The effects of lowering uric acid levels using allopurinol on markers of metabolic syndrome in end-stage renal disease patients: a pilot study

Ürik asit seviyelerinin allopurinol ile azaltılmasının son dönem böbrek hastalarındaki metabolik sendrom belirleyicilerine etkisi: Pilot çalışma

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ABSTRACT

Objective: Allopurinol was administered to end-stage renal disease (ESRD) patients with elevated uric acid levels presenting with symptoms of gout and also had risk factors of metabolic syndrome. The primary aim of this pilot study was to examine the effects of lowering uric acid levels using allopurinol on lipoprotein markers of metabolic syndrome in patients.

Methods: The study was conducted using a prospective open-label protocol. End-stage renal disease patients (n=12) (mean age: 45.8±13.6 years) undergoing chronic hemodialysis were recruited through their treating physician to participate in this study. All patients had ESRD and were prescribed allopurinol (300 mg/bid) for gout over a 3-month period. Pre-allopurinol and post-allopurinol data was obtained on low-density lipoprotein (LDL) cholesterol, LDL particle number, LDL particle size, high-density lipoprotein (HDL) cholesterol, large HDL particle number, total cholesterol, triglycerides, large very-low density lipoprotein (VLDL) particle number, and uric acid. Changes in lipid values were measured using a one-sample exact Wilcoxon rank sum test.

Results: Significant changes occurred in the primary outcome measures of serum uric acid levels (-3.53 mg/dL, p=0.01), LDL cholesterol (-14.00 mg/dL, p=0.04), and triglycerides (32.67 mg/dL, p=0.01). Trends were observed in lipid markers that warrant further investigation.

Conclusion: Novel findings of our study suggest that lowering uric acid in ESRD patients may help to reduce the risk of cardiovascular disease in this population. It should be noted than an increase in triglycerides may mitigate the reduction in risk.

(Anadolu Kardiyol Derg 2009; 9: 385-9)

Key words: Hyperuricemia, metabolic syndrome, allopurinol, end-stage renal disease

ÖZET

Amaç: Hem metabolik sendrom (SDBH) riski olan, hem de gut semptomları görülen yüksek ürik asitli hastalara allopürinol verildi. Bu pilot çalışmanın ilk hedefi, hastalarda allopürinolun, metabolik sendromun lipoprotein belirleyicilerin ve ürik asit düzeylerini düşürücü etkilerini sınamaktı.

Yöntemler: Çalışma prospektif açık-zarf protokolü ile yürütüldü. Bu çalışmada yer alan kronik hemodiyalize giren SDBH olanlar (N=12) (ortalama yaş: 45.8±13.6 yaş) doktorlarının tedavisinde iyileştiler. Tümü SDBH idi ve gut hastalığı için 3 aydan fazla (300 mg/bid) allopürinol verildi. Allopürinol öncesi ve sonrası, düşük yoğunluklu lipoprotein (LDL) kolesterol, LDL partikül sayısı, LDL partikül boyutu, yüksek yoğunluklu lipoprotein (HDL) kolesterol, büyük HDL partikül sayısı, total kolesterol, trigliseridler, çok düşük yoğunluk lipoprotein (VLDL) partikül sayısı ve ürik asit verileri elde edildi. Lipit değerlerindeki değişiklikler, tam tek örneklem Wilcoxon rank-sum testi kullanarak ölçüldü.

Bulgular: Birincil sonuç için ölçülen serum ürik asit (-3.53 mg/dL, p=0.01), LDL kolestrol (-14.00 mg/dL, p=0.04) ve triglesidlerin (32.67 mg/dL, p=0.01) değerlerinde önemli değişiklikler meydana geldi. Lipit belirleyicilerinde gözlenen eğilim ileri araştırmaları gerektirdi.

Sonuç: Çalışmamızdaki yeni bulgular SDBH'da ürik asidin düşürülmesinin, bu popülasyonda kardiyovasküler hastalık riskini azaltmaya yardımcı olabileceğini düşündürmektedir. Trigliseritteki artışın, riskte azalmayı hafifletebileceğine dikkat edilmelidir. *(Anadolu Kardiyol Derg 2009; 9: 385-9)*

Anahtar kelimeler: Hiperürisemi, metabolik sendrom, allopürinol, son dönem böbrek hastalığı

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Introduction

Published research and reviews have pointed to similarities between patients with chronic renal deficiencies and those with metabolic syndrome (1, 2). Cardiovascular risk factors grouped together as metabolic syndrome (central obesity, glucose intolerance, hyperinsulinemia, dyslipidemia, and hypertension) (3), can also be found in patients with kidney disease (1). Kidney disease and metabolic syndrome also share other metabolic abnormalities such as hyperuricemia, which is defined as ≥7 mg/dL (in men) and ≥6 (in women) (2).

A correlation between hyperuricemia and components of metabolic syndrome has been reported in previously published reports (2, 4-6). Chen et al. (2) found elevated levels of serum uric acid (SUA) to be positively correlated to waist circumference, systolic blood pressure, diastolic blood pressure, and log-transformed triglycerides and negatively correlated with high-density lipoprotein (HDL) cholesterol. Using data from the Third National Health and Nutrition Examination Survey (1988-1998) Choi and Ford (4) assessed the prevalence of metabolic syndrome among those with increased SUA and found that as SUA levels increased the prevalence of metabolic syndrome also increased. In a comparison of subjects with normal SUA levels and elevated SUA levels, those with elevated SUA levels had increases in BMI, waist to hip ratio, triglyceride levels, total cholesterol/HDL ratio, lower HDL and larger ratio of metabolic syndrome to hypertension (5). Some authors have provided evidence for including elevated SUA with impaired renal clearance as a component of metabolic syndrome (6, 7).

Although study authors report associations between elevated SUA, metabolic syndrome and kidney disease, the actual mechanism is not clearly understood. However, using animal models, Nakagawa et al. (8) and Khosla et al. (9) suggest that decreasing uric acid levels using allopurinol could reverse or inhibit the development of metabolic syndrome markers, namely hypertension, serum lipid levels, triglyceride levels and increased body weight in rats. Also, study authors have reported (8, 10) allopurinol treatment improved systolic blood pressure, triglycerides, body weight, and improved hyperinsulinemia induced by a high fructose diet.

Allopurinol has also been found to improve endothelial dysfunction in patients with hypercholesterolemia (11) and in type II diabetes patients with mild hypertension (12). One retrospective study of congestive heart failure (CHF) suggested that taking long-term high dosages (300mg) of allopurinol were associated with better mortality rates than long-term low dose usage (13). A recent study also reported improved glomerular filtration rates, blood pressures and C-reactive protein levels in patients with normal renal function (14). Finally, the role of allopurinol in lowering serum cholesterol (15), lipids (16, 17) and lipoproteins (16) in patients with primary gout was examined in the 1980s and 1970s, but was not found to be significantly effective.

Research involving hyperuricemia and allopurinol has been conducted in patients with normal renal function (14) using renal deficiency as exclusionary criteria (16) with no studies published looking at SUA, allopurinol and lipids in end-stage renal disease (ESRD) patients. Secondly, recent articles by Nakagawa et al. (8) and Khosla et al. (9), using animal models, support the need for studies in humans to explore the effects of treating uric acid levels with allopurinol as a means to control markers for metabolic syndrome. Finally, uric acid has been demonstrated to have a role is dyslipidemia, but the mechanism of action has yet to be elucidated (17). Minami et al. (18), suggests that the suppression of lipid peroxidation may be a mechanism responsible for lower lipid levels found in patients that use a xanthine oxidase inhibitor such as allopurinol. Also, increases in uric acid have been postulated to cause a decrease in lipoprotein lipase and/or hepatic triglyceride lipase activity (8).

Therefore, the purpose of this pilot study was to explore effects on lipid levels, common markers of metabolic syndrome, by lowering uric acid levels in ESRD patients by means of allopurinol use.

Methods

Patients

Twelve patients (n=12) with ESRD undergoing chronic hemodialysis in the Central Texas area volunteered to participate in this pilot study. Study participants were 66% (n=8) male, 33% (n=4) female and 18 years of age and older. The primary cause of ESRD was unspecified hypertensive renal disease for five patients; type II diabetes without complications for three patients; type II diabetes with renal manifestations for one patient; complications from kidney transplantation for one patient; and other renal disorders for one patient.

All patients presented with symptoms of gout and were treated with allopurinol to lower SUA levels. Exclusion criteria included dementia, history of previous allergic reaction to allopurinol or any of its components, positive blood tests for hepatitis B and C, triglyceride levels higher than 1000 mg/dL at pretest, patients with a life expectancy of less than six months, pregnancy, malignant hypertension, or history of previous medication non-compliance. Approval was granted by the university and clinic institutional review boards. Patients meeting eligibility criteria were informed of the requirements of the study and signed informed consent statements in compliance with the Human Subjects Guidelines.

Experimental Design and Procedures

The study was conducted using a prospective open-label protocol. Patients were prescribed 300 mg PO daily for allopurinol by their treating physician and were followed prospectively for three months. Patients who were presently on medications that could be a confounding variable (statins, niacin, fibrates, fish oil, and sevelamer hydrochloride (Renalgel)) continued with their current medications levels based on physician approval during the length of the study. Additionally, all patients consumed vitamin supplements, which contained 15 mg of B_6, 12 mg of B_{12}, and 2.5 mg of folic acid. The dialysis clinics used polysulfone membranes with 95% using the Fresenius-160 dialyzer and

5% using Fresenius-180 dialyzer at a dialysate flow rate of 800 cc/min and a mean blood flow rate of 376.49 cc/min. Dialysis dose for all patients was a Kt/V range of 1.1-2.0 with a mean of 1.35. All patients ran four hour dialysis duration per unit protocol. Patients were monitored weekly during hemodialysis by a physician concerning medication compliance and supervised by a registered and licensed dietician who had experience working with ESRD patients. The dietician followed up with each patient three times a week (at time of dialysis) during the entire study period. Patients were considered compliant if their SUA levels decreased by 20% during the course of the study (19).

Data Collection

Routine laboratory work for uric acid and lipid levels was performed prior to administration of allopurinol (baseline) and at three months following a 12-hour fast for each time period. Lipid measures included low-density lipoprotein (LDL) particle number, LDL particle size, LDL-cholesterol, HDL- cholesterol, large HDL, triglycerides, total cholesterol, and large very low density lipoprotein (VLDL) particle number. Routine monthly lipid panels and medications were recorded.

Statistical Analysis

All statistical tests were performed using R version 2.7.2 software.

The outcome of interest was the difference in blood lipid and uric acid levels from baseline to the end of the three-month allopurinol supplementation period. Due to the small sample size and apparent non-normality of many of the response variables, all biological measures were tested using the one-sample exact Wilcoxon rank sum test under the null hypothesis that no change occurred over the time period. The exact test was necessary due to ties in the data that occurred from rounding. We allowed a Type I error rate of 0.05, and thus a p-value $\leq$0.05 was considered statistically significant.

The small sample size evident in this pilot study also necessitated a close examination of individual responses to allopurinol treatment. Trends were investigated to justify or reject the need for a more comprehensive study of the effects of 300 mg of allopurinol on lipid markers of metabolic syndrome. Results for some variables represent smaller sample sizes than 12 due to missing data points.

Results

The mean age of the participants was 45.8±13.6 years old. The average time spent on dialysis was 11.504 (±1.5 SD) hours per week. Table 1 displays descriptive statistics and results for the Wilcoxon rank sum test. Mean changes in LDL cholesterol (p=0.04), triglycerides (p=0.01), and uric acid (p<0.01) were statistically significant.

Although not significant, other trends in the data warrant discussion. Increases in HDL-cholesterol was observed in six (50%) of the patients (p=0.42); decreases in total cholesterol was observed with seven (58%) patients (p=0.63); six patients (50%) had decreased LDL particle number (p=0.91) and six (50%) reported an increase in LDL particle size (p=0.75). Trends were equivocal for large VLDL particle number (p=0.16), and large HDL particle number (p=0.50).

Discussion

The purpose of this pilot study was to explore the effects on some markers of metabolic syndrome, specifically lipid levels by lowering uric acid levels in ESRD patients by means of allopurinol. Mean SUA levels (mg/dL) decreased significantly in participants from baseline (-3.53 [±2.40], p<0.01) demonstrating compliance in patients using allopurinol (19). Allopurinol is used to lower uric acid levels in gout patients and this response was not surprising, but tracking these changes was a means to demon-

Table 1. Effects of allopurinol on lipid and serum uric acid levels*

Variable	N	Baseline values (Median) (Min/Max)	Posttest values (Median) (Min/Max)	Mean change (SD)	p†
LDL particle number, mg/dL	10	1323.50 (1263.50) (614-2739)	1332.10 (1281.00) (646-2637)	8.60 (217.93)	0.91
Small LDLparticle number, mg/dL	10	751.83 (695.50) (40-1476)	818.83 (710.50) (122-1590)	67.0 (295.27)	0.36
LDL-cholesterol, mg/dL	10	103.17 (101.00) (59-233)	89.17 (79.00) (65-209)	-14.00 (20.00)	0.04*
HDL-cholesterol, mg/dL	12	46.17 (40.50) (24-94)	49.33 (38.50) (21-94)	3.17 (10.55)	0.42
Triglycerides, mg/dL	12	152.50 (100.50) (29-385)	185.17 (134.50) (42-440)	32.67 (48.19)	0.01*
Total cholesterol, mg/dL	12	178.25 (174.50) (141-289)	174.50 (161.50) (126-269)	-3.75 (29.58)	0.63
LDL particle size, nm	10	21.75 (21.20) (19.9-22.8)	23.69 (21.30) (19.7-22.5)	1.94 (7.05)	0.75
Large HDL particle number, mg/dL	10	6.97 (7.00) (2.4-14.2)	9.02 (9.00) 1.3-16.5)	2.05 (5.55)	0.50
Large VLDL particle number, mg/dL	10	2.89 (1.60) (0-12.2)	4.96 (2.15) (0.7-22.4)	2.07 (4.92)	0.16
Uric acid, mg/dL	12	10.13 (9.70) (9-12.9)	6.60 (5.80) (3.8-11)	-3.53 (2.40)	0.01*

*Significance at the 0.05 level

†All P-values from exact Wilcoxon ranked-sum test

HDL – high density lipoprotein, LDL – low density lipoprotein, VLDL – very low density lipoprotein

strate compliance and to support the supposed relationship of SUA and some metabolic syndrome markers. Findings reported by Nakagawa et al. (8) and Khosla et al. (9) using animal models suggest that using allopurinol to lower SUA levels may improve risk factors for metabolic syndrome and was partially supported in our study with human participants. The findings from our pilot study are equivocal with a multifaceted effect on lipid levels that demonstrated both an increase and decrease in risk for markers of metabolic syndrome. These unexpected results of this pilot study may be related to the clinical and therapeutic complexity of patients with ESRD and diabetes, but may also be a sample size artifact.

The mean decrease in LDL cholesterol (-14.00 [±20.00], p=0.04) in combination with a non-significant trend of an increase in LDL particle size (1.94 [±7.051], p=.75) is difficult to explain (3). A significant goal of the Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of high blood cholesterol in adults (Adult Treatment Panel III) (ATP III) (3) is to lower LDL levels, but simply lowering LDL present in the serum does not present a complete picture of risk. A recent published study (20) suggests LDL particle number is independent of LDL size and LDL cholesterol. By observing a significant decrease in LDL cholesterol with a trend of increasing LDL particle number and decreasing particle size may be partially explained by the non-significant trend in large VLDL. A defect in VLDL catabolism in ESRD patients leads to a concomitant increase in small, atherogenic LDL particles (19, 21). Consequently, significant changes in LDL cholesterol and a trend of increasing LDL particle numbers could in fact by due to this VLDL defect and produce more small, dense LDL particles. Consequently, an outcome of this defect may be that controlling uric acid levels in ESRD patients will have a positive effect on LDL cholesterol, but may not be able overcome the VLDL defect.

Another statistically significant finding was an increase in mean serum triglycerides (32.67 [±48.19], p= 0.01) which is associated with an increase in risk. These findings do not support the work of previously published reports suggesting a decrease in SUA is associated with a decrease in triglyceride levels (2, 4). Although the role of uric acid in the metabolism of triglycerides remains unclear, Nakagawa et al (8) reports that uric acid has been reported to be associated with either an overproduction in triglycerides or the reduction of clearance of triglycerides. In this study allopurinol lowered uric acid but was associated with a statistically significant increase in triglyceride levels. There is an established link between uric acid and triglyceride production in primary gout (22) and since these patients had been diagnosed with gout it may have decreased the production of lipoprotein lipase (LPL) in the endothelium. It is possible that decreases in LPL activity associated with gout contributed to a development of increased triglyceride levels that was unable to be controlled through the use of allopurinol even in the presence of decreased uric acid levels. This paradoxical finding of increased triglycerides with decreased SUA levels is contradictory to studies using animal models (8, 9) and suggests the need for further research in humans.

When comparing the increase in LDL particle number and size and the increase in triglycerides in our study these findings may also be explained by the ATP-III report. LDL particle number in our study, though not significant, displayed a trend toward an increased cardiovascular risk profile with a mean increase (67.0 [±295.27], p=0.36). LPL decreases are also associated with small dense LDL particles and may also help to explain why LDL cholesterol decreased while LDL particles became smaller and denser in our patients. Secondly, small LDL particles are formed in large part as a response to an elevation of triglycerides (19) which is associated with ESRD and gout patients. Consequently, LDL particle number and size may be more of a response to the increase in triglyceride levels associated with gout rather than a change in uric acid levels. The response of triglycerides and small LDL size should cause concern, indicating an increase risk for atherogenic outcomes. But, it should be noted that our findings of the effect of allopurinol on triglycerides does not correspond well with the literature in humans without ESRD complications (15, 16, 23, 24).

Trends in non-significant variables that indicate an improved profile were observed in HDL and total cholesterol. Mean HDL-cholesterol levels increased (3.17 [±10.55], p = 0.42) in half of the patients while mean total cholesterol decreased (-3.75 [±29.58], p = 0.63) in over half (58%) of the patients. The ATP III does not give specific goals for increasing HDL, but suggests that doing so could reduce cardiovascular risk and suggests that low levels of HDL are independent predictors for coronary heart disease. Combined with the trend for decreasing total cholesterol and the aforementioned changes in LDL may suggest an improved profile for this group of ESRD patients.

Study Limitations

Some limitations were evident in this pilot study and should be addressed in future research. The small sample size was problematic in finding significance and evident trends, but was necessary for exploring the relationship between allopurinol and markers of metabolic syndrome in a small group before expanding to a larger population of study participants. A larger sample size and an addition of a control group could be used in future studies. Secondly, some patients presented with type II diabetes, which may have been a confounding variable.

Conclusions

Our study demonstrated significant changes in LDL-cholesterol with positive trends in HDL and total cholesterol would suggest the need for large cohort trials and secondary data analysis (NHANES) for the effects of uric acid on some markers of metabolic syndrome. Additional research is warranted as well to explore the observed trends in triglycerides and the relationship between LDL particle number and LDL particle size. Since allopurinol is a common drug used to treat gout in ESRD these trends provide further reason for continued

exploration of the use of allopurinol in ESRD patients. Lastly, the clinical significance of this study is that physicians may use a novel approach to control lipids in ESRD patients. Accelerated cardiovascular disease risk is common in ESRD patients, and novel approaches are necessary to decrease morbidity and mortality rates. By using allopurinol as means to control lipids, not just gout, the physician has another option in controlling markers of metabolic syndrome.

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