Determinants of Blood Uric Acid Levels in a Dyslipidemic Arab Population

Ahoud F. Al-Meshaweh, Yaqoub Jafar, Mohammad Asem, Abayomi O. Akanji

Kuwait University Faculty of Medicine, Department of Surgery, Mubarak Al-Kabeer Hospital, and Department of Pathology, Kuwait University Faculty of Medicine, Jabriya, Kuwait

Key Words
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Abstract
Objectives: The objective of this study was to explore the relationships between circulating uric acid and lipid levels and components of the metabolic syndrome (MetS) in Arab dyslipidemic patients, a group already at high coronary artery disease risk. Subjects and Methods: The medical records of 1,229 subjects (632 men, 597 women) referred for treatment of dyslipidemia and followed up for at least 12 months were reviewed. Serum levels of uric acid and lipids (total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein) and other variables in the National Cholesterol Education Program ATP III criteria definition of MetS were assessed at initial presentation and every 4–6 months, under specific lipid-lowering treatment (statins and/or fibrates), in each of the subjects. Their respective associations were explored by appropriate logistic regression techniques with control for confounding risk factors, including age, gender and body mass index. Results: 306 subjects (24.9%) of the study population were hyperuricemic; they were more likely to be men, obese and diabetic. Also the serum uric acid level (mean ± SD) was greater in men with MetS compared with men without (377.0 ± 98.0 vs. 361.6 ± 83.1 μmol/l, p < 0.05), an observation not reproduced in women. Uric acid levels had significant associations with the presence of fasting hyperglycemia, hypertension and large waist circumference (WC) in men, but only with large WC in women. With statin treatment, uric acid levels decreased by 10% within 1 year of treatment; with fibrates, uric acid levels remained unchanged or slightly increased. Conclusion: The data showed that hyperuricemia is common in dyslipidemic patients in Kuwait, where its important determinants are male sex, obesity, diabetes and statin treatment.

Introduction
The recent interest in hyperuricemia stems from its high prevalence and increasing recognition as a risk factor for coronary artery disease (CAD). The worldwide prevalence of hyperuricemia is high, with reported rates of 35.1% (men) and 8.7% (women) in the Seychelles [1], 10.6% in Thailand [2], 7.2% (men) and 0.04% (women) in England and Scotland [3], 11.2% in the USA [4] and 8.4% in Saudi Arabia [5]. The putative associations of hyperuricemia in these populations include age, gender, smok-
An accepted risk factor for CAD is the presence of the metabolic syndrome (MetS). MetS is highly prevalent worldwide being seen in 9.1% of female Kuwaiti adolescents [7], 13–31% of Turks [8] and up to 21.8% of the adult US population [9]. In at least one study from China, a link between MetS and uric acid levels has been suggested [10], an observation worthy of further investigation. Furthermore, not all dyslipidemic disorders (especially those associated with a predominant increase in low-density lipoprotein, LDL, levels) are components of MetS, and it is of interest to see how uric acid levels relate to these non-MetS lipid components, which are typically measured routinely in lipid clinic patients. Indeed, some studies have suggested that serum uric acid fell by about 4–8% in dyslipidemic patients on specific lipid-lowering medications [11, 12].

Atherosclerotic vascular diseases (especially CAD and stroke) are common in Arab countries, undoubtedly due to the high prevalence of dyslipidemia and diabetes singly or jointly as in MetS [13, 14]. It is essential to investigate how all these latter factors interact with the high prevalence of hyperuricemia in individuals who are already at high risk for CAD. Most of the reported studies on these interactions have been from Caucasian and East Asian populations [10–12], with none from Gulf Arab countries, which are currently undergoing rapid economic and social transformation. This study therefore aimed to assess: prevalence of hyperuricemia in dyslipidemic Arab patients on follow-up in a lipid clinic; associations of uric acid levels with presence of dyslipidemia and/or MetS and its components, and changes in uric acid levels with 1-year standard treatment for dyslipidemia.

**Study Design**

The study design was retrospective and cross-sectional with at least a 1-year longitudinal component. The database of the Lipid Clinic, Mubarak Al-Kabeer Hospital, Kuwait, was used. This Lipid Clinic is the only formal service for treating dyslipidemic patients in the country, and receives referrals from all the other public and private hospitals in the country. We reviewed the records of 1,229 dyslipidemic patients, comprising 632 men and 597 women aged (mean ± SD) 48.7 ± 10.5 years. These were serially presenting subjects referred to the Lipid Clinic. The patients reviewed were those who had complete clinic follow-up data for at least 12 months and had visited regularly at about 4- to 6-month intervals. All those subjects with incomplete data were excluded, as were those under specific treatment for hyperuricemia. There were only 5 patients already on allopurinol and they were not included in the study. The study was approved by the local Research Ethics Committee of the Faculty of Medicine, Kuwait University.

**Anthropometric and Laboratory Measurements**

For each patient, at first visit (baseline) and subsequent follow-up visits at 4- to 6-month intervals, overnight fasting blood samples were collected for measurements of serum levels of lipids and lipoproteins (triglycerides [TG], total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C]), apolipoproteins A and B, glucose, uric acid and standard liver and renal function indices, as well as amylase and creatine kinase. The LDL-C levels were calculated using the Friedewald formula [15], applied in all cases with serum TG <4.50 mmol/l. These laboratory measurements were made using AutoAnalyzer (Beckman-Coulter DxC, Fullerton, Calif., USA) at the Mubarak Al-Kabeer Hospital Clinical Chemistry Laboratory, with robust quality control procedures. The routine enzymatic methods used were: glucose (hexokinase), TC and HDL-C (cholesterol esterase), TG (lipase) and uric acid (uricase).

In addition, anthropometric indices of height, weight and waist (WC) and hip circumferences were measured – WC at the umbilicus, midway between the lower rib cage and the iliac crest, and hip circumference at the greatest gluteal protuberance. The body mass index (BMI) was calculated as weight (kg) divided by height squared (m²); obesity was defined as BMI ≥30 kg/m² [16]. Similarly, the presence of MetS was diagnosed according to the National Cholesterol Education Program ATP III criteria [16] requiring at least 3 of the following 5 components: abdominal obesity (WC >102 cm in men; >88 cm in women); low HDL-C (<1.00 mmol/l in men, <1.29 mmol/l in women); elevated TG (≥1.69 mmol/l); fasting hyperglycemia (glucose ≥6.1 mmol/l) and hypertension (blood pressure, BP, ≥130/85 mm Hg). Subjects were classified as hyperuricemic with serum uric acid levels ≥416 μmol/l for men and ≥358 μmol/l for women [16].

**Statistical Analysis**

Data management and analyses were done using the Statistical Package for Social Sciences version 17.0 for Windows. The respective variables were summarized using median, range and proportion where appropriate. Age, a continuous variable, was divided into two categories according to National Cholesterol Education Program ATP III criteria for the risk of ischemic heart disease [16]. Frequency distributions were used for descriptive analysis. The associations between the categorical variables were tested for significance with the χ² test. The nonparametric Mann-Whitney U test was applied to comparing TG values, while data for the other variables, including TC, HDL-C, LDL-C, glucose and uric acid were compared using 2-sample t tests. A comparison of parameters among 4 groups according to the number of risk factors for MetS was performed by analysis of variance between groups and the Scheffé test, while the changes in uric acid and lipid parameters in all treatment groups were evaluated by repeated-measures analysis of variance and Bonferroni adjustment for multiple comparisons. A p value of <0.05 was considered significant.
Results

The demographic, anthropometric and biochemical characteristics of all the subjects considered as a whole and when subdivided into hyperuricemic and normouricemic groups are given in table 1. There were a total of 1,229 subjects with complete data – 630 (51.4%) men and 599 (48.6%) women, with a mean (±SD) age of 48.7 ± 10.5 years. Of the total subjects, 294 (23.9%) had hyperuricemia, with a preponderance of men (58.5%) as compared to women (41.5%). On analysis within gender, 27.3% of men and 20.4% of women had hyperuricemia, and in comparison to those with normouricemia, the hyperuricemia group tended to be heavier (with increased body weight, BMI and WC) and to have increased TG levels and higher diastolic BP. On the other hand, levels of TC, LDL-C, HDL-C, glucose and systolic BP did not differ significantly between the two groups.

The adjusted and unadjusted odds ratios for the putative determinants of uric acid status (hyperuricemia vs. normouricemia) for the subjects are shown in table 2. Adjustments were made for age, gender, BMI and diabetes status whenever the p values were significant. In these analyses, the age grouping was collapsed into two categories according to the National Cholesterol Education Program ATP III criteria for the definition of premature ischemic heart disease, i.e. men aged ≤45 years and women aged ≤55 years [16]. Serum uric acid levels were higher in males than in females when further compared by covariance analysis to correct for potential confounding from age, diabetes status and BMI. It was additionally noted that, in the hyperuricemia group, 168 (57%), 106 (36%) and 77 (26%) were obese, smoked regularly and/or had diagnosed diabetes, respectively. Furthermore, hypertension was present in 137 (47%) of the hyperuricemic patients in whom 113 (38%) had low HDL and 235 (80%) were hypertriglyceridemic. After adjusting for possible covariates, as shown in table 2, gender, BMI and diabetes emerged as the independent determinants of uric acid status in all the subjects considered as a whole.

The relationship between the various components of MetS and uric acid status was gender specific (table 3). In the men, since older age was associated with greater WC and presence of impaired fasting glucose (IFG) and hypertension, we adjusted for age and observed that the serum uric acid level was higher in those with MetS, large WC, IFG and hypertension. In women however, after adjusting for age, a large WC was the only significant association with the serum uric acid level. In neither gender did dyslipidemia (low HDL, high TG) contribute significantly to uric acid levels.

These disparate observations for men and women were further explored in table 4, which specifically assessed the individual effects of WC, IFG and hyperten-
sion in men and women. Different groups were identified according to the number of MetS components as follows: A = without large WC, dyslipidemia, IFG and/or high BP; B = with large WC but without dyslipidemia, IFG and/or high BP; C = with large WC and dyslipidemia but without IFG and/or high BP; D = with large WC, dyslipidemia, IFG and/or high BP. The analyses revealed significant group-based differences for both men and women; in men, group D serum uric acid was significantly higher than in group C, and group B had nonstatistically significant higher levels than group A; for the women, group D subjects had higher uric acid levels than those in group B.

The changes in serum uric acid and lipid and lipoprotein levels with specific treatment (statins, typically atorvastatin, for predominant hypercholesterolemia and fibrates, typically gemfibrozil or bezafibrate, for predominant hypertriglyceridemia) in the subjects at baseline and on follow-up at the Lipid Clinic at 4–6 months and 12–14 months are presented in Table 5. Of the 468 subjects on fibrates, 443 (95%) were on bezafibrate and 23 (5%) on gemfibrozil, mainly because the former is available free of charge to all. Only 2 (0.4%) of the subjects were on fenofibrate as it was not regularly freely available. The data were essentially similar for gemfibrozil and bezafibrate,

| Table 2. Odds ratios (OR) of hyperuricemia for potential determinants of uric acid status for all subjects |
|---------------------------------------------------------------|
| **Hyperuricemia** | **Normouricemia** | p | OR | 95% CI |
|-------------------|-------------------|---|----|-------|
| Subjects          | 294 (24.9%)       | 885 (75.1%) | -  | 0.004 |
| Gender            |                   |               |    |       |
| Female            | 122 (41.5%)       | 452 (51.1%)   | 1  | reference |
| Male              | 172 (58.5%)       | 433 (48.9%)   | 0.68 | 0.52–0.89 |
| Age groups        |                   |               |    |       |
| Men >45, women >55 years | 126 (43.0%)   | 329 (37.3%)   | 1  | reference |
| Men ≤45, women ≤55 years | 167 (57.0%)  | 554 (62.7%)   | 1.27 | 0.97–1.66 |
| BMI               |                   |               |    |       |
| Nonobese         | 119 (41.5%)       | 472 (54.8%)   | <0.001 | reference |
| Obese            | 168 (58.5%)       | 389 (45.2%)   | 1.71 | 1.31–2.25 |
| Cigarette smoking|                   |               |    |       |
| Nonsmoker        | 184 (63.4%)       | 593 (67.2%)   | 1  | reference |
| Smoker           | 106 (36.6%)       | 289 (32.8%)   | 1.18 | 0.90–1.56 |
| Diabetes status  |                   |               |    |       |
| Nondiabetic      | 216 (73.7%)       | 561 (63.4%)   | 1  | reference |
| Diabetic         | 77 (26.3%)        | 324 (36.6%)   | 0.62 | 0.46–0.83 |
| MetS status      |                   |               |    |       |
| Without          | 106 (36.1%)       | 372 (42.0%)   | 1  | reference |
| With             | 188 (63.9%)       | 513 (58.0%)   | 1.29 | 0.98–1.69 |
| WC                |                   |               |    |       |
| Men >102, women >88 cm | 94 (33.2%) | 337 (39.6%) | 1 | reference |
| Men ≤102, women ≤88 cm | 189 (66.8%) | 514 (60.4%) | 1.32 | 0.99–1.75 |
| Hypertension (BP) |                   |               |    |       |
| <130/85 mm Hg    | 157 (53.4%)       | 507 (57.3%)   | 1  | reference |
| ≥130/85 mm Hg    | 137 (46.6%)       | 378 (42.7%)   | 1.17 | 0.90–1.53 |
| HDL-C            |                   |               |    |       |
| Men >1.0, women >1.29 mmol/l | 67 (37.2%) | 269 (42.6%) | 1 | reference |
| Men ≤1.0, women ≤1.29 mmol/l | 113 (62.8%) | 363 (57.4%) | 1.25 | 0.89–1.76 |
| TG                |                   |               |    |       |
| <1.69 mmol/l     | 57 (19.5%)        | 216 (24.7%)   | 1  | reference |
| ≥1.69 mmol/l     | 235 (80.5%)       | 658 (75.3%)   | 1.36 | 0.98–1.88 |

Gender: after adjustment for age, diabetes and BMI. BMI: after adjustment for age, gender and diabetes. Diabetes: after adjustment for age, BMI and gender.
and so both were pooled for further statistical analyses. With statin treatment, mean baseline uric acid levels significantly decreased by 5.8% (p < 0.001) in 4–6 months and up to 9.0% at the end of the first year of treatment. This was accompanied by the expected major decreases in TC, LDL levels and a trivial reduction in TG levels. On the other hand, serum uric acid levels appeared to increase (albeit nonsignificantly) during the same follow-up duration in the patients administered fibrates, in spite of the expected major falls in TC and TG levels with a modest increase in HDL-C.

### Discussion

In this study, we have attempted to evaluate the associations of uric acid levels with a wide variety of clinical, anthropometric and biochemical parameters in a large group of dyslipidemic patients being followed up at a major teaching hospital in Kuwait. Dyslipidemia is itself a major CAD risk factor in Kuwait and the Arabian Gulf Region [17, 18], as elsewhere [19], and therefore our objective was to assess if the urate changes were merely incidental on the lifestyle issues resulting in dyslipidemia (such as obesity, high fat diets and poor physical activity).
The study indicated that 24% of the dyslipidemic patients had hyperuricemia, with proportionally more men (28%) than women (20%) affected. These rates are 2–4 times higher than those described for the general ‘healthy’ Arab [5] or Caucasian populations [3, 4]. Gender (male sex), obesity (as assessed with BMI) and diabetes were significant determinants of whether or not an individual would have hyperuricemia, even after adjustment for potential confounding. Of interest is the further finding that, in the whole group of subjects, important CAD risk variables such as age, MetS, large WC, atherogenic dyslipidemia (low HDL and high TG levels), cigarette smoking and high BP did not influence per se whether or not an individual would have hyperuricemia. However, these findings were gender specific – the associations of high uric acid levels in men (presence of MetS, large WC, fasting hyperglycemia and hypertension) were more robust than in women (only large WC), even after adjustment for confounding.

Table 4. Serum uric acid levels based on numbers of MetS components

| WC | Dyslipidemia | IFG ± high BP | n | Uric acid, µmol/l | p  |
|----|-------------|---------------|---|-----------------|----|
| Men |             |               |   |                 |    |
| Group A | – | – | – | 32 | 364.5 ± 76.2 | 0.045 |
| Group B | + | – | – | 161 | 370.0 ± 85.4 |    |
| Group C | + | + | – | 239 | 360.1 ± 92.0 |    |
| Group D | + | + | + | 160 | 387.0 ± 99.9 |    |
| Women |               |               |   |                 |    |
| Group A | – | – | – | 16 | 276.1 ± 84.5 | 0.026 |
| Group B | + | – | – | 75 | 277.4 ± 59.5 |    |
| Group C | + | + | – | 186 | 299.9 ± 71.3 |    |
| Group D | + | + | + | 287 | 305.2 ± 79.6 |    |

Uric acid results are expressed as means ± SD; n = number of subjects; p values derived from one-way analysis of variance.

Group A: without large WC, dyslipidemia, IFG and/or high BP. Group B: with large WC but without dyslipidemia, IFG and/or high BP. Group C: with large WC and dyslipidemia but without IFG and/or high BP. Group D: with large WC, dyslipidemia, IFG and/or high BP.

Table 5. Serum uric acid and lipid levels at diagnosis (baseline) and on follow-up at 4–6 and 12–14 months in subjects with specific treatment

|                  | Baseline       | 4–6 months     | 12–14 months   | p value  |
|------------------|----------------|----------------|----------------|---------|
| **Statins**      |                |                |                |         |
| Uric acid, µmol/l | 344.6 ± 104.6  | 324.3 ± 78.9   | 313.1 ± 79.1   | <0.001  |
| TC, mmol/l        | 8.0 ± 2.2      | 6.8 ± 1.9      | 6.3 ± 1.8      | <0.001  |
| LDL-C, mmol/l     | 6.3 ± 3.6      | 4.9 ± 2.4      | 4.3 ± 1.9      | <0.001  |
| HDL-C, mmol/l     | 1.14 ± 0.38    | 1.14 ± 0.31    | 1.14 ± 0.30    | 0.993   |
| TG, mmol/l        | 2.8 ± 2.8      | 2.3 ± 1.8      | 2.4 ± 2.7      | 0.010   |
| **Fibrates**      |                |                |                |         |
| Uric acid, µmol/l | 337.4 ± 76.1   | 346.4 ± 77.9   | 341.1 ± 86.0   | 0.502   |
| TC, mmol/l        | 8.1 ± 2.6      | 6.5 ± 1.4      | 6.4 ± 1.7      | <0.001  |
| LDL-C, mmol/l     | 4.7 ± 0.9      | 4.4 ± 0.9      | 4.0 ± 1.3      | 0.141   |
| HDL-C, mmol/l     | 1.02 ± 0.31    | 1.08 ± 0.27    | 1.01 ± 0.26    | 0.058   |
| TG, mmol/l        | 10.1 ± 9.9     | 5.0 ± 6.8      | 5.3 ± 6.2      | <0.001  |

Results are expressed as means ± SD. Analyses were performed by one-way repeated-measures analysis of variance with Bonferroni’s correction for multiple comparisons.
sulfinemia increases circulating uric acid levels possibly through one or more of: enhanced insulin action with decreased renal excretion of uric acid and increased whole-body uric acid production [20]; enhanced activity of the hexose monophosphate shunt with increased purine biosynthesis and turnover [21]; presence of hypertension and possibly decreased renal blood flow and microischemia, increased renal lactate secretion, and reduced renal uric acid excretion [22]. Furthermore, hyperuricemia could, in turn, worsen insulin resistance via effects on endothelial NO [22, 23] and potentially create a vicious cycle.

The gender-related differences in blood levels and associations of uric acid observed in this study confirmed observations elsewhere [23] and are most likely due to the hormonal (estrogen and testosterone) differences between men and women [24], with the increase in male muscle and skeletal mass and the consequent increased supply of purines.

Our results further showed that statin (but not fibrate) treatment of dyslipidemia resulted in reduction in serum uric acid levels without additional use of uricosuric or uricosuric drugs. This observation is likely to be statin specific and not due to the attendant lifestyle change advice, which was freely and generally offered to all patients, irrespective of the type of drug treatment. Similarly, it is unlikely to be due to poor compliance to therapy by patients on fibrates, since they demonstrated effectiveness of treatment with significant reductions in levels of TG and TC. Indeed, uric acid levels even tended to rise slightly with treatment using fibrates (gemfibrozil or bezafibrate), by 2.6% at 4–6 months and 1.1% at 12–14 months. However, a previous study [25] reported that serum uric acid levels decreased by almost 28% with fenofibrate treatment – with the implication that the effects of this group of drugs on uric acid levels might be specifically drug-dependent. In any case, the clear results in relation to statins, which has also been reported in other populations [11, 12], reinforce the conviction that statin effects are pleiotropic in improving endothelial function and overall vascular health, in addition to significantly reducing circulating lipid levels [26, 27]. The other drugs that have been described to potentially affect serum uric acid levels in our patients are antihypertensives (such as thiazide diuretics and losartan) and nonsteroidal anti-inflammatory drugs [25, 28]. However, the subjects in the study primarily taking either statins or fibrates had an equal likelihood of having hypertension (and being on a thiazide diuretic, with none under losartan treatment) or taking nonsteroidal anti-inflammatory drugs, so these could not have influenced our observations.

The major strength of this study was its large number of a socioculturally homogeneous population followed up in a teaching hospital environment in a country with essentially free health care and no poverty-related issues in drug compliance. However, there were some limitations to the study, in that patients were not strictly regarding clinic attendance. We did not have a control non-dyslipidemic population either, because the objective was to investigate a population already at high CAD risk. Furthermore, we did not assess alcohol intake for legal and religious reasons.

**Conclusion**

This study showed that: (i) about a quarter of dyslipidemic subjects attending the Lipid Clinic in Kuwait had hyperuricemia; (ii) the associations of hyperuricemia were gender specific, variably including different components of MetS; (iii) atherogenic dyslipidemia (low HDL, high TG), per se, was not associated with hyperuricemia; (iv) circulating uric acid levels were reduced by about 9% over a 1-year time period with statin (but not fibrate) treatment.

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Dyslipidemia

Determinants of Urate Levels in

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