Published in final edited form as:

Am J Med. 2014 June ; 127(6): e21. doi:10.1016/j.amjmed.2014.02.031.

Is Uric Acid an Underdiagnosed Mediator of Adverse Outcome in Metabolically Healthy Overweight/Obese Individuals?

Mehdi A. Fini, MD^{a,b}, Richard M. Wright, PhD^{a,b,c}, Kurt R. Stenmark, MD^{b,d}, Stephen R. Daniels, MD, PhD^d, and Richard J. Johnson, MD^{a,e}

^aDepartment of Medicine, University of Colorado Denver, School of Medicine, Aurora

^bDivision of Pulmonary and Critical Care, University of Colorado Denver, School of Medicine, Aurora

^cWebb-Waring Center, University of Colorado Denver, School of Medicine, Aurora

^dDepartment of Pediatrics, University of Colorado Denver, School of Medicine, Aurora

^eDivision of Renal Diseases and Hypertension, University of Colorado Denver, School of Medicine, Aurora

To the Editor

In their recently published observations, Kramer et al¹ have demonstrated that despite an apparently healthy metabolic state, overweight and obese individuals are still at significantly increased risk for adverse long-term outcome, suggesting that “there is no healthy pattern of increased weight.” The notion that obese and overweight individuals who exhibit a metabolically healthy profile are nonetheless at greater risk for adverse outcome begs the question of whether some undisclosed biomarker or physiologic mediator is responsible for the increased risk.² We hypothesize that uric acid may be a biomarker or underdiagnosed mediator of adverse outcome in overweight and obese individuals.

A genome-wide association study has identified numerous single nucleotide polymorphisms that are associated with elevated serum uric acid level.³ These data demonstrate that hyperuricemia and genes mediating uric acid homeostasis are significantly associated with the overweight/obese state.

Elevated serum uric acid has been found to be the best predictor of cardiovascular disease risk in metabolically unhealthy overweight and obese individuals. Data from this recent study⁴ also established the statistically significant trend between serum uric acid and healthy normal weight, healthy overweight/obese, and unhealthy overweight/obese individuals that was associated with increasing risk for cardiovascular disease. Of note, this trend was preserved in both young (<18 years) and older (>18 years) individuals with serum uric acid

Conflict of Interest: RJJ holds patent applications related to decreasing uric acid in the treatment of metabolic syndrome, kidney disease, and hypertension, and has consulted for Ardea, Novartis, Danone, and Astellas. He also holds a patent for the use of allopurinol to treat primary hypertension with the University of Washington and Merck, Inc.

Authorship: All authors had access to the data and played a role in writing this manuscript.

values of 4.5, 5.1, and 6.1 mg/dL in young individuals and 4.5, 5.2, and 6.2 mg/dL in the older cohort. Thus, serum uric acid values established a trend from healthy normal weight to healthy overweight/obese and finally unhealthy overweight/obese, suggesting that serum uric acid could mediate the trend from healthy obesity to unhealthy obesity.⁴

Analysis of serum uric acid over a broad concentration range has revealed a complex (J-shaped) dose response in cardiovascular and all-cause mortality with injurious effect when its levels reach extremes at both high and low levels.⁵ This may be of particular significance for overweight and obese individuals who may exhibit chronic long-term hyperuricemia.

Uric acid seems to be an underdiagnosed variable in the evaluation of metabolic health in overweight and obese individuals. Although further analyses are clearly warranted, the association of hyperuricemia with obesity coupled with the independent effects of uric acid on the risk for cardiovascular disease and all-cause mortality would suggest that the definition of metabolically healthy or unhealthy should include serum uric acid as an independent parameter.

Acknowledgments

Funding: National Institutes of Health HL113809 and HL007171.

References

1. Kramer CK, Zinman B, Retnakaran R, et al. Are metabolically healthy overweight and obesity benign conditions?: a systematic review and meta-analysis. *Ann Intern Med.* 2013; 159:758–769. [PubMed: 24297192]
2. Alpert JS. “So, doctor, what’s so bad about being fat?” Combating the obesity epidemic in the United States. *Am J Med.* 2010; 123:1–2. [PubMed: 20102980]
3. Kottgen A, Albrecht E, Teumer A, et al. Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. *Nat Genet.* 2013; 45:145–154. [PubMed: 23263486]
4. Mangge H, Zelzer S, Puerstner P, et al. Uric acid best predicts metabolically unhealthy obesity with increased cardiovascular risk in youth and adults. *Obesity (Silver Spring).* 2013; 21:E71–E77. [PubMed: 23401248]
5. Lapsia V, Johnson RJ, Dass B, et al. Elevated uric acid increases the risk for acute kidney injury. *Am J Med.* 2012; 125:302.e9–302.e17.