

# Serum Bilirubin Levels Predict Future Development of Metabolic Syndrome in Healthy Middle-aged Nonsmoking Men



Shao-Sung Huang, MD,<sup>a,b,c</sup> Wan-Leong Chan, MD,<sup>a,b</sup> Hsin-Bang Leu, MD, PhD,<sup>a,b,c</sup> Po-Hsun Huang, MD, PhD,<sup>a,c</sup> Shing-Jong Lin, MD, PhD,<sup>a,c,d</sup> Jaw-Wen Chen, MD<sup>a,d,e</sup>

<sup>a</sup>Department of Medicine, <sup>b</sup>Healthcare and Service Center, and <sup>d</sup>Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan; <sup>c</sup>Institute of Clinical Medicine and <sup>e</sup>Institute of Pharmacology, National Yang-Ming University, Taipei, Taiwan.

## ABSTRACT

**BACKGROUND:** Despite epidemiologic research demonstrating an inverse relationship between serum bilirubin levels and the prevalence of metabolic syndrome, prospective data on serum bilirubin as a predictor of incident metabolic syndrome are limited.

**METHODS:** Serum bilirubin was examined as a risk marker for incident metabolic syndrome in a prospective study of 468 Taiwanese middle-aged men who were free of metabolic syndrome and other systemic diseases at baseline. These subjects were followed up in annual health examinations between 2001 and 2009 for the development of metabolic syndrome, which was defined according to unified criteria set by several major organizations.

**RESULTS:** Among the study subjects, 377 were nonsmokers and 91 were current smokers. All individuals were then stratified into 3 groups according to their baseline serum bilirubin levels (low, normal, and high). During a mean follow-up period of 7.58 years, 66 subjects developed metabolic syndrome. The incidence of metabolic syndrome was significantly reduced in the high-bilirubin group compared with the low-bilirubin group (6.4% vs 22.4%,  $P < .001$ ). Multivariate Cox regression analysis revealed that the hazard ratio for incident metabolic syndrome between the highest and lowest tertiles of serum bilirubin levels was 0.246 (95% confidence interval 0.120-0.503). However, although it remained clearly evident in nonsmokers, the inverse correlation was attenuated in current smokers.

**CONCLUSIONS:** Increased serum bilirubin was associated with a reduced future risk of metabolic syndrome in apparently healthy middle-aged, nonsmoking men. Our findings support the predictive role of serum total bilirubin for future development of metabolic syndrome.

© 2015 Elsevier Inc. All rights reserved. • *The American Journal of Medicine* (2015) 128, 1138.e35-1138.e41

**KEYWORDS:** bilirubin; cohort study; metabolic syndrome

**Funding:** None.

**Conflict of Interest:** None.

**Authorship:** S-SH was responsible for study design, analysis and interpretation of data, and drafting of manuscript. W-LC and P-HH were responsible for study design. H-BL was responsible for analysis of data. S-JL was responsible for manuscript revising. J-WC was responsible for manuscript revising and final approval of the manuscript.

Requests for reprints should be addressed to Jaw-Wen Chen, MD, Taipei Veterans General Hospital, Department of Medical Research, No. 201, Sec. 2, Shih-Pai Road, Taipei, Taiwan.

E-mail address: jwchen@vghtpe.gov.tw

Metabolic syndrome represents a cluster of cardiovascular risk factors associated with cardiovascular disease and type 2 diabetes. It is associated with a 2-fold increase in cardiovascular outcomes and a 1.5-fold increase in all-cause mortality.<sup>1</sup> According to the original definition by Reaven,<sup>2</sup> metabolic syndrome consisted of obesity, insulin resistance, hypertension, impaired glucose tolerance or diabetes, hyperinsulinemia, and dyslipidemia. It is characterized by an altered oxidative/antioxidant status and a subclinical inflammatory state. The systemic proinflammatory state induces insulin resistance, leading to clinical and biochemical manifestations of metabolic syndrome.<sup>3</sup> In addition, hyperglycemia and