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Original Article

Investigation of Serum Uric Acid Levels in Individuals Eating Different Diets

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Abstract

Background: Reducing uric acid (UA) levels can provide some improvements in terms of the development risk and course of various diseases. Early diagnosis and treatment of UA elevation have become an important research area in recent years.

Objectives: The present study aimed to investigate the relationship between diets and the change in serum UA levels after diets with different carbohydrate, and fat ratios were applied in male and female patients with or without high serum UA levels.

Methods: In the study, three different diets were applied, including a low-carbohydrate diet, a low-fat diet, and a diet low in both carbohydrates and fat. The research was performed with a total of 41 patients (10 males and 31 females) who were referred to the diet polyclinic. Diet programs containing different carbohydrate and fat ratios were applied to the patients. The UA parameters of the participants were evaluated retrospectively. Afterward, pre-diet and post-diet serum UA levels were measured, and the results were compared statistically.

Results: Following diet programs, there was a significant decrease in both serum UA levels and weight loss in patients. No significant difference was found between the diets applied in terms of reducing serum UA levels. Further, no significant correlation was observed between serum UA levels and diet duration. However, in the correlation graph, there was a more pronounced reduction trend in serum UA levels with an increase in the diet period. No significant correlation was found between weight values and duration of diet. Finally, the difference between UA levels and weight changes was statistically significant ($P<0.001$).

Conclusion: In addition to examinations for various diseases, adding UA levels to the test panel in routine biochemistry screenings and evaluating the results together with clinical findings and taking necessary precautions in a timely manner are of critical importance for public health.

Keywords: Uric acid, Serum, Diet

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Background

Uric acid (UA), which is formed as a result of the breakdown of nucleic acids (DNA and RNA) and adenosine 5'-triphosphate (ATP), is the end product of purine metabolism. The renal transport of UA is in the form of glomerular filtration, presecretory reabsorption, secretion, and post-secretory reabsorption. The kidneys are responsible for most of the daily excretion of UA. If there is a problem in the excretion of UA by the renal routes, UA may crystallize and cause toxicity in the tissues (1,2). Hyperuricemia is defined as a serum UA level above 7.0 mg/dL in men and 6.0 mg/dL in women (3).

The degradation of purine nucleotides takes place mainly in the liver. Adenosine monophosphate (AMP) is converted to inosine monophosphate (IMP) by AMP deaminase or is broken down into inosine via adenosine by the 5'-nucleotidase enzyme. Adenosine deaminase is the enzyme that converts adenosine to inosine. IMP is converted to inosine by 5'-nucleotidase. Guanosine monophosphate (GMP) also forms guanosine by dephosphorylation with the 5'-nucleotidase enzyme. Inosine and guanosine are converted to hypoxanthine and guanine by the purine nucleoside phosphorylase, respectively. The resulting hypoxanthine is converted to xanthine by xanthine oxidase. Guanine is deaminated by the enzyme guanase and forms xanthine. The AMP and GMP degradation pathways intersect at this point. Xanthine is oxidized by xanthine oxidase and converted to UA to form the end product, namely, UA. Xanthine oxidase is responsible for the oxidation of purine catabolism from hypoxanthine to xanthine and from xanthine to UA. Humans and prehuman do not have an active uricase, thus UA cannot be converted to the more soluble forms of allantoin, urea, or ammonia, and is excreted in the urine

as UA (Figure 1) (4-10).

UA in the body originates from endogenous (formed by the transformation of nucleic acids of tissues such as the liver, muscle, small intestines, kidney, and vascular endothelium) and exogenous (formed mainly by the consumption of purines in animal foods). Although UA is an effective means of removing nitrogen, it is sparingly soluble in biological fluids and has a pKa of 5.8 at physiological pH. It is distributed as sodium urate in extracellular fluids and is cleared from plasma by glomerular filtration. Urate concentration is determined by the efficiency of purine metabolism and renal clearance. In addition to the effect of daily diet on purine metabolism, genetic factors have an effect as well. UA is poorly soluble in aqueous media, and its constant presence in the serum at high levels causes it to be deposited in soft tissues as urate crystals. UA must be continuously excreted to prevent toxic accumulation. Human tissues have an extremely limited ability to metabolize urate and must be eliminated by the intestines and kidneys to maintain homeostasis. The production and catabolism of purines are relatively constant between 300 and 400 mg daily. Although the kidney eliminates 2/3 of UA, it ensures the elimination of 1/3 of UA in the gastrointestinal tract (4,10,11)

In normal and non-diabetic individuals, UA is completely filtered from the glomerulus and almost completely reabsorbed in the S1 segment of the proximal tubule. This is followed by tubular secretion in the S2 segment of the proximal tubule. Post-secretion reabsorption occurs predominantly in the last portion of the proximal tubule, and 10% of the filtered UA appears in the urine (4).

UA is one of the most important endogenous antioxidants that scavenges free radicals in the body. UA contributes to approximately 60% of free radical scavenging activity in humans. In addition to having an effective radical scavenging effect, UA may also have deleterious effects on the endothelium through leukocyte activation since it stimulates granulocyte adhesion to the endothelium and the release of peroxide-superoxide free radicals at high concentrations. Indeed, a close relationship has been observed between high serum UA levels and circulating inflammatory markers. When serum UA is at normal levels, it clears toxic reactants and protects the tissue against oxidative stress (OS); however, excessive increases in serum UA levels may trigger some pathological processes (10,12-16).

It is known that UA clears toxic reactants at normal levels and is protective against OS. However, high levels of UA have also been found to have many harmful biological properties. UA sometimes plays a role in the pathogenesis of various diseases such as hypertension, heart diseases, diabetes, and metabolic syndrome by acting as a prooxidant. UA stimulates both vascular smooth muscle cell proliferation and the release of chemotactic and inflammatory substances, causes monocyte chemotaxis, inhibits endothelial cell division and migration, causes OS in adipocytes, and leads to the weakening of adiponectin secretion (17,18).

UA has been the focus of research not only because of its role in OS but also because of its association with various inflammatory diseases. A wealth of evidence suggests that elevated UA levels are strongly associated with the occurrence and development of atherosclerosis. Although previous studies have investigated the inflammatory effects of urate, they have only focused on the effects of crystalline UA. However, recent studies have shown that soluble UA has many pro-inflammatory and pro-oxidant effects. Soluble UA, an antioxidant, reacts with the free radical superoxide anion to form allantoin, thus reducing the effectiveness of superoxide and having a protective effect in vascular inflammation and dysfunction (9,15,19-24).

In glucose metabolism, ATP depletion and excessive phosphorylation are prevented by a feedback system. Fructose is directed by ongoing reactions either to glucose formation by gluconeogenesis or to *de novo* triglyceride production. There is no rate-limiting enzyme during the conversion of fructose to fructose-1 phosphate, thus fructose-derived intermediate metabolites are rapidly included in the glycolysis pathway and used in glycerol and fatty acid synthesis. There is no restrictive mechanism to prevent ATP depletion, and UA synthesis increases through the resulting AMPs, leading to the production of lactic acid and UA (Figure 2) (20,25-29).

Considering that UA is the final breakdown product of

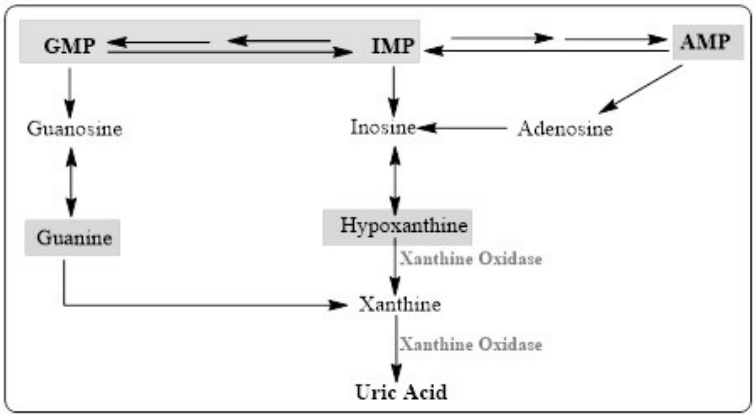

Figure 1. UA Formation. Note. GMP: Guanosine monophosphate; IMP: Inosine monophosphate; AMP: Adenosine monophosphate

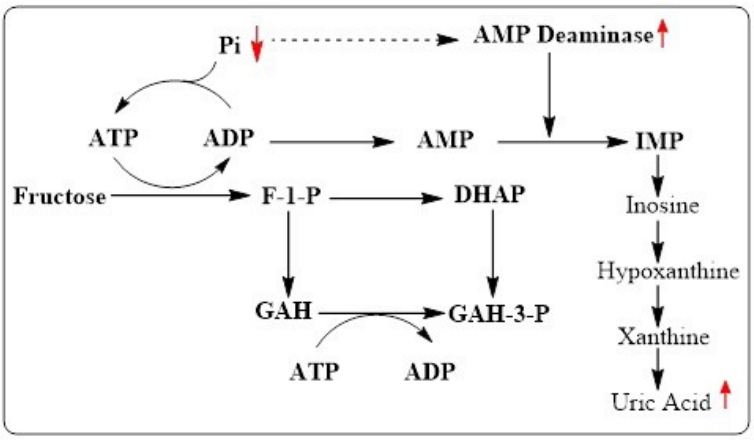

Figure 2. Fructose Increases UA Production. *Note*. UA: Uric acid; GAH: Glyceraldehyde; DHAP: Dihydroxyacetone phosphate; ATP: Adenosine triphosphate; ADP: Adenosine diphosphate; IMP: Inosine monophosphate; AMP: Adenosine monophosphate

purine metabolism, excessive intake of purine-rich foods increases serum UA levels. Although high consumption of meat and seafood significantly increases serum UA levels, this risk is relatively less in purine-rich vegetables. The reason for this is uncertain, but it may be that the fiber in vegetables reduces the absorption of purines. The bioavailability rates of purines in different foods are different. The bioavailability of adenine is higher than guanine taken with food, indicating that the strict restriction of purine intake is not practical. Studies conducted on populations that extensively use meat and alcohol in their menus while consuming extremely little vegetables have shown that UA levels are high. These menus are thought to disrupt the UA homeostatic balance; first, they provide a source of large proportions of exogenous purulent, which is converted to UA at the end of the metabolism of meat and meat products, and promote the formation of a high amount of fat, which is ketogenic due to little or no balancing carbohydrates. In addition, the lactate load increases as a result of the metabolism of consumed alcohol. Ketone bodies and lactate contribute to hyperuricemia by reducing the renal excretion of UA. In addition to the lactate load among alcoholic beverages, beer contains a high amount of purine guanosine, which can increase UA production (30-34).

Purine, which is formed as a result of the breakdown of nucleoprotein, which is the molecular unity formed by proteins with nucleic acids, is also a natural compound found in the blood. UA is the end product of purine metabolism. In simpler terms, the waste formed after digesting purine-rich foods is called UA. Although one-third of the UA emerging from the food digested by the stomach and intestines is digested by the gastrointestinal tract and excreted through the feces, the remaining two-thirds are excreted through the excretory system.

It has been explained that UA value increases with a decrease in high-density lipoprotein (HDL) cholesterol values. However, as very low-density lipoprotein cholesterol and triglyceride levels increase, UA values increase as well (35). In another study, no relationship was found between UA and lipid levels, but in subgroup analyses, triglyceride levels increased, while HDL cholesterol levels represented a decrease (36).

Materials and Methods

Place of Research

The research was performed by making a random selection among the people who applied to the State Hospital in the Kağızman District of Kars, located in the Eastern Anatolia Region, within 6 months, adhering to the principle of voluntariness.

Population and Sample of the Research

Patients in Kars province, Kağızman district applied to Kağızman State Hospital. The study was conducted on male and female patients who applied to the Internal Diseases Polyclinic of Kars Kağızman State Hospital and were referred to the diet polyclinic.

The diet to be applied to the patients was calculated using the Harris-Benedict formula after the ideal body mass index (BMI) reference intervals for the patients' age. Diets were applied to the patients by changing the carbohydrate, protein, and fat ratios.

The exclusion criteria of the study were individuals under the age of 30, pregnant women, liver patients, those with active malignancies, and those with a history of stroke.

The number of people between the working groups was not the same as the work schedule was limited by the institution where permission was taken, and the study was conducted retrospectively.

In the study, three different diets containing different carbohydrate and fat ratios (a low-carbohydrate diet, a low-fat diet, and a diet low in both carbohydrates and fat) were applied to the patients.

Age was considered as the limiting factor in the study. The study was performed with 41 patients aged between 18 and 65 years. Although the mean age of the patients was 45 ± 10.8, 10 (24.4%) of the patients included in the study were males and the remaining 31 (75.6%) were female.

The changes in serum UA levels were examined after applying 3 different diets to the patients in the study.

These groups are organized as follows:

1. Group: The group consisted of 14 patients who were fed with a diet low in carbohydrates [10 (71.4%) female and 4 (28.6%) male patients].
2. Group: It included 7 people in total who were fed with a low-fat diet [5 (71.4%) female and 2 (28.6%) male patients].
3. Group: This group contained a total of 20 patients who were fed with a diet low in carbohydrates and fat [16 (80%) female and 4 (20%) male patients].

The amount of UA was measured spectrophotometrically with the kit obtained from Roche.

In the research, the sample was chosen statistically by using the Statistical Package for Social Sciences (SPSS) applied scientific research method.

Data Collection Method of the Research

After applying to the internal medicine outpatient clinic, the purpose and method of the research were explained by interviewing the individuals who were referred to the diet outpatient clinic, and the study was started with the accepted participants. Different diet programs were applied after informing individuals that they were included in the study.

Analysis of Data

Laboratory results were uploaded to SPSS, version 20. Descriptive statistics for categorical variables were expressed as means (mean), numbers (n), and percentages (%). The chi-square (χ^2) test was used to determine the relationship between categorical variables. Seroprevalence values were presented with a 95% confidence interval (95% CA). The statistical significance level was taken as 5% in the calculations, and $P<0.05$ was considered significant.

Results

According to the results of the study, the mean serum UA levels were 4.8 ± 1.7 and 4.7 ± 1.7 in the first group before and after the diet, respectively. While its levels were 5.3 ± 1.2 and 5.0 ± 1.1 at the beginning and after the diet, respectively, in the second group. In the third group (the patient group), the mean serum UA levels at the beginning and after the diet were 5.5 ± 1.3 and 5.0 ± 0.9, respectively (Table 1).

Based on the data in Table 2, the difference between UA levels and weight changes was statistically significant ($P<0.001$).

However, there was no significant difference between the diets applied in our study in terms of reducing serum UA levels and weight ($P>0.05$, Table 3).

Moreover, mean serum UA levels decreased by 0.16 ± 0.97 mg/dL in group 1, and weight loss was observed at an average of 5.4 ± 3.3 kg. In group 2, mean serum UA levels decreased by 0.3 ± 0.4 mg/dL, and weight loss was 3.9 ± 1.9 kg on average. Further, mean serum UA levels decreased by 0.3 ± 0.66 mg/dL, and weight loss was 6.2 ± 2.4 kg on average in group 3.

Table 1. Mean and Standard Deviations of UA and Weight Values Before and After the Diet of the Groups Receiving Different Diets

Diet Type		Number	Mean	SD
Low carbohydrate diet	UA1	14	4.843	1.6924
	UA2	14	4.686	1.6947
	Weight 1	14	85.364	15.4997
	Weight 2	14	80.000	15.2986
Low fat diet	UA1	7	5.329	1.2459
	UA2	7	5.014	1.1216
	Weight 1	7	83.186	20.1090
	Weight 2	7	79.286	18.9873
Low carbohydrate and fat diet	UA1	20	5.370	1.2913
	UA2	20	5.065	0.9773
	Weight 1	20	92.340	15.4153
	Weight 2	20	86.055	15.1545

Note. UA: Uric acid; SD: Standard deviation; UA1: The uric acid values of the female in the group; UA2: The uric acid values of the male in the group; Weight 1: The weight of female in the group; Weight 2: The weight of male in the group.

Table 2. Statistically Significant Status of Different Diet Types

Diet Type		Number	Correlation	*P* Value
Low carbohydrate diet	UA1 and UA2	14	0.836	0.000
	Weight 1 and Weight 2	14	0.977	0.000
Low fat diet	UA1 and UA2	7	0.949	0.001
	Weight 1 and Weight 2	7	0.997	0.000
Low carbohydrate and fat diet	UA1 and UA2	20	0.864	0.000
	Weight 1 and Weight 2	20	0.987	0.000

Note. UA: Uric acid; UA1: The uric acid values of the female in the group; UA2: The uric acid values of the male in the group; Weight 1: The weight of female in the group; Weight 2: The weight of male in the group.

Table 3. Averages of UA and Weight Differences

Diet Type		Number	Mean	SD
Low carbohydrate diet	UA difference	14	0.1571	0.97010
	Weight difference	14	5.3643	3.33896
	Valid N (listwise)	14		
Low fat diet	UA difference	7	0.3143	0.39761
	Weight difference	7	3.9000	1.93046
	Valid N (listwise)	7		
Low carbohydrate and fat diet	UA difference	20	0.3050	0.66529
	Weight difference	20	6.2850	2.48792
	Valid N (listwise)	20		

Note. UA: Uric acid; SD: Standard deviation.

The correlation between UA levels and duration of diet was not significant ($P>0.05$, Figure 3). On the other hand, UA levels represented a more pronounced tendency to decrease as the duration of the diet increased in the correlation graph.

The correlation between weight values and duration of diet was not significant ($P>0.05$, Figure 4). However, in the correlation graph, there was a more significant decrease in weight levels with an increase in the duration

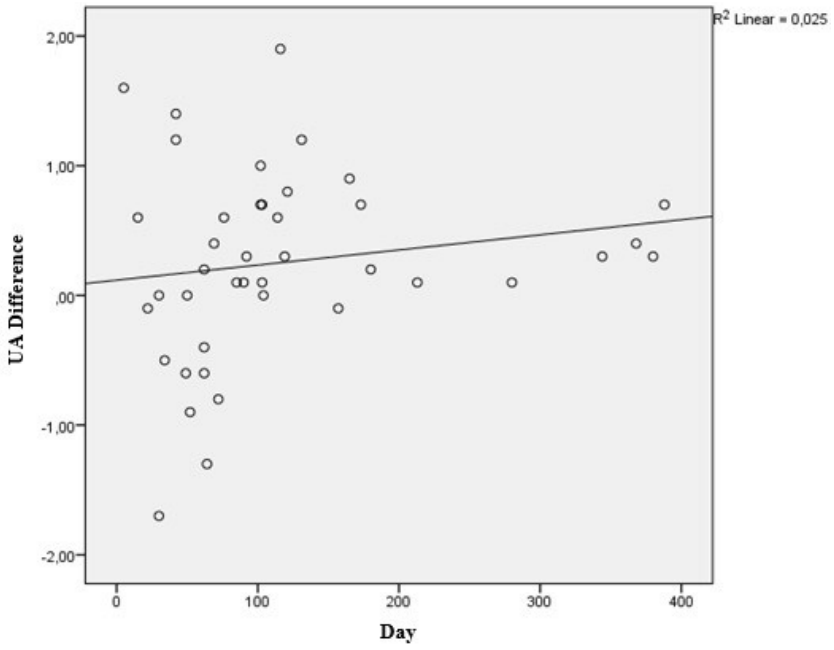

Figure 3. The Correlation Graph Between UA Levels and Duration of Diet. *Note*. UA: Uric acid

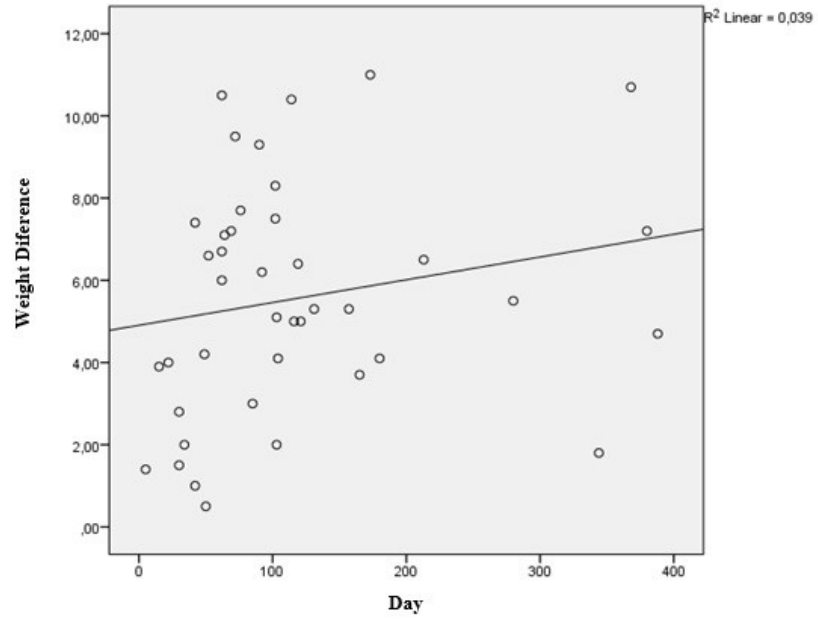

Figure 4. Correlation Graph Between Weight Values and Duration of Diet

of the diet.

No significant difference was observed between the diet groups in terms of gender distribution ($P > 0.05$) and age-height values ($P > 0.05$).

Discussion

Hyperuricemia is generally defined as blood urate concentrations higher than 7 mg/dL. UA crystallizes and precipitates when it exceeds 6.8 mg/dL. Elevated serum UA levels can be the result of excess UA production but are usually caused by the decreased excretion of UA. Many studies on the epidemiology of hyperuricemia in the world demonstrate that hyperuricemia attracts more and more attention (37-42).

UA is a positive molecule for our body at normal levels and has antioxidant and anti-inflammatory properties. However, as the positive effects of UA increase, it leaves its place to negative effects. In their study, Waring et al (43) found that increased UA levels caused the disruption of acetylcholine-induced vasodilation in the forearm in healthy people. These findings indicated that UA causes a change in nitric oxide (NO) release by decreasing NO bioavailability (44,45).

According to studies, although hyperuricemia is more commonly referred to as gout, it has also been found to be positively associated with hypertension, cardiovascular diseases, metabolic syndrome, and kidney failure (42). An independent positive correlation was found between UA

levels and the occurrence of hypertension. Hypertension can also cause microvascular disease, which can lead to local ischemia. Tissue ischemia can increase UA production, thus causing elevated serum UA levels. These mechanisms suggest that increased serum UA levels may be a consequence, not a cause, of hypertension. However, Johnson et al (46) reported that mild to moderate hyperuricemia induced by the administration of oxonic acid, a uricase inhibitor, in rats caused the development of hypertension. They further found that the development of hypertension could be prevented when elevated serum UA was treated with allopurinol or a uricosuric agent. This study supported that UA may have a causal role in the development of hypertension. Experimental studies suggest that UA may raise blood pressure by several mechanisms, including impairing endothelial function, stimulating endothelin, and activating both the renal and intracellular renin-angiotensin system. Similarly, in a prospective randomized study of 5748 healthy adolescents with 10-year follow-up, Lu et al (47) showed that high serum UA levels were positively associated with hypertension and metabolic syndrome. A recent retrospective cohort study of 3584 prehypertensive patients revealed that increased serum UA levels are a strong risk marker for the development of hypertension from a prehypertensive state. In line with the results of these studies, another large-scale meta-analysis of 55 607 subjects in 18 prospective cohort studies represented that the incidence of hypertension increased by 13% for a 1 mg/dL increase in serum UA (22,44,45,48,49).

UA is commonly associated with metabolic syndrome. The metabolic syndrome has many components that are independently mediated or can lead to kidney damage, including increased inflammation, insulin resistance, and endothelial dysfunction. In addition, a high fructose diet and hyperinsulinemia contribute to the development of hyperuricemia. In a recent prospective well-controlled study, 75 adult men were given 200 g fructose with or without allopurinol for 2 weeks. Based on the result, there were increases in both UA levels and blood pressure. However, the fact that the daily fructose amount in the diets is higher than the typical Western diets made it difficult to evaluate the results. It was reported that elevated UA levels induce insulin resistance by reducing the bioavailability of nitric oxide, which is important for insulin-stimulated glucose uptake in skeletal muscles. Considering that increased UA can induce insulin resistance, insulin can reduce renal UA excretion by stimulating urate-anion exchangers in the brush border membranes of the renal proximal tubules. A recent study evaluated the prevalence of insulin resistance and metabolic syndrome in gout patients. The results of the study demonstrated that gout patients had a higher prevalence of insulin resistance. They concluded that hyperuricemia associated with insulin resistance may be due to abdominal obesity. In another study conducted by de Miranda et al (50) on children and adolescents, it was revealed that for a 1 mg/dL increase in UA levels, there would be a 91% increase in the probability of developing insulin resistance. Although the pathophysiology between hyperuricemia and insulin resistance has not been fully determined, it is thought that hyperuricemia often increases due to the decrease in UA excretion under the influence of hyperinsulinemia (29,38,44).

Hyperuricemia may also be a risk factor for cardiovascular disease. Elevated serum UA levels detected in cardiovascular diseases may be related to the antioxidant role of UA because a high UA acid level can be a defense mechanism against atherosclerosis. On the other hand, instead of the positive effect of increased serum UA levels, it may lead to the development of cardiovascular disease by causing endothelial dysfunction. Serum UA elevation may rise as an innocent bystander as a result of cardiovascular disease. For example, kidney disease can both increase serum UA levels and promote vascular disease through the activation of the renin-angiotensin system. However, UA alone can also be vasculotoxic by triggering inflammation. In addition, UA may reduce NO bioavailability, reflecting impaired endothelial integrity, where endothelial-dependent vascular relaxation is reduced, and this contributes to the development of atherosclerosis (37,45,49).

Studies on modern monkeys and humans living on natural diets show that the mutation of the uricase enzyme only results in the elevations of serum UA in the range of 3-4 mg/dL. However, with the introduction of the Western diet, serum UA levels have increased over the past century. High serum UA levels are beginning to appear worldwide similar to the increase in the Western diet combined with the loss of uricase. Although the importance of diet in urate formation and subsequent gout exacerbations has been emphasized, a recent meta-analysis has questioned the role of purine intake in inducing hyperuricemia (39,44,45,50).

A total of 41 patients (10 females and 33 males) were included in our study. The diet to be applied to the patients was calculated using the Harris-Benedict formula after the ideal BMI reference intervals for the patients' age. Diets were applied to the patients by changing the carbohydrate and fat ratios. For a low-carbohydrate diet, carbohydrate is 45-50%, protein is 15-20%, and fat is 25%-30%. Further, for a low-fat diet, carbohydrate, protein, and fat are 55-60%, 15-20%, and 20%, respectively. Moreover, for a diet low in both carbohydrate and fat, carbohydrate is 45-55%, protein 15-20%, and fat 20-25%. Decreases in UA levels were studied after 14, 7, and 20 patients followed a low-carbohydrate, low-fat, and low-carbohydrate and low-fat diet, respectively. Based on the results of the study, although the mean serum UA level was 4.8 ± 1.7 in the group that received a low-carbohydrate diet, it was 4.7 ± 1.7 after the diet. In the patient group who received a low-fat diet, the mean serum UA level was 5.3 ± 1.2 at the beginning, whereas it was 5.0 ± 1.1 after the diet. In the last group, the patient group who received both a

low-carbohydrate and a low-fat diet, the mean serum UA level at the beginning and after the diet was 5.5 ± 1.3 and 5.0 ± 0.9, respectively. There was a significant decrease in serum UA levels after diets in all three groups ($P < 0.001$). The results also revealed that the patients who applied all three diets lost weight significantly, and both weight loss and the decrease in UA levels tended to increase with an extension in the duration of the diet.

Conclusion

Reducing UA levels may provide some improvements in terms of the development risk and course of these diseases. Early diagnosis and treatment of UA elevation have become an important research area in recent years. Therefore, in addition to the examinations for the above-mentioned diseases, it is critical for public health to add UA levels to the test panel in routine biochemistry screenings and to take the necessary measures in a timely manner by evaluating the results together with clinical findings.

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Authors' Contribution

Conceptualization: Hatice Esra Duran.
Data curation: Hatice Esra Duran.
Formal analysis: Hatice Esra Duran.
Funding acquisition: Hatice Esra Duran.
Investigation: Hatice Esra Duran.
Methodology: Hatice Esra Duran, Fatma Turğut.
Project administration: Hatice Esra Duran.
Resources: Fatma Turğut.
Software: Fatma Turğut.
Supervision: Hatice Esra Duran.
Validation: Hatice Esra Duran, Fatma Turğut.
Visualization: Hatice Esra Duran.
Writing–original draft: Hatice Esra Duran, Fatma Turğut.
Writing–review & editing: Hatice Esra Duran, Fatma Turğut.

Competing Interests

The authors declare no potential conflict of interests relevant to this article.

Ethical Approval

This study was performed with the approval of the Ethics Committee of Kafkas University Faculty of Medicine (80576354-050-99/47) and the permission of the Kars Provincial Health Directorate. It was conducted in accordance with the principles of the Declaration of Helsinki II. Informed written consent was obtained from all study subjects.

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