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ASSOCIATION BETWEEN HYPERURICEMIA, SERUM IRON LEVEL AND POSSIBILITY OF GOUT AMONG SAUDI PATIENTS: A RETROSPECTIVE STUDY

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ABSTRACT: The present study has been undertaken to evaluate the association between serum uric acid levels as a marker of iron overload in Saudi people. A retrospective cohort study was carried out at King Fahad Medical City in the Riyadh-central region of the Kingdom of Saudi Arabia for four months from 1st November 2018 to the end of February 2019 on the random sample of 117 medical files for Saudi patient of both genders. All the obtained data were analyzed by the SPSS program by considering various variables like serum uric acid, transferrin, hemoglobin, ferritin level, *etc.*, in between hyperuricemic non-hyperuricemic patients. Serum uric acid, transferrin, ferritin, and hemoglobin levels were significantly ($p > 0.05$) high *i.e.* 564.1 ± 127.7 vs. 417.6 ± 38.3 $\mu\text{mol/l}$; 3 ± 1 vs. 2.1 ± 0.8 g/dl; 658.9 ± 896 vs. 528.6 ± 920 ng/ml; 9.9 ± 2.2 vs. 9.7 ± 1.8 g/dl in hyperuricemic and non-hyperuricemic patients respectively. Pearson correlation between serum uric acid and hemoglobin, ferritin level, transferrin level indicate positive correlation ($r = 0.21$), ($r = 0.46$) and ($r = 0.23$) respectively. The findings of this study demonstrate a positive correlation between serum uric acid and iron markers (serum ferritin, transferrin, and hemoglobin) in Saudi patients. Undiagnosed hemochromatosis or iron overload should be considered as a possibility when there are elevated uric acid levels even in the absence of related symptoms.

INTRODUCTION: In the human body, serum uric acid is produced from purine metabolism; as such, serum uric acid does not play a major physiological role, but it possesses antioxidant property ¹. The ampule of scientific literature suggests that elevated serum uric acid is a causative factor for gout and other chronic diseases such as cancer, diabetes mellitus, and cardiovascular diseases, and nonalcoholic fatty liver disease ^{2,3}.

The levels of uric acid in the body rely on two variables. The primary is the rate of uric acid amalgamation in the liver, while uric acid outcome from purine corruption and its levels are impacted by both the measure of purines blended in the body and the measure of purines assimilated from the eating regimen. The second determinant of blood uric acid level is the rate of uric acid discharge from the kidneys ⁴.

Recent study reveal that human tophi and synovial membranes of chronic gout patients have shown an elevated level of iron than the healthy patients. At normal physiological pH, urate crystals complexes with the cationic iron redox-active from in a dose-dependent manner, which causes an increase in oxidative stress ⁵.

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Increased oxidative stress is a reason to activate the complement system and granulocyte and following synthesis and release of pro-inflammatory mediators like lymphokines ⁶. Moreover, it is well known that deferoxamine is an iron chelator, which completely stops response *in-vitro* and decreased urate crystal-induced foot sloe's swelling in rats *in-vivo*.

Based on these findings, this has been postulated that elevated iron level is one of the confounding factors for hyperuricemia and subsequent formation of Gout ⁶.

It's hypothesized that elevated uric acid has a positive relationship with an increase in serum iron content. So, controlling serum iron levels may be the key for prophylaxis of uric acid-dependent diseases. We hypothesized that serum uric acid concentrations would be higher in Saudi people with higher markers of iron status than those with normal or lower markers of iron status as counterparts. As per the literature survey, no previous study has been carried out to establish the correlation between the elevated iron level and circulating serum uric acid concentration.

METHODOLOGY:

Study Population and Research Design: We examined the association between elevated serum iron level and serum uric acid level on gout through prospective design in retrospective cohort studies at King Fahad Medical City in Riyadh, the central region of the Kingdom of Saudi Arabia. The study was carried out for the consecutive month *i.e.*, 1st November 2018 to February 2019, in that 117 medical files of Saudi patients of both genders were examined (IRB log number: 18-633E).

Study-related patient demographic data and physiological parameters were recorded in a data collection sheet including about age, gender, body mass index (BMI), Serum levels of serum iron, Serum ferritin, Serum transferrin, hemoglobin, total iron-binding capacity (TIBC), and C-reactive protein (CRP) levels.

We have included all the patients with gout in between the age group 40 and 60 of both the gender. All the non-Saudi patients, patients with other comorbidities, and who have high CRP were excluded from the study.

Statistical Analysis: All data entered to SPSS program for statistical analysis, mean and standard deviation calculated for numerical values and frequency, the percentage calculated for non-numerical values, t-test used to compare between means ($p > 0.05$) considered as significant, and person correlation calculated to evaluate the correlation between serum uric acid and iron indicators.

RESULTS:

Distribution of Study Subjects According to Age and Sex: The study included 117 subjects according to inclusion criteria; among them, there were 62 (53%) males and 55 (47%) females. According to age; 41 (35%) older than 60 years, 56 (35%) in the age range of 41-60 years, 20 (17%) younger than 40 years. The mean value of the study subject's age was 54.8 years **Fig. 1**.

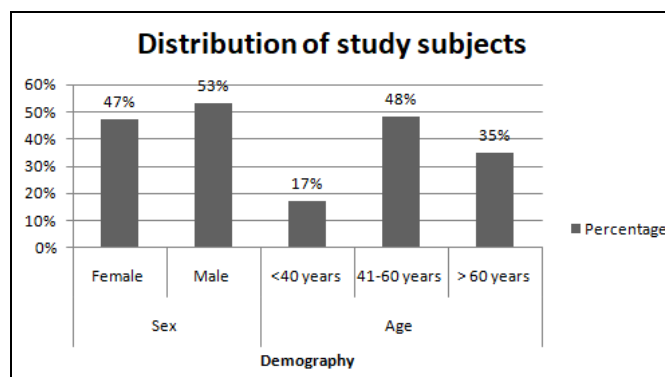


FIG. 1: DISTRIBUTION OF STUDY SUBJECTS

Distribution of Study Subjects According to Serum Uric Acid Level: The mean age was 55.6 ± 17.7 years in hyperuricemic subjects and 52 ± 17.9 years in non-hyperuricemic patients with no significant difference ($p < 0.05$). The mean BMI was 29 ± 7.4 years in hyperuricemic subjects and 21 ± 7 years in non-hyperuricemic patients with no significant difference ($p < 0.05$) **Fig. 2**. The mean value of serum uric acid was significantly ($p > 0.05$) higher in hyperuricemic patients than in non-hyperuricemic patients [564.1 ± 127.7 ($\mu\text{mol/l}$), 417.6 ± 38.3 ($\mu\text{mol/l}$) respectively]. The mean ferritin level was 658.9 ± 896 (ng/ml) in hyperuricemic subjects and 528.6 ± 920 (ng/ml) in non-hyperuricemic patients with significant difference ($p > 0.05$) **Fig. 3**. The mean hemoglobin level was 9.9 ± 2.2 (g/dl) in hyperuricemic subjects and 9.7 ± 1.8 (g/dl) in non-hyperuricemic patients with significant difference ($p > 0.05$).

Mean transferrin level was 3 ± 1 (g/dl) in hyperuricemic subjects and 2.1 ± 0.8 (g/dl) in non-hyperuricemic patients with significant difference ($p > 0.05$). The mean transferrin saturation was 28.4 ± 25.9 (%) in hyperuricemic subjects and 25.6 ± 18 (%) in non-hyperuricemic patients with significant difference ($p > 0.05$). The mean serum iron level

was 11 ± 10.3 ($\mu\text{mol/l}$) in hyperuricemic subjects and 9.3 ± 6.2 ($\mu\text{mol/l}$) in non-hyperuricemic patients with significant difference ($p > 0.05$). The Mean TIBC was 34 ± 18.1 ($\mu\text{mol/l}$) in hyperuricemic subjects and 30 ± 14.12 ($\mu\text{mol/l}$) in non-hyperuricemic patients with significant difference ($p > 0.05$) **Fig. 4**.

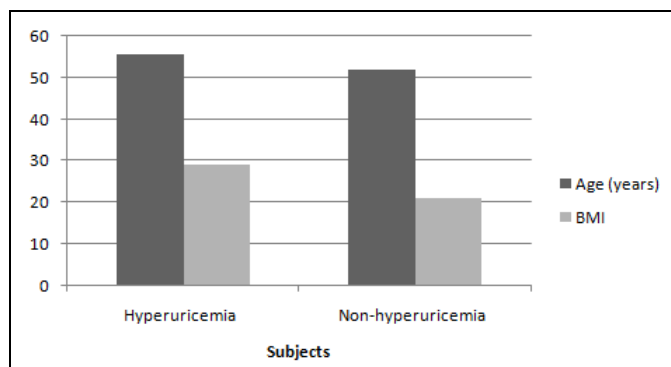


FIG. 2: DISTRIBUTION OF (AGE & BMI) IN HYPERURICEMIC AND NON-HYPERURICEMIC SUBJECTS

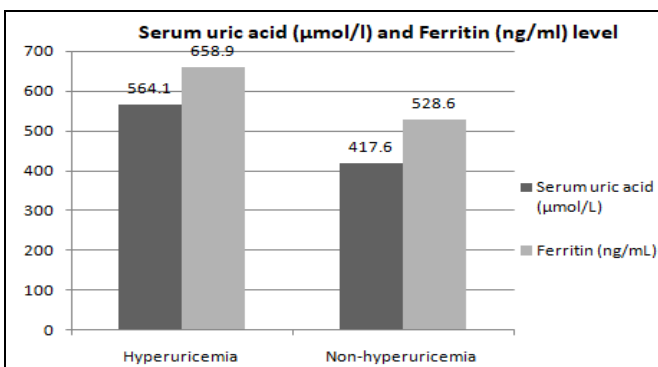


FIG. 3: SERUM URIC ACID ($\mu\text{mol/l}$) AND FERRITIN (ng/ml) LEVEL IN HYPERURICEMIA AND NON-HYPERURICEMIA PATIENTS

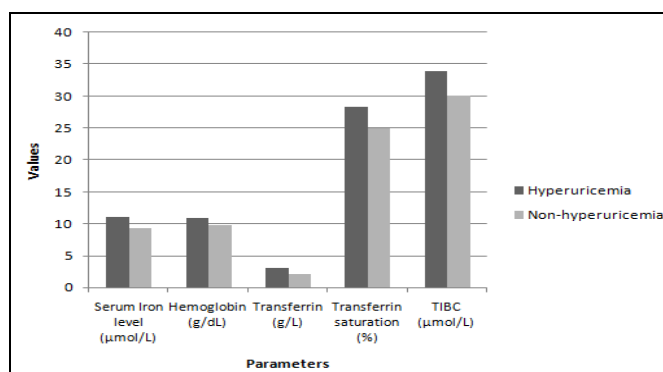


FIG. 4: DISTRIBUTION OF SERUM IRON, HEMOGLOBIN, TRANSFERRIN, TRANSFERRIN SATURATION AND TIBC LEVELS IN HYPERURICEMIA AND NON-HYPERURICEMIA PATIENTS

Distribution of Hyperuricemic Subjects According to Sex and Age: Mean level of uric acid was significantly higher ($p > 0.05$) in male subjects [580 ± 136.9 ($\mu\text{mol/l}$)] than in females [543 ± 113.4 ($\mu\text{mol/l}$)].

Additionally, the uric acid value was significantly higher in older subjects 552 ± 161 ($\mu\text{mol/l}$) in subjects > 40 years old, 563 ± 114 ($\mu\text{mol/l}$) in subjects in the age range of 41-60 years and 585 ($\mu\text{mol/l}$) in subjects older than 60 years **Fig. 5**.

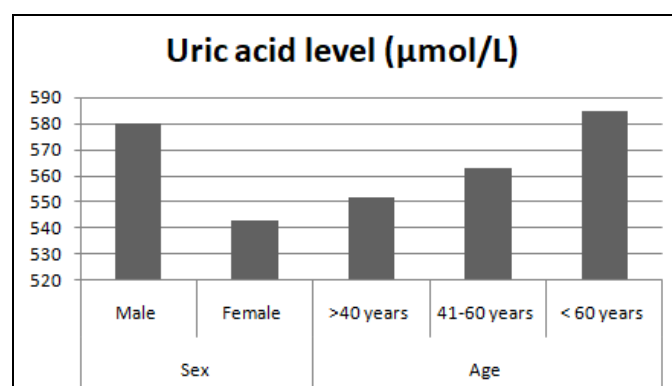


FIG. 5: DISTRIBUTION OF HYPERURICEMIC SUBJECTS ACCORDING TO SEX AND AGE

Pearson Correlation between Serum Uric Acid Level and Iron Markers in Hyperuricemic Patients:

The Pearson correlation between serum uric acid and serum Iron level ($r=0.52$) indicates a positive correlation. The Pearson correlation between serum uric acid and ferritin level ($r=0.46$) indicates a positive correlation. The Pearson correlation between serum uric acid and transferrin level ($r=0.23$) indicates a positive correlation. The Pearson correlation between serum uric acid and transferrin saturation ($r=0.56$) indicates a positive correlation.

The Pearson correlation between serum uric acid and hemoglobin ($r=0.21$) indicates a positive correlation. The Pearson correlation between serum uric acid and TIBC ($r=0.04$) indicates a positive correlation in **Table 1**.

TABLE 1: PEARSON CORRELATION BETWEEN SERUM URIC ACID LEVEL AND IRON MARKERS IN HYPERURICEMIC PATIENTS

Variable	Pearson correlation (r)
Serum Iron level ($\mu\text{mol/l}$)	0.52
Ferritin (ng/ml)	0.46
Transferrin (g/l)	0.23
Transferrin saturation (%)	0.56
Hemoglobin (g/dl)	0.21
TIBC ($\mu\text{mol/l}$)	0.04

DISCUSSION: Serum ferritin is the storage form of iron in most body organs *e.g.*, liver, pancreas, spleen, bone marrow, heart, and kidney. Physiologically, blood serum in humans contains a small quantity of ferritin⁷. Iron deposits have been reported to be present in patients with rheumatoid arthritis but not in those with other joint pathologies⁸. Previous studies in rodents have also shown an improvement in joint-related inflammation following the removal of iron by chelation treatment⁶⁻⁹. Moreover, maintaining the low serum iron level in gout patients by phlebotomy procedure has shown a significant decline in the incidence of gout flairs¹⁰.

Dietary habits play a major role in maintaining optimum serum iron levels. In humans, plant and animal sources provide non-heme and heme iron, respectively. It is interesting to know that people who consume a purine-rich diet of animal origin have shown an increased frequency of gout attack compared to patients who consume purine-rich foods from plant origin.

In Saudi Arabia, people rely more on the non-vegetarian diet compared to vegetarian food, so there is always an increased possibility of recurrence of gout flairs. Based on these observations, the present study was conducted to evaluate the association between serum ferritin, uric acid, and iron overload in Saudi patients¹¹.

The results indicated that hyperuricemia increase with advancing age and higher in males than females, which are consistent with many previous studies^{12,13,14}.

As discussed, iron overload may be a causative agent for gouty inflammation by establishing complexes with monosodium urate (MSU) crystals, provoking oxidative stress via the generation of reactive oxygen species, which contribute to granulocyte and complement activation. Uric acid scavenges free radicals of singlet oxygen and oxo-heme oxidant radicals¹⁵. So, it has been postulated that urate may decline the iron-catalyzed oxidative stress by acting as a metal ion chelator. Urate is proposed to reduce iron-catalyzed oxidative stress by acting as a metal chelator exposure of iron to the xanthine oxidase, which is the main enzyme source of xanthine oxidase and subsequent urate production^{16, 17}. This may explain a positive correlation between serum iron and serum urate levels. Previous studies have explained increase iron overload has a direct relationship in inclining in the serum urate level in both humans and rodents^{18, 19}. In fact, elevated urate level in serum is sometimes used as an indicator to screen for iron overload¹. Our results showed a positive correlation between iron levels and urate levels ($r=0.52$) with a significant difference between iron levels between patients with hyperuricemia and patients without hyperuricemia.

In another study on 9726 American patients, Ghio *et al.*, found a positive correlation between serum uric acid and serum ferritin¹. Additionally, Flais *et al.*, showed that hyperuricemia was associated with an increase in ferritin in a sample of 738 French patients with hemochromatosis²⁰. Mainous *et al.*, reached a similar conclusion that elevated levels of serum uric acid levels are associated with elevated levels of serum ferritin, which might serve as a risk stratification variable for the presence of iron overload¹⁹. Also, in China, Zhang *et al.*, conducted a 3-years cohort study on Chinese employees and found that high serum ferritin levels increase the risk of hyperuricemia²¹.

Transferrin is the iron transporter that transports iron into cells through binding to transferrin receptor (TFR)²². The results of our study indicated that transferrin as a marker for an iron load is positively correlated with uric acid levels in patients with hyperuricemia. The results showed a statistically significant difference in the ferritin level between hyperuricemia and non-hyperuricemic patients ($p>0.05$) and positive

correlation between the uric acid level and transferrin level in hyperuricemic patients ($r=0.46$). This result is consistent with the results of several previous studies; the results of national health and nutrition examination survey III included 4794 males and 4932 females aged 20 or older in good health and showed a positive correlation between uric acid levels and ferritin in serum, in which the effect was independent of the effect of age, gender, body mass index, and alcohol consumption¹. Additionally, hemoglobin level was found to be significantly elevated in patients with hyperuricemia than patients with normal uric acid levels. This result is consistent with the findings of the previous study²³.

The underlying mechanism for the effects of serum ferritin, transferrin, and hemoglobin on serum uric acid is not fully elucidated. Ferritin can convert Fe^{2+} to Fe^{3+} , owing to its high iron-binding capacity and ferroxidase activity. The iron is stored in ferritin as a compact, safe way to prevent the toxic effects of iron and make iron available when necessary; therefore, serum ferritin is widely used to evaluate iron level and status in clinical practice²¹. The relationship of serum ferritin, the hemoglobin with hyperuricemia, could be a response to oxidative stress linked with the visceral toxicity of excess non-transferrin bound iron *via* the antioxidant properties of serum uric acid¹¹.

In our study, patients with elevated C-reactive protein (CRP) were excluded. So, the association between ferritin level and serum uric acid was independent of CRP, suggesting that the relationship is not due to an elevation of ferritin in inflammation and consistent with the direct role of iron metabolism in the control of serum uric acid and gout. This is supported by the previous report of an association of transferrin receptor in gout¹¹.

This is the first study conducted to explore the relationship between serum uric acid level and iron markers in relation to gout in Saudi patients. The study included both hyperuricemia and non-hyperuricemic patients from different age groups. However, an effect of smoking, physical activity and dietary intake not studies that may act as a confounding factor. Moreover, the small number of study subjects limits the generalizability of the results.

CONCLUSION: In conclusion, the findings of this study demonstrate a positive correlation between serum uric acid and iron markers (serum ferritin, transferrin, and hemoglobin) in Saudi patients. Undiagnosed hemochromatosis or iron overload should be considered as a possibility when there are elevated uric acid levels even in the absence of related symptoms. Further large scale studies are needed to confirm these findings and to elucidate the underlying mechanisms. Additionally, studies to determine the effect of lowering serum iron overload in improving hyperuricemia and thereby reducing the risk of gout are required. The clinician should consider further tests to rule out iron overload in cases with hyperuricemia.

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CONFLICTS OF INTEREST: Declared none.

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