



## Relationship between Diabetes Mellitus and Serum Uric Acid Levels

J. Sarvesh Kumar\*, Vishnu Priya V<sup>1</sup>, Gayathri R<sup>2</sup>

\*B.D.S 1<sup>ST</sup> YEAR, Saveetha Dental College, 162, P.H road, Chennai, Tamilnadu, India.

<sup>1</sup>Associate professor, Department of Biochemistry, Saveetha Dental College, 162, P.H Road, Chennai, Tamilnadu, India.

<sup>2</sup>Assistant professor, Department of Biochemistry, Saveetha Dental College, 162, P.H Road, Chennai, Tamilnadu, India.

\*Corresponding author's E-mail: [dr.sarveshkumarj@gmail.com](mailto:dr.sarveshkumarj@gmail.com)

Accepted on: 03-05-2016; Finalized on: 30-06-2016.

### ABSTRACT

The aim of the study is to review the association between diabetes Mellitus and serum uric acid levels. The objective is to review how uric acid level is related to diabetes Mellitus. Diabetes is an increasingly important disease globally. New data from IDF showed that there are 336 million people with diabetes in 2011 and this is expected to rise to 552 million by 2030. It has been suggested that, diabetic epidemic will continue even if the level of obesity remains constant. The breakdown of foods high in protein into chemicals known as purines is responsible for the production of uric acid in the body. If there is too much of uric acid in the body it causes variety of side effects. Thus identifying risk factors of serum uric acid is required for the prevention of diabetes. The review was done to relate how serum uric acid level is associated with the risk of diabetes.

**Keywords:** Diabetes, Serum Uric Acid Level and purine.

### INTRODUCTION

Diabetes mellitus, commonly known as diabetes, is a group of metabolic disease in which there are high blood sugar levels over a prolonged period of time. It is a group of disorders characterized by chronic hyperglycemia associated with disturbance of carbohydrate, protein and fat metabolism due to absolute or relative deficiency of insulin secretion or its action.<sup>1</sup> Identifying the risk factors for the development of diabetes is essential for its screening and prevention.<sup>2</sup> For sometime it has been recognized that serum uric acid, an end product of purine metabolism is positively associated with serum glucose levels in healthy subjects with pre diabetes and early diabetes. The normal range for serum uric acid is 2.4 - 7.4 mg/dl in males and 1.4 - 5.8 mg/dl in females. Furthermore, an elevated serum uric acid level was found to increase the chances of developing diabetes in individuals impaired with glucose tolerance.<sup>3</sup> Uric acid acts as a pro oxidant and thus it is a marker of oxidative stress, but it may also have a therapeutic role as an antioxidant. Urate, the soluble form of uric acid, can scavenge the superoxide and the hydroxyl radicals and it can chelate the transition metals. Hyperuricaemia has been also added to the set of metabolic abnormalities which are associated with insulin resistance and / or hyperinsulinaemia in the metabolic syndrome. Hypouricaemia has also been implicated in the development of diabetic nephropathy.<sup>4</sup> Several studies had shown that the role of uric acid in the development of diabetes is controversial. Therefore this review was done to relate how serum uric acid level is associated with the risk of diabetes.

### Diabetes

Diabetes mellitus, commonly called as diabetes, is a

disorder in which one's body does not make enough insulin or not able to use normal amount of insulin properly. Insulin is a hormone that regulates the amount of sugar in blood. High blood sugar level will cause problems in many parts of our body.<sup>5</sup>

### Types of Diabetes

#### Type 1 diabetes

Type 1 diabetes generally occurs in children. It is also called juvenile onset diabetes mellitus or insulin-dependent diabetes mellitus. In this type, our pancreas will not be able to make enough insulin and the person has to take insulin injections for the rest of life.<sup>6</sup>

#### Type 2 diabetes

Type 2 diabetes, which is more common, usually occurs in people over 40 years of age and is called adult onset diabetes mellitus. It is also called non insulin-dependent diabetes mellitus. In Type 2, pancreas makes insulin, but body doesn't use it properly.

The high blood sugar level is often controlled by following a proper diet and/or taking medication, although some patients must take insulin. Type 2 diabetes is particularly more prevalent among Africans, Indians, Latins and Asians.<sup>6</sup>

### Insulin Resistance

Insulin resistance (IR) is generally regarded as a pathological condition in which the cells fail to respond to the normal actions of the insulin hormone.

When the body produces insulin under the conditions of insulin resistance, the cells in the body are resistant to the insulin and are not able to use it as effectively, leading to high blood sugar. Beta cells in the pancreas



subsequently increase their production of insulin, further contributing to a high blood insulin level. This often remains undetected and can lead to Type 2 diabetes.<sup>7</sup>

### Effect of Insulin Resistance

Insulin resistance often does not trigger any noticeable symptoms, especially in the early phases. One could be insulin resistant for many years without knowing, especially if a person's blood glucose levels aren't checked. Some people with insulin resistance may develop a condition known as acanthosis nigricans. This condition creates dark patches on the back of the neck, armpits and groin. It also puts a person at higher risk for type 2 diabetes. There is no cure for acanthosis nigricans, but if the cause is treated, some of their natural skin color may return. Insulin resistance may also damage blood vessels without the person realizing it. This can increase the risk of heart disease and stroke.<sup>8</sup> If a person has insulin resistance; they are at significant risk for progressing to diabetes. The symptoms of type 2 diabetes can be mild, so they may not know that they have the condition until a doctor runs diagnostic tests on them.

### The symptoms pertaining to diabetes are:-

- extreme thirst or hunger
- feeling hungry even after a meal
- frequent or increased urination
- tingling sensations in hands or feet
- feeling more tired than usual

### Relation between Insulin Resistance and Diabetes

Insulin resistance increases the risk of developing type 2 diabetes and prediabetes. Prediabetes usually occurs in people who already have insulin resistance.

Although insulin resistance alone does not cause type 2 diabetes, it often acts as the stage for the disease by placing a high demand on the insulin-producing beta cells. In prediabetes, the beta cells will not be able to produce enough insulin to overcome insulin resistance, causing blood glucose levels to rise above the normal range.<sup>9</sup>

Once a person has pre diabetes, the continued loss of beta cell function usually leads to type 2 diabetes. People with type 2 diabetes have high blood glucose.

Over the time, high blood glucose damages the nerves and blood vessels, leading to complications such as heart disease, kidney failure, blindness, stroke, and lower-limb amputations.<sup>10</sup>

Studies have shown that most of the people with pre diabetes develop type 2 diabetes within 10 years, unless they change their lifestyle.

Lifestyle changes include losing 5 to 7 percent of their body weight—10 to 14 pounds for people who weigh 200 pounds and by making changes in their diet and the level of physical activity.<sup>10</sup>

### Uric Acid

Uric acid is a heterocyclic compound of carbon, hydrogen, nitrogen and oxygen, with the formula  $C_5H_4N_4O_3$ . It forms salts and ions known as urates and acid urates, such as ammonium acid urate. Uric acid is the final product obtained by the metabolic breakdown of purine nucleotides. High blood concentrations of uric acid can lead to gout and are associated with other medical conditions including diabetes and the formation of ammonium acid urate kidney stones.

Uric acid is the waste product that is normally found in the blood. High amounts of uric acid in the blood can cause crystal formation in the joints, leading to the condition gout. However, only a small portion of people with high uric acid levels are possibly to get gout.<sup>11</sup>

Researches have shown that there are strong links between the uric acid levels and metabolic syndrome. Studies in people with pre-diabetes and among elderly people have suggested that high uric acid levels raise a person's chances of getting diabetes.

### Uric Acid and Type 2 Diabetes

People who had higher uric acid levels are more likely to get type 2 diabetes. Uric acid is measured as milligrams per deciliter. For every 1 milligram per deciliter increase in uric acid, the risk of type 2 diabetes is increased by 20 percent in elderly people and by 15 percent in their children.<sup>12</sup>

### Hyperuricemia

Hyperuricemia is condition with increased uric acid levels in the body. It is common in elderly, male patients. Associated diseases and renal impairment can be found frequently.<sup>13</sup> It has been seen that hyperuricemia is commonly associated with obesity, hypertriglyceridemia, diabetes mellitus, development and progression of coronary artery disease<sup>14,15</sup> and hypertension.<sup>16</sup> Serum Uric Acid is as independent risk factor for development and progression of Coronary Artery Disease.<sup>15</sup> Marked hyperuricemia is known to cause acute renal failure via intra renal crystal deposition.<sup>17</sup>

Hyperuricemia is associated with renal disease, but it is usually considered a marker of renal dysfunction rather than a risk factor for progression. Recent studies have reported that mild hyperuricemia in normal rats induced by the uricase inhibitor, oxonic acid (OA), results in hypertension, intrarenal vascular disease, and renal injury. This led to the hypothesis that uric acid may be a true mediator of renal disease and progression.<sup>18</sup>

Male gender is associated with a more rapid progression of renal disease independent of blood pressure, dietary protein intake, or serum lipid levels.<sup>18</sup>

Although hyperuricemia has long been associated with renal disease, uric acid has not been considered as a true mediator of progression of renal Disease. The observation that hyperuricemia is commonly associated with other

risk factors of cardiovascular and renal disease, especially hypertension, has made it difficult to dissect the effect of uric acid itself. However, recent epidemiologic evidence suggests a significant and independent association between the level of serum uric acid and renal disease progression with beneficial effect of decreasing uric acid levels. Furthermore, our experimental data using hyperuricemic animals and cultured cells have provided robust evidence regarding the role of uric acid on progression of renal disease.

Recent data also suggest hyperuricemia may be one of the key and previously unknown mechanisms for the activation of the renin-angiotensin and cyclooxygenase-2 (COX-2) systems in progressive renal disease. Although we must be cautious in the interpretation of animal models to human disease, these studies provide a mechanism to explain epidemiologic data that show uric acid is an independent risk factor for renal progression. Although there is no concrete evidence yet that uric acid bears a causal or reversible relationship to progressive renal disease in humans, it is time to reevaluate the implication of hyperuricemia as an important player for progression of renal disease and to try to find safe and reasonable therapeutic modalities in individual patients based on their clinical data, medication history, and the presence of cardiovascular complications.<sup>19,20</sup>

Hyperuricemia is commonly associated with traditional risk factors such as abnormalities in glucose metabolism, dyslipidemia, and hypertension.

### Hyperuricemia with Insulin Resistance

Despite the fact that many studies have demonstrated an association between high serum uric acid and insulin resistance, the causal effect between them has not been fully explained. Uric acid – the end product of purine catabolism – was found to be associated with hypertension, obesity, dyslipidemia as well as hyperinsulinemia.<sup>21</sup> Those with higher serum uric acid were associated with a higher prevalence of insulin resistance even among normal fasting glucose and normal glucose tolerance patients.<sup>21</sup> Vuorinen Markkola and Yki-Jarvinen<sup>22</sup> indicated that serum uric acid level is inversely correlated with insulin sensitivity, and uric acid was suggested to play an important role in the function of the  $\beta$  cell in patients with type 2 diabetes even in states prior to hyperuricemia.<sup>23</sup>

A large epidemiologic study<sup>24</sup> also showed that high serum uric acid levels had a positive correlation with fasting serum insulin levels, and Tsouli<sup>25</sup> have reviewed the association between elevated uric acid and insulin resistance.

Even though the association between hyperuricemia and insulin resistance has been well demonstrated, the causal effect between them should be further explored. Carnethon<sup>26</sup> revealed a significantly higher risk of developing hyperinsulinemia with increased baseline uric acid level in a follow-up study among nondiabetic

participants. In a recent study, Krishnan<sup>27</sup> also demonstrated that those with hyperuricemia have 1.36 times the risk of developing insulin resistance in a 15-year follow-up study. Furthermore, in a mice study, Baldwin<sup>28</sup> demonstrated that lowering uric acid in obese mice can reduce insulin resistance. All the data suggest that hyperuricemia can be detected prior to the development of hyperinsulinemia.

Although regarding the progressing causal effect of insulin resistance leading to hyperuricemia, hyperuricemia is usually the result of under-excretion of urate,<sup>29</sup> and the renal clearance of urate has been shown to be inversely related to the degree of insulin resistance.<sup>30</sup> Moreover, hyperinsulinemia may decrease uric acid clearance by the kidneys.<sup>31,32</sup> Reaven<sup>33</sup> attributed the presence of hyperuricemia in metabolic syndrome to a secondary response to hyperinsulinemia. The association has been attributed to the effects of insulin on proximal tubular urate transport of the kidney. In addition, drug treatments for improving insulin sensitivity were also shown to lower serum uric acid levels.<sup>34–37</sup>

Therefore, one mechanism linking the association between hyperinsulinemia with hyperuricemia is a decrease of renal excretion of uric acid. Insulin can also enhance renal tubular sodium reabsorption,<sup>32,38</sup> which in turn can reduce renal excretion of uric acid. Whatever the mechanisms of insulin on the renal tubules, be it direct stimulation of tubular ion exchange or acceleration of cellular metabolism,<sup>39</sup> insulin can modify the handling of uric acid by the kidney, thus leading to hyperuricemia.

Nakagawa<sup>40</sup> showed that uric acid blocked acetylcholine-mediated arterial dilation, suggesting that uric acid can impair endothelial function. Moreover, in mice studies, endothelial nitric oxide synthase deficiency results in the features of insulin resistance and metabolic syndrome<sup>41</sup> because uric acid has been shown to reduce nitric oxide bioavailability,<sup>42,43</sup> and reducing endothelial nitric oxide supply is a known mechanism for inducing insulin resistance,<sup>44</sup> hyperuricemia may thus have a key role in the pathogenesis of insulin resistance.

In summary we have reviewed the evidence that insulin may modify the handling of uric acid by the kidney, and contribute to hyperuricemia and the evidence that hyperuricemia may have a key role in the pathogenesis of insulin resistance by blocking endothelial nitric oxide supply. Thus, we speculate that hyperuricemia and insulin resistance share bidirectional causal effects.

### Hyperuricemia with Type 2 Diabetes

Hyperuricemia is a risk factor for type 2 diabetes, but the causal association between them is controversial. A large epidemiological study<sup>45</sup> of Japanese adult men showed that an elevation of serum uric acid levels increased the risk of type 2 diabetes. Although obesity has been recognized as a potential risk factor for type 2 diabetes, some studies<sup>46–48</sup> have documented high rates of type 2 diabetes in the absence of classical obesity among some



populations. These results suggest that other independent pathogenic factors may exist that could contribute to the occurrence of type 2 diabetes, such as hyperuricemia, and many studies<sup>27,49,50</sup> have suggested that elevated uric acid levels, hyperuricemia, or gout, have associations with the development of type 2 diabetes.

Dehghan<sup>51</sup> demonstrated that serum uric acid is a strong and independent risk factor for diabetes in a 10-year follow-up study. Other studies<sup>51,52</sup> demonstrated a significant linear regression between serum uric acid levels and incident type 2 diabetes. However, diabetic patients who continue to be hyperuricemic appear to be at increased risk of developing diabetic complications, especially renal disease.<sup>53</sup> Although decreased kidney function can be highly associated with hyperuricemia, based on some epidemiological studies, hyperuricemia is an independent risk factor for kidney dysfunction in patients with diabetes mellitus. The causal association between hyperuricemia and type 2 diabetes may be mediated by kidney dysfunction as well as insulin resistance. However, not all studies have reached the same conclusion; a large prospective study<sup>54</sup> did not show an association between uric acid levels and type 2 diabetes, and an inverse association between serum uric acid levels and diabetes mellitus has also been observed.<sup>55,56</sup>

## CONCLUSION

The present review clearly explains that the serum uric acid level is directly proportional to the risk associated with type 2 diabetes and even a small increase in uric acid level causes a more than 10 times increase in the risk associated with pre diabetes and type 2 diabetes, also high uric acid level is associated with a higher prevalence of insulin resistance, increased risk of cardiovascular mortality and metabolic syndrome. It is clear that serum uric acid level serves as an important biomarker for impaired glucose metabolism and is found to be high in patients with impaired renal function, also further research should be attempted to investigate whether serum uric acid levels can be used as a diagnostic test to identify the presence of diabetes and in its early prevention.

## REFERENCES

1. Sudhindra Rao M, Bino John Sahayo. A study of serum uric acid in diabetes mellitus and pre diabetes in south Indian tertiary care hospital. *NUJHS* 2.2 (2012).
2. Kodama, S., K. Saito, Y. Yachi, M. Asumi, A. Sugawara, K. Totsuka, A. Saito, and H. Sone. "Association between Serum Uric Acid and Development of Type 2 Diabetes." *Diabetes Care* 32.9 (2009), 1737-742. Web.
3. A. Cauaevic, S. Semiz, A.M. Dzankovic, B. Cico, T. Dujic, M. Malenica, T. Bego. Relevance of uric acid in progression of type 2 diabetes mellitus. *Bosnian journal of basic medical sciences*, 10(1), 2010, 54-59.
4. Shabana S, Sireesha M, Satyanarayana U. Uric acid in relation to type 2 diabetes mellitus association with hypertension. *Journal of clinical and diagnostic research*, vol-6(7), 2012 September (suppl), 1140-1143.
5. Harris, M. I. "Diabetes in America: Epidemiology and Scope of the Problem." *Diabetes Care* 21. Supplement\_3 (1998).
6. Dewitt, Dawn E., and Irl B. Hirsch. "Outpatient Insulin Therapy in Type 1 and Type 2 Diabetes Mellitus." *Jama* 289.17 (2003), 2254.
7. Chiu H. K., Tsai E. C., Juneja R., Stoever J., Brooks-Worrell B., Goel A., & Palmer J. P. (2007). Equivalent insulin resistance in latent autoimmune diabetes in adults (LADA) and type 2 diabetic patients. *Diabetes Research and Clinical Practice*, 77(2), 237-244. doi:10.1016/j.diabres.2006.12.013
8. Kahn, C. Ronald, Jeffrey S. Flier, Robert S. Bar, Juanita A. Archer, Phillip Gordon, Malcolm M. Martin, and Jesse Roth. "The Syndromes of Insulin Resistance and Acanthosis Nigricans." *New England Journal of Medicine* *N Engl J Med* 294.14 (1976), 739-45.
9. Seidell, Jacob C. "Obesity, Insulin Resistance and Diabetes — a Worldwide Epidemic." *BJN British Journal of Nutrition* 83.S1 (2000).
10. Tuomilehto, Jaakko, Jaana Lindström, Johan G. Eriksson, Timo T. Valle, Helena Hämäläinen, Pirjo Ilanne-Parikka, Sirkka Keinänen-Kiukaanniemi, Mauri Laakso, Anne Louheranta, Merja Rastas, Virpi Salminen, Sirkka Aunola, Zygimantas Cepaitis, Vladislav Moltchanov, Martti Hakumäki, Marjo Mannelin, Vesa Martikkala, Jouko Sundvall, and Matti Uusitupa. "Prevention of Type 2 Diabetes Mellitus by Changes in Lifestyle among Subjects with Impaired Glucose Tolerance." *New England Journal of Medicine* *N Engl J Med* 344.18 (2001), 1343-350.
11. Herman, Joseph B., and Uri Goldbourt. "Uric Acid and Diabetes: Observations in a Population Study." *The Lancet* 320.8292, (1982), 240-43.
12. Dehghan, A., M. Van Hoek, E. J.g. Sijbrands, A. Hofman, and J. C.m. Witteman. "High Serum Uric Acid as a Novel Risk Factor for Type 2 Diabetes." *Diabetes Care* 31.2, (2007), 361-62.
13. Akkasilpa S, Avihingsanon Y, Hanvivadhanakul P, Wonchinsri J. Clinical manifestations of patients with hyperuricemia. *J Med Assoc Thai*, 87(Suppl 2), 2004, S41–4.
14. Short RA, Johnson RJ, Tuttle KR. Uric acid, micro albuminuria and cardiovascular events in high-risk patients. *Am J Nephrol*, 25(1), 2005, 36–44.
15. Madsen TE, Muhlestein JB, Carlquist JF, Horne BD, Bair TL, Jackson JD, et al. Uric acid independently predicts mortality in patients with significant, angiographically defined coronary disease. *Am J Nephrol*, 25(1), 2005, 45–9.
16. Kelley NW, Palella TD. Gout and Other Disorders of Purine Metabolism. *Harrison's Principles of Internal Medicine*. 12th Ed. New York: McGraw Hill Book Company; 1991, 1834–7.
17. Roncal CA, Mu W, Croker B, Reungjui S, Ouyang X, TabahFisch I, Johnson RJ, Ejaz AA. Effect of elevated serum uric acid on cisplatin-induced acute renal failure. *Am J Physiol Renal Physiol*, 292, 2007, F116–22.
18. Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, Truong L, Harris R, Johnson RJ. A role for uric acid in the



- progression of renal disease. *J Am Soc Nephrol*, 13, 2002, 2888–97.
19. Kang DH, Yu ES, Yoon KI, Johnson R. The impact of gender on progression of renal disease: potential role of estrogen-mediated vascular endothelial growth factor regulation and vascular protection. *Am J Pathol*, 164, 2004, 679–88.
  20. Nakagawa T, Kang DH. Uric acid and chronic renal disease: possible implication of hyperuricemia on progression of renal disease. *Semin Nephrol*, 25(1), 2005, 43–9.
  21. Meshkani R, Zargari M, Larijani B. The relationship between uric acid and metabolic syndrome in normal glucose tolerance and normal fasting glucose subjects. *Acta Diabetologica*, 48, 2011, 79–88.
  22. Vuorinen-Markkola H, Yki-Jarvinen H. Hyperuricemia and insulin resistance. *J Clin Endocrinol Metab*, 78, 1994, 25–29.
  23. Robles-Cervantes JA, Ramos-Zavala MG, Gonzalez-Ortiz M, E. Martínez-Abundis, C. Valencia-Sandoval, A. Torres-Chávez, C. Espinel-Bermúdez, N. J. Santiago-Hernández, and S. O. Hernández-González. Relationship between serum concentration of uric acid and insulin secretion among adults with type 2 diabetes mellitus. *Int J Endocrinol* 2011; 2011:107904. The article revealed the opinion that uric acid can play an important role in the function of the beta cell in patients with type 2 diabetes, even in states prior to hyperuricemia.
  24. Yoo TW, Sung KC, Shin HS, Kim BJ, Kim BS, Kang JH, Lee MH, Park JR, Kim H, Rhee EJ, Lee WY, Kim SW, Ryu SH, Keum DG. Relationship between serum uric acid concentration and insulin resistance and metabolic syndrome. *Circ J*, 69, 2005, 928–933.
  25. Tsouli SG, Liberopoulos EN, Mikhailidis DP, Athyros VG, Elisaf MS. Elevated serum uric acid levels in metabolic syndrome: an active component or an innocent bystander? *Metabolism*, 55, 2006, 1293–1301.
  26. Carnethon MR, Fortmann SP, Palaniappan L, Duncan BB, Schmidt MI, Chambless LE. Risk factors for progression to incident hyperinsulinemia: the Atherosclerosis Risk in Communities Study, 1987–1998. *Am J Epidemiol*, 158, 2003, 1058–1067.
  27. Krishnan E, Pandya BJ, Chung L, Hariri A, Dabbous O. Hyperuricemia in young adults and risk of insulin resistance, prediabetes, and diabetes: a 15-year follow-up study. *Am J Epidemiol*, 176, 2012, 108–116.
  28. Baldwin W, McRae S, Marek G, Wymer D, Pannu V, Baylis C, Johnson RJ, Sautin YY. Hyperuricemia as a mediator of the proinflammatory endocrine imbalance in the adipose tissue in a murine model of the metabolic syndrome. *Diabetes*, 2011.
  29. Yamanaka H. Gout and hyperuricemia in young people. *Curr Opin Rheumatol*, 23, 2011, 156–160.
  30. Facchini F, Chen YD, Hollenbeck CB, Reaven GM. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. *Jama*, 266, 1991, 3008–3011.
  31. Quinones Galvan A, Natali A, Baldi S, Frascerra S, Sanna G, Ciociaro D, Ferrannini E. Effect of insulin on uric acid excretion in humans. *Am J Physiol*, 268, 1995, E1–E5.
  32. Muscelli E, Natali A, Bianchi S, Bigazzi R, Galvan AQ, Sironi AM, Frascerra S, Ciociaro D, Ferrannini E. Effect of insulin on renal sodium and uric acid handling in essential hypertension. *Am J Hypertens*, 9, 1996, 746–752.
  33. Reaven GM. The kidney: an unwilling accomplice in syndrome X. *Am J Kidney Dis*, 30, 1997, 928–931.
  34. Tsunoda S, Kamide K, Minami J, Kawano Y. Decreases in serum uric acid by amelioration of insulin resistance in overweight hypertensive patients: effect of a low-energy diet and an insulin-sensitizing agent. *Am J Hypertens*, 15, 2002, 697–701.
  35. Filippatos TD, Kiortsis DN, Liberopoulos EN, Mikhailidis DP, Elisaf MS. A review of the metabolic effects of sibutramine. *Curr Med Res Opin*, 21, 2005, 457–468.
  36. Tambascia MA, Geloneze B, Repetto EM, Geloneze SR, Picolo M, Magro DO. Sibutramine enhances insulin sensitivity ameliorating metabolic parameters in a double-blind, randomized, placebo-controlled trial. *Diabetes Obes Metab*, 5, 2003, 338–344.
  37. Kiortsis DN, Filippatos TD, Elisaf MS. The effects of orlistat on metabolic parameters and other cardiovascular risk factors. *Diabetes Metab*, 31, 2005, 15–22.
  38. Ter Maaten JC, Voorburg A, Heine RJ, Ter Wee PM, Donker AJ, Gans RO. Renal handling of urate and sodium during acute physiological hyperinsulinaemia in healthy subjects. *Clin Sci (Lond)*, 92, 1997, 51–58.
  39. Mandel LJ. Primary active sodium transport, oxygen consumption, and ATP: coupling and regulation. *Kidney Int*, 29, 1986, 3–9.
  40. Nakagawa T, Hu H, Zharikov S, Tuttle KR, Short RA, Glushakova O, Ouyang X, Feig DI, Block ER, Herrera-Acosta J, Patel JM, Johnson RJ. A causal role for uric acid in fructose-induced metabolic syndrome. *Am J Physiol Renal Physiol*, 290, 2006, F625–F631.
  41. Cook S, Hugli O, Egli M, Vollenweider P, Burcelin R, Nicod P, Thorens B, Scherrer U. Clustering of cardiovascular risk factors mimicking the human metabolic syndrome X in eNOS null mice. *Swiss Med Wkly*, 133, 2003, 360–363.
  42. Baldus S, Köster R, Chumley P, Heitzer T, Rudolph V, Ostad MA, Warnholtz A, Staude HJ, Thüneke F, Koss K, Berger J, Meinertz T, Freeman BA, Münzel T. Oxypurinol improves coronary and peripheral endothelial function in patients with coronary artery disease. *Free Radic Biol Med*, 39, 2005, 1184–1190.
  43. Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, Krotova K, Block ER, Prabhakar S, Johnson RJ. Hyperuricemia induces endothelial dysfunction. *Kidney Int*, 67, 2005, 1739–1742.
  44. Roy D, Perreault M, Marette A. Insulin stimulation of glucose uptake in skeletal muscles and adipose tissues *in vivo* is NO dependent. *Am J Physiol*, 274, 1998, E692–E699.
  45. Nakanishi N, Okamoto M, Yoshida H, Matsuo Y, Suzuki K, Tataru K. Serum uric acid and risk for development of hypertension and impaired fasting glucose or Type II diabetes in Japanese male office workers. *Eur J Epidemiol*, 18, 2003, 523–530.
  46. Pan WH, Flegal KM, Chang HY, Yeh WT, Yeh CJ, Lee WC. Body mass index and obesity-related metabolic disorders in

- Taiwanese and US whites and blacks: implications for definitions of overweight and obesity for Asians. *Am J Clin Nutr*, 79, 2004, 31–39.
47. Sone H, Mizuno S, Ohashi Y, Yamada N. Type 2 diabetes prevalence in Asian subjects. *Diabetes Care*, 27, 2004, 1251–1252.
48. Jiang Y, Chen Y, Mao Y, Group COW. The contribution of excess weight to prevalent diabetes in Canadian adults. *Public Health*, 122, 2008, 271–276.
49. Lai HM, Chen CJ, Su BY, Chen YC, Yu SF, Yen JH, Hsieh MC, Cheng TT, Chang SJ. Gout and type 2 diabetes have a mutual interdependent effect on genetic risk factors and higher incidences. *Rheumatology (Oxford)*, 51, 2012, 715–720.
50. Chien KL, Chen MF, Hsu HC, Chang WT, Su TC, Lee YT, Hu FB. Plasma uric acid and the risk of type 2 diabetes in a Chinese community. *Clin Chem*, 54, 2008, 310–316.
51. Dehghan A, Van Hoek M, Sijbrands EJ, Hofman A, Witteman JC. High serum uric acid as a novel risk factor for type 2 diabetes. *Diabetes Care*, 31, 2008, 361–362.
52. Choi HK, De Vera MA, Krishnan E. Gout and the risk of type 2 diabetes among men with a high cardiovascular risk profile. *Rheumatology (Oxford)*, 47, 2008, 1567–1570.
53. Rosolowsky ET, Ficociello LH, Maselli NJ, Niewczas MA, Binns AL, Roshan B, Warram JH, Krolewski AS. High-normal serum uric acid is associated with impaired glomerular filtration rate in nonproteinuric patients with type 1 diabetes. *Clin J Am Soc Nephrol*, 3, 2008, 706–713.
54. Taniguchi Y, Hayashi T, Tsumura K, Endo G, Fujii S, Okada K. Serum uric acid and the risk for hypertension and Type 2 diabetes in Japanese men: The Osaka Health Survey. *J Hypertens*, 19, 2001, 1209–1215.
55. Tuomilehto J, Zimmet P, Wolf E, Taylor R, Ram P, King H. Plasma uric acid level and its association with diabetes mellitus and some biologic parameters in a biracial population of Fiji. *Am J Epidemiol*, 127, 1988, 321–336.
56. Herman JB, Medalie JH, Goldbourt U. Diabetes, prediabetes and uricaemia. *Diabetologia*, 12, 1976, 47–52.

**Source of Support:** Nil, **Conflict of Interest:** None.