



Original Article



Serum Electrolytes and Their Combined Effect on Hyperuricemia among Type 2 Diabetic Patients

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ABSTRACT

Hyperuricemia (HU) is a metabolic and kidney dysfunction that is rapidly prevailing. To compare the diabetic, gender, and age-based response of magnesium and potassium in patients with diabetes mellitus (DM) type 2. **Objectives:** To compare the diabetic, gender, and age-based response of magnesium and potassium in patients with diabetes mellitus (DM) type 2. **Methods:** It was a randomized controlled trial (single-blinded) conducted on 290 patients. Four groups were formed: T1 (control), T2 (Magnesium), T3 (Potassium), and T4 (Magnesium + Potassium). Supplements were given for a period of two months. Blood samples from subjects were taken before (phase I) and after (phase II) the supplements. Unpaired t-test and multivariate Analysis of Variance (MANOVA) were applied. **Results:** Among 290 participants, 195 were female (67.2%) and 95 male (32.7%), with 159 (54.8%) of all participants in the age range of 46-65 years. The mean uric acid levels dropped from 5.5 mg/dL to 4.6 mg/dL after medication intervention. Significant differences in BSF/R, HbA1c, and uric acid levels were reported between phase I and phase II; p-values <0.001, 0.0025, and 0.04, respectively. MANOVA determined that T3 was highly significant with respect to gender (0.005) and T4 with respect to age (0.01). While the control group showed the largest absolute drop in uric acid, potassium supplementation (T3) demonstrated a consistent and statistically significant reduction relative to baseline and across gender groups. **Conclusions:** Potassium substantially plays an effective role in lowering the BSF/R and uric acid levels of T2DM patients and is controlled by gender.

INTRODUCTION

Diabetes mellitus type 2 is a complex metabolic condition categorized by elevated levels of blood sugar and changes in carbohydrates, lipids, and protein metabolism, primarily due to insulin resistance (IR). T2DM is a prolonged disease that affects adults and can cause symptomatic hyperglycemia, which may be life-threatening. Insulin deficiency, either complete or partial, also disrupts the balance of various minerals and electrolytes. These minerals have an essential role in maintaining the body's

electrical gradients, acid-base stability, nerve signaling, blood clotting, and muscle function [1]. In 2011, T2DM was identified in 366 million individuals. Diabetic complications can result in disability and decrease quality of life. Diabetes increases the number of microvascular and macrovascular complications. T2DM is primarily associated with cardiovascular disease (CVD), kidney diseases and is a major cause of mortality [2, 3]. By 2040, it is estimated that T2DM, a significant lifestyle disease, will affect over 640



million adults worldwide, posing a global burden [4]. Research evidence suggests a direct relationship between serum uric acid (SUA) levels and the development of diabetes. Obesity and diet are well-known risk factors for this association. Hyperuricemia promotes insulin resistance partly through inhibition of endothelial function. Approximately 17% more people are at risk of developing diabetes for every SUA increment of 59.5 mm/L [5]. In addition to DM, CVD, and CKD, HU is involved in the origin and progression of various chronic diseases, commonly associated with gout [6]. Uric acid and metabolic diseases are closely related. To maintain optimal insulin sensitivity and glucose tolerance, uric acid levels should be monitored and managed [7]. Data from epidemiological studies show roughly 21.4% of adult's experience hyperuricemia, while prevalence rates in several Asian countries range from 13% to 25.8% [6, 7]. Those with diabetes may experience both hyper- and hypo-electrolyte levels due to electrolyte imbalances [8-10]. Hyperuricemia is characterized by serum urate concentrations above 400 μM . Magnesium (Mg^{2+}) regulates excitability in the central nervous system through ion channel conductivity, and significant amounts are lost during food processing [11]. Mg^{2+} is one of the body's fourth most abundant positive ions and is involved in over 300 enzymatic reactions [12]. Potassium (K^+) is abundant in saliva, and its concentration is regulated by cellular transporters in the salivary duct. Although the mechanisms regulating salivary creatinine and uric acid are not fully understood, increased plasma UA and creatinine may facilitate their diffusion through cell membranes or intercellular junctions [13].

This study aims to evaluate the role of magnesium and potassium in regulating uric acid levels in type 2 diabetic patients and improving their quality of life.

METHODS

A randomized controlled trial (single-blinded) was conducted for nine months from September 2022 to May 2023 on the use of supplements of magnesium and potassium and their combined effect on hyperuricemia of diabetic patients. The study setting was Lahore Garrison University (LGU) (RCT trial registration: NCT04642313). Each participant received the assigned intervention (magnesium, potassium, or their combination) for a duration of 2 months. Participants were randomly assigned to one of the four intervention groups (T1-T4) using a computer-generated simple randomization sequence with equal allocation. The trial was single-blinded: participants were unaware of their group allocation, and outcome assessors analyzing blood samples were blinded, while investigators administering the supplements were aware

of group assignments." Blood samples of 290 subjects were collected from Akhuwat Medical Services, Lahore, with written consent. All diabetic patients of both genders and an age range of 26-85 years were included in the study. Individuals with the following condition(s) were not included: gestational diabetes, diabetic nephropathy, and psychiatric illness. To test the effects of potassium and magnesium supplements on hyperuricemia in T2DM patients, four groups were formed. Group I (T1) called as placebo group was administered with inert placebo capsule containing starch (250mgx2); Group II (T2), magnesium group, was provided with magnesium in form of Ostin (250mgx2); Group III (T3) received potassium supplements in form of Paravit (250mgx2); and Group IV (T4) received both magnesium and potassium through Bionta administration (250mgx2). Samples were taken before the intervention of supplements (Phase I) and after 60 days of intervention (Phase II). Serum uric acid was measured by the uricase-peroxidase method, blood glucose by the glucose oxidase-peroxidase method, and HbA1c by HPLC, using standard protocols with internal quality control. Statistical analysis was performed using IBM SPSS® version 26.0. Ethical Approval was taken from LGU.

RESULTS

Among 290 participants, 195 were female (67.2%) and 95 were male (32.7%), with 159 (54.8%) of all participants in the age range of 46-65 years. The mean uric acid levels dropped from 5.5 mg/dL to 4.6 mg/dL after the medication intervention. A significant p-value <0.001 shows that there are significant differences in the BSF/R (fasting blood sugar, random blood sugar) of subjects before and after the medication intervention. The R-squared value implies that 88.2% of the significant change observed in BSF/R values during Phase II is due to the medication intervention. Moreover, the T3 group has the highest drop in BSF/R levels, i.e., by 41 units. Further, the significant p-value of 0.0025<0.05 highlights that the variance between phase I and phase II HbA1C levels was due to the intervention medication. Moreover, the R-squared value indicates that 70% of this significant variance was affected by the supplements. HbA1c levels drop substantially in the T4 group, i.e., by 1.3 units (Table 1).

Table 1: Unpaired t-Test for BSF/R Levels and HbA1C Levels

Variables	Phase I	Phase II	p-Value	R-Squared Value
BSF/R Levels				
T1	160.6 ± 67.12	134.6 ± 27.1	<0.001	0.8812
T2	179.6 ± 80.96	138.9 ± 32.29		
T3	186.6 ± 88.66	137.9 ± 32.6		
T4	185.5 ± 83.96	146.5 ± 58.22		
Overall	178.4 ± 81.04	139.5 ± 39.57		

HbA1C Levels				
T1	7.816 ± 2.115	6.783 ± 1.385	0.0025	0.7003
T2	6.881 ± 1.711	6.492 ± 1.145		
T3	7.965 ± 2.079	6.777 ± 1.448		
T4	8.244 ± 2.155	6.968 ± 1.458		
Overall	7.72 ± 2.075	6.705 ± 1.3		

The differences between phase I and phase II uric acid levels are statistically significant ($0.04 < 0.05$). The significant differences are due to the supplementation intervention, which is responsible for 40% of the differences. The highest drop is observed in the T3 group, i.e., by 0.9 units in uric acid levels (Table 2).

Table 2: Unpaired t-Test for Uric Acid Levels

Variables	Phase I	Phase II	p-Value	R-Squared Value
Uric Acid Levels				
T1	6.718 ± 1.804	4.2 ± 1.445	<0.001	0.8812
T2	5.216 ± 0.9887	4.724 ± 1.427		
T3	5.443 ± 1.083	4.520 ± 1.362		
T4	4.433 ± 1.313	4.514 ± 1.082		
Overall	5.538 ± 1.644	4.641 ± 1.339		

To compare the gender and age-based response of the medication intervention on hyperuricemia in T2DM patients, MANOVA (Multivariate Analysis of Variance) was applied on the uric acid levels for each group (T1, T2, T3, T4). The data was adjusted for normality. The homogeneity of variances in uric acid levels across different categories of gender and age group is validated by the insignificant p-values for Levene's Test of Equality of Error Variances for all the intervention groups. i.e. 0.595 (T1), 0.136 (T2), 0.652 (T3), and 0.709 (T4). The Multivariate Test table 4 indicates significant differences in uric acid levels pre- and post-medication intervention with respect to gender, age, and the combined effect of gender and age. The results manifest that in the control group, the uric acid levels are significantly affected by whether the subject is male or female ($0.01 < 0.05$). Similarly, when only K⁺ is given, uric acid levels deviate significantly with respect to gender ($0.005 < 0.05$). However, when Mg²⁺ and K⁺ are ingested together, age will largely affect the uric acid balance (Table 3).

Table 3: Multivariate Test Results for Age, Gender, and Combined Effect

Intervention Groups	Multivariate Testa, Wilk's Lambda P-Values		
	Age	Gender	Age * Gender
T1	0.519	0.01	0.599
T2	0.099	0.407	0.153
T3	0.242	0.005	0.268
T4	<0.001	0.193	0.191

The study indicates the shift in the proportions of males and females with low, normal, and high uric acid levels after receiving the medical intervention. There is an increase in

the frequency of both male (by 7.4%) and female (by 21.5%) with normal uric acid after the treatment. Whereas, drastic drops are observed in the high uric acid of male (by 13.7%) and female (by 14.3%) (Table 4).

Table 4: Cross Tabulations Between Uric Acid Levels, Age, and Weight

Uric Acid Levels		Phase I, n (%)	Phase II, n (%)
Male (n=95)	Low	0	6 (6.3%)
	Normal	71 (74.7%)	78 (82.1%)
	High	24 (25.2%)	11 (11.5%)
Female (n=195)	Low	0	4 (2.0%)
	Normal	125 (64.1%)	167 (85.6%)
	High	70 (35.8%)	24 (21.5%)

Cutoff values for uric acid categories: Low (<4.0 mg/dL), Normal (4.0–6.0 mg/dL), High (>6.0 mg/dL)

DISCUSSION

The current study is a trial-based investigation into the effects of serum electrolytes' administration on hyperuricemia regulation, which poses a grave danger in escalating T2DM-associated hormones. This is evident by a study which stated that among the various investigative variables in T2DM patients, hyperuricemia causes the worst diabetic outcomes if left unattended [14]. The reason for reporting the values of BSF/R and HbA1C along with uric acid levels lies in the findings of a study that for each 0.1mmol/l increase in serum uric acid, the risk of diabetic complications increased by 28% [15]. The results in this study further add that the medication intervention not only combats hyperuricemia but also manages diabetes. The increased levels of serum magnesium reduce the serum uric acid levels, as the odds of the prevalence of HU were decreased by 0.65 times [6]. This supports our general idea of the study, where Mg administration reduced uric acid levels along with levels of BSF/R and HbA1C. In research on a predictive model for hyperuricemia among T2DM patients, sex was included among the risk factors for hyperuricemia as reported by LASSO regression analysis [16]. This study also entails that the effect of K supplementation in reducing hyperuricemia is controlled by gender. The control group (T1) exhibited a larger absolute reduction in uric acid compared to potassium alone, which suggests that the role of potassium may be less direct than initially assumed. The apparent benefit may therefore be influenced by baseline variation or unmeasured confounders, and this should be interpreted with caution. This study is the first of its kind that explores the effectiveness of Mg, K, and their combined effect on hyperuricemia in managing T2DM as suggested in a review [17]. Previous studies regarding this topic have explored hyperuricemia in predicting the risk of T2DM, hypertension, and CVD. A study concludes that

serum uric acid levels strongly varied with hyperinsulinemia and plasma glucose levels in female. This supports our gender-based frequency distribution findings of the drops in uric acid levels after the intervention, where more female had reduced serum uric acid levels and ultimately reduced glucose levels. The present study showed a higher baseline prevalence of hyperuricemia in females (35.8%), several large-scale studies have reported the opposite trend, with higher prevalence in males (up to 69.55%) [18–20]. This apparent contradiction may reflect differences in study population, dietary patterns, or regional factors. This study highlights that more females had hyperuricemia (35.8%) before the medication trial, whereas other studies declare that hyperuricemia was abundant in males (69.55%) [18–20]. Taken together, these findings suggest possible sex-specific responses to electrolyte supplementation that merit further investigation in larger and more diverse populations. This study had some limitations, including a relatively small sample size, short trial duration, and lack of detailed control for dietary intake, lifestyle factors, and electrolyte dosage levels. These may have influenced both uric acid and glycemic outcomes. The potassium dose used was modest and selected for safety; stronger reductions in serum uric acid may require higher therapeutic doses. Future studies should evaluate dose-response effects.

CONCLUSIONS

Potassium supplementation was associated with reductions in BSF/R and modest decreases in uric acid among T2DM patients, while combined potassium and magnesium showed age-related effects. However, since the control group showed a greater uric acid decline than the intervention groups, these findings should be interpreted cautiously. Larger, well-controlled studies are required to clarify whether potassium has a specific role in uric acid regulation in T2DM.

Authors Contribution

Conceptualization: NB

Methodology: NB

Formal analysis: NB, SH, RHU

Writing review and editing: UR, SK, NI, TAF

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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