Rheumatology 2008;47:1567–1570
Advance Access publication 18 August 2008
doi:10.1093/rheumatology/ken305

Gout and the risk of type 2 diabetes among men with a high cardiovascular risk profile

H. K. Choi[1,2,3], M. A. De Vera[2,3] and E. Krishnan[4]

Objective. Our objective was to evaluate the independent relation between a history of gout and the future risk of type 2 diabetes among men with a high cardiovascular risk profile.
Methods. We prospectively examined over a 6-yr period the relation between gout and the risk of incident type 2 diabetes in 11 351 male participants from the Multiple Risk Factor Intervention Trial (MRFIT). Incident diabetes was defined based on the American Diabetes Association (ADA) criteria for epidemiological studies. Cox proportional hazards regression was used to adjust for potential confounders.
Results. We documented 1215 new cases of type 2 diabetes. After adjusting for age, BMI, smoking, family history of type 2 diabetes, alcohol intake, dietary factors and presence of individual components of the metabolic syndrome, the multivariate relative risk (RR) for incident type 2 diabetes among men with gout at baseline, as compared with men without gout, was 1.34 (95% CI 1.09, 1.64). When we further adjusted for serum uric acid levels, the association remained significant (RR 1.26; 95% CI 1.02, 1.54). When we updated the status of gout annually during follow-up as a time-varying covariate, the association remained similar. The association also remained similar in our subgroup analyses by major covariates (*P*-values for interaction >0.16).
Conclusions. These findings from men with a high cardiovascular risk profile suggest that men with gout are at a higher future risk of type 2 diabetes independent of other known risk factors. These data expand on well-established, cross-sectional associations between hyperuricaemia, gout and the metabolic syndrome, and extend the link to the future risk of type 2 diabetes.

Key words: Uric acid, Gout, Diabetes, Insulin, Metabolic syndrome.

Introduction

There are strong cross-sectional associations between hyperuricaemia, gout and the metabolic syndrome [1–7]. This link is important to note because the metabolic syndrome increases the risk for atherosclerotic cardiovascular disease (CVD) and type 2 diabetes [8–11] as well as mortality from CVD and from all causes [12–16]. While prospective studies have investigated the independent impact of serum uric acid levels [17] and gout [18, 19] on the risk of CVD, little information is available on the risk of type 2 diabetes. Recently, the Finnish diabetes prevention study, based on 557 overweight or obese individuals with impaired glucose tolerance, reported that baseline uric acid predicted the risk of diabetes after adjusting for age, gender, blood pressure, BMI, triglyceride levels, baseline creatinine, physical activity and dietary variables ($P=0.037$) [20]. However, we are not aware of any study that investigated the potential, independent relation between a history of gout and future risk of type 2 diabetes. To examine this link, we analysed a prospective cohort of 11 351 male participants from the Multiple Risk Factor Intervention Trial (MRFIT) [18, 21–25].

Materials and methods

Study population

The MRFIT was a randomized clinical trial designed to examine the efficacy of a coronary risk reduction programme among men at high risk of adverse coronary events [22–25]. Subjects were eligible if scores for the combination of three risk factors (smoking, hyperlipidaemia and hypertension) were sufficiently high to place them in the upper 15% of a risk score distribution based on data from the Framingham Heart Study. Detailed descriptions of the MRFIT have been published elsewhere [22–25]. Briefly, between 1973 and 1976, the MRFIT investigators screened 361 662 men for eligibility at 22 US clinical centres. Of this group, 12 866 men between the ages of 35 and 57 yrs were randomly assigned to either a special intervention group ($n=6428$) or a usual care group ($n=6438$). Participants were followed for six annual visits and the follow-up rate was >90%.

We excluded 508 men with evidence of diabetes at baseline (i.e. fasting glucose level of $\geq$7 mmol/l ($\geq$126 mg/dl), a glucose level of $\geq$16.65 mmol/l ($\geq$300 mg/dl) 1 h after a 75-g oral glucose load, or those who were taking insulin) [21]. We additionally excluded from our analyses 531 men with fewer than two fasting glucose values (i.e. end point) throughout the trial [21], 12 men with missing serum uric acid levels at baseline (i.e. exposure of interest) and 464 men with missing covariate data included in our final multivariate model (see subsequently), leaving a final sample of 11 351 men for our analysis.

Ethical approval for the present study was obtained from the University of Pennsylvania Medical Centre and informed patient consent was also obtained.

Assessment of gout and uric acid levels

We used a case definition of gout based on an affirmative answer to the question, 'Have you been told by your physician that you have gout?', which was the definition used in the Meharry–Hopkins Study [26]. It was not feasible to demonstrate IA crystals to prove a diagnosis of gout because participants seldom presented at a study visit with acute gouty arthritis. We evaluated the robustness of our results by using alternative case definitions of gout that required: (i) co-presence of hyperuricaemia ($\geq$416 μmol/l [7.0 mg/dl]) and (ii) use of any gout-specific medications (allopurinol, probenecid or colchicine). Serum uric acid levels and other laboratory tests, including lipid profiles, blood

[1]Department of Medicine, Division of Rheumatology, Vancouver General Hospital, [2]Arthritis Research Centre of Canada, [3]Department of Health Care and Epidemiology, Vancouver, BC, Canada and [4]Department of Medicine, Division of Rheumatology, University of Pittsburgh, Pittsburgh, PA, USA.

Submitted 21 April 2008; accepted 3 July 2008.

Correspondence to: H. K. Choi, Department of Medicine, Division of Rheumatology, University of British Columbia, Arthritis Research Centre of Canada, 895 West 10th Avenue, Vancouver, BC V5Z 1L7, Canada.
E-mail: hchoi@partners.org

glucose levels and blood chemistry tests were performed at baseline and annually thereafter [27]. Blood samples were sent to a central laboratory for analysis, and the results were determined as previously described [27].

Definition of diabetes

A fasting blood sample was taken at each annual examination, from which serum glucose concentration levels were measured. At each annual examination, participants were asked whether a physician had told them that they had diabetes at any time in the previous 12 months. Each participant was also asked whether he was using insulin or oral hypoglycaemic agents.

The definition of incident diabetes followed the American Diabetes Association (ADA) guidelines [28], as adopted in the recent report of this cohort [21]. With this definition, participants were considered to have developed diabetes if at any annual visit their fasting glucose level was $\geq$7 mmol/l ($\geq$126 mg/dl) or they reported taking insulin or any oral hypoglycaemic agents.

Assessment of covariates

At baseline, subjects provided a detailed medical history, including medication and social histories, and underwent a full physical examination. Standard and random-zero blood pressure measurements were recorded as the average of two measurements. BMI was calculated as the weight in kilograms divided by the square of the height in metres. In the MRFIT, 24-h dietary recalls were obtained at baseline and during follow-up visits [21, 29].

Statistical analysis

We calculated the risk of incident type 2 diabetes according to the presence and absence of gout at baseline. We computed person-time of follow-up for each participant from the MRFIT baseline up to the date of diagnosis of type 2 diabetes, death from any cause, loss to follow-up (<10%) or end of the study period, whichever came first.

We used Cox proportional hazards modelling to estimate the relative risk (RR) for incident type 2 diabetes in all multivariate analyses (Version 8.2, STATA Corporation, College Station, TX, USA). We used baseline gout status and covariate information in our primary analyses. Multivariate models were adjusted for age (continuous), the presence or absence of a family history of diabetes (yes or no), smoking status (never smoked, former smoker and current smoker), BMI (<23.0, 23.0–23.9, 24.0–24.9, 25.0–26.9, 27.0–28.9, 29.0–30.9, 31.0–34.9 or $\geq$35.0), presence of hypertension [$\geq$130/85 mmHg (yes or no) or current use of anti-hypertensive medication], physical activity (five categories), dietary variables (intake [quintiles] of total energy, cereal fibre, coffee, polyunsaturated fat, monounsaturated fat, saturated fat) [20], daily alcohol consumption (0, 0.01–0.09, 0.1–0.49, 0.5–0.99, 1.0–2.9 and $\geq$3.0 drinks per day) and presence (yes or no) of biomarker components of the metabolic syndrome [i.e. high fasting blood glucose, hypertriglyceridaemia and low high-density lipoprotein (HDL) cholesterol] [8, 30]. An assumption of clustering within the two arms of the trial was made, since the medical and non-medical interventions differed systematically across these groups but were homogeneous within the groups [18]. Accordingly, a cluster option was specified in the Cox regression models. We also conducted subgroup analyses stratified by treatment group, BMI (<25 kg/m^2 *vs* $\geq$25 kg/m^2), family history of diabetes, presence of hypertension and presence of the metabolic syndrome to assess possible effect modification. We tested the significance of the interaction using the likelihood ratio test by comparing a model with the main effects (i.e. history of gout and the stratifying variable) and the interaction terms with a reduced model with only the main effects. For all RRs, we calculated 95% CIs. All *P*-values were two-sided.

Results

Baseline characteristics

The characteristics of the cohort according to presence of gout at baseline are shown in Table 1. Men with gout tended to have a higher BMI and consumed more alcohol and less coffee. The prevalence of the metabolic syndrome among those with gout was 63% and individual components of the metabolic syndrome were more often present among those with gout than those without (Table 1).

Gout and incident type 2 diabetes

During 6 yrs of follow-up, we documented 1215 new cases of type 2 diabetes (annual incidence, 1.90 per 100 person-years). Compared with men without history of gout at baseline, the age-adjusted RR for incident type 2 diabetes was 1.66 (95% CI 1.37, 2.02) among men with history of gout. When we adjusted for other covariates, the multivariate RRs became attenuated but remained significant, including the final model that adjusted for biomarker components of the metabolic syndrome (RR 1.34; 95% CI 1.09, 1.64) (Table 2). This multivariate RR remained

TABLE 1. Baseline characteristics according to presence of gout in MRFIT

	Baseline disease status	
	No gout	Gout
N	10 707	644
Age, mean ± S.D., yrs	46.1 ± 5.9	47.4 ± 5.8
Race (Caucasian), %	90.1	91.9
BMI, mean ± S.D., kg/m^2	27.6 ± 3.4	28.7 ± 3.6
Current smokers, %	61.4	56.4
Alcohol intake (drinks/day)	1.8	2.1
Family history of diabetes, %	18.5	16.3
Proportion in special intervention group, %	50	47
Metabolic syndrome variables		
Obesity, %	21.5	32.5
High blood pressure or medication use, %	86.9	90.2
Low HDL cholesterol, %	46.8	50.6
Hypertriglyceridaemia, %	58.9	71.3
Fasting glucose $\geq$100 mg/dl or medication use, %	40.7	45.8
Metabolic syndrome[a], %	51	63
Dietary variables		
Cereal fibre intake, g/day	16.2	15.9
Saturated fat, g/day	37.1	34.9
Monounsaturated fat, g/day	39.5	37.7
Polyunsaturated fat, g/day	16.6	16.5
Coffee, servings/day	3.5	2.9

[a]According to revised National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) guidelines.

TABLE 2. Relative risk of type 2 diabetes among men in MRFIT according to presence of gout at baseline

	Baseline disease status	
	No gout	Gout
No. of type 2 diabetes cases	1104	111
Incidence/100 person-years	1.79	3.08
Age-adjusted model (95% CI)	1.0	1.66 (1.37, 2.02)
Multivariate model[a] (95% CI)	1.0	1.49 (1.22, 1.82)
Dietary factors-added multivariate model[b] (95% CI)	1.0	1.43 (1.17, 1.75)
Final multivariate model with all covariates[c] (95% CI)	1.0	1.34 (1.09, 1.64)

[a]Adjusted for age (continuous), the presence or absence of a family history of diabetes (yes or no), smoking status (never smoked, former smoker, current smoker, 1–14 cigarettes per day, or current smoker, 15–24 and >25 cigarettes per day), BMI (<23.0, 23.0–23.9, 24.0–24.9, 25.0–26.9, 27.0–28.9, 29.0–30.9, 31.0–34.9 or >35.0), hypertension (yes or no) and physical activity (five categories).

[b]Adjusted for all variables in the multivariate model above plus intakes (quintiles) of total energy, cereal fibre, polyunsaturated fat, monounsaturated fat, saturated fat, coffee and alcohol (daily consumption: 0, 0.01–0.09, 0.1–0.49, 0.5–0.99, 1.0–2.9 and >3.0 drinks per day).

[c]Adjusted for all variables in the multivariate models above plus presence of biomarker components of the metabolic syndrome (i.e. high fasting blood glucose, hypertriglyceridaemia and low HDL cholesterol).

significant when we used an alternative definition of gout that additionally required presence of hyperuricaemia (RR 1.31; 95% CI 1.05, 1.65) and use of anti-gout medication (RR 1.48; 95% CI 1.12, 1.96). When we further adjusted for serum uric acid levels in our final model, the association remained significant (multivariate RR 1.26; 95% CI 1.02, 1.54). When we updated the status of gout annually during follow-up (as a time-varying covariate), the RRs for type 2 diabetes among men with gout remained similar (multivariate RR of the full model, 1.35; 95% CI 1.10, 1.66).

Serum uric acid levels and incident type 2 diabetes

The incidence of type 2 diabetes increased with increasing serum urate levels at baseline. The incidence rates of type 2 diabetes per 100 person-years from the bottom quintile of serum uric acid levels (<333 μmol/l [5.6 mg/dl]) to the top (≥464 μmol/l [7.8 mg/dl]) were 1.32, 1.63, 1.80, 2.07 and 2.47, respectively (P-values for trend <0.001). Compared with men with the lowest quintile of serum uric acid levels at baseline, the age-adjusted RR for incident type 2 diabetes was 1.88 (95% CI 1.52, 2.32) among men in the highest quintile of serum uric acid level. When we adjusted for other covariates, the RRs became attenuated but remained significant in multivariate models that did not include baseline fasting blood sugar (P-values for trend <0.001), but after adjusting for this variable, the association became insignificant (P-values for trend, 0.43). When we updated the status of gout annually during follow-up (as a time-varying exposure variable), all multivariate RRs between the extreme quintiles were significant (multivariate P-values for trend <0.001; multivariate RR of the final model including fasting hyperglycaemia, 1.70; 95% CI 1.38, 2.11).

Subgroup analyses and potential interactions

The association between history of gout and type 2 diabetes did not vary significantly by treatment group, presence of obesity, family history of type 2 diabetes, history of hypertension or presence of the metabolic syndrome (P-values for interaction >0.16). Similarly, the association between serum uric acid levels and type 2 diabetes did not vary significantly by these factors (P-values for interaction >0.61).

Discussion

In this large prospective cohort of men with a high cardiovascular risk profile, we found that men with gout had a higher future risk of type 2 diabetes. This association was independent of age, BMI, smoking, family history of type 2 diabetes, alcohol intake, dietary factors and presence of the metabolic syndrome or its individual components. The current study provides the first prospective data on the independent association between gout and the risk for type 2 diabetes. These findings provide support for aggressive management of cardiometabolic risk factors including hypertension, dyslipidaemia and lifestyle factors in patients with gout.

Overall, our findings on the impact of serum uric acid levels on the risk of type 2 diabetes were consistent with the recent data from the Finnish diabetes prevention study [20]. In this lifestyle intervention study of high-risk middle-aged subjects with impaired glucose tolerance, baseline uric acid and its changes predicted a two fold increase in the likelihood of developing type 2 diabetes [20]. Our study found that the risk of type 2 diabetes increased with increasing serum urate levels at similar magnitudes, particularly with updated serum uric acid level as a time-varying exposure variable.

A conceivable mechanism behind the link between hyperuricaemia and the risk of type 2 diabetes may occur at the renal level [20]. Higher insulin levels are known to reduce renal excretion of urate [31–34]. For example, exogenous insulin can reduce the renal excretion of urate in both healthy and hypertensive subjects [1, 31, 32]. Insulin may enhance renal urate reabsorption via stimulation of the urate–anion exchanger URAT1 [35] and/or the Na^+-dependent anion cotransporter in brush border membranes of the renal proximal tubule [36]. Urinary uric acid clearance decreases with decreasing insulin-mediated glucose disposal and decreased uric acid excretion leads to hyperuricaemia [20]. Hyperuricaemia has been found to be an independent risk factor for progression to hyperinsulinaemia and thereby preceded hyperinsulinaemia in the 11-yr follow-up of non-diabetic participants of the Atherosclerosis Risk in Communities Study [20, 37].

The link between the presence of gout and the risk of type 2 diabetes may also stem from the shared metabolic factors of the two conditions, including the factors associated with the metabolic syndrome. While we found that the association was significant even after adjusting for individual biomarker components of the metabolic syndrome according to the revised National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) criteria [8], it remains conceivable that other unmeasured factors associated with the metabolic syndrome may explain the link between gout and the risk of type 2 diabetes. Furthermore, the independent association with gout, despite adjusting for serum uric acid levels, suggests that the impact of gout itself may go beyond the potential influence of serum uric acid levels. A possible explanation for this excess risk is that ongoing low-grade inflammation among patients with gout may promote the diabetogenic process [18].

Strengths and limitations of our study deserve comment. Men in the MRFIT were at relatively high risk of developing coronary artery disease, and thus, these results are most directly generalizable to men with a similar cardiovascular risk profile. Although the demographic characteristics of our study participants (i.e. men aged ≥36 yrs) reflect a population at a high risk for gout and type 2 diabetes [38], the generalizability of our findings to men with different demographic profile or a lower cardiovascular risk remains to be studied. Furthermore, given the potential influence of female hormones on the risk of gout in women [39, 40], prospective studies of female populations would be valuable. The self-reported diagnosis of gout by a physician was not validated in this study. However, it is unlikely that misclassification of the diagnosis would explain the associations observed in this population study. These results could become stronger with more specific case definitions of gout, which would likely reduce random misclassification. For example, findings from the Health Professionals Follow-up Study showed that the associations with suspected risk factors for self-reported gout were underestimated compared with gout diagnosed based on the ACR survey criteria [41, 42]. Furthermore, our results remained robust with alternative case definitions of gout that required presence of hyperuricaemia and anti-gout medications. Nevertheless, confirming these results using specific case definitions of gout would be valuable.

In conclusion, these findings from men with a high cardiovascular risk profile suggest that men with gout are at a higher future risk of type 2 diabetes independent of other known risk factors. These data expand on well-established, cross-sectional associations between hyperuricaemia, gout and the metabolic syndrome, and extend the link to a major complication of this syndrome, type 2 diabetes. These findings provide support for aggressive management of diabetes risk factors in men with gout, which is largely in line with the life-style measures for gout [36, 43].

Rheumatology key messages

- Men with gout are at a higher future risk of type 2 diabetes.
- This association is independent of other risk factors.
- These findings support the aggressive management of diabetes risk factors in gout.

Acknowledgements

H.K. Choi holds the Mary Pack Arthritis Society of Canada Chair in Rheumatology.

Funding: M.A. De Vera receives training support from the Canadian Arthritis Network, the Michael Smith Foundation for Health Research, and the Canadian Institutes of Health Research.

Disclosure statement: The authors have declared no conflicts of interest.

References

1 Emmerson B. Hyperlipidaemia in hyperuricaemia and gout. Ann Rheum Dis 1998;57:509–10.
2 Lee J, Sparrow D, Vokonas PS, Landsberg L, Weiss ST. Uric acid and coronary heart disease risk: evidence for a role of uric acid in the obesity-insulin resistance syndrome. The Normative Aging Study. Am J Epidemiol 1995;142:288–94.
3 Rathmann W, Funkhouser E, Dyer AR, Roseman JM. Relations of hyperuricemia with the various components of the insulin resistance syndrome in young black and white adults: the CARDIA study. Coronary Artery Risk Development in Young Adults. Ann Epidemiol 1998;8:250–61.
4 Vazquez-Mellado J, Conrado GG, Vazquez SG *et al.* Metabolic syndrome and ischemic heart disease in gout. J Clin Rheumatol 2004;10:105–9.
5 Rho YH, Choi SJ, Lee YH *et al.* The prevalence of metabolic syndrome in patients with gout: a multicenter study. J Korean Med Sci 2005;20:1029–33.
6 Choi HK, Ford ES. Prevalence of the metabolic syndrome in individuals with hyperuricemia. Am J Med 2007;120:442–7.
7 Choi HK, Ford ES, Li C, Curhan G. Prevalence of the metabolic syndrome in patients with gout: the Third National Health and Nutrition Examination Survey. Arthritis Rheum 2007;57:109–15.
8 Grundy SM, Cleeman JI, Daniels SR *et al.* Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735–52.
9 American Heart Association. http://www.americanheart.org/presenter.jhtml?identifier=3033454 (15 December 2005, date last accessed).
10 Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation 2005;112:3066–72.
11 Haffner SM. Risk constellations in patients with the metabolic syndrome: epidemiology, diagnosis, and treatment patterns. Am J Med 2006;119:S3–9.
12 Malik S, Wong ND, Franklin SS *et al.* Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. Circulation 2004;110:1245–50.
13 Lakka HM, Laaksonen DE, Lakka TA *et al.* The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. J Am Med Assoc 2002;288:2709–16.
14 Trevisan M, Liu J, Bahsas FB, Menotti A. Syndrome X and mortality: a population-based study. Risk Factor and Life Expectancy Research Group. Am J Epidemiol 1998;148:958–66.
15 Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. J Am Med Assoc 2002;287:356–9.
16 Ford ES. Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. Diabetes Care 2005;28:1769–78.
17 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.
18 Krishnan E, Baker JF, Furst DE, Schumacher HR. Gout and the risk of acute myocardial infarction. Arthritis Rheum 2006;54:2688–96.
19 Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. Circulation 2007;116:894–900.
20 Niskanen L, Laaksonen DE, Lindstrom J *et al.* Serum uric acid as a harbinger of metabolic outcome in subjects with impaired glucose tolerance: the Finnish Diabetes Prevention Study. Diabetes Care 2006;29:709–11.
21 Davey Smith G, Bracha Y, Svendsen KH, Neaton JD, Haffner SM, Kuller LH. Incidence of type 2 diabetes in the randomized Multiple Risk Factor Intervention Trial. Ann Intern Med 2005;142:313–22.
22 The Multiple Risk Factor Intervention Trial Group. Statistical design considerations in the NHLI Multiple Risk Factor Intervention Trial (MRFIT). J Chronic Dis 1977;30:261–75.
23 Multiple Risk Factor Intervention Trial Research Group. Multiple Risk Factor Intervention Trial: risk factor changes and mortality results. J Am Med Assoc 1982;248:1465–77.
24 Sherwin R, Kaelber CT, Kezdi P, Kjelsberg MO, Thomas HE Jr. The Multiple Risk Factor Intervention Trial (MRFIT) II. The development of the protocol. Prev Med 1981;10:402–25.
25 Neaton JD, Grimm RH Jr, Cutler JA. Recruitment of participants for the multiple risk factor intervention trial (MRFIT). Control Clin Trials 1987;8:41S–53S.
26 Gelber AC, Klag MJ, Mead LA *et al.* Gout and risk for subsequent coronary heart disease. The Meharry–Hopkins Study. Arch Intern Med 1997;157:1436–40.
27 Multiple Risk Factor Intervention Trial Research Group. Coronary heart disease death, nonfatal acute myocardial infarction and other clinical outcomes in the Multiple Risk Factor Intervention Trial. Am J Cardiol 1986;58:1–13.
28 Supplement 1. American Diabetes Association: clinical practice recommendations 2000. Diabetes Care 2000;23:S1–116.
29 Dolecek TA, Stamler J, Caggiula AW, Tillotson JL, Buzzard IM. Methods of dietary and nutritional assessment and intervention and other methods in the Multiple Risk Factor Intervention Trial. Am J Clin Nutr 1997;65:196S–210S.
30 Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004;109:433–8.
31 Ter Maaten JC, Voorburg A, Heine RJ, Ter Wee PM, Donker AJ, Gans RO. Renal handling of urate and sodium during acute physiological hyperinsulinaemia in healthy subjects. Clin Sci 1997;92:51–8.
32 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.
33 Facchini F, Chen YD, Hollenbeck CB, Reaven GM. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. J Am Med Assoc 1991;266:3008–11.
34 Dessein PH, Shipton EA, Stanwix AE, Joffe BI, Ramokgadi J. Beneficial effects of weight loss associated with moderate calorie/carbohydrate restriction, and increased proportional intake of protein and unsaturated fat on serum urate and lipoprotein levels in gout: a pilot study. Ann Rheum Dis 2000;59:539–43.
35 Enomoto A, Kimura H, Chairoungdua A *et al.* Molecular identification of a renal urate anion exchanger that regulates blood urate levels. Nature 2002;417:447–52.
36 Choi HK, Mount DB, Reginato AM. Pathogenesis of gout. Ann Intern Med 2005;143:499–516.
37 Carnethon MR, Fortmann SP, Palaniappan L, Duncan BB, Schmidt MI, Chambless LE. Risk factors for progression to incident hyperinsulinemia: the Atherosclerosis Risk in Communities Study, 1987–1998. Am J Epidemiol 2003;158:1058–67.
38 Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. Am J Med 1987;82:421–6.
39 Nicholls A, Snaith ML, Scott JT. Effect of oestrogen therapy on plasma and urinary levels of uric acid. Br Med J 1973;1:449–51.
40 Gibson T, Hannan SF, Hatfield PJ *et al.* The effect of acid loading on renal excretion of uric acid and ammonium in gout. Adv Exp Med Biol 1977;76B:46–56.
41 Choi HK, Atkinson K, Karlson EW, Willett WC, Curhan G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. N Engl J Med 2004;350:1093–103.
42 Choi HK, Atkinson K, Karlson EW, Willett WC, Curhan G. Alcohol intake and risk of incident gout in men - a prospective study. Lancet 2004;363:1277–81.
43 Choi HK. Diet, alcohol, and gout: how do we advise patients given recent developments? Curr Rheumatol Rep 2005;7:220–6.