Uric Acid, Type 2 Diabetes, and Cardiovascular Diseases: Fueling the Common Soil Hypothesis?

Uric acid is the final oxidation product of purine catabolism. Excess serum accumulation can lead to various diseases, and most notably uric acid is causally involved in the pathogenesis of gouty arthritis. Also, for more than 50 years, increased serum concentrations of uric acid have been implicated in cardiovascular disease. Uric acid's contribution to atherosclerotic vascular disease, however, is still somewhat controversial. Various mechanisms have been suggested through which uric acid may be implicated in the atherosclerotic process and its clinical complications. Uric acid can act as a prooxidant, particularly at increased concentrations, and may thus be a marker of oxidative stress (1, 2), but it may also have a therapeutic role as an antioxidant (3, 4). Plasma uric acid concentrations correlate with longevity in primates and other mammals (5), a characteristic that is presumably a function of urate's antioxidant properties. Thus, it is unclear whether increased concentrations of uric acid in diseases associated with oxidative stress, such as atherosclerotic coronary heart disease (CHD), stroke, and peripheral arterial occlusive disease, are a protective response or a primary cause. Some researchers have proposed that hyperuricemia-induced oxidative stress represents a cause of the metabolic syndrome (6). Hyperuricemia has been found to be associated with obesity and insulin resistance, and consequently with type 2 diabetes (7, 8). Further potentially important biological effects of uric acid relate to endothelial dysfunction by inducing antiproliferative effects on endothelium and impairing nitric oxide production and inflammation, e.g., through increased C-reactive protein expression, although these issues are considered controversial (9, 10). Finally, uric acid may play a role in immune activation with subsequent increased chemokine and cytokine expression (11, 12). Thus, although there are plausible mechanisms to suggest uric acid as a potential direct mediator of cardiometabolic and other chronic diseases (except for gout), this is still a controversial area. Metabolic syndrome, type 2 diabetes, and atherosclerotic vascular disease are characterized by various established but also emerging risk factors, and interestingly, these three disorders have several risk factors in common. This has led Stern in 1995 (13) to put forward his "common soil" hypothesis. As mentioned above, uric acid presents one of the candidates that may be involved in these three cardiometabolic disorders.

In this issue of Clinical Chemistry, reports from two prospective studies may support this concept. Chien et al. (14), in a well-conducted, large, population-based study, investigated the association between increased plasma concentrations of uric acid and the incidence of type 2 diabetes in Chinese subjects followed for a median of 9 years, during which 548 new cases occurred. In cross-sectional analysis, they found an association with the metabolic syndrome (defined according to ATP III guidelines using an Asian-specific cut point for waist circumference) and, in their prospective approach, could demonstrate a 63% increased risk for incident type 2 diabetes across extreme quintiles of uric acid in multivariable analyses. Including the presence of metabolic syndrome in their analyses led to a moderate attenuation of the association, which was however still statistically significant, suggesting that part of the effect of uric acid on the incidence of diabetes was mediated by various components of the metabolic syndrome, in particular insulin resistance. Such results may not be contrary to the suggested protective effects of uric acid. It is quite conceivable, as the authors suggest, that, in the context of the complex cellular environment of the metabolic syndrome—which is clearly associated with oxidative stress—antioxidant properties of uric acid might convert to a prooxidant state owing to reactive oxygen species (ROS) accumulation (6). This may also lead to adverse effects on endothelial function and a proinflammatory response, both of which are known to be associated with new onset of type 2 diabetes (15, 16). In addition, renal effects of uric acid (such as increased glomerular pressure and sodium reabsorption), which are enhanced by high plasma insulin (17), may further adversely affect glucose tolerance.

The second study, by Strasak et al. (18), investigated the association between increased uric acid concentrations in serum and mortality from cardiovascular causes in more than 80 000 Austrian men followed for a median of 13.6 years. Whereas increased uric acid was associated with increased risk of death from CHD, congestive heart failure (CHF), and stroke in univariate models, the association with CHD disappeared completely in multivariate models. Uric acid remained a statistically significant and clini-

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cally relevant predictor of mortality from CHF and stroke if extreme quintiles of the uric acid distribution were compared. A number of reports have looked at CHD as an end point, with conflicting results, and a few at stroke (2), but this is the first prospective study to convincingly demonstrate an association between increased concentrations of uric acid and CHF. Would this fit with the mechanisms within the cardiometabolic field that we know uric acid is involved in? Indeed, oxidative stress, endothelial dysfunction, an activated immune system, and inflammation are also implicated in the pathogenesis of CHF and stroke. But why is uric acid not independently related to CHD in this very large cohort? Probably because of the consistent relationship with established cardiometabolic risk factors, the strongest correlations of which were seen with γ-glutamyltransferase, triglycerides, and obesity, all of which are implicated in the metabolic syndrome. Again, uric acid might act as a strong oxidant in such environment (6). For stroke, hypertension represents the major risk factor, and the correlation with uric acid was much smaller for systolic and diastolic blood pressure than for metabolic variables, which may explain why uric acid was still an independent predictor for stroke mortality in multivariable analyses.

What can we learn from these studies? Although neither study collected detailed information on food intake and renal function (which are known codeterminants of serum uric acid), and also were incomplete concerning assessment of medication (especially for hypertension and CHD), they were prospective in their design, investigated large samples over a long follow-up period, and used well-standardized protocols. Still, they will not be able to finally resolve the issue of whether increased serum uric acid is causally involved in cardiometabolic diseases, although they present suggestive evidence that it may at least contribute. Measurement of uric acid is easy in terms of preanalytics, can be performed with simple methods in routine laboratories, and is inexpensive. Thus, a preventive, cost-effective approach is available with potential implications for public health. Because the metabolic environment seems to be crucial for the adverse effects of uric acid, patients with advanced atherosclerotic disease may present an even more attractive group, with a potentially larger benefit from intervention, than subjects from the general population. Such high-risk groups need to be studied in more detail, and a randomized controlled trial to test the effect of uric acid reduction on clinical end points may be warranted (2). Developments in medicine are not always straightforward, and sometimes a new look at an old candidate may facilitate change.

– **Wolfgang Koenig**[1*]
– **Christa Meisinger**[2,3]

[1]*Department of Internal Medicine II–Cardiology*
University of Ulm Medical Center
Ulm, Germany
[2]*Helmholtz Center Munich*
German Research Center for Environmental Health
(GmbH)
Institute of Epidemiology
Germany
[3]*MONICA/KORA Myocardial Infarction Registry*
Central Hospital
Augsburg, Germany
*Address correspondence to this author at
Department of Internal Medicine II–Cardiology
University of Ulm Medical Center
Robert-Koch Str. 8
D-89081 Ulm, Germany
Fax ++49-731-500-45021
E-mail wolfgang.koenig@uniklinik-ulm.de

References

1. Becker BF. Towards the physiological function of uric acid. Free Radic Biol Med 1993;14:615–31.
2. Strazzullo P, Puig JG. Uric acid and oxidative stress: relative impact on cardiovascular risk? Nutr Metab Cardiovasc Dis 2007;17:409–14.
3. Becker BF, Reinholz N, Leipert B, Raschke P, Permanetter B, Gerlach E. Role of uric acid as an endogenous radical scavenger and antioxidant. Chest 1991;100(3 suppl):176S–81S.
4. Strasak AM, Rapp K, Hilbe W, Oberaigner W, Ruttmann E, Concin H, et al. on behalf of the VHM&PP Study Group. The role of serum uric acid as an antioxidant protecting against cancer: prospective study in more than 28 000 older Austrian women. Ann Oncol 2007;18:1893–7.
5. Cutler RG. Urate and ascorbate: their possible roles as antioxidants in determining longevity of mammalian species. Arch Gerontol Geriatr 1984; 3:321–48.
6. Hayden MR, Tyagi SC. Uric acid: a new look at an old risk marker for cardiovascular disease, metabolic syndrome, and type 2 diabetes mellitus: the urate redox shuttle. Nutr Metab (Lond) 2004;1:10.
7. Baker JF, Krishnan E, Chen L, Schumacher HR. Serum uric acid and cardiovascular disease: recent developments, and where do they leave us? Am J Med 2005;118:816–26.
8. Dehghan A, van Hoek M, Sijbrands EJ, Hofman A, Witteman JC. High serum uric acid as a novel risk factor for type 2 diabetes mellitus. Diabetes Care 2007 Oct 31 [Epub ahead of print]
9. Kanellis J, Kang DH. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. Semin Nephrol 2005;25:39–42.
10. Waring WS, McKnight JA, Webb DJ, Maxwell SR. Uric acid restores endothelial function in patients with type 1 diabetes and regular smokers. Diabetes 2006;55:3127–32.
11. Gersch MS, Johnson RJ. Uric acid and the immune response. Nephrol Dial Transplant 2006;21:3046–7.
12. Sanchez-Lozada LG, Nakagawa T, Kang DH, Feig DI, Franco M, Johnson RJ, et al. Hormonal and cytokine effects of uric acid. Curr Opin Nephrol Hypertens 2006;15:30–3.
13. Stern MP. Diabetes and cardiovascular disease. The "common soil" hypothesis. Diabetes 1995;44:369–74.
14. Chien K-L, Chen M-F, Hsu H-C, Chang W-T, Su T-C, Lee Y-T, Hu FB. Plasma uric

acid and risk of type 2 diabetes in a Chinese community. Clin Chem 2008;54: 310–6.

15. Thorand B, Baumert J, Chambless L, Meisinger C, Kolb H, Döring A, et al. MONICA/KORA Study Group. Elevated markers of endothelial dysfunction predict type 2 diabetes mellitus in middle-aged men and women from the general population. Arterioscler Thromb Vasc Biol 2006;26:398–405.

16. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001; 286:327–34.

17. Quinones GA, Natali A, Baldi S, Frascerra S, Sanna G, Ciociaro D, et al. Effect of insulin on uric acid excretion in humans. Am J Physiol 1995;268:E1–5.

18. Strasak A, Ruttmann E, Brant L, Kelleher C, Klenk J, Concin H, et al. Serum uric acid and risk of cardiovascular mortality: a prospective long-term study in 83 683 Austrian men. Clin Chem 2008;54:273–84.