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Serum uric acid and metabolic risk factors in three ethnic groups: Asian Indians and Creoles in Mauritius and Chinese in Qingdao, China

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ACADEMIC DISSERTATION

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ABBREVIATIONS

AMP	Adenosine monophosphate
ATP	Adenosine triphosphate
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
FCG	Fasting Capillary whole blood Glucose
FPG	Fasting plasma glucose
HDL-C	High-density lipoprotein cholesterol
IFG	Impaired fasting glycemia
IGT	Impaired glucose tolerance
IR	Insulin resistance
IDF	International Diabetes Federation
MNCDS	Mauritius Non-Communicable Diseases Survey
NADPH	Nicotinamide adenine dinucleotide phosphate
NCEP	National Cholesterol Education Program adult treatment expert panel III
NHANES	National Health and Nutrition Examination Survey
OGTT	Oral glucose tolerance test
QDS	Qingdao Diabetes Survey
SD	Standard deviation
UA	Uric acid
WHO	World Health Organization
2-hPG	2-hour plasma glucose

ABSTRACT

In humans with a loss of uricase the final oxidation product of purine catabolism is uric acid (UA). The prevalence of hyperuricemia has been increasing around the world accompanied by a rapid increase in obesity and diabetes. Since hyperuricemia was first described as being associated with hyperglycemia and hypertension by Kylin in 1923, there has been a growing interest in the association between elevated UA and other metabolic abnormalities of hyperglycemia, abdominal obesity, dyslipidemia, and hypertension. The direction of causality between hyperuricemia and metabolic disorders, however, is unceertain. The association of UA with metabolic abnormalities still needs to be delineated in population samples.

Our overall aims were to study the prevalence of hyperuricemia and the metabolic factors clustering with hyperuricemia, to explore the dynamical changes in blood UA levels with the deterioration in glucose metabolism and to estimate the predictive capability of UA in the development of diabetes.

Four population-based surveys for diabetes and other non-communicable diseases were conducted in 1987, 1992, and 1998 in Mauritius, and in 2001-2002 in Qingdao, China. The Qingdao study comprised 1 288 Chinese men and 2 344 women between 20-74, and the Mauritius study consisted of 3 784 Mauritian Indian and Mauritian Creole men and 4 442 women between 25-74. In Mauritius, re-exams were made in 1992 and/or 1998 for 1 941 men (1 409 Indians and 532 Creoles) and 2 318 non-pregnant women (1 645 Indians and 673 Creoles), free of diabetes, cardiovascular diseases, and gout at baseline examinations in 1987 or 1992, using the same study protocol. The questionnaire was designed to collect demographic details, physical examinations and standard 75g oral glucose tolerance tests were performed in all cohorts. Fasting blood UA and lipid profiles were also determined.

The age-standardized prevalence in Chinese living in Qingdao was 25.3% for hyperuricemia (defined as fasting serum UA > 420 μmol/l in men and > 360 μmol/l in women) and 0.36% for gout in adults between 20-74. Hyperuricemia was more prevalent in men than in women. One standard deviation increase in UA concentration was associated with the clustering of metabolic risk factors for both men and women in three ethnic groups. Waist circumference, body mass index, and serum triglycerides appeared to be independently associated with hyperuricemia in both sexes and in all ethnic groups except in Chinese women, in whom triglycerides, high-density lipoprotein cholesterol, and total cholesterol were associated with hyperuricemia. Serum UA increased with increasing fasting plasma glucose levels up to a value of 7.0-mmol/l, but significantly decreased thereafter in mainland Chinese. An inverse relationship occurred between 2-h plasma glucose and serum UA when 2-h plasma glucose higher than 8.0 mmol/l. In the prospective study in Mauritius, 337 (17.4%) men and 379 (16.4%) women developed diabetes during the follow-up. Elevated UA levels at baseline increased 1.14-fold in risk of incident diabetes in Indian men and 1.37-fold in Creole men, but no significant risk was observed in women.

In conclusion, the prevalence of hyperuricemia was high in Chinese in Qingdao, blood UA was associated with the clustering of metabolic risk factors in Mauritian Indian, Mauritian Creole, and Chinese living in Qingdao, and a high baseline UA level

independently predicted the development of diabetes in Mauritian men. The clinical use of UA as a marker of hyperglycemia and other metabolic disorders needs to be further studied.

Keywords: Uric acid, Hyperuricemia, Risk factors, Type 2 Diabetes, Incidence, Mauritius, Chinese

1 INTRODUCTION

As an end product of the purine metabolism in humans, the serum uric acid (UA) concentration is determined by an interaction of genetic and environmental factors. The UA levels are higher in humans and the Great and Lesser Apes due to parallel mutations of the uricase gene that occurred during the mid Miocene era (Wu et al. 1992). The consequence of the mutation is that humans not only have higher UA levels than most other mammals but they can not regulate UA levels as effectively as others either (Johnson et al. 2004; Johnson et al. 2005b).

The uricase mutation may have conferred a survival advantage by helping to maintain blood pressure (BP), stimulate salt-sensitivity, and induce insulin resistance (IR) and mild obesity, thereby helping promote survival during a period of famine or stress (Johnson et al. 2008). Western lifestyle, however, including western diet and physical inactivity have swept the world during the past few decades. Since the current western diet is high in meat and fructose, both which generate UA, humans today have higher UA levels (range 238–595 μmol/l) compared with primates that lack uricase (whose UA levels are typically in the 178–238 μmol/l range) (Johnson et al. 2005b).

Hyperuricemia is defined as a serum UA concentration in excess of urate solubility, which is about 420 μmol/l in men and 360 μmol/l in women (Fang et al. 2000). People with elevated UA, but without the symptoms of gout, nephropathy, or kidney stones are classified as having asymptomatic hyperuricemia. If the gouty symptom does not occur, people with asymptomatic hyperuricemia are usually unaware of their condition and the possible consequences such as hypertension, diabetes, renal disease, and cardiovascular diseases.

Increased urbanization, westernization, and economic development have already contributed to a worldwide substantial rise in obesity and diabetes. Interestingly, the prevalence of hyperuricemia has shown a rise in both developing and developed countries, accompanied by a rapid increased rate in obesity and diabetes (Chang et al. 2001; Conen et al. 2004; Darmawan et al. 1992). The prevalence of hyperuricemia and gout has reportedly been increasing recently in large Chinese cities, even though it was once considered to be rare in China (Chen et al. 1998; Fang et al. 1983; Li et al. 1997). To our knowledge this is the first study on the prevalence of hyperuricemia and gout in Qingdao, one of the largest harbor cities in China, with a high consumption rate of seafood and beer.

Since hyperuricemia was first described as being associated with hyperglycemia and hypertension by Kylin in 1923 (Kylin 1923), there has been a growing interest in the association between elevated UA and other metabolic abnormalities of hyperglycemia, abdominal obesity, dyslipidemia, and hypertension, as well as a continuing debating on hyperuricemia as an additional component of the metabolic syndrome (Liou et al. 2006; Zavaroni et al. 1993). Serum UA is positively associated with plasma glucose in healthy subjects (Facchini et al. 1991; Modan et al. 1987). This association, however, is not consistent between healthy and diabetic individuals (Nakanishi et al. 2003; Taniguchi et al. 2001; Tuomilehto et al. 1988). Since most individuals experience a phase of impaired glucose tolerance (IGT) before progression to diabetes, it is unclear to what extent serum UA independently predicts the development of diabetes during

the pre-diabetes period. Hyperuricemia is associated with BP in middle-aged men without diabetes, glucose intolerance, and the metabolic syndrome (Krishnan et al. 2007). Elevated UA is significantly associated with several indices of coronary heart disease risk and a number of the metabolic abnormalities (Coutinho et al. 2007; Ishizaka et al. 2005). Other studies, however, provided conflicting results in general populations (Baker et al. 2005; Culleton et al. 1999; Wheeler et al. 2005). Hyperuricemia occurs with increased frequency in several important metabolic disorders in which no clear or direct cause–and-effect relationship in either direction has been established. The association of UA with metabolic abnormalities still needs to be delineated in other population samples.

The prevalence of obesity, hypertension, diabetes, dyslipidemia, and hyperuricemia have been increasing over the last few decades in the southern Indian Ocean island of Mauritius and in China due to rising living standards occurring with modernization and urbanization (DECODE Study Group 2003; Dong et al. 2005; Li et al. 1997; Soderberg et al. 2005). Population-based surveys with focus on diabetes were conducted in Mauritius in 1987, 1992, and 1998 (Soderberg et al. 2004), and in Qingdao, China in 2001-2002. These data create a unique opportunity for description of the prevalence of hyperuricemia and gout, evaluation of the association of UA levels with glucose concentrations, estimation of the associations between serum UA and metabolic abnormalities in the different ethnic groups from these two countries, and exploration of the predictive value of UA for incident type 2 diabetes.

2 REVIEW OF THE LITERATURE

2.1 UA

2.1.1 Physiology of UA

UA is an end product of purine metabolism and is related to the purine bases of the nucleic acids in humans. Nearly 15 million years ago, one of our hominid ancestors acquired a mutation in the gene for uricase, the hepatic enzyme that degrades UA into allantoin. As a consequence, having lost the ability to express urate oxidase, humans are exposed to higher serum UA levels than other mammals (Marangella 2005; Wu et al. 1992) with UA levels in the 59-119 μmol/l range. The serum UA level is determined by the balance between purine intake and UA production on the one hand and UA elimination by renal and extrarenal routes on the other. Approximately two thirds of total body urate are produced endogenously, the remaining one third is accounted for by dietary purines. Approximately 70% of the urate produced daily, however, is excreted by the kidneys. The rest is eliminated by the intestines. Normal serum UA levels are less than 420 μmol/l in men and 330-360 μmol/l in women (Johnson et al. 1999). UA levels are lower in premenopausal women because estrogen is uricosuric (Nicholls et al. 1973). After menopause, UA levels in women are similar to men. They also increase with age (Glynn et al. 1983). Furthermore, UA levels may vary in the same individual by as much as 59 to 119 μmol/l during the course of a day, due to the effects of diet and exercise.

Hyperuricemia is arbitrarily defined as a serum UA concentration in excess of urate solubility, which is about 420 μmol/l in men and 360 μmol/l in women. Hyperuricemia may occur from excessive production of urate (overproduction) or decreased elimination (underexcretion), and frequently a combination of both processes occur in the same patient. Long-term hyperuricemia is a causal factor to damage development in the joints, connective tissues, and kidney. Those with elevated UA levels, but without gout, nephropathy or kidney stone symptoms, are classified as having asymptomatic hyperuricemia.

Gout management is well identified. It includes rapid and safe termination of the acute attacks of gouty arthritis, protection against further attacks prior to and during urate lowering, and establishment and long-term maintenance of subsaturating serum UA levels that will eventually normalize the extracellular urate pool. Nevertheless so far it has not been determined whether the urate-lowering therapy suits asymptomatic hyperuricemia. Allopurinol is arguably the most effective urate-lowering agent available today and is generally well tolerated. About 2% of those individuals receiving allopurinol develop hypersensitivity reactions, however, and 20% of those are severe. Severe reactions include severe rash, toxic epidermal necrolysis, hepatitis, interstitial nephritis, and death (Wortmann 2002). Recently, additional urate-lowering agents have been developed and are currently undergoing clinical trials. These include febuxostat, a xanthine oxidase inhibitor, structurally distinct from allopurinol and metabolized mainly in the liver (Becker et al. 2004) and pegloticase (pegylated recombinant porcine uricases), biological agents that replace the activity of uricase (Sundy et al. 2007). The safety of these agents, however, is under evaluation.

The rise in UA concentration has historically been viewed as simply a potential risk factor for inducing gout, however, clinical gout is only the tip of the iceberg. If the gouty symptom does not occur, people with asymptomatic hyperuricemia are usually unaware of their condition. Hyperuricemia is associated with, and may predispose to, hypertension, diabetes, renal disease, and cardiovascular disease.

Table 1 Prevalence (%) of hyperuricemia in different ethnic groups and geographic regions

Ethnicity	Survey year	Geographic locations	Age (years)	Number men/women	Prevalence (%) men	Prevalence (%) women	Reference
Caucasian	1970	Birminham, Winfrish and Glasgow, UK	Adult	849/254	7.2	0.4 [a]	(Sturge et al. 1977)
Caucasian	1989	Southern Germany			28.6 [b]	2.6 [b]	(Gresser et al. 1990)
Caucasian	1990-1992	New Zealand	≥19	139/176	9.4	10.5	(Klemp et al. 1997)
Chinese	1980	Beijing, Shanghai and Guangzhou, China	≥20	267/235	1.4	1.3	(Fang et al. 1983)
Chinese	1987-1988	Beijing urban area, China	40-58	1 062/951	15.4	11.0	(Li et al. 1997)
		Beijing rural area, China	40-58	558/949	11.3	8.4	(Li et al. 1997)
Chinese	1995-1996	Littoral area, Shandong, China	≥20	-	5.8	0.05	(Jiang et al. 1999)
Chinese	1998	Shanghai, China	≥15	913/1 124	14.2	7.1	(Chen et al. 1998)
Chinese	2004-2006	Hangzhou, China	Adult	1 468/906	19.1	3.4	(Chen et al. 2007)
Chinese (Han and Muslim)	2006	Beijing, China	Adult	1 217/780	13.8	6.0	(Fang et al. 2006)
Chinese, Han	1991-1992	Taiwan Kin-Hu, Kinmen	≥30	1 515/1 670	25.8	15.0	(Lin et al. 2000)
Chinese, Han	1993-1996	Taiwan	≥19	1 348/1 498	42.1	27.4	(Chang et al. 2001)
					26.1[b]	17.0 [b]	(Chang et al. 2001)
Taiwanese	1993-1996	Taiwan Metropolitan cities	≥19	204/201	48.0	20.7	(Chang et al. 2001)
Taiwanese	1993-1996	Taiwan Mountainous area	≥19	206/233	82.0	64.3	(Chang et al. 2001)
Taiwan aborigines	1990	Taiwan Mountainous area	≥18	145/197	53.8	30.7	(Chou et al. 1998)

Table 1 Continues

Ethnicity	Survey year	Geographic locations	Age (years)	Number men/women	Prevalence (%) men	women	Reference
Taiwan aborigines	1994-1999	Taiwan	12-15	476/464	50.4	37.7	(Ko et al. 2002)
Chinese and Taiwan aborigines	1999-2000	Taiwan	≥65	1 225/1 167	46.0	26.0	(Lee et al. 2005)
Thailander	1999-2000	Bangkok, Thailand	≥15	376/1 005	18.4	7.8	(Lohsoonthorn et al. 2006)
Melanesian	1980	Fiji	≥20	643/697	26.7	27.1	(Tuomilehto et al. 1988)
Asian Indian	1980	Fiji	≥20	598/700	21.7	10.9	(Tuomilehto et al. 1988)
Maori	1963	New Zealand	≥15	388/378	49.0	42.0	(Brauer et al. 1978)
Maori	1990-1992	New Zealand	≥19	130/212	27.1	26.6	(Klemp et al. 1997)
Micronesian-Polynesian	1978	Urban area in Nauru	≥20	217/238	63.6	60.0	(Zimmet et al. 1978)
Malayo-Polynesian	1992	Rural area in Java		Total: 4 683	24.3	12.2	(Darmawan et al. 1992)
African descent	1994	Seychelles	25-64	482/529	35.2	8.7	(Conen et al. 2004)
Arab	1998-1999	Saudi Arabia	≥14	250/237	8.0	8.9	(Al-Arfaj 2001)
Parkateje Indian	1997	Amazon region, Brazil	≥20	56/34	5.6	-	(Tavares et al. 2003)
Japanese	2000	Okinawa, Japan	18-89	2 927/1 562	32.6	9.0	(Nagahama et al. 2004a)
White and African-American	1987-1989	4 community, US	45-64	Total:14 481	11.2 [c]		(Schmidt et al. 1996)

[a] Hyperuricemia defined as UA >420 μmol/l for women, [b] Hyperuricemia defined as UA ≥458 μmol/l for men and ≥393 μmol/l for women;
[c] Hyperuricemia defined as UA ≥480 μmol/l; the rest using uric acid >420 μmol/l for men and >360 μmol/l for women.

2.1.2 Epidemiology of hyperuricemia

The prevalence of hyperuricemia varies markedly depending on the difference in ethnic groups, geographic regions and survey years (Table 1). Among twenty three studies (Al-Arfaj 2001; Brauer et al. 1978; Chang et al. 2001; Chen et al. 2007; Chen et al. 1998; Chou et al. 1998; Conen et al. 2004; Darmawan et al. 1992; Fang et al. 1983; Fang et al. 2006; Jiang et al. 1999; Klemp et al. 1997; Ko et al. 2002; Lee et al. 2005; Li et al. 1997; Lin et al. 2000; Lohsoonthorn et al. 2006; Nagahama et al. 2004a; Sturge et al. 1977; Tavares et al. 2003; Tuomilehto et al. 1988; Zimmet et al. 1978) that used the hyperuricemia definition of > 420 μmol/l for men and of > 360 μmol/l for women, the prevalence of hyperuricemia ranged from 0.05% in Chinese women in Shandong in 1995-1996 to 82.0% in male aborigines in Taiwan in 1993-1996. The prevalence was lowest among Mainland Chinese and Indians in the Amazon region of Brazil and highest among aborigines in Taiwan Mountainous area and Maori in New Zealand in both men and women.

Trend studies in Caucasian (Gresser et al. 1990) and Han Chinese in Taiwan (Chang et al. 2001; Lin et al. 2000) showed that the prevalence of hyperuricemia has increased over past decades. A follow-up study of southern Germany (Gresser et al. 1990) showed the UA levels have increased in both sexes over secular periods, since 1962, 1971, 1984, and 1989. The prevalence of hyperuricemia reached 2.6% for women and 28.6% for men in southern Germany in 1989. Early historical evidence suggests that the Maori people of New Zealand were virtually untroubled by gout or obesity at the time when these disorders were rife in the best fed and hardest drinking sections of the northern European population (Rose 1975). During the past decades, with the introduction of a western culture and diet, there has been a significant change. By the mid 20th century, however, with an apparent decline of gout in Europe and North America, hyperuricemia and gout appeared on a large scale in Maori and in other indigenous inhabitants of the Pacific islands. Half the Polynesian population of New Zealand, Rarotonga, Puka Puka, and the Tokelau Islands had hyperuricemia by accepted European and North American standards. The associated gout rate reached 10.2% in Maori males aged 20 and over (Rose 1975). Studies of indigenous Pacific populations have also documented that the serum UA is higher in Maori in New Zealand (Brauer et al. 1978; Klemp et al. 1997), Filipinos in Hawaii and Alaska (Healey et al. 1966), and Chamorros and Carolinians in the Marianas Islands (Burch et al. 1966).

The increase in serum UA levels, or the prevalence of hyperuricemia, appears to be associated with the economic development (Wortmann 2002). For instance, the Chinese emigrants in Malaya and western Canada have higher serum UA concentrations than their relatives who live still in Taiwan (Ford et al. 1964), the urban African black populations have higher serum UA levels than those with the same ethnicities, but living in the rural community (Beighton et al. 1974).

It has also been noticed that serum UA levels tend to be higher in certain populations (e.g., Pacific Islanders and Taiwan aborigines in high Mountainous area), with certain phenotypes (obesity, metabolic syndrome), and with special diets (meat eaters) (Brauer

et al. 1978; Chang et al. 1997; Klemp et al. 1997). Australian indigenous (Emmerson et al. 1969) and Taiwanese aborigines have higher UA levels than Caucasian and Chinese population in the same residential area, respectively (Chang et al. 2001). Taiwanese aborigines are genetically related to the Malayo-Polynesians (Chang et al. 2001), having a different genetic background compared to the Chinese population in Taiwan, most of whom came from southern mainland China some 400 years ago and some of whom arrived from the central and northern areas of mainland China 50 years ago (Chou et al. 1998; Chungtei 2003). In addition, the higher prevalence of hypericemia in Taiwanese aborigines, compared to other populations in Taiwan, is also associated with a higher body mass index (BMI), and a higher consumption of alcohol and organ meat, such as heart, kidney, and liver sweetbread (Chang et al. 2001; Chou et al. 1993).

2.2 Hyperuricemia associated with non-metabolic factors

2.2.1 Dietary factors

Dietary purine is an important exogenous source of UA. The transition of Western lifestyle in developing counties or areas has been associated with increases in serum UA levels and the prevalence of hyperuricemia (Kagan et al. 1974; Lennane et al. 1960). During the past couple centuries, large amounts of research demonstrated meat, beef liver, seafood, haddock, and mushrooms as purine-rich food. An experimental study (Brule et al. 1992) showed that a purine-rich diet increases serum UA 2-4 hours post meals with a transient elevation with serum UA levels of 59-118 μmol/l, whereas, a purine-free diet, containing the same amount of calories, will take 7-10 days to decrease serum UA levels by the same amount. The National Health and Nutrition Examination Survey (NHANES) III (1988-1994) in the US, including 14 809 participants (6 932 men and 7 877 women) over 20, indicated that higher levels of meat and seafood consumption are associated with higher serum UA levels, but that total protein intake is not and dairy consumption is inversely associated (Choi et al. 2005). This was confirmed by a Dutch elder population study (Loenen et al. 1990). Actually, a diet low in meat and high in dairy products had been considered protective against gout since the 17th-19th centuries (Schlesinger 2005). Since dairy products are low in purine content, dairy protein (casein and lactalbumin) may exert its uricosuric effect without providing the concomitant purine load contained in other protein sources, such as meat and seafood (Garrel et al. 1991).

Fructose is consumed in significant amounts in Western diet. An increase in fructose consumption over the past 10-20 years has been linked with a rise in obesity and metabolic disorders (Johnson et al. 2007; Le et al. 2006). Fructose intake may raise serum UA levels by increasing adenosine triphosphate (ATP) degradation to adenosine monophosphate (AMP), prompting activation of the pathway of purine degradation to urate (Hallfrisch 1990; Mayes 1993). In contrast, glucose and other simple sugars do not have this effect (Nakagawa et al. 2005). It is also suspected that the cellular mechanisms underlying the metabolic effects of fructose involve the production of reactive oxygen species, activation of cellular stress pathways, and possibly an increase in UA synthesis (Le et al. 2006). After studying recent research on association of fructose, hyperuricemia, and cardiovascular diseases in humans, Johnson et al. concluded that fructose and UA associated mechanisms are likely to be of more importance in the initial development of the metabolic syndrome phenotype and may

become less important once obesity, hypertension, and renal disease became established (Johnson et al. 2007).

Tofu (soybean curd), a popular food among vegetarians in the Asian population, is rich in protein, but most of the purines are lost during processing, and ingestion of tofu produces only a small rise of serum UA in both healthy individuals and gout sufferers (Yamakita et al. 1998). A study of Chinese vegetarians and omnivores found that the omnivores had higher serum UA levels and lower insulin sensitivity than vegetarians, and the degree of insulin sensitivity appeared to correlate with years on a vegetarian diet (Kuo et al. 2004). A controlled randomized crossover designed trail evaluating the metabolic effects of diets high in vegetable protein (specifically, wheat gluten) found that high intakes of vegetable protein of gluten reduced oxidized low density lipoproteins, triglycerides, and serum UA levels (Jenkins et al. 2001).

Alcohol consumption

Alcohol consumption is independently and significantly associated with hyperuricemia and gout (Drum et al. 1981; Loenen et al. 1990; Lyu et al. 2003). In a 12-year cohort study (Choi et al. 2004) using biannual questionnaires, Choi et al. found that moderate regular consumption of beer was associated with gout incidence (the multivariate adjusted relative risk of 1.49 per 12-oz beer serving per day). In contrast, moderate wine consumption of 1-2 glasses per day did not increase the risk of development of gout. Beer has a high purine content, predominantly as readily absorbable guanosine and its intake enhances urate production, compounding the stimulatory effects of alcohol metabolites on renal urate reabsorption (Yamamoto et al. 2002).

A number of mechanisms have been implicated in the pathogenesis of alcohol-induced hyperuricemia. Ethanol increases urate synthesis by enhancing the turnover of adenine nucleotides (Faller et al. 1982). Acute alcohol excess may cause temporary lactic acidaemia, reduced renal urate excretion and induced hyperuricemia. Chronic alcohol intake stimulates purine production by accelerating the degradation of ATP to AMP via the conversion of acetate to acetyl-coA in the metabolism of alcohol (Sharpe 1984).

2.2.2 Other dietary and non-dietary factors

Cherries reportedly significantly reduce the plasma UA levels, irrespectively of remaining time of consumption over hours or months (Jacob et al. 2003; Johnson et al. 2004), whereas, other fruits such as grapes, strawberries, and kiwifruit did not produce the same effect. Using the same NHANES III data, Choi and Curhan (Choi et al. 2007a) examined the association of serum UA with coffee and tea intake. The results showed that coffee consumption is associated with lower serum UA levels and hyperuricemia frequency, but tea consumption is not. Serum UA levels associated with the coffee intake of 4 to 5 and 6 cups or more daily was lower than that associated with no intake by 15.5 μmol/l (95% CI 6.5-24.4) and 25.6 mg/dl (95% CI 13.7-38.7), after adjustments. Correspondingly, in the Health Professionals Follow-up Study (HPFS) of 47 150 males over a 12-year period follow-up, increasing coffee intake was inversely associated with the risk of gout and a modest inverse association was also found for decaffeinated coffee, but not tea comsumption (Choi et al. 2007c). The absence of association between serum urate levels and total caffeine and tea intake suggests that components other than caffeine in the coffee have contributed to the inverse

association. The mechanism behind this decreased risk of gout may be due to the effect of coffee on insulin sensitivity (Hak et al. 2008). Higher long-term coffee intake is associated with lower insulin levels (Wu et al. 2005) and improved insulin sensitivity (Arnlov et al. 2004), whereas renal UA clearance is inversely related to the degree of IR (Facchini et al. 1991; Muscelli et al. 1996; Ter Maaten et al. 1997). Thus increased insulin sensitivity may lead to lower urate levels.

Diuretics are associated with hyperuricemia. Diuretics have an inhibitory effect on renal excretions of UA. Some foods, including cranberry juice and asparagus, celery, eggplant, lemon, garlic, cucumbers, and licorice, have a diuretic property that can potentially increase serum UA levels (Schlesinger 2005). Fasting is also associated with a rise in serum UA levels. This is presumably due to the inhibitory effect of ketones on UA excretion by the renal tubules for a short period (Maclachlan et al. 1967) and the dehydration for the month of Ramadan (Roky et al. 2004).

2.3 Hyperuricemia associated with metabolic risk factors

The main causes of high UA are shown in Table 2 (Becker et al. 2005). Non-modifiable risk factors for hyperuricemia include genes, age, sex, and ethnic group. Some studies of restricted populations (i.e., racially selected, geographically isolated, or families of gouty probands) have shown a bimodal distribution of serum urate values, supporting a single dominant gene hypothesis (Laskarzewski et al. 1983). Nevertheless, abundant data indicate that serum UA concentration is continuously distributed in both male and female general populations (Mikkelsen et al. 1965), although skewed slightly toward higher values. Whether a single or multiple genes determine the UA level in primary gout patients remains controversial (Becker 2002).

Table 2 Major causes of high uric acid concentration

Genetic causes
Familial hyperuricemic nephropathy (mutation of uromodulin)
Lesch-Nyan syndrome (HGPRT mutation)
Phosphoribosyl pyrophosphate synthetase (PRPPS) mutation
Dietary causes
Diet high in purines (organ meats, shellfish, fatty meats)
Diet high in fructose (high fructose corn syrup, table sugar, honey)
Ethanol
Low sale diet
Drugs
Thiazides
Loop diuretics
Calcineurin inhibitors (cyclosporine > tacrolimus)
Pyrizinamide
Low-dose aspirin
Volume depletion
Hypoxia (systemic or tissue)
Increased cell turnover (myeloproliferative disorders, polycythemia vera)
Conditions associated with higher uric acid levels
Renal failure
Obesity/metabolic syndrome
Untreated hypertension
African American race
Preeclampsia
Vigorous exercise

Reference:(Becker et al. 2005)

2.3.1 Obesity

Obesity has reached epidemic proportions in the past decade and possibly represents the most important component of the metabolic syndrome and an important risk factor for type 2 diabetes. The association of hyperuricemia with obesity has been recognized for hundreds of years (Wynagaarden et al. 1983). Hyperuricemia has been associated with increasing BMI in early studies. A high correlation between serum UA and weight and body surface area was found in American Indians in 1966 (O'Brien et al. 1966). In the same year a similar association was discovered in European populations (Krizek 1966) and in a population of the Marian Island (Burch et al. 1966). The concept of central obesity was first introduced by Vague in the 1940s (Vague 1947). Later on, in 1956, central obesity was indicated for the first time as being more important than peripheral obesity in relation to diabetes, atherosclerosis, gout, and urate calculus diseases. It has been shown in limited numbers of healthy and obese Japanese men (n = 50) that accumulation of visceral fat may have a greater adverse effect on the metabolism of UA than BMI or accumulation of subcutaneous fat (Takahashi et al. 1997). Another study of obese Japanese men (n = 36) revealed that hyperuricemia in those subjects with visceral fat obesity is related to UA overproduction, but not low 24-hour urinary urate excretion (Matsuura et al. 1998).

Recent follow-up studies further clarify the relationship between serum UA and obesity. The Coronary Artery Risk Development In young Adults (CARDIA) cohort study (n = 4 053) has shown that BMI is definitely the strongest positive factor correlating with serum UA among components of the metabolic syndrome. The significant associations of hyperuricemia with the metabolic risk factors appeared in all sex-race groups. They persisted after controlling for possible confounders, including age, education, physical activity, smoking, alcohol intake, oral contraceptive use, and creatinine, but largely decreased further adjustment for BMI (Rathmann et al. 1998). In the NHANES I epidemiologic follow-up study (n = 5 926) (Fang et al. 2000), serum UA values in the higher quartiles were associated with higher values of BMI in both men and women. Another prospective study consisting of 433 young, non-obese, normotensive men was able to measure BMI, BP, serum UA, and other items every year for 5 years and demonstrated that serum UA levels predict subsequent weight gain and BP elevation (Masuo et al. 2003). In a 12-year follow-up study of 17 155 male students at Okayama University in Japan (Ogura et al. 2004), the incidence of hyperuricemia markedly increased in parallel with BMI and was also associated with other metabolic risks, including hypercholesterolemia, fatty liver, and hypertension.

Obesity has several effects on UA metabolism, including increased UA production and decreased renal UA clearance (Emmerson 1973). In obese subjects, hyperuricemia is attributable to the overproduction of UA and impairment in the renal clearance of UA owing to the influence of hyperinsulinemia secondary to IR (Matsuura et al. 1998; Quinones Galvan et al. 1995; Yamashita et al. 1986). Weight reduction is associated with a modest lowering of serum UA concentration and a decrease in the rate of de novo purine synthesis (Emmerson 1973). In addition, the weight loss associated with moderate calorie and carbohydrate restriction and increased proportional intake of protein and unsaturated fat (as recommended for insulin-resistant states) is reported to be accompanied by a decrease in serum UA levels and dyslipidemia in gout patients (Dessein et al. 2000). Similarly, the amelioration of IR, by either a low-energy diet or

troglitazone, decreased the serum UA levels in overweight hypertensive individuals (Tsunoda et al. 2002).

A possible role of leptin in the relationship among hyperuricemia, obesity, and IR has been addressed recently. Leptin, a hormone product of the OB (obese) gene, is expressed in adipocytes and acts through the hypothalamus to regulate food intake and energy expenditure. Most obese people show leptin resistance, and increased levels are significantly associated with IR among nondiabetic individuals (Donahue et al. 1999). Insulin responses, triglyceride levels, and BMI are independently and significantly associated with leptin concentrations (Ruige et al. 1999). Serum UA levels correlate positively with serum leptin in healthy male adolescents (Ogura et al. 2000) and in moderately obese women (Garcia-Lorda et al. 2001). Matsubara et al. (Matsubara et al. 2002) found an independent relationship between serum leptin and UA among Japanese women, even after adjusting for BMI and the percentage of body fat. Similar findings were also observed among obese children (Moreno et al. 2002). Bedir et al. have recently discussed the role of leptin as a possible regulator of UA concentrations in humans and suspect that it might be a candidate for the missing link between obesity and hyperuricemia (Bedir et al. 2003). These studies imply that the association of serum UA, obesity, and IR may, at least in part, be mediated by leptin expression.

2.3.2 Dyslipidaemia

An association between hypertriglyceridemia and hyperuricemia is well established (Barlow 1968). Up to 80% of individuals with hypertriglyceridemia have hyperuricemia and 50% to 75% of gouty patients have hypertriglyceridemia. Obesity and excessive alcohol intake may be confounders of the relations between hypertriglyceridemia and hyperuricemia. In 108 gouty Japanese men, hyperlipoproteinemia was seen in 56% and appeared to be independent of both alcohol intake and obesity (Jiao et al. 1986).

Irrespective of central or peripheral type of obesity, however, it is not suspected that dyslipidemia, especially hypertriglyceridemia to be involved and interacted in the association of serum UA. More recently, free fatty acids have been discovered to be related to hyperuricemia independently of hypertriglyceridemia, obesity and central body fat distribution (Bonora et al. 1996; Conen et al. 2004). Elevated serum total cholesterol and triglycerides concentrations were observed among patients in the highest tertile of serum UA levels compared to those in the lowest tertile, and an inverse relationship was seen between HDL-C and serum UA levels (Matsubara et al. 2002). Concentrations of serum lipoprotein Lp(a) and apolipoproteins A-II, B, C-II, C-III, and E were also reported as increased, while HDL–C decreased in patients with gout (Takahashi et al. 1995). The prevalence of apolipoprotein E2 allele was greater in gout patients, and its presence was associated with higher triglyceride levels in very low-density lipoprotein and intermediate-density lipoproteins and with reduced renal UA excretion (Cardona et al. 2003).

The potential mechanisms relating hyperuricemia to fasting hypertriglyceridemia are unknown. It has been speculated that it may be due to an increase in nicotinamide adenine dinucleotide phosphate oxidase (NADPH) requirement for de novo fatty acid synthesis in obese subject (Vuorinen-Markkola et al. 1994). As noted elsewhere, UA is produced by an enzyme, xanthine oxidoreductase, which catalyzes the reaction:

Xanthine + NAD^+ + H_2O = UA +NADH + H^+. With increasing NADPH, UA production is enhanced possibly increasing the serum UA level (Vuorinen-Markkola et al. 1994). The current consensus is that the strongest association of UA is with fasting triglyceride concentrations rather than with any direct measure of insulin sensitivity (Schachter 2005). A corollary of these observations is that individuals with both hyperuricemia and hyperlipidemia, particularly those with abdominal obesity, may be at high-risk for type 2 diabetes and the cardiovascular diseases.

2.3.3 Hypertension

The relationship of UA to hypertension is independent of obesity, renal function, or anti-hypertensive medications, especially thiazide diuretics (Heinig et al. 2006). This association has been well demonstrated in many clinical and epidemiological studies (Conen et al. 2004; Fang et al. 2000; Li et al. 1997). Hyperuricemia is common in patients with essential hypertension. It appears that overall about 25% of hypertensive individuals have hyperuricemia and this figure increases to 75% in those with malignant hypertension (Cannon et al. 1966; Johnson et al. 2003). Studies suggest that hyperuricemia in hypertensive subjects reflect early renal vascular involvement associated with hypertension (Frohlich 1993; Messerli et al. 1980). Several studies, however, found that elevated serum UA appeared in hypertension patients without clinical renal dysfunction.

Univariate associations of hyperuricemia with both systolic and diastolic BP were observed, but these relationships were attenuated after adjustment for BMI, suggesting a major role of adiposity in this association (Wannamethee et al. 1997; Wannamethee 2005). Furthermore, results from most of population-based epidemiological studies support hyperuricemia as a significant independent predictor for incident hypertension by higher relative risk in Korean (Yoo et al. 2005), Italian (Jossa et al. 1994), Canadian (Forman et al. 2007), black and white from US (Dyer et al. 1999; Mellen et al. 2006), native Japanese (Nagahama et al. 2004a), and Japanese immigrants in US (Imazu et al. 2001).

On the other hand, new findings from a number of animal model experimental studies shed light on a causal role for hyperuricemia in hypertension (Nakagawa et al. 2003; Sanchez-Lozada et al. 2005; Sanchez-Lozada et al. 2006). For example, in Sprague-Dawley rats (n = 69) (Mazzali et al. 2001), mild hyperuricemia was induced by providing a uricase inhibitor (oxonic acid) in the diet. Experimentally induced hyperuricemic rats developed elevated BP after 3 weeks, whereas control rats retained normal BP. A dose-response relationship was observed between serum UA levels and BP ($r = 0.75$), with a 10 mm Hg BP increase for each 30 μmol/l increment in serum UA levels. The induced elevation in BP in experimental rats was, however, partially reversed by administration of enalapril, an angiotensin converting enzyme inhibitor, or L-arginine, a substrate for nitric oxide production (Mazzali et al. 2001). This strongly suggests that both angiotensin II and nitric oxide are involved in the pathogenesis of the hypertension induced by UA.

The underlying mechanisms of increases in the UA level with essential hypertension are still not well understood. Recent studies proposed the role of IR being the possible pathophysiological link between an altered tubular sodium handling and UA metabolism in humans (Cappuccio et al. 1993; Facchini et al. 1991; Frohlich 1993;

Lee et al. 1995; Rathmann et al. 1998). The epidemiologic support for such a role in humans has also been reviewed by Johnson et al. (Johnson et al. 2005b). The relationship between serum UA and BP was hypothesized as resulting from a uricase mutation that occurred during early hominoid evolution, which was originally advantageous because it helped to maintain BP both acutely (via stimulation of the renin angiotensin system) and chronically (by inducing salt-sensitivity via the development of renal microvascular and interstitial disease) (Watanabe et al. 2002). In modern society, the switch to a westernized diet rich in high salt and fatty meat, coupled with this mutation, may have played an important role in the current epidemic of hypertension and cardiovascular diseases (Johnson et al. 2005b). Acute hyperinsulinemia does not affect serum UA levels, but it does cause a marked decrease in the urinary excretion of UA accompanied by decreased sodium and potassium excretion (Muscelli et al. 1996). Furthermore, it has been demonstrated that high UA levels are independently associated with increased tubular sodium resorption in men (Cappuccio et al. 1993). The predictive value of hyperuricemia in respect to cardiovascular outcome does not weaken by adjustment for the components of metabolic syndrome, including fasting insulin levels (Niskanen et al. 2004).

2.3.4 Insulin resistance

The Bruneck Study, based on a random sample of the general population (n = 888, aged 40-79), reported that the prevalence of IR is 62.8% in subjects with hyperuricemia (Bonora et al. 1998). IR is probably one of the underlying conditions triggering the development of the above metabolic disorders. It has been reported that the degree of IR (measured in everyday practice by the homeostasis model assessment index and the quantitative insulin sensitivity check index) (Pacini et al. 2003) may be directly related to serum UA levels (Modan et al. 1987; Vuorinen-Markkola et al. 1994).

The increased purine biosynthesis and turnover, with consequent increases in serum UA concentrations caused by the increased activity of the hexose monophosphate shunt, may be linked to IR and/or hyperinsulinemia (Modan et al. 1987). Especially, the impairment of the glycolytic pathway can increase the flux of glucose-6-phosphate through the hexose monophosphate shunt, resulting in the accumulation of ribose-5-phosphate and other intermediates, which are major substrates for UA production (Fox 1981; Fox et al. 1985). 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.

Moreover, a recent study (Nakagawa et al. 2006) showed that UA plays an important role in the pathogenesis of metabolic syndrome, probably due to its ability to inhibit endothelial function through inhibiting nitric oxide bioavailability (Baldus et al. 2005). Since insulin needs nitric oxide to stimulate glucose uptake, the investigators hypothesized that hyperuricemia may have a key role in the pathogenesis of IR (Nakagawa et al. 2006).

In addition, drugs that improve insulin sensitivity, such as metformin (Gokcel et al. 2002), troglitazone (Tsunoda et al. 2002), sibutramine (Filippatos et al. 2005; Tambascia et al. 2003), and orlistat (Gokcel et al. 2002; Kiortsis et al. 2005) can also lower UA levels. Furthermore, insulin receptors were found in different tubular segments of human kidney (Nakamura et al. 1983). Insulin can enhance renal proximal

tubular UA reabsorption in humans due to an active transport mechanism closely linked to the tubular reabsorption of sodium (Cappuccio et al. 1993; Muscelli et al. 1996; Quinones Galvan et al. 1995). Whatever the site of the tubular effects of insulin, the possible mechanisms linking hyperinsulinemia (a consequence of IR) with hyperuricemia include the direct stimulations of tubular ion (UA-Na) exchange or the acceleration of cellular metabolism (Mandel 1986).

2.3.5 Hyperglycemia and diabetes

Diabetes mellitus is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both (World Health Organisation 1999). Diabetes is defined according to elevated glucose levels, FPG $\geq$ 7.0 mmol/l and/or 2-hour plasma glucose (2-hPG) $\geq$ 11.1 mmol/l by the latest WHO criteria (World Health Organisation/International Diabetes Federation 2006). Type 2 diabetes is characterized by IR and relative insulin deficiency, either of which may be present at the time that diabetes becomes clinically manifested (Reaven et al. 1976; Tuomilehto et al. 2001). The specific reasons for the development of these abnormalities are not yet known, but the general reasons are population aging, unhealthy diet, overweight and obesity, and a sedentary lifestyle.

In 2007, it was estimated that 7.3% of adults aged 20-79 in all International Diabetes Federation (IDF) member countries had diabetes. In 1985, an estimated 30 million people worldwide had diabetes. In 2000, a little over a decade later, the figure had risen to over 150 million. By 2025, the figure is expected to rise to 380 million (International Diabetes Federation 2008). Approximately 85% to 95% of all diabetes cases are estimated to be type 2 diabetes in developed countries, and account for an even higher percentage in developing countries.

The long-term effects of diabetes are largely due to the fact that virtually all tissues of the body are exposed to high glucose, and include a progressive development of the specific microvascular complications such as retinopathy with potential blindness, nephropathy that may lead to renal failure, and neuropathy with risk of foot ulcers, amputation, and features of autonomic nervous dysfunction. In addition, people with diabetes are at an increased risk of macrovascular complications including coronary heart disease, peripheral vascular and cerebrovascular disease, and most diabetic patients die from cardiovascular disease. Therefore, huge premature morbidity and mortality are associated with the disease (Boyko et al. 2000).

Since World War II, the southern Indian Ocean island of Mauritius has experienced a rising standard of living associated with industrialization, and there has been a marked secular increase in prevalence of diabetes. The prevalence of type 2 diabetes increased significantly from 12.8% in 1987 to 15.2% in 1992 and 17.9% in 1998 (Soderberg et al. 2005). China, which is the largest developing country and has the largest population in the world, has also experienced high-speed socio-economic development during past two decades, accompanied by a rapid increase in the prevalence of obesity and diabetes. National population based studies made in mainland China, indicate sharply rising prevalence rates of diabetes in Chinese adults, three-fold from approximately 1% in 1980 to 3.2% in 1996 (National Diabetes Co-operative Study Group 1981; Xiang et al. 1998). In Qingdao city a diabetes survey in 2001-2002 showed that the

age-standardized prevalence of diabetes was 6.1% (4.1% for undiagnosed and 2.1% for previous diagnosed diabetes) in adults aged 20-74 (Dong et al. 2005).

2.3.5.1 UA and its changes with pre-diabetes and type 2 diabetes

Previous cross-sectional studies have shown that diabetic patients have low UA levels. In the Japanese-American population in Hawaii (n = 8 000, men), subjects with a prior history of diabetes have lower serum UA levels than those without (Yano et al. 1977). UA was significantly elevated in people with IGT and significantly lower in those with diabetes in Melanesians and Asian Indians (Tuomilehto et al. 1988), increased with FPG up to 7.0 mmol/l in men and to 9.0 mmol/l in women but significantly decreased thereafter in Caucasians (Whitehead et al. 1992), and increased with increasing FPG levels up to 8.0 mmol/l in middle-aged British men (Cook et al. 1986). Cook et al. concluded that the positive relationship between serum UA and plasma glucose could not be explained by associations with BMI, alcohol intake, age, social class, gout, or treatment for hypertension. It probably reflected the biochemical interaction between plasma glucose and purine metabolism, with increased excretions of UA during hyperglycemia and glycosuria (Cook et al. 1986). Another population-based cross-sectional study indicated serum UA strongly correlated with 2-hPG ($p < 0.001$) in nondiabetic Mauritian men ($r = 0.15$) and women ($r = 0.22$) (Hodge et al. 2001).

In the Israeli Heart Disease Study, 10 000 men, age 40, from a random selection of government and municipal workers were examined at the baseline in 1963 and re-examined in 1965 and 1968 by using a same glucose tolerance test. This study showed that baseline serum UA levels were higher in individuals who were pre-diabetes at baseline, but developed diabetes at the end of follow-up, as compared to individuals who were free of diabetes at the end of follow-up. In those who developed diabetes during the follow-up, the UA levels were lower at the diagnosis of diabetes than at baseline and the UA levels continued to decrease with the duration of diabetes (Herman et al. 1976).

2.3.5.2 UA and incident type 2 diabetes

A few studies have investigated the association of serum UA with incident type 2 diabetes (Table 3), but most of these studies were conducted only on the male population. In those early prospective studies, for example, it was reported that for a 1 mg/dl increase in baseline UA levels a 1.14-fold increase in risk of incident diabetes was observed during a 5-year follow-up period in middle-aged Israeli men (Medalie et al. 1975). Among a randomized sample (n = 766) of men, age 54, from an urban area in Sweden, the multivariate adjusted risk for the development of diabetes during a 13.5-year follow-up was 5.8-fold for those in the top quintile of serum UA values compared to those in the lowest quintile (Ohlson et al. 1988).

The British Regional Heart Study (BRHPS) was designed to determine the risk factors for type 2 diabetes during a 12.8-year follow-up period in a cohort of 7 735 men, age 40-59, drawn from the age-sex register of one general practice in each of 24 towns in England, Wales, and Scotland between January 1978 and June 1980 (Perry et al. 1995). The BRHPS found that subjects whose baseline serum UA values were in top quintile of the distribution had 1.5-fold higher risk for diabetes than those in the lowest quintile. Similar to BRHPS, a Japanese study has shown that a high baseline UA level

was associated with an increased risk of diabetes over a 6-year follow-up in male office workers, age 35-39, who did not have hypertension, impaired fasting glycemia (IFG), type 2 diabetes, or past history of cardiovascular disease (Nakanishi et al. 2003).

A few population-based prospective studies have assessed the relationship between UA and diabetes in women (Table 3). Monica Augsburg Cohort Study is the first population-based prospective study that explored the prediction of serum UA for development of diabetes in Germany (Meisinger et al. 2002). This study reported that baseline serum UA was a strong independent risk factor for diabetes in women, with a multivariable adjusted hazard ratio (95% CI) of 2.1 (1.5-2.8). Another study in the Chinese population of Taiwan (Lin et al. 2004) indicated that high UA levels at baseline examination independently predicted the development of diabetes in women with an odds ratio of 1.44, but not in men. More recently, it has been shown that baseline plasma UA is an independent predictor of future type 2 diabetes incidence in a community-based prospective cohort study of 2 690 Chinese participants (age 35-97) in Chin-Shan town, Taiwan (Chien et al. 2008). The relationship between FPG and 2-hPG concentration and serum UA level in nondiabetic population, however, is still unknown. The baseline serum UA levels have been found to independently predict the 2-hPG level 13.5 years later in Swedish male population, with a low regression coefficient of 0.01 ($p = 0.026$) (Ohlson et al. 1988). In the Finnish Diabetes Prevention Study (Niskanen et al. 2006) in high-risk middle-aged subjects with IGT, baseline UA and its changes predicted a 2-fold increase in the likelihood of developing type 2 diabetes. Furthermore, UA and its changes during follow-up were related to corresponding changes in FPG and 2-hPG (Niskanen et al. 2006).

Table 3 Prospective studies on the relationship between serum uric acid and incident diabetes

Study	Study region	Baseline study year	Population, Age (y)	Follow-up years	Hazard ratio (95% CI)	Adjustment variables	Reference
Israeli Heart Disease Study	Israel	1963	10 000 Men, age ≥40	5	1.14 per 1 mg/dl	Age, BMI, SBP, total cholesterol, hemoglobin, education, and birthplace	(Medalie et al. 1975)
Swedish Study	Gothenburg, Sweden	1967	766 Men, mean age 54	13.5	Q5 vs. Q1 5.8(2.2-16.0)	Age, BMI (WHR), SBP (DBP), FPG, triglycerides, GOT(GPT), and Bilirubin	(Ohlson et al. 1988)
British Regional Heart Study	Great Britain	1977-1980	7 735 Men, age 40-59	12.8	Q5 vs. Q1 1.5 (0.9-2.5)	Age, BMI, SBP, HDL-C, smoking and alcohol drinking status, prevalent CHD, heart rate, and physical activity	(Perry et al. 1995)
Monica Augsburg Cohort Study	Augsburg, Germany	1984-1995	3 052 Men and 3 114 Women, age 35-74	3-15	Men 1.1 (0.9-1.4), women 2.2 (1.6-3.0) per 1mmol/l	Age, BMI, SBP, HDL-C, smoking and alcohol drinking status, family history of DM, physical activity, and cohort	(Meisinger et al. 2002)
Japanese office worker Study	Japan	1994	2 310 Men, age 39-59	6	Q5 vs. Q1 1.78 (1.11-2.85)	Age, BMI, family history of diabetes, cigarette smoking, alcohol intake, regular physical exercise, mean BP, FPG, triglycerides, total cholesterol, and HDL-C	(Nakanishi et al. 2003)
Hyperuricemic Chinese Study	Taiwan	1991-1992	391 Men and 250 Women, age ≥30	7	Men 0.76 (0.51-1.22), Women 1.44 (1.13-2.25) per 1 mg/dl	Age, FPG, BMI, SBP (DBP), menopause status (women), HDL-C, serum creatinine, triglyceride, total cholesterol, and fasting serum insulin	(Lin et al. 2004)
Community Cardiovascular Cohort Study	Taiwan	1990	1 392 Men and 1 566 Women, age ≥35	9	Q5 vs. Q1 1.40 (1.02-1.92) for total population	Age, sex, BMI, SBP (DBP), FPG, triglycerides, HDL-C, alcohol intake, marital status, education level, occupation, and family history of diabetes.	(Chien et al. 2008)
Rotterdam Study	Netherlands	1990-1993	4 536 Men and women, age ≥55	10.1	Quartile 4 vs. Quartile 1 1.68 (1.22-2.30)	Age, sex, BMI, waist circumference, SBP. DBP, and HDL-C	(Dehghan et al. 2008)

Q5, quintile 5 or top quintile; Q1, quintile 1 or the lowest quintile. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WHR, waist to hip ratio; HDL-C, high density lipoprotein -cholesterol; FPG, fasting plasma glucose; GOT/GPT, human aspartate aminotransferase.

2.3.6 Metabolic syndrome

The clustering of resistance to insulin-stimulated glucose uptake, hyperinsulinemia, hyperglycemia, hyperuricemia, increased very low-density lipoprotein, triglycerides, decreased high-density lipoprotein cholesterol (HDL-C), and hypertension has been noticed and described since 1923 (Kylin 1923) named later as "syndrome X" (Reaven 1988) or “IR syndrome” (Haffner et al. 1992) or more recently the “metabolic syndrome” (Grundy 1999). The co-morbidities associated with hyperuricemia include obesity, hyperlipidemia, hypertension, IR, hyperglycemia, cardiovascular diseases (coronary artery disease and stroke), and chronic renal disease (Johnson et al. 2003). Although hyperuricimia was not included in the recent major definitions for the metabolic syndrome by the WHO, the National Cholesterol Education Program Adult Treatment Expert Panel III (NCEP), and the IDF (Adult Treatment Panel III 2002; Alberti et al. 2005, 2006; Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults 2001; World Health Orgnisation 1999), continuing debating ensues on whether hyperuricemia is an additional component of the metabolic syndrome (Liou et al. 2006; Zavaroni et al. 1993). This indicates the role of the hyperuricemia is still less known.

The prevalence of the metabolic syndrome varies markedly depending on the definitions used and populations studied (Qiao et al. 2007). Among 22 studies that used the original full definition of the NCEP, the prevalence of the metabolic syndrome ranged from 5.6% in Chinese women in Hong Kong to 52.8% in Polynesian men in New Zealand. A more recent study (Lee et al. 2008) aiming to compare the age-adjusted prevalence of metabolic syndrome by different definitions in Asia-Pacific populations from Australia, Japan, Korea, and Samoa, indicated that Japanese people had the lowest prevalence of metabolic syndrome regardless of the definition and Samoans generally had the highest prevalence. Regarding the differences in the prevalence of metabolic syndrome and its components by using the various definitions, both within and between populations, researchers concluded that standardization of the methodology is gravely required when comparing studies from different countries.

The metabolic syndrome increased the risk of the development of type 2 diabetes and cardiovascular disease (DECODE Study Group 2006; Ford 2004), and the prediction is stronger for type 2 diabetes than for cardiovascular disease (Stern et al. 2004). Studies have also shown, however, that individual metabolic components predicted the cardiovascular diseases risk by a similar magnitude to that of the actual syndrome (DECODE Study Group 2006; Ford 2004; Hunt et al. 2004; Lawlor et al. 2006). Research addressing the issue regarding the cardiovascular disease risk prediction of an actual syndrome and its single individual component are required. In addition, to what extent the other factors that are not included in the current definition of the metabolic syndrome, including hyperuricemia, have contributed to the cluster and the increased risk of diabetes and cardiovascular disease is much less known.

Prevalence of metabolic syndrome in Mauritius and China

According to the non-communicable diseases surveys in 1987 in Mauritius, including known or newly diagnosed diabetes, the metabolic syndrome prevalence varied between 14.1% (95% CI 13.0–15.3) for the IDF, 19.6% (95% CI 18.3–20.9) for the

NCEP and 20.4% (95% CI 19.1–21.7) for the WHO definition (Cameron et al. 2007). The corresponding figures, after exclusion of those with diabetes, were 10.7% (9.6-11.7), 14.2% (13.0–15.4) and 14.6% (13.4–15.8) in the same study. The prevalence of the NCEP and IDF metabolic syndrome definitions were significantly higher among Creoles [19.2% (16.4–21.9) and 14.2% (11.8–16.6)] than Indians [12.2% (10.8–13.6) and 9.5% (8.2–10.7); both $p < 0.05$], however, no significant difference in the prevalence of the WHO definition of the metabolic syndrome was observed among the three ethnic groups of Indian, Creole and Chinese (Cameron et al. 2007).

The International Collaborative Study of Cardiovascular Disease in Asia was conducted in China and Thailand between 2000 and 2001, including a nationally representative sample of 15 540 individuals from ten provinces of China. The study revealed that 19.4% of Chinese adults, age 35-74, have hypertension, 24.8% have raised triglycerides levels, and 33.9% have low HDL cholesterol (Gu et al. 2005; He et al. 2004; Huang et al. 2004). A recent study (He et al. 2007) reported that according to the WHO definition for overweight (BMI $\geq$ 25.0 kg/m^2) and the IDF criteria for metabolic syndrome, prevalence rates for overweight and metabolic syndrome were 56.3% (53.9% in men and 57.9% in women) and 46.3% (34.8% in men and 54.1% in women), in individuals 60-year old or younger living in a community in Haidian District, a metropolitan area representative of the geographic and economic characteristics in Beijing, China. In mainland China, in 2000-2001 (Yang et al. 2007), the overall age-standardized prevalence of the metabolic syndrome among a nationally representative sample of 15 838 Chinese adults, age 35-74, was 16.5% and 23.3%, according to the IDF and revised NCEP definitions. The prevalence significantly increased with age and was higher in women than in men by both definitions (23.3% vs. 10.0% for IDF and 29.1% vs. 17.7% for revised NCEP, $p < 0.001$). Compared to men, women had a significantly higher prevalence of central obesity (37.6% vs. 16.0%) and reduced HDL-C (46.5% vs. 21.9%), whereas men had a significantly higher prevalence of raised BP (44.2% vs. 38.0%) compared to women (Yang et al. 2007).

UA associated with metabolic syndrome

The association between serum UA and the metabolic syndrome is also illustrated by the fact that the prevalence of metabolic syndrome shows a graded increase with increased serum UA levels from large population based epidemiologic studies in different ethnic groups (Boyko et al. 2000; Ishizaka et al. 2005; Klein et al. 2002; Yoo et al. 2005). A recent analysis of the NHANES III (Choi et al. 2007b) showed that the prevalence of the metabolic syndrome increases substantially with increasing levels of serum UA. The prevalence of the metabolic syndrome (NCEP criteria) ranged from 18.9% (95% CI 16.8–21.0) for UA levels less than 6.0 mg/dl, to 70.7% (95% CI 51.4–89.9) for UA levels equal to or above 10.0 mg/dl, and the increasing trends persisted in subgroups stratified by sex, age, alcohol intake, BMI, hypertension, and diabetes. Recently, a cross-sectional study in the healthy Thai population (inclusion criteria: no previously diagnosed diabetes, hypertension, gout, and not taking UA- lipid- or BP-lowering medication) addressed that elevated serum UA (top quartile) conveyed a 3.9-fold high risk of the metabolic syndrome (defined by the modified NCEP criteria) in men and 2-fold in women (Lohsoonthorn et al. 2006). The association of UA with metabolic syndrome, however, still needs to be delineated in other population samples.

2.4 Hyperuricemia and cardiovascular diseases

2.4.1 Associations of hyperuricemia with cardiovascular diseases

The positive association between serum UA and coronary heart disease and cardiovascular disease has been recognized for 50 years (Gertler et al. 1951; Klein et al. 1973). The issue of hyperuricemia as an independent risk factor for atherosclerotic cardiovascular disease has received much renewed interest in recent years with many reviews and editorials providing different views (Alderman et al. 2004; Dobson 1999; Johnson et al. 1999; Yusuf et al. 2002), and some studies providing conflicting results (Culleton et al. 1999; Fang et al. 2000; Liese et al. 1999; Wannamethee et al. 1997).

The Framingham study (Culleton et al. 1999), including 6 763 subjects whose baseline serum UA levels were tested from 1971 to 1976, supported the contention that traditional risk factors, rather than hyperuricemia, are the primary casual factors in development of atherosclerotic heart disease during follow-up. In this study, hyperuricemia was not associated with an increased risk for adverse outcomes (coronary heart disease, death from cardiovascular disease, or death from all causes) after adjustment for other cardiovascular risk factors in men and women.

Nevertheless in another nationwide survey, the NHANES I study of 5 926 subjects followed-up for an average of 16.4 years found that the increasing serum UA concentration was related to increased cardiovascular mortality in both sexes and ethnic groups (Fang et al. 2000). Death due to ischemic heart disease and overall cardiovascular mortality rates increased in relation to UA quartiles (relative risk, 1.77 in men and 3.00 in women), even after adjustment for age, race, BMI, smoking, alcohol intake, cholesterol, hypertension, and diabetes. Recently, a study of 1 017 patients with angiographically proven coronary artery disease has shown a 5-fold increase in overall mortality rates among patients with serum UA levels in the top quartile, compared to those in the lowest quartile. In addition, serum UA was an independent predictor of mortality in patients with coronary artery disease after adjustment for 12 variables (including diuretic use) that influence overall cardiovascular mortality (Bickel et al. 2002). In patients with well-controlled hypertension, cardiovascular mortality was significantly greater among hyperuricemic individuals than among their normouricemic counterparts (Alderman et al. 1999).

More recently, elevated serum UA has been shown as being an independent predictor of mortality in high-risk groups including subjects with hypertension, coronary heart disease (Hoieggen et al. 2004), stroke (Weir et al. 2003), diabetes, and heart failure (Gerber et al. 2006). The similar result has been further confirmed in a population-based cohort study of a 12-year follow-up in middle-aged healthy Finnish men (Niskanen et al. 2004).

Johnson et al. (Johnson et al. 2003) summarized that hyperuricemia predicted the development of cardiovascular disease, not only in individuals with hypertension or pre-existing cardiovascular disease but also in the general population. Whereas, Wheeler et al. (Wheeler et al. 2005) considered that measurement of serum UA levels is unlikely to usefully enhance the prediction of coronary heart disease nor to be a major determinant of the disease in general populations based on the results of a meta-

analysis of data from 15 prospective studies. Although some studies suggested that serum UA is an independent risk factor for coronary heart disease (Fang et al. 2000; Freedman et al. 1995; Gertler et al. 1951; Liese et al. 1999), there is still more evidence that the association of hyperuricemia with coronary heart disease events is dependent on the association between serum UA and other risk factors, such as hypertension, obesity, and elevated levels of triglycerides (Culleton et al. 1999; Freedman et al. 1995; Jee et al. 2004; Wannamethee et al. 1997; Yano et al. 1984). This evidence suggests that the influence of UA on coronary heart disease is explained by the secondary association of UA with other established etiological risk factors (hypertension, dyslipidemia, hyperinsulinemia, obesity, and pre-existing disease) (Wannamethee 2005).

A causal role for hyperuricemia in cardiovascular disease events and mortality has not been unequivocally established (Johnson et al. 2003). Serum UA may, however, provide useful prognostic information in subjects with hypertension and vascular disease (Wannamethee 2005).

2.4.2 Underlying mechanisms

2.4.2.1 Antioxidant – prooxidant UA redox shuttle

The term “Oxidative Stress” generally was denoted “the disturbance in prooxidant-antioxidant balance in favor of the former” in 1985 by Helmut Sies (Sies et al. 1985). The interest for elucidating the molecular mechanisms underlying the effects of oxidative stress on cells has been greatly increased during the past few years, mainly due to proposals indicating its involvement in many physiological and pathological conditions, including aging, cancer, and atheriosclerosis (Glantzounis et al. 2005). It should be noted that low levels of reactive oxygen species are continuously present in cells under physiological conditions and the cellular redox state is tightly regulated. The toxic effects of reactive oxygen species become apparent only when the rate of their generation increases and the defence capacity of cells are overwhelmed. Oxidative stress has been regarded broadly as a mediator in the process of development of cardiovascular disease (Berges et al. 2003; Linke et al. 2003). Oxidative stress may also play a role in the pathogenesis of diabetes, associated cardiac dysfunction, general vascular dysfunction, and the metabolic syndrome (Channon et al. 2002; Deedwania 2003).

Serum UA in the early stages of the atherosclerotic process is known to act as an antioxidant and may be one of the strongest contents of plasma antioxidative capacity (Glantzounis et al. 2005; Nyyssonen et al. 1997). Intriguingly, the simple concept is that serum UA in patients with cardiovascular disease, the metabolic syndrome, type 2 diabetes, hypertension, and renal disease may reflect a compensatory mechanism to counter oxidative stress. This is not, however, able to explain why higher serum UA levels in patients with these diseases are generally associated with worse outcomes (Johnson et al. 2003).

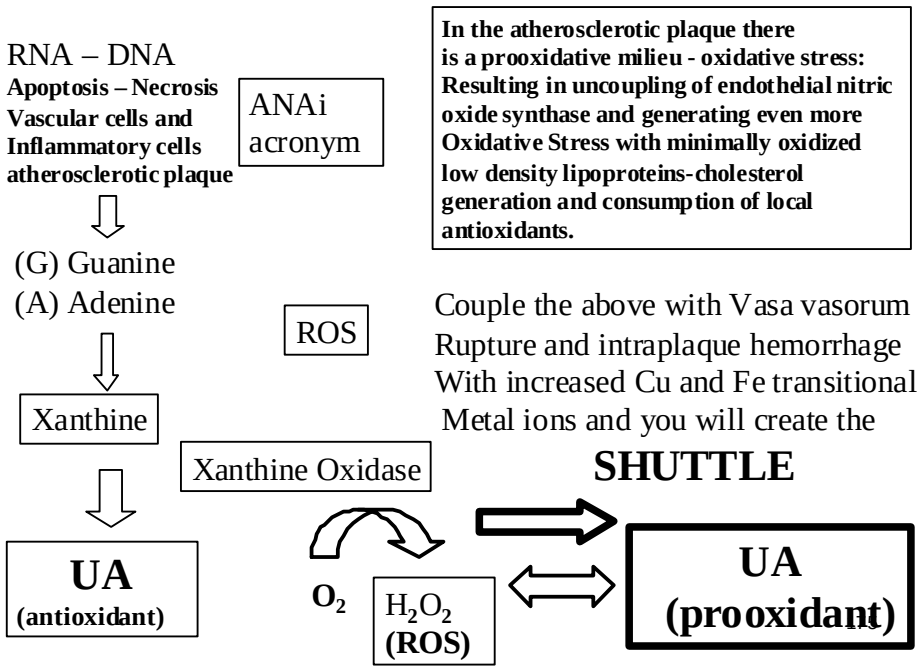


Figure 1. (Hayden et al. 2004) Antioxidant – prooxidant urate redox shuttle. This shuttle is important in understanding the role of how the antioxidant uric aicd (UA) becomes prooxidant in this environmental milieu, which results in its damaging role to the endothelium and arterial vessel wall remodeling with an elevated tension of oxidative – redox stress (ROS), accelerated atherosclerosis and arterial vessel wall remodeling.

Unfortunately, later in the atherosclerotic process when serum UA levels reach above the normal range 357 μmol/l in females and 387–416 μmol/l in males, the previously antioxidant (UA) paradoxically becomes prooxidant (Fang et al. 2000; Niskanen et al. 2004). This antioxidant – prooxidant UA redox shuttle (Figure 1) seems dependent on its surrounding environment such as timing (early or late in the disease process), location of the tissue and substrate, acidity (acidic–, basic– or neutral PH value), the surrounding oxidant milieu, the depletion of other local antioxidants, and the supply and duration of oxidant substrate and its oxidant enzyme. Depletion of local antioxidants with an underlying increase in oxidantive-redox stress is associated with the uncoupling of the endothelial nitric oxide synthase enzyme, then a decrease in the locally produced naturally occurring antioxidants, endothelial nitric oxide and endothelial dysfunction (Hayden et al. 2004). This process is also occurs within the microvascular bed at the level of the capillaries within various affected hypertensive and diabetic end organs (Bagnati et al. 1999; Hayden et al. 2004; Patterson et al. 2003).

Recent experimental studies (Bagnati et al. 1999; Nyyssonen et al. 1997; Patterson et al. 2003; Sanguinetti et al. 2004) have explored the formation of UA being connected with the conversion of xanthine dehydrogenase to xanthine oxidase leading to concomitant production of free radicals. Glantzounis et al. (Glantzounis et al. 2005) showed that besides well-known reasons for an increase in the serum UA level stands another poorly recognized factor, i.e. local ischemia, from the metabolism of hypoxanthine-xanthine by the enzyme xanthine oxidoreductase. In this respect, it is worth noting that xanthine oxidoreductase occurs in two different forms. Xanthine

dehydrogenase is the prevalent operative form under physiological conditions and has greater affinity for oxidized nicotinamide adenine dinucleotide compared with oxygen, as the electron acceptor. Under ischemic conditions, in parallel to the degradation of ATP into adenine, an interconversion of xanthine dehydrogenase to xanthine oxidase takes place. The latter utilizes molecular oxygen in place of oxidized nicotinamide adenine dinucleotide as an electron acceptor, leading to the formation of superoxide anion and hydrogen peroxide in parallel with UA production (Glantzounis et al. 2005).

2.4.2.2 Serum UA and inflammation

Increased serum UA was closely associated with systemic inflammation, such as elevated C-reactive protein (Anker et al. 2003), stimulation of release of chemokine monocyte chemoattractant protein-1(Kanellis et al. 2003), interleukin-6, and tumor necrosis factor-α synthesis (Johnson et al. 2005a). Serum UA has been shown to have a significant positive correlation with C-reactive protein in Japanese men (n = 3 692, aged 34–69) (Tamakoshi et al. 2003), in a German population-based study (n = 1 703, aged 18-89) (Frohlich et al. 2000), and in a representative random sample of 957 individuals, age 65-95, of the Italian general population (Ruggiero et al. 2006). In the Italian study (Ruggiero et al. 2006), the association between UA and C-reactive protein was independent of multiple confounders of white blood cells, neutrophil count, interleukin-6, interleukin-1 receptor antagonist, interleukin-18, and tumor necrosis factor-α. The relationship of UA with inflammatory markers is linear across the entire range of UA level.

Moreover, a follow-up study (Ruggiero et al. 2007) in the same Italian cohort found that: (1) baseline UA and changes in UA from baseline to follow-up were significant predictors of C-reactive protein changes during a 3-year follow-up, independently of baseline inflammatory markers and relevant confounders; (2) subjects in the fourth and fifth UA quintiles had a higher probability of developing clinically relevant increased interleukin-6 (> 2.5 pg/ml) and C-reactive protein (> 3 mg/l) during the 3-year follow-up period, compared to those in the second quintile. A clinical study of a sample of 30 patients concluded that serum UA may reflect the severity of systolic dysfunction and the activation of inflammation in patients with congestive heart failure (Olexa et al. 2002).

Serum UA elevation may indeed be a sensitive marker for underlying vascular inflammation and remodeling within the arterial vessel wall and capillary interstitium. Some evidence suggests that UA may exert a negative effect on cardiovascular disease by stimulating inflammation, which is clearly involved in the pathogenesis of cardiovascular disease (Festa et al. 2005; Hansson 2005). Is it possible that serum UA levels could be as similarly predictive as C-reactive protein since it is a sensitive marker for underlying inflammation and remodeling within the arterial vessel wall and the myocardium? It is not surprising that these two markers of risk track together within the metabolic syndrome and cardiovascular disease (Hayden et al. 2004). In spite of the evidence that UA might contribute to the development of human vascular disease and atherosclerosis, through a pro-inflammatory pathway, the relationship between UA and inflammation has been less investigated and needs further exploration.

2.4.2.3 Endothelial dysfunction

The endothelium represents a single layer of cells that line all vessels in the body, including the conduit vessels, the resistance vessels, precapillary arterioles, and capillaries (Vane et al. 1990). By virtue of its direct contact with the circulating blood, the endothelial layer provides a critical interface between the elements of blood and the tissues. The function of each vessel and the role of its respective endothelium vary according to its location in the body. Vascular endothelial dysfunction may occur at any level in the arterial system and contributes to the development and progression of atherosclerosis by favoring coagulation, cell adhesion and inflammation, through promoting inappropriate vasoconstriction and/or vasodilation, and by enhancing transendothelial transport of atherogenice lipoproteins.

Furthermore, endothelial dysfunction involves a very early stage of vascular disease (Aengevaeren 1999). Since one of the major sites of the production of UA in the cardiovascular system is the vessel wall and particularly the endothelium (Becker 1993) and UA's ability to inhibit endothelial function through inhibiting nitric oxide bioavailability (Baldus et al. 2005), elevated serum UA may be a marker of endothelial dysfunction. It has been shown that UA concentrations correlated inversely with flow-mediated brachial artery vasodilation in vivo (Maxwell et al. 2001). Moreover, in a controlled setting of dietary treatment with an arginine-enriched nutrient bar, which enhances nitric oxide activity, the increased flow-mediated vasodilation was associated with the reduction of UA levels (Maxwell et al. 2001).

In summary, experimental evidence suggest a complex but potentially direct causal relationship between serum UA and numerous deleterious biologic functions involved in the pathogenesis of metabolic syndrome and atherosclerosis (Kang et al. 2002; Mazzali et al. 2001; Mazzali et al. 2002; Watanabe et al. 2002). For example, in in vitro studies UA stimulates both vascular smooth muscle cell proliferation and the release of chemotactic and inflammatory substances (Mazzali et al. 2002; Rao et al. 1991; Watanabe et al. 2002), induces monocyte chemotaxis (Zare et al. 2006), inhibits endothelial cell proliferation and migration (Kang et al. 2005; Khosla et al. 2005), and causes oxidative stress in adipocytes resulting in the impaired secretion of adiponectin (Sautin et al. 2007). The role of serum UA in development of metabolic abnormalities is summarized in Table 4.

Table 4 Hyperuricemia possible roles in the metabolic syndrome and cardiovascular diseases

Components	Potential mechanisms
Hypertension	1. Urate reabsorption increased in setting of increased renal vascular resistance, microvascular disease predisposes to tissue ischemia that leads to increased urate generation (excess purine metabolism) and reduced excretion (due to lactate competing with urate transporter in the proximal tubule) 2. Increased oxidative – redox stress 3. Antioxidant – Prooxidant Paradox:Urate Redox Shuttle 4. UA effect on the renin-angiotensin system.
Obesity – Insulin resistance	1. Overproduction of UA and impairment in renal clearance of UA 2. Leptin may induce hyperuricemia. 3. Insulin increases sodium reabsorption and is tightly linked to urate reabsorption.
Glucose intolerance and/or Diabetes	Acting through obesity and insulin resistance.
Dyslipidaemia	Link between fatty acid synthesis and production of NADPH.
Accelerated atherosclerosis	1. Endothelial dysfunction 2. Accelerated atherosclerosis with increased vascular cell apoptosis 3. Inflammatory necrosis with increased purine metabolism resulting in hyperuricemia 4. Increased oxidative stress through ischemia-reperfusion and xanthine oxidase 5. Antioxidant – Prooxidant Paradox: Urate Redox Shuttle 6. UA effect on the renin-angiotensin system.

3 AIMS OF THIS STUDY

Our overall aims were to study the prevalence of hyperuricemia and the metabolic factors clustering with hyperuricemia, to explore the dynamical changes in blood UA levels with the deterioration in glucose metabolism and to estimate the predictive capability of UA in the development of diabetes.

The specific objectives of the study are:

1. To determine the prevalence of hyperuricemia and gout and the risk factors associated with hyperuricemia in Chinese population in an urban community in Qingdao, China (Study I).

2. To explore the association of serum UA levels with the metabolic abnormalities based on cross-sectional data in non-diabetic subjects of Indian and Creole living in Mauritius, and in Chinese living in Qingdao (Study II)

3. To estimate the association between FPG, 2-hPG levels and serum UA concentrations in a Chinese adult population (Study III).

4. To investigate the predictive value of baseline blood UA for the development of diabetes in Asian Indians and Creoles living in Mauritius (Study IV).

4 POPULATIONS AND METHODS

4.1 Study Populations

Qingdao Diabetes Survey (QDS)-2001

A stratified, random cluster sampling method was used to select a representative sample of the general population aged 20-74 years in Qingdao in April-June, 2001 and in April-May, 2002. Street blocks were randomly drawn from rural and urban communities to serve as clusters for the survey. From each selected block, families were randomly selected, and a total of 12 210 subjects who had lived in Qingdao for at least 5 years were invited to take part in the survey (Figure 2).

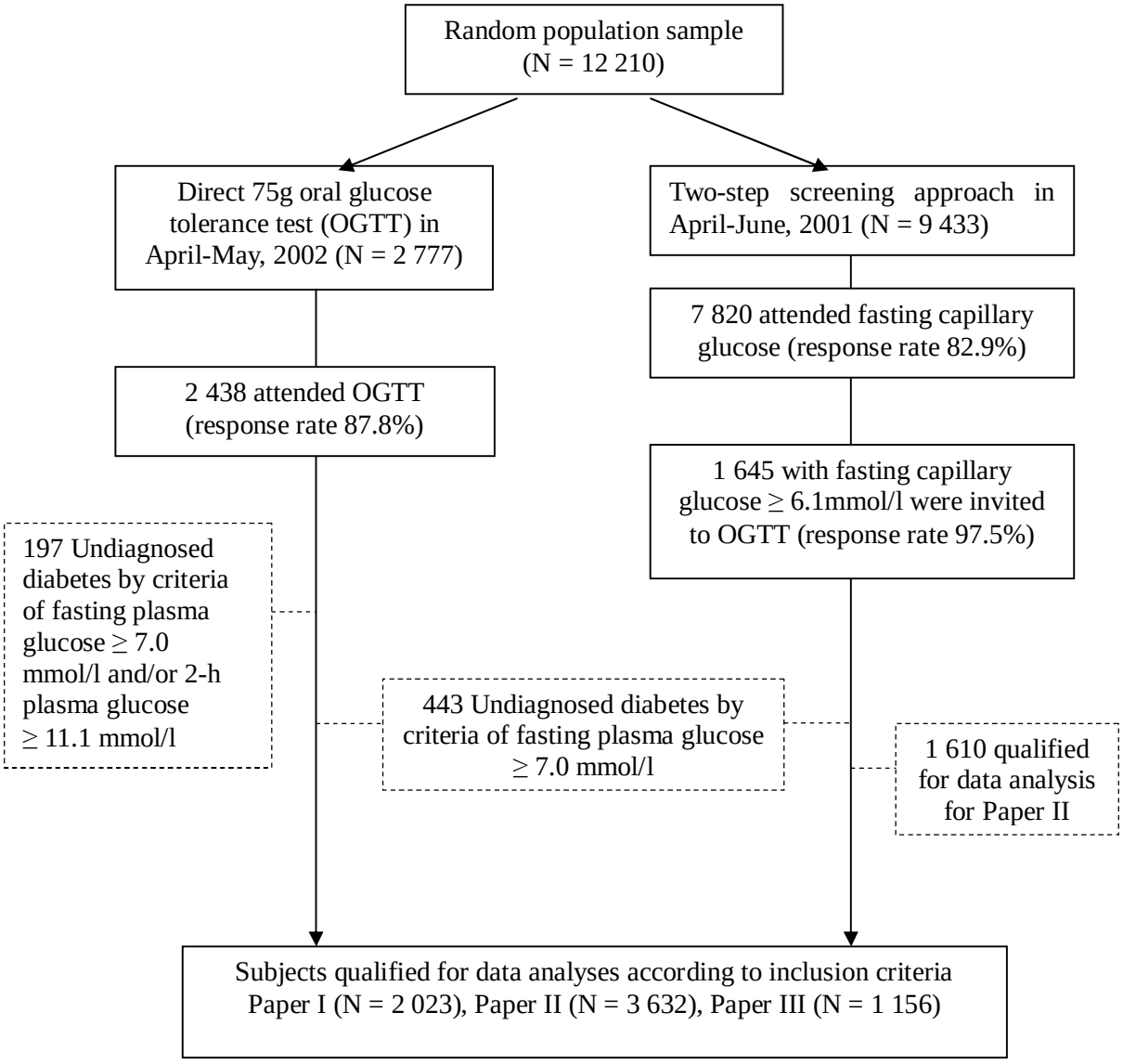


Figure 2. The sampling procedure and the participation rate in the survey in Qingdao, China, in 2001-2002.

Two screening strategies for diabetes were applied. In April-June, 2001, a two-step screening strategy was applied to the target populations (n = 9 433). A fasting capillary whole blood glucose (FCG) test was first administrated to all participants between 7:00-9:30 in the morning. The participation rate for the FCG test was 82.9%. A total of 1 645 subjects who had a FCG value of ≥ 6.1mmol/l were further invited to a standard 75g 2-hour oral glucose tolerance test (OGTT); 1 610 subjects with complete data for the data analysis were included in the Study III.

In April-May, 2002, a total of 2 777 eligible subjects were invited to take part a standard OGTT directly in an urban community, Zhanshan. Of these, 2 438 (903 men and 1 535 women) participated, with an overall response rate of 87.8%. Among participants in Zhanshan community, 415 subjects were excluded due to missing data on glucose or other lab measurements, leaving 2 023 subjects in the data analysis for Study I and 1 156 non-diabetic subjects free of hypertension and cardiovascular diseases for Study II. A total of 3 632 (1 288 men and 2 344 women) subjects with data on both FPG and serum UA were included in the current data analysis for the association of serum UA and plasma glucose (Study III), after further excluded those with a previous history of physician diagnosed gout.

Mauritius 1987, 1992 and 1998 Non-Communicable Diseases Surveys (MNCDS)

The population of Mauritius consists of 70% Asian Indians (both Hindus and Muslims), 28% Creoles (predominantly African ancestry), and 2% Chinese, with varying amount of European, Malagasy and Indian admixture (Central Intelligence Agency. 2003). Population based surveys for prevention and control of chronic non-communicable diseases were undertaken in 1987, 1992, and 1998. Details of the survey methodology have been published previously (Dowse et al. 1995; Soderberg et al. 2005).

In 1987, 10 randomly selected (with probability proportional to size) population clusters were examined, and all eligible residents were invited to participate. In both 1992 and 1998, all previous participants were invited, plus all other current eligible residents in each cluster and with three new clusters added in 1992. Briefly, all residents aged 25-74 years in randomly selected population clusters were invited to participate (Soderberg et al. 2005). The response rate was 86 %, 90 %, 87 %, respectively, in the 1987, 1992, and 1998 survey. The numbers of Mauritian Indian and Mauritian Creole who attended baseline surveys were 4 661 in 1987, 2 638 in 1992, and 1 440 in 1998. The following groups of participants were excluded: 193 participants with missing data on the measurements required for the current data analysis, 1 161 participants with a personal history of hypertension, gout and cardiovascular diseases including coronary heart disease, stroke, peripheral vascular disease, 1 178 individuals with known or newly diagnosed diabetes. Therefore, a total of 6 207 subjects (2 867 men) of Mauritian Indian and Mauritian Creole were included in the data analysis for the association of serum UA with metabolic risk factors in Study II.

Individuals participating in the study in 1987 or 1992 were invited to attend re-examination in 1992 and/or 1998 using the same study protocol. According to the date of entering (free of diabetes) and the date of exiting (developed diabetes) the study,

participants were divided into four sub-cohorts: 1987 to 1992, 1987 to 1998, 1987 through 1992 to 1998, and 1992 to 1998. Among 5083 individuals who were free of diabetes in the 1987 baseline survey, 22.5 % attended the re-examination in 1992, 3.5 % in 1998, 51.7 % both in 1992 and 1998, which gave an overall follow-up rate of 77.7 %. Among 2845 individuals who were free of diabetes in the 1992 baseline survey, 60.6 % attended the re-examination in 1998 (Nyamdorj et al. 2008). A total of 1 941 men (1 409 Indians, 532 Creoles) and 2 318 non-pregnant women (1 645 Indians, 673 Creoles) aged 25-74 years at baseline qualified for studying the incidence of diabetes (Study IV). The inclusion criteria for Study IV were: (1) UA determined at both baseline and follow-up survey, (2) data on BMI, systolic and diastolic blood pressure, fasting and 2h plasma glucose, serum lipids, creatinine, smoking and alcohol consumption at baseline, and (3) free of diabetes, cardiovascular diseases, renal failure and gout at baseline.

The demographic, clinical and metabolic characteristic of the study population in general are summarized in Table 5. For all these studies, informed consent was obtained from all participants in each of the surveys, and the survey protocols were reviewed and approved by each of the local ethics committees (Melbourne, Australia and Qingdao, China).

Table 5 Characteristics of the study population in Mauritius and in Qingdao, China

Men	Mauritian Indian			Mauritian Creole			Chinese	
Baseline survey (year)	1987	1992	1998	1987	1992	1998	2001*	2002
Total Number	1 517	842	354	571	347	153	568	720
Undiagnosed diabetes (%)	141 (9.3)	81 (9.6)	46 (13.0)	41 (7.2)	38 (11.0)	12 (7.8)	90 (15,8)	57 (7.9)
Age (years)	42 (13)	43 (12)	43 (11)	44 (13)	44 (12)	43 (12)	52 (12)	53 (12)
Waist circumference (cm)	77.8 (9.2)	86.5 (8.8)	88.0 (10,6)	77.2 (8.9)	85.5 (9.7)	85.1 (11.8)	92.0 (9.3)	90.0 (9.5)
Body mass index (kg/m^2)	22.7 (3.7)	24.0 (3.8)	24.5 (4,1)	22.8 (3.5)	24.1 (4.2)	24.0 (4.6)	26.3 (3.6)	26.4 (3.4)
Systolic blood pressure (mmHg)	126 (18)	122 (18)	125 (20)	133 (21)	127 (19)	126 (19)	133 (21)	129 (19)
Diastolic blood pressure (mmHg)	79 (12)	75 (12)	76 (14)	82 (13)	79 (13)	75 (13)	86 (13)	85 (11)
Fasting plasma glucose (mmol/l)	5.7 (2.0)	6.1 (2.0)	6.4 (2,3)	5.7 (1.5)	6.1 (2.1)	6.5 (2.8)	7.1 (3.5)	5.7 (1.7)
2h plasma glucose (mmol/)	6.9 (3.5)	7.3 (4.0)	7.4 (4,0)	6.5 (2.9)	6.7 (3.1)	7.1 (4.4)	9.6 (5.9)	6.7 (3.9)
Triglycerides (mmol/l)	1.8 (1.3)	1.6 (1.1)	1.7 (1,0)	1.7 (1.4)	1.6 (1.0)	1.7 (1.0)	1.7 (1.5)	1.8 (1.5)
Total cholesterol (mmol/l)	5.6 (1.6)	4.9 (0.8)	5.1 (1,1)	5.7 (1.8)	4.9 (0.9)	5.1 (1.2)	5.4 (1.2)	5.6 (1.2)
HDL-cholesterol (mmol/l)	1.3 (0.4)	1.2 (0.3)	0.9 (0,3)	1.3 (0.4)	1.3 (0.4)	1.0 (0.39	1.56 (0.52)	1.49 (0.28)
Serum uric acid (μmol/l)	398 (84)	362 (84)	351 (79)	399 (86)	368 (90)	366 (83)	363 (98)	390 (89)
Creatinine (μmol/l)	85 (31)	110 (46)	99 (229	85 (16)	111 (20)	99 (12)	NA	NA
Current smokers (%)	863 (56.9)	400 (47.5)	153 (43.2)	380 (66.5)	194 (55.9)	83 (54.2)	308 (54.3)	326 (45.3)
Current drinkers (%)	1 134 (74.8)	455 (54.0)	200 (56.5)	496 (86.9)	263 (75.8)	123 (80.4)	261 (46.0)	300 (41.7)
Follow-up	Yes	Yes	No	Yes	Yes	No	No	No

*Among subjects who with fasting capillary glucose ≥6.1mmol/l at the first step screening. Data are crude mean (SD) and number (percentage)

Table 5 Continues

Women	Mauritian Indian			Mauritian Creole			Chinese	
Baseline survey (year)	1987	1992	1998	1987	1992	1998	2001*	2002
Total Number	1 688	956	435	727	441	195	1 042	1 302
Undiagnosed diabetes (%)	119 (7.0)	77 (8.1)	38 (8.7)	72 (9.9)	34 (7.7)	22 (11.3)	210 (20.2)	86 (6.6)
Age (years)	42 (13)	43 (12)	43 (11)	45 (14)	46 (13)	42 (12)	54 (11)	52 (12)
Waist circumference (cm)	74.0 (11.4)	83.9 (11.4)	78.1 (10.6)	77.6 (11.9)	84.6 (10.8)	81.7 (12.4)	87.3 (10.3)	83.5 (9.9)
Body mass index (kg/m^2)	23.9 (4.7)	25.6 (5.2)	25.2 (4.8)	24.9 (5.0)	26.7 (5.3)	26.9 (5.9)	26.6 (4.0)	26.1 (3.8)
Systolic blood pressure (mmHg)	122 (19)	121 (19)	121 (21)	133 (24)	129 (25)	125 (22)	135 (24)	128 (21)
Diastolic blood pressure (mmHg)	74 (11)	73 (12)	71 (12)	79 (13)	79 (15)	73 (13)	84 (11)	82 (11)
Fasting plasma glucose (mmol/l)	5.6 (1.9)	6.2 (2.6)	5.9 (2.0)	6.0 (2.2)	6.1 (2.4)	5.9 (2.2)	7.2 (3.7)	5.7 (1.8)
2h plasma glucose (mmol/l)	7.4 (3.4)	7.5 (3.4)	7.4 (3.0)	7.6 (3.4)	7.4 (3.2)	7.0 (2.7)	9.5 (5.8)	6.5 (3.3)
Triglycerides (mmol/l)	1.3 (0.9)	1.3 (0.7)	1.2 (0.6)	1.3 (0.8)	1.3 (0.7)	1.2 (0.6)	1.6 (1.1)	1.5 (0.9)
Total cholesterol (mmol/l)	5.3 (1.5)	4.8 (0.9)	4.7 (1.1)	5.8 (1.8)	5.0 (0.9)	4.6 (1.1)	5.5 (1.2)	5.7 (1.1)
HDL-cholesterol (mmol/l)	1.3 (0.3)	1.3 (0.3)	1.0 (0.3)	1.3 (0.3)	1.4 (0.3)	1.0 (0.3)	1.67 (0.55)	1.52 (0.28)
Uric acid (μmol/l)	305 (73)	275 (76)	258 (68)	318 (80)	294 (77)	290 (70)	298 (83)	316 (70)
Creatinine (μmol/l)	67 (19)	85 (41)	77 (15)	69 (13)	90 (44)	78 (10)	NA	NA
Current smokers (%)	37 (2.2)	6 (0.6)	1 (0.2)	138 (19.0)	54 (12.2)	20 (10.3)	202 (19.4)	46 (1.2)
Current drinkers (%)	620 (36.7)	178 (18.6)	66 (15.2)	484 (66.6)	192 (43.5)	92 (47.2)	56 (5.4)	21 (1.6)
Follow-up	Yes	Yes	No	Yes	Yes	No	No	No

*Among subjects who with fasting capillary glucose ≥6.1mmol/l at the first step screening. Data are crude mean (SD) and number (percentage)

4.2 Survey procedures and physical examinations

The QDS was conducted during the months of April to June in 2001 and April to May in 2002. The survey team consisted of nurses and physicians, who were trained for one week before the fieldwork. Nurses distributed survey questionnaires to all participants during a house visit. The questionnaire contained questions on demographic, dietary, drinking and smoking information, personal and family history of diabetes, gout and hyperuricemia, previous history of hypertension, cardiovaslular disease and dyslipdemia. A participant was classified as an alcohol drinker if he/she currently drank beer, wine, or liquors during the last half a year.

Height and weight was measured with light clothes and without shoes. BMI was calculated by dividing the weight (kg) by the height (m) squared. Waist circumference at the mid-point between the lower margin of rib and the iliac crest, and hip circumference at the maximal horizontal girth between the waist and thigh were measured. The measurements were made to the nearest 0.5 cm. Two consecutive measurements were performed, and if the variation was greater than 2.0 cm between the two readings, a third measurement was taken. The two most consistent readings were used in the analysis. Waist to hip ratio was calculated by waist circumference divided by hip circumference. Three consecutive BP readings, at least 5 min apart, were taken from the right arm of seated subjects and the average of the three readings was used in data analysis.

The survey methodology was similar in all three MNCDS in 1987, 1992, and 1998. All eligible adults were asked to attend a survey site during 8:00-10:00 A.M. after an overnight fast. After registration, local nurses trained for the survey administered a questionnaire and measured anthropometric parameters (Soderberg et al. 2005). Ethnicity was determined by self-report. Menstruation information was collected in the follow-up surveys. Pregnancy status was determined based on a self-reported pregnancy history. Every participant was asked whether or not anyone of first or second relatives in his/her family ever had diabetes. If the answer was yes, the family history of diabetes was considered positive.

Waist circumference was measured twice at the midpoint between the lower margin of the ribs and the iliac crest to the nearest 0.5 cm. The third measurement was taken if the first two readings were different, greater than 2 cm. The mean of the closest two measurements was used to calculate waist circumference. Hip circumference was measured as the maximum circumference around the buttocks posteriorly and symphysis pubis anteriorly by viewing it from the side. BMI was calculated by dividing the weight (kg) by the height (m) squared. BP was measured twice on the right arm of the participant with elbow level at heart, after sitting for five to ten minutes using a standard mercury sphygmomanometer, using the first and fifth Korotkoff sounds to the nearest 2 mmHg. The mean of the two measurements was used in data analysis. Personal history of hypertension was based on self-reported use of antihypertensive drugs. Information on smoking and alcohol drinking were obtained by interview.

4.3 Laboratory methods

In the QDS, Individuals were instructed to fast for at least 10 hours before the blood was drawn. Blood samples were collected at the local community health clinic. Fasting blood specimens were collected for measurement of serum UA, plasma glucose, serum total cholesterol, triglycerides, and HDL-C. After fasting blood sample was drawn, each participant was asked to drink 75g glucose dissolved in 300 ml water (World Health Organisation 1999) between 7:00-9:30 A.M. Venous blood samples were collected from the antecubital vein into a vacuum tube containing sodium fluoride before and 120 min after the ingestion of 75g glucose. The specimens were put into ice-cooled containers and transported immediately to clinical laboratory of the Qingdao Endocrine and Diabetes Hospital. The plasma glucose was determined by glucose oxidase method within 3 hours after the blood sample was collected. Serum was frozen at –20°C and serum UA was measured by the uricase method within a month in the same clinical laboratory. Fasting serum lipid profile, including triglycerides, total, HDL-C was determined by the enzymatic method.

In the MNCDS, participants not taking antidiabetic drugs were examined with a 75g OGTT. Plasma glucose concentrations were measured immediately after the blood sampling at the survey site using Yellow Springs Instruments (YSI, OH, USA) glucose analyzers in both 1987 and 1992. In 1998, plasma was frozen immediately and glucose was measured approximately 4 months later in Newcastle upon Tyne, UK, using the YSI glucose analyzers. Considering the delay in analysis, the glucose concentrations of 1998 values were adjusted upwards using an equation (adjusted glucose = 0.0288 + 1.037 × measured glucose) based on the difference between on-site values and quality controls from the 1987 and 1992 surveys (Soderberg et al. 2005). Fasting and 2-h serum insulin was measured in Newcastle upon Tyne, UK. A modified radioimmunoassay method proposed by Soeldner and Slone (Soeldner et al. 1965) was used. The interassay and intraassay coefficients of variation were 6% and 4%, respectively. Cross reactivity with intact proinsulin and 32,33-split proinsulin was 27% and 16%, respectively (Soderberg et al. 2007). The homeostasis model assessment of IR (HOMA-IR) was calculated as fasting serum insulin (μU/ml) x FPG (mmol/l)/22.5 and was used as an index of IR. UA, triglycerides, total cholesterol, and HDL-C concentrations were measured at a central laboratory, in Mauritius, in fresh heparin plasma (1987) and serum (1992 and 1998). In 1987, manual enzymatic methods were used, but in 1992 and in 1998 a Chemistry Profile Analyser Model LS (Coultronics, Port Louis, Mauritius) was used. For quality assessment, every 10th sample was also analyzed in Newcastle upon Tyne, UK. On the basis of the external quality assurance data, total cholesterol and triglycerides were adjusted downwards by using calculated regression equations (Dowse et al. 1995), while uncorrected HDL-C and UA were used here as quality controls showed similar results.

4.4 Definitions

Hyperuricemia

Hyperuricemia was defined as serum UA > 420 μmol/l for men and > 360 μmol/l for women according to the common guidelines (Fang et al. 2000). The diagnosis of gout was based on self-reported information that was confirmed by reading the patients' hospital diagnosis record (in Qingdao, China) or clinic record (in Mauritius).

Diabetes

Diabetes was determined according to WHO/IDF 2006 criteria (World Health Organisation/International Diabetes Federation 2006). Known diabetes was diagnosed if participants reported a history of a physician diagnosis of diabetes and was either taking hypoglycemic medication, or the FPG level of ≥ 7.0 mmol/l and/or the 2-hPG value of ≥ 11.1 mmol/l at the survey. Newly diagnosed diabetes was diagnosed if one of these glucose values exceeded the above cut-off points and there was no a prior history of diabetes. Participants without known diabetes were divided into glucose categories according to either FPG or 2-hPG distributions. Both known and newly diagnosed diabetic individuals at the baseline survey were excluded from the current data analysis on the prediction of UA for incident diabetes. Incident cases of diabetes were identified at the end of follow-up among those who were free of diabetes at baseline. Subjects with a FPG of < 7.0 mmol/l but a 2-hPG of 7.8-11.0 mmol/l were defined as having IGT; those with a FPG of 6.1-6.9 mmol/l but a 2-hPG of < 11.1 mmol/l were categorized as having IFG.

Metabolic abnormalities

Taking into account the differences both chronologically and methodologically between studies, metabolic syndrome variables were categorized into sex-, ethnic- and cohort-specific quintiles. We defined the top quintile of waist circumference, BMI, BP, triglycerides, total cholesterol and glucose levels, and the bottom quintile of HDL-C as abnormal. Elevated BP was defined as either systolic or diastolic BP in the top quintile distributions. Hyperuricemia was defined as top quintile of UA values in each cohort in data analysis (Study II).

4.5 Statistical analyses

The standard world population for 10-year intervals was adopted to calculate age-standardized prevalence of hyperuricemia and self-reported gout (Waterhouse 1976). Analysis of covariance was used for comparison of the differences in continuous variables between subgroups in the Qingdao data, a general linear model adjusting for age, ethnicity and cohort for continuous variables in the Mauritius data, and Chi-square test for categorical variables were used to compare the differences between subgroups. Serum triglycerides, FPG, 2hPG, fasting and 2h insulin were log10-transformed to reduce skewness and geometric means were reported. The multiple linear regression analysis was applied to study the association of serum UA with other related variables for men and women (Study I, III), separately. The log-likelihood ratio test was performed to compare the association of each of the metabolic syndrome variables with hyperuricemia (Study II). SPSS package (Chicago, IL) for Windows version 14.0 was used. A p-value of < 0.05 (two-tailed) was considered statistically significant in all analyses.

In Mauritius data, taking into account the differences between cohorts both chronologically and methodologically, sex-, ethnicity- and cohort-specific standard deviation (SD) of continuous variables and their Z scores were calculated and fitted into the models. Cox proportional hazards model for an interval censored survival analysis using the 'interval censoring' package in R 2.2.4 program (http://www.r-project.org/) was fitted to estimate the hazard ratios and their 95% CIs for the incidence of diabetes corresponding to a one SD increase in UA concentration at baseline, using age as time scale (Study IV). Except for the pooled analysis, meta-analysis using the method detailed by Fleiss (Fleiss 1993) was also performed based on individual cohort data (Study II). Individual β-coefficients for each cohort and combined β-coefficients for all cohorts with three or more metabolic syndrome related disorders vs. fewer than three factors, corresponding to a one SD increase in serum UA concentration, were calculated and reported. Q statistic for measuring study-to-study variation in effect size was performed. Since Q was not statistically different from zero ($Q = 0.38$ for Indian men and $Q = 2.96$ for Creole men, and $Q = 3.35$ and $Q = 0.89$, for Indian and Creole women, respectively, with 2 df all $p > 0.10$), fixed effect approach was chosen.

5 RESULTS

5.1 The prevalence of hyperuricemia and its risk factors in Chinese populations in 2002 (Study I)

Age-adjusted mean serum UA (389 μmol/l for men and 316 μmol/l for women), triglycerides (1.76 mmol/l for men and 1.45 mmol/l for women), waist circumference (89.9 cm for men and 83.6 for women) and waist to hip ratio (0.90 for men and 0.84 for women) were significantly higher in men (n = 720) than in women (n = 1 302) (all $p < 0.05$). A total of 215 men and 294 women were found with hyperuricemia in the survey in 2002 in Qingdao. The crude prevalence of hyperuricemia was 29.9% (95% CI 26.6-33.2) for men and 22.6% (95% CI 20.4-25.0) for women. The age-standardized prevalence of hyperuricemia was 25.3% (95% CI 23.5-27.2) in the adult population aged 20-74 years. It was higher in men than women below age 55 years ($p < 0.001$), but no sex difference was observed above age 55 years. Postmenopausal women had a much higher prevalence of hyperuricemia compared to premenopausal women (29.1% vs. 15.4%, $p<0.001$). There were 11 gout patients. The mean UA among them was higher than that for subjects without gout (416.1 μmol/l vs. 341.6 μmol/l, $p = 0.004$). The age-standardized prevalence of gout was 0.63% (95% CI 0.05-1.21) in men, 0.23% (95% CI 0.0-0.49) in women and 0.36 % (95% CI 0.10-0.62) in the total study population.

In multivariate regression analysis, BMI, triglycerides, and alcohol drinking, with standardized β-coefficient of 0.23, 0.23, and 0.10, respectively, were significantly and positively associated with increase in serum UA concentration in men, explaining 15.0% of the variation in serum UA. In women, BMI, triglycerides, total cholesterol, and systolic BP were positively, whereas FPG negatively associated with the serum UA levels, with standardized β-coefficient of 0.17, 0.18, 0.05, 0.08, and -0.05, respectively, which explained 11.0% of serum UA variations. Systolic and diastolic BP, and hypertension was found to have significant direct correlation with UA.

5.2 Mean UA levels in Mauritian populations in 1987, 1992 and 1998 (unpublished data)

The prevalence (95% CI) of hyperuricemia defined as UA > 420 μmol/l for men and UA > 360 μmol/l for women was 36.0% (33.7-38.3), 20.4% (17.7-23.1) and 20.3 (16.1-24.5) for men and 18.2 (16.5-19.9), 9.3 (7.5-11.1) and 4.3 (2.5-6.1) for women in 1987, 1992 and 1998, respectively. Since the laboratory measures differ between surveys, a direct comparison between cohorts can not be made. To make the data comparable, cohort- and sex-specific Z scores of UAs were calculated. The UA levels escalated from the year 1987 to 1992 then to 1998 in Mauritian Creole men and women, with the trend p value of 0.04 and 0.03, respectively, but not in Mauritian Indian men and women (Table 6).

Table 6 Cohort- and sex-specific mean Z-score of uric acid (95% CI) in Mauritian Indian and Creole populations

Cohort	Mauritian Indian			Mauritian Creole		
Men	N	Mean	(95% CI)	N	Mean	(95% CI)
1987	1186	0.02	(-0.04, 0.08)	452	-0.05	(-0.15, 0.04)
1992	619	0.00	(-0.08, 0.08)	260	0.01	(-0.12, 0.13)
1998	245	-0.08	(-0.20, 0.05)	105	0.18	(-0.02, 0.37)
p value for trend		0.20			0.04	
Women						
1987	1364	-0.04	(-0.09, 0.02)	511	0.10	(0.01, 0.18)
1992	677	-0.08	(-0.15, -0.01)	323	0.17	(0.06, 0.28)
1998	327	-0.13	(-0.24, -0.03)	138	0.32	(0.15, 0.49)
p value for trend		0.09			0.03	

5.3 Association of UA with metabolic abnormalities (Study II)

Hyperuricemia (defined as top quintile of UA values in each cohort) and metabolic risk factors

In multivariate regression analysis, the association of hyperuricemia with each of the metabolic risk factors was estimated and compared using the log-likelihood ratio test. Waist circumference, BMI, and triglycerides were statistically strongly associated with hyperuricemia in all groups except in Chinese women, in whom triglycerides, HDL-C, and total cholesterol were associated with hyperuricemia. Adding creatinine to the model did not change the association of hyperuricemia with waist circumference, BMI, triglycerides, HDL-C, total cholesterol, and BP, although creatinine by itself associated with hyperuricemia in both Indians and Creoles ($p < 0.05$).

UA and metabolic syndrome components

Prevalence (95% CI) of a cluster of three or more metabolic disorders was 9.6% (8.3-10.9), 9.4% (7.4-11.4) and 12.0% (8.9-15.1) for Indian, Creole and Chinese men, and 10.5% (9.3-11.7), 10.1% (8.2-12.0) and 13.0% (10.6-15.4) for women, respectively. The prevalences did not differ significantly between Mauritian Indians, Creoles and mainland Chinese in either sex ($p > 0.05$ for both).

Multivariate adjusted odds ratios (95% CIs) for with three or more metabolic syndrome related disorders vs. fewer than three factors, corresponding to a one SD increase in UA concentration were 1.75 (1.51 to 2.02), 2.19 (1.71 to 2.82) and 2.30

(1.68 to 3.16) in Indian, Creole and Chinese men, and 1.74 (1.52 to 2.00), 1.75 (1.40 to 2.19) and 1.72 (1.37 to 2.16) in women, respectively, after adjustment for age, cohort, smoking and alcohol consumption. These associations remained statistically significant after further adjustment for BMI (Figure 3 B1 and B2) or both BMI and waist circumference simultaneously in the same model, with odds ratios (95% CIs) of 1.39 (1.18 to 1.63), 1.59 (1.23 to 2.07) and 1.76 (1.23 to 2.53) in Indian, Creole and Chinese men, and 1.29 (1.11 to 1.49), 1.39 (1.10 to 1.76) and 1.63 (1.27 to 2.09) in women.

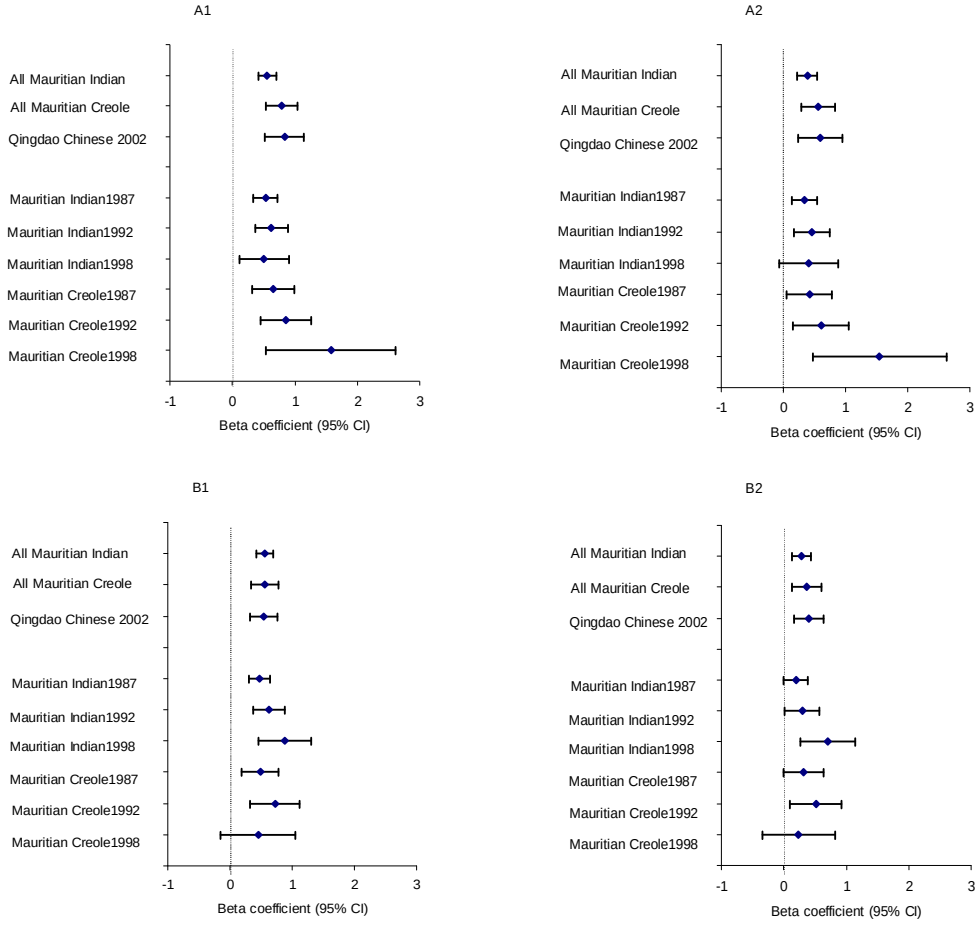


Figure 3. Beta coefficients (black square) and 95% CIs (bar) for with three or more metabolic syndrome variables of waist circumference, elevated blood pressure, fasting glucose, triglycerides and high density lipoprotein cholesterol vs. fewer than three factors, corresponding to a one SD increase in serum uric acid in: (A) men without (A1) and with (A2) body mass index adjustment; and in (B) women without (B1) and with (B2) body mass index adjustment

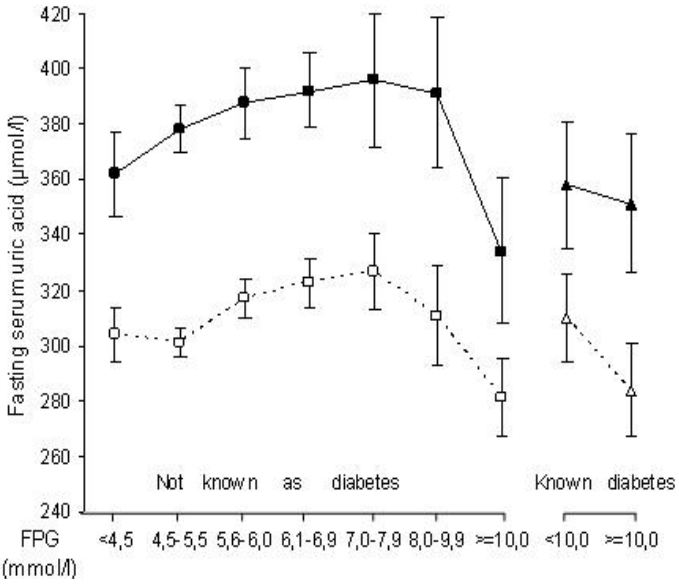
5.4 Association of UA with plasma glucose (Study III, IV)

5.4.1 The pattern of changes in serum UA levels with plasma glucose in Chinese population (cross-sectional study, Study III)

There was an increasing trend in serum UA concentration when the levels of FPG increased from low to high up to the FPG level of 7.0mmol/l; thereafter, the UA concentration started to decrease with further increases in FPG levels (Figure 4A). After multivariate adjustments for age, residential areas, BMI, and triglycerides, the increasing trend in UA at the low FPG level (< 7.0 mmol/l) leveled off in men, but still remained in women (Figure 4B). The declining trend of UA at the higher FPG concentration remained significant after further adjusting for the previous disease history of hypertension, cardiovascular disease, and dyslipidemia in both genders, with a β value of -0.26 in men and -0.20 in women ($p < 0.01$) (Figure 4C).

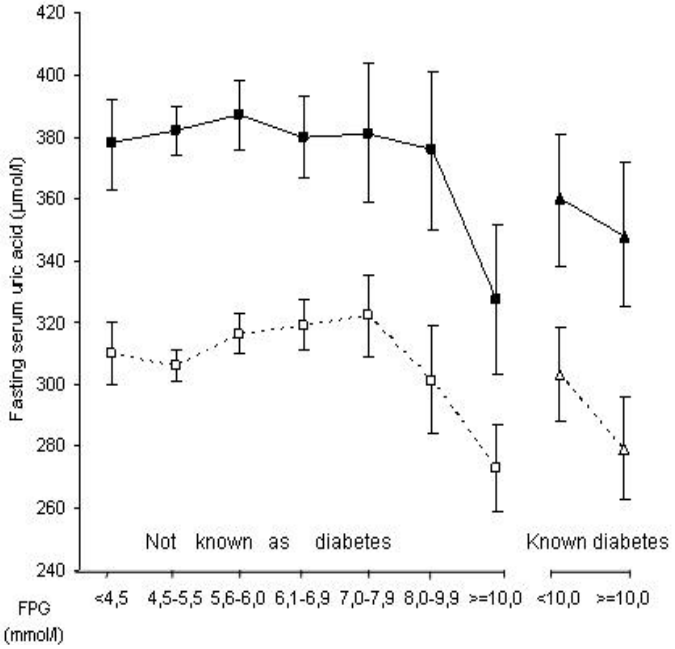
The lowest UA level appeared in subjects with the highest FPG concentrations ($\geq$ 10 0 mmol/l) in previously undiagnosed diabetic men and women ($p < 0.001$). Adjustment for BP or a history of hypertension did not alter the observed relationship. A decreasing trend of serum UA levels with increasing 2-hPG at range of 2-hPG $\geq$ 8.0mmol/l approximately was also observed, with a multivariate adjusted β coefficient of -0.13 ($p < 0.05$) in men and -0.15 in women ($p < 0.001$). We did not, however, observe an upward positive relationship between UA and 2-hPG in the low 2-hPG range.

Figure 4A



n (men)	142	483	221	169	56	43	47	64	56
n (women)	231	890	442	314	121	66	109	90	77

Figure 4B



n (men)	142	483	221	169	56	43	47	64	56
n (women)	231	890	442	314	121	66	109	90	77

Figure 4C

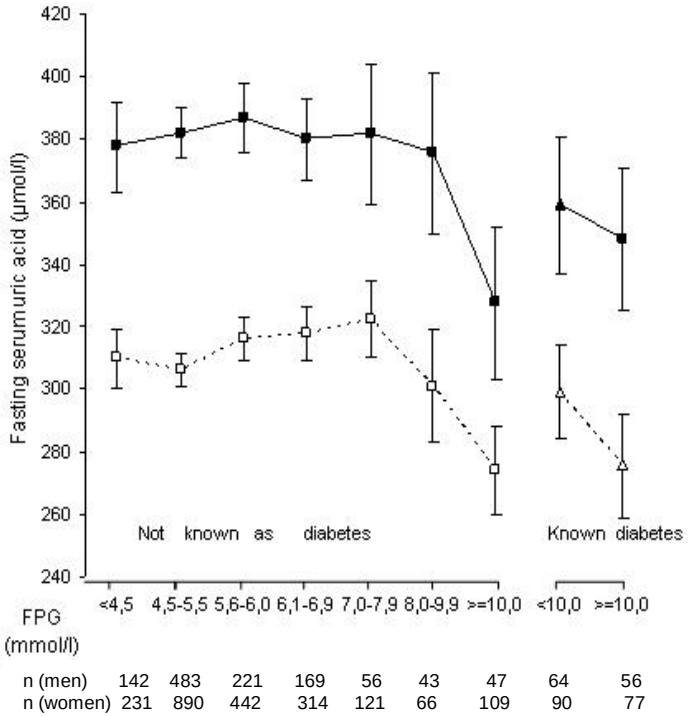


Figure 4. Mean serum uric acid (µmol/l) and their 95% confidence intervals (bar) in men (solid line) and women (dashed line) according to fasting plasma glucose categories, after adjustment for age and resident areas (A); additional adjustment for body mass index and triglycerides (B); and further adjustment for previous history of hypertension, cardiovascular disease, and dislipidemia (C).

5.4.2 Baseline UA predicted the development of diabetes during the follow-up in Mauritian populations (Study IV)

Changes in UA with the development of incident diabetes

A total of 337 (17.4%) men (252 Indians and 85 Creoles) and 379 (16.4%) women (257 Indians and 122 Creoles) were diagnosed with diabetes at the end of the follow-up. The incidence of diabetes did not differ significantly between Mauritian Indians and Creoles in either sex ($p > 0.05$ for both).

Baseline UA levels were significant higher in individuals with incident diabetes (423 μmol/l in men and 311 μmol/l in women) than in those who retained free of diabetes at the end of the follow-up (384 μmol/l in men and 292 μmol/l in women). Regarding to the difference between cohorts both chronologically and methodologically, Z scores of blood UA and other measures of interest at both baseline and follow-up were used in the following data analyses. The UA levels fell significantly from baseline to follow-up in the men (0.35 to 0.02) and the pre-menopausal women (0.04 to -0.21) who developed diabetes ($p < 0.001$ for both), but not in the post-menopausal women (0.38 to 0.45).

High UA at baseline predicted incident diabetes

Multivariate adjusted hazard ratios for the incidence of diabetes corresponding to a one SD increase in UA at baseline in Indians, Creoles and both combined were 1.32, 1.62 and 1.40 in men, and 1.26, 1.20 and 1.23 in women, respectively, after adjusting for FPG, serum creatinine, alcohol consumption, history of hypertension, family history of diabetes, and cohort (Table 7). Further adjustment for BMI, triglycerides, and fasting insulin attenuated the risk related to the baseline UA in both men and women, but the hazard ratios still remained statistically significant in Mauritian Indians and Creoles in men. Replacing BMI, history of hypertension, triglycerides, fasting insulin, and FPG with waist circumference, systolic or diastolic BP, HDL-C or total cholesterol, HOMA-IR, and 2-hPG, did not change the results substantially. Adjustment for the baseline smoking consumption did not alter the relationships observed between UA and diabetes either. In those postmenopausal women at the end of the follow-up, the findings were consistent with that for premenopausal women.

Table 7 Hazard ratios (95% CI) for diabetes incidence corresponding to a one SD increase in covariates at baseline (Study IV)

	Mauritian Indian (n, case)	Mauritian Creole (n, case)	Total (n, case)
Men	(1409, 252)	(532, 85)	(1941, 337)
Model 1			
Uric acid (μmol/l)	1.32 (1.18, 1.49)	1.62 (1.34, 1.96)	1.40 (1.27, 1.55)
Fasting plasma glucose (mmol/l)	1.99 (1.80, 2.20)	1.50 (1.25, 1.79)	1.82 (1.68, 1.98)
Model 2			
Uric acid (μmol/l)	1.14 (1.01, 1.30)	1.37 (1.11, 1.68)	1.19 (1.07, 1.34)
Body mass index (kg/m^2)	1.41 (1.26, 1.58)	1.69 (1.40, 2.05)	1.46 (1.32, 1.61)
Triglycerides (mmol/l)	1.14 (1.03, 1.27)	1.35 (1.14, 1.59)	1.18 (1.08, 1.28)
Fasting plasma glucose (mmol/l)	1.97 (1.79, 2.17)	1.53 (1.27, 1.82)	1.81 (1.66, 1.96)
Women	(1645, 257)	(673, 122)	(2318, 379)
Model 1			
Uric acid (μmol/l)	1.26 (1.13, 1.40)	1.20 (1.02, 1.41)	1.23 (1.13, 1.35)
Fasting plasma glucose (mmol/l)	1.99 (1.85, 2.14)	1.79 (1.58, 2.03)	1.92 (1.80, 2.06)
Model 2			
Uric acid (μmol/l)	1.07 (0.95, 1.22)	1.01 (0.84, 1.22)	1.05 (0.95, 1.16)
Body mass index (kg/m^2)	1.32 (1.17, 1.49)	1.33 (1.12, 1.58)	1.32 (1.19, 1.45)
Triglycerides (mmol/l)	1.27 (1.14, 1.41)	1.32 (1.15, 1.52)	1.27 (1.17, 1.38)
Fasting plasma glucose (mmol/l)	1.92 (1.77, 2.09)	1.71 (1.50, 1.96)	1.86 (1.73, 2.00)

Model 1 adjusted for cohort, serum creatinine, alcohol consumption, history of hypertension, family history of diabetes, and ethnicity (for total population). Model 2 adjusted for cohort, serum creatinine, alcohol consumption, history of hypertension, family history of diabetes, fasting serum insulin, and ethnicity (for total population).

6 DISCUSSION

6.1 Study design and methodology

The strength of the MNCDS was that the sampling procedure, anthropometric measurements, and laboratory tests followed the similar protocol in all cohorts. The large random representative population sample covers 13 areas of Mauritius. Considering the larger sample size drawn from large areas and the high participation rate, the results may represent the characteristics of the general Mauritian Indian and Mauritian Creole population. A representative sample of the general population was selected using a stratified, random cluster sampling method in three urban districts and four rural counties in Qingdao city. Considering the diversity in culture, diet, and climate in China, however, the study result may not be representative of the general Chinese population. More studies in other areas are required.

The large simple size enables a comprehensive data analysis by exclusion of subjects with a personal history of hypertension, cardiovascular diseases including coronary heart disease, stroke and peripheral vascular disease, renal failure, gout, and individuals with diagnosed and undiagnosed diabetes at baseline. The serial measurments of UA, FPG, 2-hPG, lipids and other covariates provides an opportunity to study the trends and changes in the parameters of interest. The meansurement of the 75g 2-h OGTTs have been conducted for all eligible participants to define diabetes status. Differences, however, exist in the laboratory measurements. To minimize the discrepancy between study cohorts, we have tried to use sex- and cohort-specific SD and Z scores for factors studied. In addition, a homogeneity test was performed to check whether the effect sizes between cohorts differ, and the results showed that the effect sizes of interest are quite homogenous between cohorts and therefore, we have pooled the Mauritian cohorts together for certain data analyses to increase the power.

In our study, some potential confounding variables such as detailed dietary information, detailed antihypertensive medication (especially thiazide diuretics, beta-blockers), menstruation information at baseline, socioeconomic factors, C-reactive protein, and urinary UA clearance were not available. To what extent these factors may affect the results obtained was not explored.

Our study is the first prospective investigation of UA and the risk of incident diabetes among Mauritian Indian and Mauritian Creole populations. The results of the study were consistent with the previous findings in other ethnic groups (Chien et al. 2008; Meisinger et al. 2002; Perry et al. 1995). Nevertheless, since the re-examinations were made in intervals and the exact date of a diagnosis of diabetes was not available, we can not obtain the actual changes in blood UA concentration in relation to the onset of diabetes and the duration of diabetes. This is also the first detailed report on the association of the serum UA with the FPG and 2-hPG in the Chinese population in mainland China. The study is cross-sectional, however, and predictive value of the UA in the development of future diabetes is not known.

6.2 Interpretation of Findings

6.2.1 The high prevalence of hyperuricemia in Chinese populations

Our study revealed a higher prevalence of hyperuricemia in Qingdao compared to those previously reported in mainland China, but the prevalence in this study was lower than most of the reports from studies in Taiwan, and much lower than in Taiwanese Aborigines (Chang et al. 2001; Chang et al. 1997; Chungtei 2003) (Table 1). The high UA levels in Taiwanese aborigines is due to the factors that they are genetically more similar to the Malayo-Polynesians and have a higher BMI and relatively higher amounts of alcohol consumption compared with non-aborigines (Chang et al. 2001). In the past decades obesity and dyslipidemia have reportedly increased in mainland China (Liu et al. 2004), which may to a large extent explain the higher prevalence of hyperuricemia in our survey as compared to surveys made in 1990s. In addition, seafood is a major part of the food components in Qingdao. This may also contributed to the high levels of UA observed in Qingdao.

6.2.2 Associations between high UA and metabolic risk factors

In study I, the associations of BMI and triglycerides with serum UA were highly significant for both sexes in general population in Qingdao, China. Serum UA was demonstrated as significant in relation to hypertension, which was consistent with findings in other clinical and epidemiological studies (Conen et al. 2004; Fang et al. 2000; Johnson et al. 2003; Li et al. 1997). Age appeared related to hyperuricemia in women in our study, which was consistent with a report from a study in Beijing (Li et al. 1997). In other Asian studies, age was also reported as being a risk factor for hyperuricemia in women, but in men hyperuricemia has been found to decrease with age (Chang et al. 2001; Nakanishi et al. 1999). The mechanisms relating hyperuricemia to aging remains unclear. Estrogen may play a role in inducement increase UA elimination (Nicholls et al. 1973; Yahyaoui et al. 2008). Alcohol consumption was associated with hyperuricemia only in men in our study. This may be due to the fact that women seldom drink alcohol in China.

In study II, high serum UA was significantly associated with several metabolic factors such as a large waist circumference (or BMI), dyslipidemia, high BP, and both individually and the clustering of these metabolic risk factors in the nondiabetic population. These results were consistent with findings in the Japanese (Ishizaka et al. 2005; Nagahama et al. 2004b; Nakanishi et al. 2003), non-Hispanic Caucasians from the US (Coutinho et al. 2007; Krishnan et al. 2007), and European people (Bonora et al. 1998), despite different assays used for UA and different ethnic backgrounds. It was recently reported that Korean men, age 30-39, with serum UA levels in the top quintile, compared to the bottom quintile, had an approximately 1.6-fold increased risk for metabolic syndrome (Ryu et al. 2007). Our study found an association of serum UA with plasma glucose in the nondiabetic population, but these associations also depended on the level of obesity and triglycerides as indicated by others (Chou et al. 2001; Johnson et al. 2003).

In obese individuals, high serum UA is due to an overproduction of UA and impairment in renal clearance of UA owing to the influence of hyperinsulinemia secondary to IR (Matsuura et al. 1998; Quinones Galvan et al. 1995; Yamashita et al.

1986). The potential mechanisms relating hyperuricemia to fasting hypertriglyceridemia are unknown. It has been speculated that it may be due to an increase in NADPH requirement for de novo fatty acid synthesis. With increasing NADPH, UA production is enhanced, and this may increase the serum UA level (Vuorinen-Markkola et al. 1994). In addition, UA may play a role in the pathophysiology of IR and cellular disturbances in glucose and lipid metabolism. UA is also known to be an endogenous antioxidant and its efficacy in antioxidative capacity in the early stages of the atherosclerotic process is strong (Nyyssonen et al. 1997). With advancing atherosclerosis, circulating UA levels increase and this previous antioxidant paradoxically may become prooxidant (Hayden et al. 2004), contributing to the pathogenesis of the metabolic syndrome (Sautin et al. 2007). In contrast, it has also been reported that acute exposure to the high concentrations of UA did not impair endothelial function in healthy men (Waring et al. 2004), suggesting that high UA may not be a causal factor in vascular disease, but rather a marker of an existing problem.

6.2.3 UA was lower after diabetes developed

In the cross-sectional study (III) we found that serum UA increased with increasing FPG levels up to the FPG level of 7.0 mmol/l, but decreased when FPG was over 7.0 mmol/l. An inverse relationship existed between 2-hPG and serum UA when 2-hPG was higher than 8.0 mmol/l, but an upward increasing trend in UA levels was not observed in the low 2-hPG range. These findings further confirmed previous findings (Herman et al. 1976; Tuomilehto et al. 1988; Whitehead et al. 1992; Yano et al. 1977) despite differences in assays used for UA and in diagnostic criteria for diabetes in different studies. Furthermore, in the Mauritius longitudinal study (IV), UA levels decreased from baseline levels in the same individuals who developed diabetes at the end of the follow-up, except for menopausal women. After menopause the UA levels increased (Nicholls et al. 1973), possibly compensating for the decrease in UA in women who developed diabetes at the end of the follow-up.

Few studies have investigated the relationship between 2-hPG and UA due to the fact that 2-h OGTT have not been widely applied. UA declined with increasing 2-hPG at the upper range of the 2-hPG distribution, but did not find an increasing trend at the lower 2-hPG range. Our study showed a stronger association between FPG and serum UA than that for 2-hPG. The finding needs to be further examined. The physiological bases of isolated IFG and isolated IGT are somewhat different (Davies et al. 2000; DeFronzo 1999; Weyer et al. 1999). Although both isolated IFG and isolated IGT are insulin-resistant states, they differ in their site of IR (Abdul-Ghani et al. 2006; Qiao et al. 2003). People with isolated IFG predominantly have hepatic IR and normal muscle insulin sensitivity, whereas individuals with isolated IGT have normal to slightly reduced hepatic IR and moderate to severe muscle IR. Individuals with both IFG and IGT manifest both muscle and hepatic IR. The pattern of insulin secretion also differs between IFG and IGT (Nathan et al. 2007). People with isolated IFG have a decrease in first-phase (0–10 min) insulin secretory response to intravenous glucose and a reduced early-phase (first 30 min) insulin response to oral glucose. The late-phase (60–120 min) plasma insulin response during the OGTT, however, is normal in isolated IFG. Isolated IGT also has a defect in early-phase insulin secretion in response to an oral glucose load and in addition has a severe deficit in late-phase insulin secretion. Therefore, the extent of which the difference in glucose regulations at fasting and postprandial conditions has contributed to the observed relationship between UA and

glucose levels requires further investigation.

Studies have revealed that insulin can enhance renal proximal tubular UA reabsorption in humans, linking to the tubular reabsorption of sodium (Cappuccio et al. 1993; Muscelli et al. 1996; Quinones Galvan et al. 1995). In addition, IR increases serum UA through the hexose monophosphate shunt connecting with UA production (Fox 1981; Modan et al. 1987). Thus, high insulin levels can lead to hyperuricemia. In our study, the high fasting insulin levels may explain the high baseline UA levels in individuals with diabetes at follow-up, but can not explain the decrease in UA levels after the onset of diabetes. The reduction in UA levels after the onset of diabetes may be a consequence of the excess excretion of UA due to the hyperosmotic effect caused by high blood glucose concentration and glycosuria (Cook et al. 1986).

6.2.4 High UA at baseline predicted incident diabetes in Mauritian Indian and Creole

In the population-based longitudinal study from Mauritius (IV), baseline UA, after multivariate adjustments, independently predicted the development of diabetes in Mauritian men, but not in Mauritian women. Aging and sex hormones (estrogen and androgen) may contribute to gender difference, but the mechanism is uncertain. In addition, the difference in smoking and diet between men and women may be involve, since smoking and drinking alcohol were more popular for men than women in Mauritius. This can not be investigated, however, because the detailed dieting information (e.g. meat and seafood) was not collected. A previous study reported a direct and graded relationship between UA and the risk of diabetes in the Mauritian population over 5 years (Boyko et al. 2000), and our findings confirm it in a more detailed analysis of data collected over a maximum of 11 years of follow-up.

UA may play a direct role in the pathogenesis of diabetes by the possible inhibition of endothelial function (Nakagawa et al. 2006), inhibition of nitric oxide bioavailability (Baldus et al. 2005) and stimulation of vascular smooth muscle cell proliferation (Price et al. 2006). Furthermore, deficiency of endothelial-derived nitric oxide is believed to be the primary defect that links IR and cellular disturbances in glucose and lipid metabolism (Cersosimo et al. 2006). The underlying mechanism of UA in the process of deterioration of glucose metabolism is still not clear, and needs to be further investigated.

6.3 Implications for further research and clinical management

We found serum UA levels clearly strongly associated with metabolic risk factors, tended to increase with increasing FPG concentration in nondiabetic individuals, but decreased in diabetic individuals. Moreover, high baseline UA concentrations predicted the development of diabetes in Mauritian Indian and Creole. Nonetheless, the prognostic value of UA in the development of type 2 diabetes is not clear, and the direction of causality between hyperuricemia and metabolic disorders is uncertain. Although prospective cohort studies are useful in establishing temporal relationship between exposure and a discrete disease endpoint, the direction of the association between hyperuricemia and metabolic disorders is more difficult to ascertain because all those variables are continuous and correlated with each other. Further studies to investigate the pathophysiological mechanism underlying the relationship between

glucose and UA, and between metabolic syndrome and UA, may help to understand the formation of these metabolic disorders and find a way to stop or delay the development of diabetes and cardiovascular diseases.

Regardless of the pathophysiological explanations, these observations raise an important clinical question. Is it possible to prevent/postpone the onset of type 2 diabetes by reducing serum UA in people with pre-diabetes? Recently, in a short-term, crossover designed clinical trail of adolescents with newly diagnosed hypertension, treatment with allopurinol resulted in reduction of BP (Feig et al. 2008). The results represent a new potential therapeutic approach, although not a fully developed therapeutic strategy due to potential adverse effects. These preliminary findings require confirmation in larger randomized, controlled clinical trails. Allopurinol and other agents of febuxostat, or pegylated, would be potential candidate drugs for intervention, but the safety and cost-effectiveness of these medications in pre-diabetes individuals first need to be studied.

It would be important to advise subjects with hyperuricemia and gout to control or loss weight, to increase physical activity, and to follow healthy dietary recommendations (Hak et al. 2008), in order to reduce the risk of type 2 diabetes and metabolic syndrome, and improve overall long-term outcomes.

7 CONCLUSIONS

The conclusions related to the specific objectives are:

1. The prevalence of hyperuricemia was high in the urban Chinese populations in Qingdao. Obesity, dyslipidemia, and hypertension were important risk factors related to the hyperuricemia.

2. Blood UA was associated with the clustering of metabolic risk factors in nondiabetic populations of Mauritian Indian, Mauritian Creole, and Chinese living in Qingdao. Whether including UA in the definition of the metabolic syndrome would improve the ability of the metabolic syndrome to predict cardiovascular disease and diabetes needs further investigation.

3. Serum UA levels tended to increase with increasing FPG concentrations in nondiabetic individuals, but decreased in diabetic individuals. The relationship between UA and 2-hPG levels was not as strong as that for FPG. It would be interesting to explore to the extent of which the difference in glucose regulations at fasting and postprandial conditions has contributed to the observed relationship.

4. A high baseline UA level predicted the development of future diabetes, independently of major confounding or mediating risk factors in Mauritian in men, but not in Mauritian women. The clinical use of UA as a marker of glucose and other metabolic risk factors needs to be further studied.

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