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Serum bilirubin levels are lower in overweight asymptomatic middle-aged adults: An early indicator of metabolic syndrome?

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ABSTRACT

Objective. Low levels of bilirubin have recently been associated with obesity, diabetes mellitus, and metabolic syndrome. Here, we hypothesized that serum bilirubin levels might be already altered in overweight asymptomatic middle-aged individuals before full development of the metabolic syndrome.

Methods. Healthy nonsmoking adults aged 25–49 (64 women and 32 men) participated in this cross-sectional study. All participants who reported stable weight within the last three months underwent standard anthropomorphological measurements of body composition, blood pressure measurements, aerobic and anaerobic capabilities assessment, dietary intake evaluation, and fasting serological measurements of total and direct bilirubin, glucose, insulin, triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and C-reactive protein. Participants were divided into normal-weight and overweight groups. Linear correlation and multiple regression analyses were used to examine the association of serum bilirubin levels with all metabolic syndrome risk factor changes.

Results. Serum bilirubin levels were lower in overweight healthy individuals of both sexes, and were negatively associated with abdominal obesity, insulin resistance, fasting glucose, fasting insulin, fasting triglycerides, total cholesterol, low-density lipoprotein cholesterol, and C-reactive protein levels but positively associated with aerobic body capabilities.

Conclusion. Our findings suggest that serum bilirubin levels have the potential to be employed as an early biomarker for indicating asymptomatic individuals at increased risk of developing metabolic syndrome.

1. Introduction

Overweight and obesity are common conditions affecting health in all age and gender groups. Obesity is correlated with systemic inflammation, and accompanied by high-oxidative status [1,2]. Moreover, overweight can be considered as a pre-disease state that can compromise the antioxidant defense system on a long-term basis. From this perspective, low serum concentrations of endogenous antioxidants can be an early sign of disease-prone conditions in apparently healthy asymptomatic middle-aged individuals.

Abbreviations: AMA, American Medical Association; ANOVA, analysis of variance; BF, body fat; BMI, body mass index; BSME, Biering–Sørenson muscular endurance; CRP, C-reactive protein; DSP, diastolic blood pressure; FI, fitness index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MetS, Metabolic Syndrome; NSAID, non-steroidal anti-inflammatory drug; TF, trunk fat; SBP, systolic blood pressure; UDP, uridine diphosphate.

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Bilirubin, the end product of heme metabolism, is an endogenous antioxidant with anti-inflammatory properties. Indeed, high bilirubin serum concentrations are associated with increased total antioxidant capacity, and confer protection against oxidative stress-induced diseases [3–5]. Bilirubin serum levels are determined, on the one hand, by genetic factors, such as the intrinsic activity of enzymatic steps in bilirubin homeostasis (heme oxygenase-1, biliverdin reductase, bilirubin UDP-glucuronosyltransferase), serum albumin concentration, and its bilirubin-binding properties; and on the other hand, by external factors like dietary status, fasting, tobacco smoking, intake of drugs or plant products, living at altitude, age, fitness level, and general health status [4].

Recent studies have shown that serum bilirubin levels are inversely associated with the metabolic syndrome (MetS) and systemic inflammation in adults [6–10], as well as in children and adolescents [11]. In particular, abdominal obesity alone has been correlated with low serum bilirubin levels [9–11].

In this study, we tested the hypothesis that serum bilirubin levels might be already decreased in overweight asymptomatic young adults. Thus, MetS components, nutritional intake, physical fitness level, and core muscle endurance were analyzed together with serum bilirubin in the studied group. As an outcome, we identified bilirubin as a potential early serum biomarker for indicating healthy individuals at increased risk of developing MetS.

2. Methods

2.1. Subjects and methods

In this cross-sectional study, we recruited 182 individuals (Caucasian origin), aged 25–49 years, from the general population (70 males and 112 females) by advertisement (Internet forums, e-mail and newspaper advertisements) to participate in the study. Only subjects who met the following criteria were eligible to participate in the study: 1) nonsmokers aged 25-49; 2) body mass index (BMI) higher than 19, but lower than 35; 3) healthy with no cardiovascular, endocrine, and acute or chronic inflammatory diseases; 4) not taking medications for lipid metabolism, or anti-inflammatory drugs (NSAID); and 5) reporting a stable weight within the last three months. Among 182 potential subjects, 86 were excluded from the study. A total of 96 healthy Caucasian adults (64 females and 32 males), resident in the coastal part of Slovenia, participated in the study. The study was approved by the Slovenian National Medical Ethics Committee (No. 56/08/11 bis), and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All volunteers were fully informed of the procedures before affording their written consent. The study was carried out in October–December 2011 at the Faculty of Health Sciences, University of Primorska, Izola, Slovenia.

2.1.1. Serum measurements

Venous blood samples for biochemical and hormonal determinations were taken on an empty stomach in the morning (between 8 and 9 A.M.) in 4 mL vacuum test tubes (Becton-Dickinson, Rutherford, USA). Serum was immediately separated, frozen and stored at −20 °C until subsequent analysis. Serum concentrations of direct and total bilirubin, glucose, triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and C-reactive protein (CRP) were measured using Olympus reagents and performed on an AU 680 Chemistry System analyzer (Beckman Coulter, Nyon, Switzerland). Serum insulin and folic acid concentrations were measured using Abbott reagents, and performed on an ARCHITECT i2000SR analyzer (Abbott Diagnostics, Illinois, USA). The homeostasis model assessment (HOMA) was used as a measure of insulin resistance (HOMA-IR) and β cell function (HOMA-β). HOMA-IR was calculated as [insulin (milli-international units per liter) × glucose (millimoles per liter)]/22.5 and HOMA-β was calculated as [20 × insulin (milli-international units per liter)/(glucose (millimoles per liter) − 3.5)] [12].

2.1.2. Measurement of body composition

Subjects' height, weight, waist and hip circumference, as well as blood pressure were measured using a standardized protocol. All measurements were performed by the same examiner between 7 A.M. and 8 A.M. Subject height was measured to the nearest 0.1 cm in a standing position, without shoes, using a Leicester Height Measure (Invicta Plastics, Oadby, England). Body weight was measured with ± 0.1 kg precision, with participants wearing only underwear and without shoes. Waist was measured in a standing position halfway between the costal edge and iliac crest, whereas hip was measured as the greatest circumference around the buttocks. BMI and waist to hip ratios were calculated using the formulas weight (kg)/height^2 (m^2) and waist (cm)/hip (cm), respectively. Body composition (total percentage body fat (% BF) and percentage trunk fat (% TF)) were assessed using bioelectrical impedance analysis (BIA) using a Tanita BC 418MA (Tanita, Arlington Heights, IL), and data were analyzed with the software provided by the producer (Tanita Corporation). Although % BF and % TF are highly correlated, % TF represents visceral fat better than does % BF. In addition, the same analysis also provided data on visceral fat rating. Participants with at least two of the following characteristics were classified as members of the overweight group: BMI ≥25 kg/m^2, large waist circumference (≥94 cm in men and ≥80 cm in women), and/or high % of total fat (≥21.5% in men and ≥32% in women). The MetS was evaluated according to the Harmonization definition, which takes into account the following five components: hypertriglyceridemia (≥1.7 mmol/l), HDL levels (<1 mmol/l in men and <1.3 mmol/l in women), large waist circumference (≥94 cm in men and ≥80 cm in women), elevated blood pressure (systolic ≥130 mmHg and/or diastolic ≥85 mmHg) and elevated plasma glucose (≥5.6 mmol/l) [13].

2.1.3. Assessment of aerobic capabilities using the Fitness index

Physical fitness was assessed to predict maximal oxygen uptake and to measure the ability of brisk walking. Functional status was assessed by estimating the ability to perform low intensity walking for 2 km according to the UKK Walk Test