed that the SUA levels were significantly different between the groups, with higher SUA levels in the severe tinnitus group than in the mild tinnitus group and the control group, but no difference between the mild tinnitus and control groups. The results can be considered reliable due to the normal distribution of SUA data and the application of parametric tests in the statistical analysis. The p value of $< 0.001$ in the analysis of the SUA levels also indicates a strong relationship. All these results suggest that SUA levels might be a marker only for severe tinnitus.

Severe tinnitus is quite difficult to treat. There is no licensed medication in Europe or North America for treatment of IST, although many have been trialed (11). Standard care is to inform the patient about the disease (including both causation and the progress of related distress), and the use of medication such as betahistine or antidepressants, hyperbaric oxygen therapy, masking devices, and cognitive behavioral therapy (CBT) to reduce the distress (11 ,23, 24). Psychology-based therapies, especially those based on CBT are often cited as the most efficacious of current tinnitus treatments, but nevertheless, there is no definitive cure (25). The presence of an association between high SUA level and severe tinnitus may lead to the consideration of new treatment modalities such as the use of diuretic drugs that reduce SUA or a UA-restricted diet.

There were some limitations to this study. The research was carried out with a small number of subjects because of the limited number of patients matching the inclusion and exclusion criteria during the planned period. Another limitation was that a high frequency audiometry test was not administered to the patients. According to the literature, high frequency hearing loss may cause an inclination to microangiopathic events (26). If patients with hearing loss above 8 kHz had been identified and excluded, the study population would have been more specific.

The results of this study demonstrated that there is a strong association between severe tinnitus and higher SUA levels even if it is within the normal range. However, this relationship has not shown that SUA levels are a definite biological marker for tinnitus. SUA can only be considered as a marker for disease severity. There is a need for further multicenter studies with larger samples to confirm these results. In addition, further investigation of the association between uric acid and tinnitus will shed light on whether diet and/or diuretics might have a place in the treatment of tinnitus.

**Ethics Committee Approval**: Erzincan Binali Yıldırım University Clinical Research Local Ethics Committee's approval was obtained on 20.03.2020 with the decision numbered 03/24 prior to this prospective clinical trial.

**Informed Consent:** Written informed consent was obtained.

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