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Elevated serum uric acid levels in metabolic syndrome: an active component or an innocent bystander?

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Abstract

Elevated serum uric acid (SUA) levels are commonly seen in patients with the metabolic syndrome (MetS). Several mechanisms, both direct and indirect, connect the increased SUA levels with the established diagnostic criteria of MetS. It is possible that the increased cardiovascular disease risk associated with the MetS is partially attributed to elevated circulating SUA concentration. Several drugs used in the treatment of MetS may alter SUA levels. Thus, lifestyle measures together with the judicious selection of drugs for the treatment of hypertension, dyslipidemia, and insulin resistance associated with MetS may result in a reduction of SUA levels and possibly cardiovascular disease risk. This review summarizes the pathophysiologic association between SUA and MetS and focuses on the prevention of hyperuricemia and its cardiovascular consequences.

1. Introduction

The metabolic syndrome (MetS) is a modern "epidemic" leading to increased risk of cardiovascular disease (CVD) and diabetes mellitus (DM) [1-4]. The principal underlying pathophysiologic abnormality is insulin resistance (IR), which is mainly associated with abdominal obesity. Insulin resistance eventually results in dyslipidemia, hypertension, impaired carbohydrate metabolism, and other metabolic abnormalities [5]. At least 5 organizations have recommended clinical criteria for the diagnosis of MetS [6-12]. These criteria are similar in many aspects, but they also have differences concerning the predominant causes of MetS and the definition of obesity.

Serum uric acid (SUA) levels are often increased in subjects with MetS [13,14]. However, none of the proposed sets of diagnostic criteria include SUA levels in the definition of MetS. In 2001, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) published the most widely used set of diagnostic criteria [6]. These criteria include elevated plasma triglyceride (TRG) levels (≥150 mg/dL [1.69 mmol/L]), decreased levels of high-density lipoprotein cholesterol (HDL-C) (<40 mg/dL [1.04 mmol/L] in men and <50 mg/dL [1.29 mmol/L] in women), elevated blood pressure (BP) (≥130/85 mm Hg), increased fasting plasma glucose levels (≥ 110 mg/dL [6.1 mmol/L]), and abdominal obesity (waist circumference >102 cm in men and >88 cm in women). Recently, the International Diabetes Federation (IDF) proposed a new MetS definition [10]. The IDF definition suggested that abdominal obesity (plus other 2 criteria) is required for the diagnosis of MetS. Furthermore, IDF lowered waist circumference values defining abdominal obesity (≥94 cm in Europid men and ≥80 cm in Europid women) and fasting plasma glucose levels defining impaired fasting glucose (≥100 mg/dL [5.54 mmol/L]). However, it is believed that the NCEP ATP III criteria are currently the most useful for the diagnosis of MetS, as IDF definition seems to unacceptably increase the incidence of MetS in the general population [15]. Moreover, a recent American Heart Association/National Heart, Lung, and Blood Institute

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statement maintains the NCEP ATP III criteria except for defining glucose levels as ≥100 mg/dL (5.54 mmol/L) [12]. It also adopts the IDF-proposed criteria for the definition of abdominal obesity in certain ethnic groups (eg, Asians).

Large epidemiologic studies underlined the association of hyperuricemia with the components of MetS, suggesting that SUA levels could be included in the definition of MetS [13,16-21]. Moreover, as the number of MetS variables increased, so did the SUA concentration [14]. Serum uric acid levels may also be a reliable predictor of the "pre-MetS" in obese youths [22].

Therefore, we undertook this review of current literature on the relationship between uric acid (UA) and IR/MetS aiming to answer the question of whether elevated SUA levels are an active component or just an associative link to the MetS. In addition, we briefly review the effect of drugs used in the treatment of MetS on SUA levels.

2. Direct association of SUA levels with MetS and IR

Large epidemiologic studies demonstrated that the prevalence of MetS showed a graded increase according to SUA levels [14,17,18,23,24]. Moreover, SUA concentration was positively correlated with BP, waist-to-hip ratio, homeostasis model assessment index (an index of IR), body mass index, and levels of fasting plasma glucose, insulin, TRG, high-sensitivity C-reactive protein, and inversely correlated with HDL-C levels [14,17,18,20,21,23-26]. Insulin resistance is probably the underlying condition triggering the development of the above metabolic disturbances. Thus, the degree of IR (measured in everyday practice by the homeostasis model assessment index and the quantitative insulin sensitivity check index) [27] may be directly related to SUA levels [28-32]. In addition, drugs that improve insulin sensitivity, such as metformin [33], troglitazone [34,35], sibutramine [36-39], and orlistat [33,40] can also lower SUA levels. Furthermore, after multiple logistic regression analysis, only SUA levels and fasting insulin were independent predictors of nonalcoholic fatty liver disease, which is another common characteristic of MetS [41]. In the same context, SUA concentration was an independent predictor of hypertension incidence and longitudinal BP progression at 4-year follow-up in Framingham study participants [42].

Several studies revealed that IR is inversely related to 24-hour urinary UA clearance [43-45]. Therefore, one mechanism linking hyperinsulinemia (a consequence of IR) with hyperuricemia is a decreased renal excretion of UA. In fact, insulin can enhance renal tubular sodium reabsorption in humans [44-46]. Furthermore, renal excretion of UA is reduced in situations with increased renal tubular reabsorption of sodium [45-47]. This finding could be explained by the fact that proximal tubular reabsorption of UA occurs by an active transport mechanism closely linked to, or identical with, the tubular reabsorption of sodium [47]. Moreover, insulin receptors were found in different tubular segments [48]. Whatever the site of the tubular effects of insulin, possible mechanisms include direct stimulation of tubular ion exchange or acceleration of cellular metabolism [49]. Therefore, insulin can modify the handling of UA by the kidney, thus leading to hyperuricemia. In the same context, we recently showed that patients with MetS exhibited significantly lower serum phosphate and magnesium levels compared with healthy individuals [50].

In addition, there are other mechanisms connecting increased SUA levels and hyperinsulinemia. Indeed, increased purine biosynthesis and turnover, with its attendant increase in SUA concentrations caused by increased activity of the hexose monophosphate shunt, may be linked to IR and/or hyperinsulinemia [29]. Specifically, impairment of the glycolytic pathway can increase flux of glucose-6-phosphate through the hexose monophosphate shunt, resulting in accumulation of ribose-5-phosphate and other intermediates, which are major substrates for UA production [51,52]. Furthermore, glucose-6-phosphatase deficiency has been reported to be associated with increased SUA levels through multiple mechanisms [51].

On the other hand, there is evidence that UA may not only be a consequence of IR, but it may actually promote or worsen IR. Specifically, a recent study [53] showed that UA plays an important role in the pathogenesis of MetS, possibly due to its ability to inhibit endothelial function. In detail, UA has been shown to inhibit nitric oxide (NO) bioavailability [54]. Because insulin requires NO to stimulate glucose uptake, the investigators hypothesized that hyperuricemia may have a key role in the pathogenesis of IR [53]. Further experiments from the same group confirmed the above statement. Firstly, they demonstrated that fructose intake can induce features of MetS (hyperinsulinemia, hypertriglyceridemia) and also hyperuricemia. Moreover, they administered allopurinol (a xanthine oxidase inhibitor) and noticed that this drug could prevent fructose-induced hyperinsulinemia and hypertriglyceridemia [53].

Metabolic syndrome is associated with increased oxidative stress [55] and CVD risk [56,57]. Because UA is considered to be an effective antioxidant [58,59], the elevated SUA levels encountered in individuals with MetS may reflect a compensatory mechanism counteracting the increased oxidative stress associated with the MetS.

Other factors may also contribute to the association of elevated SUA levels with MetS. Serum uric acid concentration may depend on food and alcohol intake [60]. Indeed, alcohol abuse may increase urate generation [61] and decrease urate excretion [62] resulting in hyperuricemia. Furthermore, a diet rich in purines (eg, overconsumption of meat and seafood), complex carbohydrates, and saturated fat may lead to both MetS and hyperuricemia [1,63]. Commonly used drugs, such as diuretics, may also lead to elevated SUA levels [63]. In addition, postmenopausal women have higher incidence of hypertension, diabetes, obesity, and MetS as well as hyperuricemia [64]. A possible explanation is that estrogens are uricosuric [65].

The association between smoking and SUA levels is not known. It is well established that smoking is associated with an increased risk of vascular events [66]. Furthermore, there is also evidence showing that smoking is associated with IR [32,67] and increased risk of type 2 diabetes mellitus development [68,69]. However, in a 6-year longitudinal study of middle-aged Japanese men (n = 1445) free of hyperuricemia at baseline, smoking was a protective risk factor against the development of hyperuricemia (hazard ratio [HR], 0.65, 95% confidence interval [CI], 0.46-0.92) even after adjustment for body mass index [70]. In another study [71], SUA levels were influenced by smoking status during pregnancy: nonsmokers had the lowest SUA concentration, whereas women who quit smoking had the highest level.

3. Indirect association of SUA levels with MetS and IR

Hypertension, commonly encountered in MetS, could mediate an indirect relationship between MetS and SUA levels. Indeed, hypertension could lead to hyperuricemia by several mechanisms [72].

Hypertension leads to vascular disease and increased renal vascular resistance [73], both resulting in decreased renal blood flow, which in turn stimulates urate reabsorption [73]. Moreover, microvascular disease leads to local ischemia and release of lactate, which compete with urate transporter in the proximal tubule, thus blocking urate excretion [74]. In addition, ischemia induces the degradation of adenosine to adenine and xanthine, whereas increased generation of xanthine oxidase may be observed [51]. The increased generation of the substrate (xanthine) and the enzyme (xanthine oxidase) can lead to increased UA production [75]. Furthermore, high SUA levels have been associated with an increased generation of free radicals [76] and oxidative stress, which may abolish endothelium-dependent vasodilatation, thus leading to hypertension [77]. However, as already stated, other studies have suggested that UA is an effective antioxidant [58,59] and elevated SUA levels encountered in individuals with MetS may reflect a compensatory mechanism to the increased oxidative stress associated with the MetS. One possible mechanism could be that xanthine oxidase, the enzyme responsible for UA production, is one of the main producers of reactive oxygen species in the endothelium. All things considered, the exact role of UA in oxidation (ie, antioxidant vs prooxidant) is largely unknown and remains to be elucidated.

Uric acid may not only be the result, but also a mediator of hypertension [42]. Endothelial dysfunction and impaired NO production due to increased SUA levels [78,79], as well as the possible proinflammatory and prooxidative capacity of UA [80,81] may explain the pathogenic role of UA in hypertension. In addition, large clinical trials demonstrated that UA predicts renal dysfunction, which is associated with the development of hypertension [81-85].

Hypertriglyceridemia is one of the main abnormalities in MetS. The association between UA and IR may be secondary to the association between UA levels and hypertriglyceridemia. Many studies underlined the independent association of TRG and SUA levels [28,52,86-89]. In this context, increased TRG levels may be associated with decreased UA renal excretion [87].

Several studies revealed a genetic association between hypertriglyceridemia and hyperuricemia. Apolipoprotein (Apo) E polymorphism may affect SUA levels; the ApoE2 allele was independently associated with increased SUA levels in healthy individuals in one study [90]. On the other hand, an uncommon allelic variant of the ApoC-III gene (S2 allele) [91] as well as the ApoE4 allele [92] have been found more frequently in individuals with elevated TRG and SUA levels. In addition, a recent study showed that patients with MetS who do not have the E3/3 genotype have a greater risk of hyperuricemia and postprandial hypertriglyceridemia after a fat overload [93]. The above findings suggested that the association between high UA and TRG levels may be partially genetic.

Dyslipidemia per se represents a significant aggravating factor for renal dysfunction [94]. Atherogenic dyslipidemia (increased TRGs, decreased HDL-C levels, and, consequently, increased small-dense low-density lipoprotein cholesterol particle concentration) is a common characteristic of the MetS. High serum cholesterol binds to glomerular mesangial cells, and this may lead to renal function decline [95-98]. A reduction in glomerular filtration rate is another mechanism that increases SUA [99]. The above mechanism could also partially explain the association between dyslipidemia and hyperuricemia.

Of interest, MetS may be associated with an increased prevalence of kidney dysfunction [100], thus resulting in an increase in SUA levels. Elevated serum glucose levels [101,102], hypertension [103,104], and obesity [105,106] have been associated with an increased risk for chronic kidney disease and microalbuminuria. These findings provide more explanation for the high incidence of hyperuricemia in MetS. On the other hand, elevation of SUA levels could be a risk factor for the development of chronic kidney disease [107]. Thus, reducing SUA levels may prevent kidney function decline in MetS.

Another inherent part of MetS is visceral obesity, which has been proposed to play a key role in the development of the syndrome. An indirect relationship between UA and MetS may be mediated via visceral obesity. Except for IR, which seems to be the main mechanism connecting visceral obesity with hyperuricemia [108], elevated levels of leptin may also lead to an increase in SUA concentration. Recent studies assessed the role of leptin in hyperuricemia [109-111]. Leptin has been demonstrated to induce oxidative stress in endothelial cells and this, as already mentioned, could increase SUA concentration [112]. The involvement of leptin in sodium tubular reabsorption [113] may result in an increase in SUA

levels [47]. However, these observations were derived from animal models. Further studies are needed to elucidate the relationship between urate homeostasis and leptin in humans.

4. Uric acid and CVD risk

Many studies have underlined the positive association between SUA and CVD risk. Indeed, SUA concentration was shown to be an independent risk factor for CVD [114-118]. In the Augsburg cohort of the MONICA (World Health Organization Monitoring Trends and Determinants in Cardiovascular Diseases) study (including 1044 men) [119], increased SUA levels independently from other known risk factors predicted all-cause (HR, 2.8; 95% CI, 1.6-5.0) and CVD mortality (HR, 2.2; 95% CI, 1.0-4.8). Furthermore, in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study [120], SUA concentration as a time-varying covariate was strongly ($P < .0001$) associated with CVD events, particularly in women.

One possible mechanism could be that elevated SUA levels may induce renal disease [107], which seems to progress in parallel with CVD [121]. Furthermore, xanthine oxidase is one of the main producers of reactive oxygen species in the endothelium, providing another possible linkage between SUA, endothelium dysfunction, and CVD. On the other hand, MetS is associated with increased risk of CVD [122], and the number of the MetS diagnostic criteria provides a more informative graded assessment of CVD risk [123]. One may speculate that increased risk of CVD associated with MetS could be partially mediated by the elevated SUA levels [124]. In this context, the reduction of SUA levels may result in a decrease in CVD risk [121,125,126].

5. The effect of drugs used in the treatment of MetS on SUA levels

A selection of cardiovascular drugs that have a neutral or even lowering effect on SUA levels may be important in decreasing CVD risk in MetS. Several drugs can influence SUA concentration [63,127] (Table 1). Firstly, diuretics, even in low doses, may increase SUA concentration by increasing the net reabsorption of UA in the nephron proximal tubule [128]. The diuretic-induced SUA elevation is evident within a few days after initiating treatment [129,130]. β-Blockers (propranolol [131], atenolol [132], metoprolol [133], timolol [134], and alprenolol [135]) also increased SUA concentrations in some studies. However, this was not confirmed in others [136-138]. The mechanisms by which β-blockers influence SUA levels are not known. On the other hand, angiotensin-converting enzyme inhibitors (captopril [139], enalapril [140], and ramipril [141]) can reduce SUA levels [142]. The hypouricemic effect of these drugs is possibly mediated by the reduction of angiotensin II, which increases the UA net reabsorption in the proximal tubule [143]. Angiotensin II receptor blockers (valsartan [144], candesartan [145], telmisartan [146], irbersartan [147], and erprosartan [148]) do not lower SUA levels as they do not decrease angiotensin II

Table 1
The effect of drugs used in the treatment of MetS on SUA levels

Drug	Effect on SUA levels	Mechanism of action
Diuretics	Increase	Increase of the net reabsorption of UA in the proximal tubule of the nephron
β-Blockers	Increase or no change	Unknown
ACEIs	Reduction	Reduction of angiotensin II, which increases the UA net reabsorption in the proximal tubule
ARBs	No change	
-Except for losartan	-Reduction	-Losartan reduces the net reabsorption of UA in the proximal tubule. However, the mechanism of its action is unknown.
Calcium channel blockers	Reduction	Increase in urate excretion, possibly by increasing creatinine clearance
-Except for nifedipine and verapamil	-No change	
Fenofibrate	Reduction	Augments uricosuria by reducing the net reabsorption of UA in the proximal tubule
-Other fibrates	-No change	
Statins	No change	
-Except for atorvastatin and simvastatin	-Reduction	-Atorvastatin increases the fractional urate excretion
Metformin	Reduction	Improved insulin sensitivity that leads to increased urinary excretion of UA
Sulfonylureas	No change	
Troglitazone	Reduction	Improved insulin sensitivity that leads to increased urinary excretion of UA
-Newer glitazones	-No data available	
Weight-lowering drugs (sibutramine and orlistat)	Reduction	The fall in SUA levels may be associated with the observed weight loss per se, with an improvement in renal function, but also with a direct uricosuric effect of these drugs or a decrease in insulin resistance.
Aspirin	Biphasic effect: reduction at high doses (>3 g/d), increase in lower doses	Unknown

ACEIs indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; SUA, serum uric acid; metS, metabolic syndrome.

concentration [142]. Of interest, losartan is the only drug from this category that can reduce the net reabsorption of UA in the proximal tubule and lower SUA levels [149-152]. In the LIFE study [120], the increase in SUA concentration over 4.8 years was attenuated by losartan compared with atenolol treatment, appearing to explain 29% of the treatment effect on the primary composite end point. The underlying mechanism for this uricosuric action of losartan remains unknown.

Calcium channel blockers (eg, amlodipine [153], felodipine [154]) significantly decrease SUA levels by increasing urate excretion. Nifedipine [155] and verapamil [156] are the only drugs from this category that seem to have a neutral effect on SUA levels.

Among lipid-lowering agents, fenofibrate may lower SUA levels, whereas the other fibrates do not seem to influence urate homeostasis [151,157-161]. Fenofibrate augments uricosuria by reducing the net reabsorption of uric acid in the proximal tubules [161]. Moreover, fenofibrate may counterbalance the SUA-raising effect of diuretics [162]. Among statins, atorvastatin has a hypouricemic action by increasing fractional urate excretion [163]. In the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study this was dependent on the atorvastatin dose [126]. Similarly, the improvement in calculated creatinine clearance in GREACE was related to atorvastatin dose and to baseline levels [164,165]. Simvastatin administration also reduced SUA levels in patients with peripheral arterial disease [166].

As already mentioned, hyperinsulinemia may decrease the urinary excretion of UA [43-45]. Therefore, drugs that improve insulin sensitivity may lower SUA levels. For example, metformin in some, but not all, studies lowered SUA levels [33,167]. In contrast, sulfonylureas do not have a hypouricemic effect [168]. In addition, troglitazone has been shown to improve IR and decrease SUA levels [25,34,35]. There are no clinical data regarding the effect of the newer thiazolidinediones on UA metabolism.

Clinical studies have shown that 2 drugs used for weight loss, sibutramine [37,38] and orlistat [33,40], can also lower SUA levels. The fall in SUA concentration may be associated with the observed weight loss per se, with an improvement in renal function but also with a direct uricosuric effect of these drugs or a decrease in IR [36,40].

Aspirin at high doses (> 3 g/d) exhibits uricosuric properties, whereas lower doses cause urate retention [169,170]. At 75 mg/d (a dose commonly used in high-risk patients to prevent vascular events), aspirin caused a slight but significant increase in SUA levels [169,170]. The mechanism of this biphasic effect of aspirin on the renal excretion of UA is not fully understood.

Lifestyle changes are of paramount importance in the context of MetS treatment [1,2]. Weight loss has been associated with a fall in SUA levels [171]. Furthermore, regular physical exercise may also lower SUA concentration [172,173].

6. Conclusions and suggestions for future work

Raised SUA levels are associated with the MetS. Data presented herein clearly show that UA is not just an innocent bystander in MetS, but it is strongly interrelated with metabolic disarrangements of MetS. Specifically, IR leads to elevated SUA levels through both direct and indirect mechanisms, which include increased urate production as well as decreased renal urate excretion. Increased SUA levels may in turn worsen IR and associated features, such as hypertension, dyslipidemia, endothelial dysfunction, nonalcoholic fatty liver disease, and chronic kidney disease, thus increasing CVD risk.

The exact prevalence of elevated SUA levels in patients with MetS as well as the incidence of gout in these patients should be studied. Further studies are needed to define the exact association between SUA and CVD and determine whether inclusion of SUA concentration in the MetS definition would improve its power to predict CVD risk independently of other associated features.

A judicious selection of drugs used for the treatment of hypertension, dyslipidemia, and IR associated with MetS may result in a reduction of SUA levels and, possibly, in a further reduction in CVD risk. An aggressive implementation of lifestyle changes could also reduce the adverse impact of SUA in MetS.

References

[1] Daskalopoulou SS, Mikhailidis DP, Elisaf M. Prevention and treatment of the metabolic syndrome. Angiology 2004;55:589-612.
[2] Liberopoulos EN, Mikhailidis DP, Elisaf MS. Diagnosis and management of the metabolic syndrome in obesity. Obes Rev 2005;6:283-96.
[3] Gazi I, Liberopoulos E, Mikhailidis DP, et al. Metabolic syndrome: clinical features leading to therapeutic strategies. Vasc Dis Prevent 2004;1:243-53.
[4] Liberopoulos EN, Tsouli SG, Mikhailidis DP, et al. Preventing type 2 diabetes in high risk patients: an overview of lifestyle and pharmacological measures. Curr Drug Targets 2006;7:211-28.
[5] Reaven GM. Role of insulin resistance in human disease. Diabetes 1988;37:1595-607.
[6] Expert Panel on Detection, Evaluation and treatment of high blood cholesterol in adults. Executive summary 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). JAMA 2001;285:2486-97.
[7] Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabet Med 1998;15:539-53.
[8] Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European group for the study of insulin resistance. Diabet Med 1999;16:442-3.
[9] Einhorn D, Reaven GM, Cobin RH, et al. American College of Endocrinology position statement on the insulin resistance syndrome. Endocr Pract 2003;9:237-52.
[10] The IDF consensus worldwide definition of the metabolic syndrome. (accessed 29 June 2006) www.idf.org/webdata/docs/MetSyndrome_FINAL.pdf.
[11] Liberopoulos EN, Elisaf MS. Diagnosis of the metabolic syndrome: which definition should we use? Hellenic J Cardiol 2005;46:258-62.

[12] Grundy SM, Cleeman JI, Daniels SR, et al. American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart. Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735-52.
[13] Schmidt MI, Duncan BB, Watson RL, et al. A metabolic syndrome in whites and African-Americans. The Atherosclerosis Risk in Communities baseline study. Diabetes Care 1996;19:414-8.
[14] Yoo TW, Sung KC, Shin HS, et al. Relationship between serum uric acid concentration and insulin resistance and metabolic syndrome. Circ J 2005;69:928-33.
[15] Athyros VG, Ganotakis ES, Elisaf M, et al. The prevalence of the metabolic syndrome using the National Cholesterol Educational Program and International Diabetes Federation definitions. Curr Med Res Opin 2005;21:1157-9.
[16] Zimmet PZ, Collins VR, Dowse GK, et al. Is hyperinsulinaemia a central characteristic of a chronic cardiovascular risk factor clustering syndrome? Mixed findings in Asian Indian, Creole and Chinese Mauritians. Mauritius Noncommunicable Disease Study Group. Diabet Med 1994;11:388-96.
[17] Klein BE, Klein R, Lee KE. Components of the metabolic syndrome and risk of cardiovascular disease and diabetes in beaver dam. Diabetes Care 2002;25:1790-4.
[18] Leyva F, Godsland IF, Worthington M, et al. Factors of the metabolic syndrome: baseline interrelationships in the first follow-up cohort of the HDDRISC Study (HDDRISC-1). Heart Disease and Diabetes Risk Indicators in a Screened Cohort. Arterioscler Thromb Vasc Biol 1998;18:208-14 [Erratum in: Arterioscler Thromb Vasc Biol 18 (1998) 1198].
[19] Tang W, Miller MB, Rich SS, et al. National heart, lung, and blood institute family heart study. Linkage analysis of a composite factor for the multiple metabolic syndrome: the National Heart, Lung, and Blood Institute Family Heart Study. Diabetes 2003;52:2840-7.
[20] Conen D, Wietlisbach V, Bovet P. Prevalence of hyperuricemia and relation of serum uric acid with cardiovascular risk factors in a developing country. BMC Public Health 2004;4:9.
[21] Chen J, Wildman RP, Hamm LL, et al. Third National Health and Nutrition Examination Survey. Association between inflammation and insulin resistance in U.S. nondiabetic adults: results from the Third National Health and Nutrition Examination Survey. Diabetes Care 2004;27:2960-5.
[22] Denzer C, Muche R, Mayer H, et al. Serum uric acid levels in obese children and adolescents: linkage to testosterone levels and pre-metabolic syndrome. J Pediatr Endocrinol Metab 2003;16:1225-32.
[23] Ishizaka N, Ishizaka Y, Toda E, et al. Association between serum uric acid, metabolic syndrome, and carotid atherosclerosis in Japanese individuals. Arterioscler Thromb Vasc Biol 2005;25:1038-44.
[24] Boyko EJ, de Courten M, Zimmet PZ, et al. Features of the metabolic syndrome predict higher risk of diabetes and impaired glucose tolerance: a prospective study in Mauritius. Diabetes Care 2000;23:1242-8.
[25] Taniguchi Y, Hayashi T, Tsumura K, et al. Serum uric acid and the risk for hypertension and type 2 diabetes in Japanese men: The Osaka Health Survey. J Hypertens 2001;19:1209-15.
[26] Nakanishi N, Okamoto M, Yoshida H, et al. Serum uric acid and risk for development of hypertension and impaired fasting glucose or type II diabetes in Japanese male office workers. Eur J Epidemiol 2003;18:523-30.
[27] Pacini G, Mari A. Methods for clinical assessment of insulin sensitivity and β-cell function. Best Pract Res Clin Endocrinol Metab 2003;17:305-22.
[28] Vuorinen-Markkola H, Yki-Jarvinen H. Hyperuricemia and insulin resistance. J Clin Endocrinol Metab 1994;78:25-9.
[29] Modan M, Halkin H, Karasik A, et al. Elevated serum uric acid—a facet of hyperinsulinaemia. Diabetologia 1987;30:713-8.
[30] Donahue RP, Bean JA, Donahue RD, et al. Does insulin resistance unite the separate components of the insulin resistance syndrome? Evidence from the Miami Community Health Study. Arterioscler Thromb Vasc Biol 1997;17:2413-7.
[31] Costa A, Iguala I, Bedini J, et al. Uric acid concentration in subjects at risk of type 2 diabetes mellitus: relationship to components of the metabolic syndrome. Metabolism 2002;51:372-5.
[32] Carnethon MR, Fortmann SP, Palaniappan L, et al. Risk factors for progression to incident hyperinsulinemia: the Atherosclerosis Risk in Communities Study, 1987-1998. Am J Epidemiol 2003;158:1058-67.
[33] Gokcel A, Gumurdulu Y, Karakose H, et al. Evaluation of the safety and efficacy of sibutramine, orlistat and metformin in the treatment of obesity. Diabetes Obes Metab 2002;4:49-55.
[34] Tsunoda S, Kamide K, Minami J, et al. Decreases in serum uric acid by amelioration of insulin resistance in overweight hypertensive patients: effect of a low-energy diet and an insulin-sensitizing agent. Am J Hypertens 2002;15:697-701.
[35] Iwatani M, Wasada T, Katsumori K, et al. Troglitazone decreases serum uric acid concentrations in type II diabetic patients and non-diabetics. Diabetologia 2000;43:814-5.
[36] Filippatos TD, Kiortsis DN, Liberopoulos EN, et al. A review of the metabolic effects of sibutramine. Curr Med Res Opin 2005;21:457-68.
[37] Tambascia MA, Geloneze B, Repetto EM, et al. Sibutramine enhances insulin sensitivity ameliorating metabolic parameters in a double-blind, randomized, placebo-controlled trial. Diabetes Obes Metab 2003;5:338-44.
[38] McMahon FG, Weinstein SP, Rowe E, et al. Sibutramine is safe and effective for weight loss in obese patients whose hypertension is well controlled with angiotensin-converting enzyme inhibitors. J Hum Hypertens 2002;16:5-11.
[39] Krejs GJ. Metabolic benefits associated with sibutramine therapy. Int J Obes Relat Metab Disord 2002;26:34-7.
[40] Kiortsis DN, Filippatos TD, Elisaf MS. The effects of orlistat on metabolic parameters and other cardiovascular risk factors. Diabetes Metab 2005;31:15-22.
[41] Lonardo A, Loria P, Leonardi F, et al. Policentrica Steatosi Epatica Non Alcolica. Fasting insulin and uric acid levels but not indices of iron metabolism are independent predictors of non-alcoholic fatty liver disease. A case-control study. Dig Liver Dis 2002;34:204-11.
[42] Sundstrom J, Sullivan L, D'Agostino RB, et al. Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence. Hypertension 2005;45:28-33.
[43] Facchini F, Chen YD, Hollenbeck CB, et al. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. JAMA 1991;266:3008-11.
[44] Muscelli E, Natali A, Bianchi S, et al. Effect of insulin on renal sodium and uric acid handling in essential hypertension. Am J Hypertens 1996;9:746-52.
[45] Quinones Galvan A, Natali A, Baldi S, et al. Effect of insulin on uric acid excretion in humans. Am J Physiol 1995;268:E1-E5.
[46] Ter Maaten JC, Voorburg A, Heine RJ, et al. Renal handling of urate and sodium during acute physiological hyperinsulinaemia in healthy subjects. Clin Sci (Lond) 1997;92:51-8.
[47] Cappuccio FP, Strazzullo P, Farinaro E, et al. Uric acid metabolism and tubular sodium handling. Results from a population-based study. JAMA 1993;270:354-9.
[48] Nakamura R, Emmanouel DS, Katz AI. Insulin binding sites in various segments of the rabbit nephron. J Clin Invest 1983;72:388-92.
[49] Mandel LJ. Primary active sodium transport, oxygen consumption, and ATP: coupling and regulation. Kidney Int 1986;29:3-9.
[50] Kalaitzidis R, Tsimihodimos V, Bairaktari E, et al. Disturbances of phosphate metabolism: another feature of metabolic syndrome. Am J Kidney Dis 2005;45:851-8.
[51] Fox IH. Metabolic basis for disorders of purine nucleotide degradation. Metabolism 1981;30:616-34.

[52] Fox IH, John D, De Bruyne S, Dwosh I, et al. Hyperuricemia and hypertriglyceridemia: metabolic basis for the association. Metabolism 1985;34:741-6.
[53] Nakagawa T, Hu H, Zharikov S, et al. A causal role for uric acid in fructose-induced metabolic syndrome. Am J Physiol Renal Physiol 2006;290:625-31.
[54] Baldus S, Koster R, Chumley P, et al. Oxypurinol improves coronary and peripheral endothelial function in patients with coronary artery disease. Free Radic Biol Med 2005;39:1184-90.
[55] Evans JL, Maddux BA, Goldfine ID. The molecular basis for oxidative stress-induced insulin resistances. Antioxid Redox Signal 2005;7:1040-52.
[56] Milionis HJ, Rizos E, Goudevenos J, et al. Components of the metabolic syndrome and risk for first-ever acute ischemic non-embolic stroke in elderly subjects. Stroke 2005;36:1372-6.
[57] Milionis HJ, Liberopoulos E, Goudevenos J, et al. Risk factors for first-ever acute ischemic non-embolic stroke in elderly individuals. Int J Cardiol 2005;99:269-75.
[58] Nieto FJ, Iribarren C, Gross MD, et al. Uric acid and serum antioxidant capacity: a reaction to atherosclerosis? Atherosclerosis 2000;148:131-9.
[59] Nyyssonen K, Porkkala-Sarataho E, Kaikkonen J. Ascorbate and urate are the strongest determinants of plasma antioxidative capacity and serum lipid resistance to oxidation in Finish men. Atherosclerosis 1997;130:223-33.
[60] Liberopoulos EN, Miltiadous GA, Elisaf MS. Alcohol intake, serum uric acid concentrations, and risk of gout. Lancet 2004; 364:246-7.
[61] Faller J, Fox IH. Ethanol-induced hyperuricemia. Evidence for increased urate production by activation of adenine nucleotide turnover. N Engl J Med 1982;307:1598-602.
[62] Lieber CS, Jones DP, Losowsky MS, et al. Interrelation of uric acid and ethanol metabolism in man. J Clin Invest 1962;41:1863-70.
[63] Daskalopoulou SS, Tzovaras V, Mikhailidis DP, et al. Effect on serum uric acid levels of drugs prescribed for indications other than treating hyperuricaemia. Curr Pharm Des 2005;11:4161-75.
[64] Simon JA, Lin F, Vittinghoff E, et al. For the Heart and Estrogen-Progestin Replacement Study (HERS) Research Group. The relation of postmenopausal hormone therapy to serum uric acid and the risk of coronary heart disease events: the Heart and Estrogen-Progestin Replacement Study (HERS). Ann Epidemiol 2006;16: 138-45.
[65] Nicholls A, Snaith ML, Scott JT. Effect of estrogen therapy on plasma and urinary urate levels. BMJ 1973;1:449-51.
[66] Tsiara S, Elisaf M, Mikhailidis DP. Influence of smoking on predictors of vascular disease. Angiology 2003;54:507-30.
[67] Eliasson B, Mero N, Taskinen MR, et al. The insulin resistance syndrome and postprandial lipid intolerance in smokers. Atherosclerosis 1997;129:79-88.
[68] van Dam RM. The epidemiology of lifestyle and risk for type 2 diabetes. Eur J Epidemiol 2003;18:1115-25.
[69] Eliasson B. Cigarette smoking and diabetes. Prog Cardiovasc Dis 2003;45:405-13.
[70] Nakanishi N, Tatara K, Nakamura K, et al. Risk factors for the incidence of hyperuricaemia: a 6-year longitudinal study of middle-aged Japanese men. Int J Epidemiol 1999;28:888-93.
[71] Lain KY, Markovic N, Ness RB, et al. Effect of smoking on uric acid and other metabolic markers throughout normal pregnancy. J Clin Endocrinol Metab 2005;90:5743-6.
[72] Johnson RJ, Kang DH, Feig D, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension 2003;41:1183-90.
[73] Messerli FH, Frohlich ED, Dreslinski GR, et al. Serum uric acid in essential hypertension: an indicator of renal vascular involvement. Ann Intern Med 1980;93:817-21.
[74] Puig JG, Ruilope LM. Uric acid as a cardiovascular risk factor in arterial hypertension. J Hypertens 1999;17:869-72.
[75] Friedl HP, Till GO, Trentz O, et al. Role of oxygen radicals in tourniquet related ischemia reperfusion injury of human patients. Klin Wochenschr 1991;69:1109-12.
[76] Vasquez-Vivar J, Santos AM, Junqueira VB, et al. Peroxynitrite-mediated formation of free radicals in human plasma: EPR detection of ascorbyl, albuminthiyl and uric acid–derived free radicals. Biochem J 1996;314:869-76.
[77] Auch-Schwelk W, Katusic ZS, Vanhoutte PM. Contractions to oxygen-derived free radicals are augmented in aorta of the spontaneously hypertensive rat. Hypertension 1989;13:859-64.
[78] Farquharson CA, Butler R, Hill A, et al. Allopurinol improves endothelial dysfunction in chronic heart failure. Circulation 2002; 106:221-6.
[79] Doehner W, Schoene N, Rauchhaus M, et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. Circulation 2002; 105:2619-24.
[80] Kanellis J, Watanabe S, Li JH, et al. Uric acid stimulates monocyte chemoattractant protein–1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. Hypertension 2003;41:1287-93.
[81] Abuja PM. Ascorbate prevents prooxidant effects of urate in oxidation of human low density lipoprotein. FEBS Lett 1999;44: 305-8.
[82] Beck LH. Requiem for gouty nephropathy. Kidney Int 1986;30: 280-7.
[83] Bo S, Cavallo-Perin P, Gentile L, et al. Hypouricemia and hyperuricemia in type 2 diabetes: two different phenotypes. Eur J Clin Invest 2001;31:318-21.
[84] Syrjanen J, Mustonen J, Pasternack A. Hypertriglyceridaemia and hyperuricaemia are risk factors for progression of IgA nephropathy. Nephrol Dial Transplant 2000;15:34-42.
[85] Johnson RJ, Segal MS, Srinivas T, et al. Essential hypertension, progressive renal disease, and uric acid: a pathogenetic link? J Am Soc Nephrol 2005;16:1909-19.
[86] Giacomello A, Di Sciascio N, Quaratino CP. Relation between serum triglyceride level, serum urate concentration, and fractional urate excretion. Metabolism 1997;46:1085-9.
[87] Tinahones JF, Perez-Lindon G, Soriguer C-FJ, et al. Dietary alterations in plasma very low density lipoprotein levels modify renal excretion of urates in hyperuricemic-hypertriglyceridemic patients. J Clin Endocrinol Metab 1997;82:1188-91.
[88] Clausen JO, Borch-Johnsen K, Ibsen H, et al. Analysis of the relationship between fasting serum uric acid and the insulin sensitivity index in a population-based sample of 380 young healthy Caucasians. Eur J Endocrinol 1998;138:63-9.
[89] Matsubara K, Matsuzawa Y, Jiao S, et al. Relationship between hypertriglyceridemia and uric acid production in primary gout. Metabolism 1989;38:698-701.
[90] Liberopoulos EN, Miltiadous GA, Athyros VG, et al. Effect of apolipoprotein E polymorphism on serum uric acid levels in healthy subjects. J Investig Med 2005;53:116-22.
[91] Ferns GA, Lanham J, Dieppe P, et al. A DNA polymorphism of an apoprotein gene associates with the hypertriglyceridaemia of primary gout. Hum Genet 1988;78:55-9.
[92] Moriwaki Y, Yamamoto T, Takahashi S, et al. Apolipoprotein E phenotypes in patients with gout: relation with hypertriglyceridaemia. Ann Rheum Dis 1995;54:351-4.
[93] Cardona F, Morcillo S, Gonzalo-Marin M, et al. The apolipoprotein E genotype predicts postprandial hypertriglyceridemia in patients with the metabolic syndrome. J Clin Endocrinol Metab 2005;90:2972-5.
[94] Moorhead JF, Chan MK, El Nahas M, et al. Lipid nephrotoxicity in chronic progressive glomerular and tubulo-interstitial disease. Lancet 1982;2:1309-11.
[95] Gin H, Rigalleau V, Aparicio M. Lipids, protein intake, and diabetic nephropathy. Diabetes Metab 2000;26:45-53.

[96] Elisaf M, Mikhailidis DP. Statins and renal function. Angiology 2002;53:493-502.
[97] Guijarro C, Kasiske BL, Kim Y, et al. Early glomerular changes in rats with dietary-induced hypercholesterolemia. Am J Kidney Dis 1995;26:152-61.
[98] Liberopoulos E, Siamopoulos K, Elisaf M. Apolipoprotein E and renal disease. Am J Kidney Dis 2004;43:223-33.
[99] Vaziri ND, Freel RK, Hatch M. Effect of chronic experimental renal insufficiency on urate metabolism. J Am Soc Nephrol 1995; 6:1313-7.
[100] Chen J, Muntner P, Hamm L, et al. The metabolic syndrome and chronic kidney disease in US adults. Ann Intern Med 2004; 140:167-74.
[101] Nelson RG, Bennett PH, Beck GJ, et al. Development and progression of renal disease in Pima Indians with non–insulin dependent diabetes mellitus. Diabetic Renal Disease Study Group. N Engl J Med 1996;335:1636-42.
[102] Humphrey LL, Ballard DJ, Frohnert PP, et al. Chronic renal failure in non–insulin-dependent diabetes mellitus. A population-based study in Rochester Minnesota. Ann Intern Med 1989;111: 788-96.
[103] Whelton PK, Perneger TV, He J, et al. The role of blood pressure as a risk factor for renal disease: a review of the epidemiologic evidence. J Hum Hypertens 1996;10:683-9.
[104] Perneger TV, Nieto FJ, Whelton PK, et al. A prospective study of blood pressure and serum creatinine. Results from the "Clue" Study and the ARIC Study. JAMA 1993;269:488-93.
[105] Hall JE, Brands MW, Henegar JR. Mechanisms of hypertension and kidney disease in obesity. Ann N Y Acad Sci 1999;892: 91-107.
[106] Kopple JD, Greene T, Chumlea WC, et al. Relationship between nutritional status and the glomerular filtration rate: results from the MDRD study. Kidney Int 2000;57:1688-703.
[107] Iseki K, Ikemiya Y, Inoue T, et al. Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort. Am J Kidney Dis 2004;44:642-50.
[108] Matsuura F, Yamashita S, Nakamura T, et al. Effect of visceral fat accumulation on uric acid metabolism in male obese subjects: visceral fat obesity is linked more closely to overproduction of uric acid than subcutaneous fat obesity. Metabolism 1998;47:929-33.
[109] Bedir A, Topbas M, Tanyeri F, et al. Leptin might be a regulator of serum uric acid concentrations in humans. Jpn Heart J 2003;44: 527-36.
[110] Matsubara M, Chiba H, Maruoka S, et al. Elevated serum leptin concentrations in women with hyperuricemia. J Atheroscler Thromb 2002;9:28-34.
[111] Fruehwald-Schultes B, Peters A, Kern W, et al. Serum leptin is associated with serum uric acid concentrations in humans. Metabolism 1999;48:677-80.
[112] Rahmouni K, Haynes WG. Endothelial effects of leptin: implications in health and diseases. Curr Diab Rep 2005;5:260-6.
[113] Jackson EK, Li P. Human leptin has natriuretic activity in the rat. Am J Physiol 1997;1272:333-8.
[114] Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey. JAMA 2000; 283:2404-10.
[115] Culleton BF, Larson MG, Kannel WB, et al. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. Ann Intern Med 1999;131:7-13.
[116] Niskanen LK, Laaksonen DE, Nyyssonen K, et al. Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study. Arch Intern Med 2004;16: 1546-51.
[117] Milionis HJ, Kalantzi KJ, Goudevenos JA, et al. Serum uric acid levels and risk for acute ischaemic nonembolic stroke in elderly subjects. J Intern Med 2005;258:435-41.
[118] Kawamoto R, Tomita H, Oka Y, et al. Association between uric acid and carotid atherosclerosis in elderly persons. Intern Med 2005; 44:787-93.
[119] Liese AD, Hense HW, Lowel H, et al. Association of serum uric acid with all-cause and cardiovascular disease mortality and incident myocardial infarction in the MONICA Augsburg cohort. World Health Organization Monitoring Trends and Determinants in Cardiovascular Diseases. Epidemiology 1999;10:391-7.
[120] Hoieggen A, Alderman MH, Kjeldsen SE, et al. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. Kidney Int 2004;65:1041-9.
[121] Daskalopoulou SS, Athyros VG, Elisaf M, et al. Uric acid levels and vascular disease. Curr Med Res Opin 2004;20:951-4.
[122] Athyros VG, Mikhailidis DP, Papageorgiou AA, et al. Prevalence of atherosclerotic vascular disease among subjects with the metabolic syndrome with or without diabetes mellitus: the METS-GREECE Multicentre Study. Curr Med Res Opin 2004;20:1691-701.
[123] L'ltalien G, Ford I, Norrie J, et al. The cardiovascular event reduction tool (CERT)—a simplified cardiac risk prediction model developed from the West of Scotland Coronary Prevention Study (WOSCOPS). Am J Cardiol 2000;85:720-4.
[124] Lee J, Sparrow D, Vokonas PS, et al. Uric acid and coronary heart disease risk: evidence for a role of uric acid in the obesity-insulin resistance syndrome. Am J Epidemiol 1995;142:288-94.
[125] Daskalopoulou SS, Athyros VG, Elisaf M, et al. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. Kidney Int 2004;66:1714-5.
[126] Athyros VG, Elisaf M, Papageorgiou AA, et al. Effect of statins versus untreated dyslipidemia on serum uric acid levels in patients with coronary heart disease: a subgroup analysis of the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. Am J Kidney Dis 2004;43:589-99.
[127] Reyes AJ. Cardiovascular drugs and serum uric acid. Cardiovasc Drugs Ther 2003;17:397-414.
[128] Iwaki K, Yonetani Y. Decreased renal excretion of uric acid following diuretic administration in rats. Jpn J Pharmacol 1984; 34:389-96.
[129] Savage PJ, Pressel SL, Curb JD, et al. Influence of longterm, low-dose, diuretic-based, antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic hypertension: The Systolic Hypertension in the Elderly Program. Arch Intern Med 1998;158:741-51.
[130] Franse LV, Pahor M, Di Bari M, et al. Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). J Hypertens 2000; 18:1149-54.
[131] Medical Research Council Working Party on Mild to Moderate Hypertension. Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension. Lancet 1981;2:539-53.
[132] Andersen GS. Atenolol versus bendroflumethiazide in middle-aged and elderly hypertensives. Acta Med Scand 1985;218:165-72.
[133] Aurell M, Bengtsson C, Bjorck S. Enalapril versus metoprolol in primary hypertension—effects on the glomerular filtration rate. Nephrol Dial Transplant 1997;12:2289-94.
[134] Leren P, Foss PO, Nordvik B, et al. The effect of enalapril and timolol on blood lipids. A randomized multicenter hypertension study in general practice in Norway. Acta Med Scand 1988;223:321-6.
[135] Bengtsson C. Comparison between alprenolol and chlorthalidone as antihypertensive agents. Acta Med Scand 1972;191:433-9.
[136] Rizos E, Bairaktari E, Kostoula A, et al. The combination of nebivolol plus pravastatin is associated with a more beneficial metabolic profile compared to that of atenolol plus pravastatin in hypertensive patients with dyslipidemia: a pilot study. J Cardiovasc Pharmacol Ther 2003;8:127-34.
[137] Chrysant SG, Chappei C, Farnham DJ. Antihypertensive and metabolic effects of single and combined atenolol regimens. J Clin Pharmacol 1992;32:61-5.

[138] Lehtonen A. Comparison of the metabolic effects of long-term treatment with pindolol or atenolol by hypertensive patients. Cardiovasc Drugs Ther 1998;1:549-51.
[139] Leary WP, Reyes AJ, van der Byl K, et al. Effects of captopril, hydrochlorothiazide and their combination on timed urinary excretions of water and electrolytes. J Cardiovasc Pharmacol 1985;7:56-62.
[140] Lant AF, McNabb RW, Noormohamed FH. Kinetic and metabolic aspects of enalapril action. J Hypertens 1984;2:37-42.
[141] Labeeuw M, Pozet N, Zech PY, et al. Influence de l'administration aigüe de ramipril sur l'excretion d'acide urique. Arch Mal Coeur Vaiss 1987;80:870-4.
[142] Tsouli SG, Liberopoulos EN, Kiortsis DN, et al. Combined treatment with angiotensin converting enzyme inhibitors and angiotensin II receptor blockers: a review of the current evidence. J Cardiovasc Pharmacol Ther 2006;11:1-15.
[143] Moriwaki Y, Yamamoto T, Tsutsumi Z, et al. Effects of angiotensin II infusion on renal excretion of purine bases and oxypurinol. Metabolism 2002;51:893-5.
[144] Gonzalez-Ortiz M, Mora-Martinez JM, Martinez-Abundis E, et al. Effect of valsartan on renal handling of uric acid in healthy subjects. J Nephrol 2000;13:126-8.
[145] Manolis AJ, Grossman E, Jelakovic B, et al. Effects of losartan and candesartan monotherapy and losartan/hydrochlorothiazide combination therapy in patients with mild to moderate hypertension. Losartan Trial Investigators. Clin Ther 2000;22:1186-203.
[146] Burgess ED, Buckley S. Acute natriuretic effect of telmisartan in hypertensive patients. Am J Hypertens 2000;13:183.
[147] Wurzner G, Gerster JC, Chiolero A, et al. Comparative effects of losartan and irbesartan on serum uric acid in hypertensive patients with hyperuricaemia and gout. J Hypertens 2001;19:1855-60.
[148] Ilson BE, Martin DE, Boike SC. The effects of eprosartan, an angiotensin II AT1 receptor antagonist, on uric acid excretion in patients with mild to moderate essential hypertension. J Clin Pharmacol 1998;38:437-41.
[149] Nakashima M, Uematsu T, Kosuge K, et al. Pilot study of the uricosuric effect of DuP-753, a new angiotensin II receptor antagonist, in healthy subjects. Eur J Clin Pharmacol 1992;42:333-5.
[150] Alderman M, Aiyer KJ. Uric acid: role in cardiovascular disease and effects of losartan. Curr Med Res Opin 2004;20:369-79.
[151] Elisaf M, Tsimichodimos V, Bairaktari E, et al. Effect of micronized fenofibrate and losartan combination on uric acid metabolism in hypertensive patients with hyperuricemia. J Cardiovasc Pharmacol 1999;34:60-3.
[152] Liberopoulos E, Christides D, Elisaf M. Comparative effects of losartan and irbesartan on serum uric acid in hypertensive patients with hyperuricemia and gout. J Hypertens 2002;20:347.
[153] Sennesael JJ, Lamote JG, Violet I, et al. Divergent effects of calcium channel and angiotensin converting enzyme blockade on glomerulotubular function in cyclosporine treated renal allograft recipients. Am J Kidney Dis 1996;27:701-8.
[154] Hulthen UL, Katzman PL. Renal effects of acute and long-term treatment with felodipine in essential hypertension. J Hypertens 1988;6:231-7.
[155] Zawadzki J, Grenda R, Januszewicz P. Effect of nifedipine on tubular handling of uric acid in transplanted kidney on cyclosporine a treatment. Nephron 1995;70:77-82.
[156] Benjamin N, Phillips RJ, Robinson BF. Verapamil and bendrofluazide in the treatment of hypertension: a controlled study of effectiveness alone and in combination. Eur J Clin Pharmacol 1988;34:249-53.
[157] Melenovsky V, Malik J, Wichterle D, et al. Comparison of the effects of atorvastatin or fenofibrate on nonlipid biochemical risk factors and the LDL particle size in subjects with combined hyperlipidemia. Am Heart J 2002;144:E6.
[158] Milionis HJ, Elisaf MS. Management of hypertension and dyslipidaemia in patients presenting with hyperuricaemia: case histories. Curr Med Res Opin 2000;16:164-70.
[159] Elisaf M. Effects of fibrates on serum metabolic parameters. Curr Med Res Opin 2002;18:269-76.
[160] Filippatos TD, Kiortsis DN, Liberopoulos EN, et al. Effect of orlistat, micronised fenofibrate and their combination on metabolic parameters in overweight and obese patients with the metabolic syndrome: the FenOrli study. Curr Med Res Opin 2005;21:1997-2006.
[161] Liamis G, Bairaktari ET, Elisaf MS. Effect of fenofibrate on serum uric acid levels. Am J Kidney Dis 1999;34:594.
[162] Achimastos A, Liberopoulos E, Nikas S, et al. The effects of the addition of micronised fenofibrate on uric acid metabolism in patients receiving indapamide. Curr Med Res Opin 2002;18:59-63.
[163] Milionis HJ, Kakafika AI, Tsouli SG, et al. Effects of statin treatment on uric acid homeostasis in patients with primary hyperlipidemia. Am Heart J 2004;148:635-40.
[164] Athyros VG, Mikhailidis DP, Papageorgiou AA, et al. The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease. A subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. J Clin Pathol 2004;57:728-34.
[165] Liberopoulos EN, Athyros VG, Mikhailidis DP, et al. The effect of cholesterol-lowering treatment on renal function. Am J Kidney Dis 2006;47:561.
[166] Youssef F, Gupta P, Seifalian AM, et al. The effect of short-term treatment with simvastatin on renal function in patients with peripheral arterial disease. Angiology 2004;55:53-62.
[167] Fruehwald-Schultes B, Oltmanns KM, Toschek B, et al. Short-term treatment with metformin decreases serum leptin concentration without affecting body weight and body fat content in normal-weight healthy men. Metabolism 2002;51:531-6.
[168] Kilo C, Dudley J, Kalb B. Evaluation of the efficacy and safety of Diamicron in non–insulin-dependent diabetic patients. Diabetes Res Clin Pract 1991;14:79-82.
[169] Caspi D, Lubart E, Graff E, et al. The effect of mini-dose aspirin on renal function and uric acid handling in elderly patients. Arthritis Rheum 2000;43:103-8.
[170] Louthrenoo W, Kasitanon N, Wichainun R, et al. Effect of minidose aspirin on renal function and renal uric acid handling in healthy young adults. J Clin Rheumatol 2002;8:299-304.
[171] Hainer V, Stunkard AJ, Kunesova M, et al. Intrapair resemblance in very low calorie diet-induced weight loss in female obese identical twins. Int J Obes Relat Metab Disord 2000;24:1051-7.
[172] Lippi G, Brocco G, Franchini M, et al. Comparison of serum creatinine, uric acid, albumin and glucose in male professional endurance athletes compared with healthy controls. Clin Chem Lab Med 2004;42:644-7.
[173] Church TS, Finley CE, Earnest CP, et al. Relative associations of fitness and fatness to fibrinogen, white blood cell count, uric acid and metabolic syndrome. Int J Obes Relat Metab Disord 2002;26:805-13.