

# Prevalence of Hyperuricemia and the Relationship Serum Uric Acid with a Musculoskeletal Complication in Patients with $\beta$ Thalassemia Intermedia

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## ABSTRACT

**Background:** Beta thalassemia ( $\beta$ -thalassemia), which is one of the most common monogenic diseases in the world, is caused by a decrease or lack of synthesis of the beta-globin chain. Patients with thalassemia major are associated with ineffective erythropoiesis, chronic hemolysis of erythrocytes, and increased production of uric acid. Complications such as musculoskeletal complications, osteoporosis have been reported in these patients. Studies in general populations have also shown that elevated serum uric acid levels are associated with increased bone mineral density.

**Patients and methods:** This cross-sectional descriptive and analytical study was performed on 48 patients in Yasuj City (Southwest Iran). We collect the information in the patients' file and analyzed blood samples of patients Thalassemia Intermedia referring to Yasuj city. The tests were performed by the reference laboratory of the Blood Transfusion Organization of Iran. Statistical significance was based on two-sided design-based tests evaluated at the 0.05 level of significance. All the statistical analyses were performed by SPSS 20 software.

**Results:** The mean age of the patients was  $46.15 \pm 13.05$  years. The uric acid level had a significant relationship with the Lumbar Z score in men patients ( $p$ -value=0.02). The mean Lumbar Z score in people with uric acid levels less than 6.1 was in the osteoporotic range and people with uric acid levels more were equal to 6.2 in the osteopenia range. Most people with thalassemia intermedia had osteopenia, but no significant relationship was found between blood uric acid levels in women and bone mineral density.

**Conclusion:** Most people with thalassemia intermedia had osteopenia, but no significant relationship was found between blood uric acid levels in women and bone mineral density.

**Keywords:** Osteopenia; Uric acid; Thalassemia intermedia

## INTRODUCTION

Thalassemia is a heterogeneous group of inherited disorders that was first proposed as a disease in 1925 by the American scientist Thomas Cooley. This disease is caused by a small defect in globin chains and occurs in two forms: alpha thalassemia and beta thalassemia [1].

Beta thalassemia ( $\beta$ -thalassemia), which is one of the most common monogenic diseases in the world, is caused by a decrease or lack of synthesis of the beta-globin chain.  $\beta$ -thalassemia in three forms 1- Thalassemia minor or so-called thalassemia (associated with mild asymptomatic hemolytic anemia) 2- Intermediate or interstitial thalassemia (which occurs as an enlargement of the spleen and moderate to severe anemia and form Homozygous is a disease) and 3- thalassemia major occurs [1].

Patients with thalassemia major are associated with ineffective erythropoiesis, chronic hemolysis of erythrocytes and impaired maturity and survival of erythrocytes. Complications such as diabetes mellitus, musculoskeletal complications, osteoporosis, and decreased bone density have been reported in these patients [2]. Also, studies have shown that due to high cellular transducer in patients with thalassemia major and intermediate hyperuricemia (hyperuricemia or high serum uric acid) is expected in this group of patients [3].

Blood uric acid is a final product of purine metabolism that has strong antioxidant properties and also stimulates the adhesion of granulocytes to endothelial cells. Uric acid acts like normal antioxidants at normal serum levels and is a strong factor in plasma antioxidant capacity. However, at abnormal levels and above normal levels (above 6 mg/dL in women and above 7 in men)

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due to increased production of uric acid or decreased urinary excretion, its antioxidant properties are the opposite. And acts as a prooxidant (prooxidants are compounds that can potentially cause reactions in the body that result in harmful compounds, inflammation, and chronic disease) [4].

In recent decades, the prevalence of hyperuricemia has been increasing worldwide (> 15-20%) and many studies have been conducted in this field. These studies showed that there is a strong and positive indirect correlation between serum uric acid and white blood cell (WBC) levels, neutrophil counts, monocytes, C-reactive protein (CRP) and interleukin-6 (IL-6) and that hyperosmia is associated with many diseases including diabetes mellitus, chronic kidney disease, stroke, cardiovascular disease, gout (gout or gouty arthritis) and musculoskeletal disorders, although the results are contradictory. There is also a relationship [5, 6].

Studies in general populations have also shown that elevated serum uric acid levels in older men (70 and older) and premenopausal and postmenopausal women are associated with increased bone mineral density and are thought to increase serum uric acid levels. It has a protective role [7]. According to the results of these studies, which introduce hyperosmia as a risk factor for musculoskeletal disorders and also state that increased levels of uric acid can play a protective role in bone density in general populations. Now, what is the relationship between hyperuricemia and elevated uric acid levels in patients with thalassemia, and the musculoskeletal disorders and osteoporosis that are common in these patients?

Due to the limited studies in this field, this study aimed to determine the prevalence of hyperuricemia and the relationship between hyperuricemia and bone mineral density and musculoskeletal complications (including bone fractures, chronic joint pain, osteoporosis, decreased bone density and extramedullary bleeding) in patients Thalassemia Intermedia referring to Yasuj city.

**MATERIALS AND METHODS**

The study population consisted of 48 thalassemic patients registered and followed in a comprehensive thalassemia clinic in Shahid Beheshti Hospital, Yasuj, Iran. 5 ml of venous blood were taken after 8-h overnight fasting. Serum calcium (Ca), phosphorous (P), Hb, Cr, MCV, RBC, WBC, Retic, Urea, UA, Total Bilirubin, Direct Bilirubin, Ferritin, Vit D, PTH, Liver MRI, Bone Densitometry, and Hepatic iron load were assessed. We collected the necessary information by reviewing the patients' medical files.

Blood samples were assessed by the Sysmex KX21 cell counter, in the Iranian Blood transfer organization hematology reference lab. Hormonal and biochemical analysis tests were taken by Auto Analyzer at the Biochemical lab part. The logic system dual-energy X-ray absorptiometry (DXA) (Discovery QDR, USA) was used to measure the lumbar spine left hip BMD. The International Society for Clinical Densitometry (ISCD) defined low bone mass (LBM) as a Z-score of - 2 or lower than the expected range for

age. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 22 (SPSS Inc. Chicago IL, USA). Descriptive data were presented as mean, standard deviation, frequency, and percentage. We used the Chi-square test and Fisher exact test to compare qualitative data, and the Student t-test to compare quantitative data between the two groups. Variables with a P -a value of less than 0.05 in univariate analysis were entered in the multivariable analysis. Multiple logistic regression analysis was done to determine associated factors independently related to low bone mass in the femur and lumbar area. A p-value of less than 0.05 was considered to be statistically significant.

**RESULTS**

In this study, 48 patients with thalassemia intermedia were studied. The study population included: 24 patients (50% of patients) who were female and 24 patients (50% of patients) were male with thalassemia intermediate (Table 1). The mean age of the subjects in this study was 46.15 ±13.05 years. The study of patients' hemoglobin showed that the mean hemoglobin of the subjects in the present study was 8.73 ± 3.39 mg/dL. Laboratory studies showed that 27 patients (56%) had uric acid above 6.2 and 18 patients (37.5%) had uric acid less than 6.1. The prevalence of hyperuricemia in our patients was 56%.

**Table 1:** Prevalence of hyperuricemia and serum uric acid levels among β-thalassemia intermedia patients.

<b>Abnormal uric acid levels</b>	
Women	≥ 6 mg / dL
Men	≥ 7 mg / dL
Hyperuricemia prevalence	>15%-20% worldwide
<b>Study parameters and results</b>	
No. of thalassemia intermedia patients	48 [24 Males (50%) + 24 Females (50%)]
Hyperuricemia prevalence	56%
Area of study	Yasuj City, Southwest Iran
Age, mean ± SD	46.15 ± 13.05
Haemoglobin, mean ± SD	8.73 ± 3.39 mg / dL
<b>Uric acid levels</b>	
Uric acid ≥ 6.2	27 patients (56%)
s acid ≤ 6.1	18 patients (37.5%)
<b>Bone density parameters</b>	
Z-score	≥ -1 (Normal bone density)
Z-score	-1 to -2.5 (Osteopenia)
Z-score	≤ -2.5 (Osteoporosis)
<b>Radiographic examination, Lumbar region</b>	
No. of patients osteopenia	24 (50%)
No. of patients osteoporosis	17 (35.4%)
<b>Radiographic examination, Pelvic region</b>	
No. of patients osteopenia	31 (64.6%)
No. of patients osteoporosis	2 (4.2%)

A normal person's Z-scores are similar in age, gender, and race, and if low, this could indicate an increased risk of future fractures. The Z-score compares each person's bone density to the average bone density of people of their age and gender. The z score is three levels higher than -1, which indicates normal bone density, from -1 to -2.5, which indicates osteopenia or decreased bone density, and less than -2.5, which indicates a severe decrease in bone density, It means osteoporosis. The results of the radiographic examination of bone density in the lumbar region showed that (n=24) 50% of the subjects in the present study had a decrease in bone density (osteopenia) in the lumbar region and people with osteoporosis in the lumbar region with a high percentage (n=17) 35.4 had the highest frequency. The lowest frequency was related to people with normal lumbar bone density. The results of radiography of bone density in the left pelvic region showed that only 4.2% (2 people) of the subjects had osteoporosis (based on Z score) in the left pelvic region. Like bone density in the lumbar region, the highest frequency with 64.6%, and the frequency of 31 was related to people with osteopenia in the left pelvic region. Normal subjects without reduction of bone density in the left pelvic region constituted 31.3% of the subjects (n=15) in the study. The majority of subjects with a frequency of 89.58 (43 patients) had a history of bone fractures. Patients were divided into two groups based on uric acid levels. One group was divided with the uric acid level above 6.2 and the other with the uric acid level below 6.1. Then, in each group, patients were divided into male and female groups, and the relationship between laboratory factors and uric acid levels in each male and female group was investigated. These results showed that the relationship between blood uric acid level and none of the studied variables except blood urea (BUN) was significant. Urea level in people with the uric acid level above 6.2 was 32.36 77 9.77 and in people with uric acid level, less than 6.1 was 22.69.  $\pm$  5.62. The relationship between blood uric acid level and blood urea level was statistically significant (p-value=0.02). Therefore, it can be assumed the higher the blood uric acid level, the higher the blood urea level. Also, hemoglobin, MCV, MCH, reticulocyte, creatinine, calcium, phosphorus, bilirubin, Vitamin D, and iron levels in females had no significant relationship with blood uric acid levels (p value>0.05). The degree of enhancement due to MRI contrast in the heart had no significant relationship with blood uric acid level (p-value=0.1). Also, blood uric acid level was not significantly associated with the rate of contrast-induced enhancement in patients' livers (p-value=0.7). The rate of osteoporosis was higher in people with uric acid levels above 6.2 than in people with uric acid levels below 6.1. The decreased bone density (absence of osteoporosis) was greater in people with uric acid above 6.2 than in people with uric acid levels below 6.1. But none of these relationships were statistically significant (p-value=0.58).

## DISCUSSION

Blood uric acid is a final product of purine metabolism that has strong antioxidant properties [8]. Uric acid acts like normal antioxidants at normal serum levels and is a strong factor in

plasma antioxidant capacity. However, at abnormal levels and above normal levels due to increased production of uric acid or decreased urinary excretion, its antioxidant properties are reversed and it acts as a pro-oxidant. Studies in the general population also show Elevated serum uric acid levels in older men (70 and older) and women before and after menopause are associated with increased bone density and are thought to increase serum uric acid levels in them [9]. The relationship between uric acid and hemoglobin levels of the women was in line with the results of a study by Pu Su et al. There is a positive correlation between uric acid levels and white blood cells, red blood cells, hemoglobin, and hematocrit counts. In the mentioned study, there was a significant relationship between blood indices and gender, but in the present study, these relationships are not statistically significant [4]. This case may be due to the small size of our study population, so it is suggested that in the future this study be performed on a larger population of thalassemia intermedia patients. Several studies [10-16] have demonstrated the usefulness of uric acid in bone health, and uric acid in physiological concentrations has been considered a potent antioxidant to protect against oxidative stress associated with bone loss and osteoporosis. Uric acid is an effective balancer for oxidative stresses such as superoxide, hydroxyl radicals, and the strongest oxidizer of nitrite peroxide. Oxidative stress has been identified to reduce bone regeneration and is a risk factor for osteoporosis. The antioxidant properties of UA can also protect against free radical damage to blood vessels, heart, and nerve cells [17]. Our study also showed that in general, the majority of people with thalassemia intermedia with a prevalence of 58.3% have osteopenia. Also, in the present study, an increase in serum uric acid levels were associated with an increase in osteoporosis and a decrease in bone mineral density in women and also with a decrease in bone mineral density in men, although this was not statistically significant. This case is a self-confirmation of the usefulness of uric acid in physiological concentrations if it is significant. However, the present study shows that at higher concentrations, bone density decreases, which can be a reason for the dual role of uric acid in different concentrations, although the results of the study were not statistically significant. Therefore, conducting studies with larger populations and analyzing the results at different levels of uric acid may help to better understand its behavior. However, in the present study, in males, the level above 6.2 mg/dl uric acid was associated with an increase in lumbar z score compared to the group with a level of uric acid less than 6.1 mg/dl. Which was statistically significant? This could also confirm the role of uric acid in bone health. Epidemiological evidence has shown that uric acid is positively associated with bone mineral density and protects against osteoporosis [12]. In the present study, individuals with higher uric acid levels were more associated with decreased bone density in both sexes, although this relationship was not statistically significant. However, in males, uric acid levels above 6.2 mg/dL were associated with an increase in Lumbar Z score, which was statistically significant. This may confirm the

protective role of uric acid.

## CONCLUSION

Blood factors, except blood urea level in women and Lumbar Z-score in men, who had a positive relationship with a uric acid level higher than 6.2 mg/dL, the other factors had no significant relationship with the studied uric acid levels. Also, in the MRI of the subjects, no significant relationship was observed between the amounts of enhancement due to contrast in the heart and liver of patients with thalassemia intermedia and blood uric acid levels. In general, most people with thalassemia intermedia had osteopenia, but no significant relationship was found between blood uric acid levels and bone mineral density. In males, an increase in uric acid level was significantly associated with an increase in lumbar z score. Finally, it is suggested that this study be performed on a larger population based on different age groups and also according to the drugs used by patients.

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