Diabetes & Metabolism xxx (2017) xxx–xxx

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Original article

Total serum bilirubin and 8-year incident type 2 diabetes mellitus: The Korean Genome and Epidemiology Study

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ARTICLE INFO

Article history:
Received 10 April 2017
Received in revised form 7 July 2017
Accepted 14 July 2017
Available online xxx

Keywords:
Bilirubin
Impaired fasting glucose
Impaired glucose tolerance
KoGES
Type 2 diabetes mellitus

ABSTRACT

Aim. – In this study, the impact of serum bilirubin on new-onset type 2 diabetes mellitus (T2DM) in Korean adults was investigated.
Methods. – Data were obtained from the Korean Genome and Epidemiology Study (KoGES), a population-based prospective cohort study. The study enrolled 8650 adults (4015 men and 4635 women), aged 40 to 69 years, who underwent a mean follow-up of 8.4 years. The study population was divided into quartiles (Q) of serum bilirubin levels, with cut-off points at 0.46, 0.61 and 0.82 mg/dL for men, and 0.35, 0.47 and 0.61 mg/dL for women. T2DM was defined based on the following data: fasting blood glucose $\geq$ 7.0 mmol/L, HbA_{1c} level $\geq$ 6.5% or 2-h plasma glucose $\geq$ 11.1 mmol/L during a 75-g oral glucose tolerance test.
Results. – Over the mean 8.4-year follow-up, 786 participants (9.1%) developed T2DM. Compared with Q1, the odds ratios (ORs) and 95% confidence intervals (CIs) for T2DM incidence were 0.52 (0.36–0.74) in men and 0.56 (0.38–0.83) in women aged $\geq$50 years, respectively, in the highest Q group after adjusting for possible confounding factors. These significant results persisted in those with impaired glucose tolerance and impaired fasting glucose.
Conclusion. – The results of this study reveal a protective role for serum total bilirubin on new-onset T2DM in Korean men and women. In addition, serum total bilirubin had favourable effects on new-onset T2DM in those with impaired glucose tolerance and impaired fasting glucose.

Introduction

Bilirubin, the end product of the haem catabolic pathway, has been considered a potent antioxidant with an anti-inflammatory capacity [1]. Haem oxygenase (HO), one of the key enzymes in bilirubin metabolism, leads to haem degradation and to biliverdin production [2]; subsequently, biliverdin is reduced to bilirubin by biliverdin reductase (BVR) [3]. Many studies have found that bilirubin has antioxidant properties through the bilirubin–biliverdin redox cycle [4]. Serum bilirubin levels are determined by genetic factors, and influenced by age, gender, fasting, smoking and oxidative stress [1,5].

Type 2 diabetes mellitus (T2DM) has become a global epidemic disease and is rapidly increasing in Asia [6]. The prevalence of T2DM is predicted to further increase worldwide by 54% from 2010 to 2030 [7]. The World Health Organization (WHO) has called diabetes the 21st century's leading healthcare challenge [8]. The disorder can lead to health-threatening complications and premature death [8]. The prevalence of diabetes in Koreans was estimated as 5.8% in 2010 and is expected to rise to 6.8% by 2030 [7]. The characteristics of T2DM include insulin resistance and a relative lack of insulin secretion [9]. Emerging evidence shows that elevated serum bilirubin is inversely associated with the risks of cardiovascular disease (CVD) and the metabolic syndrome [10,11]. There have also been considerable advances made by researches into the role of serum bilirubin in diabetes. Bilirubin directly and indirectly affects glucose metabolism and insulin sensitivity through crucial enzymes, such as HO type 1 (HO-1) and BVR [12].

Several clinical and epidemiological studies have established a relationship between serum bilirubin levels and T2DM

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http://dx.doi.org/10.1016/j.diabet.2017.07.004
1262-3636/

[13,14]. However, prospective longitudinal studies to clarify the causal relationship between serum bilirubin and diabetes are limited. A Dutch population-based cohort study indicated that serum bilirubin acts as a protective factor against the development of diabetes [15]. However, only one prospective study has been conducted in an Asian population. A 4-year prospective longitudinal study identified a protective role for serum total bilirubin in the development of diabetes in Korean men [16], but the study was conducted at a single centre and excluded women. In addition, impaired glucose tolerance at baseline was not assessed. Otherwise, several prospective studies have shown no significant associations between serum bilirubin and diabetes, while Vozarova et al. [17] found that bilirubin did not predict the development of T2DM. These inconsistent findings remain a subject of debate [18]. Nevertheless, to the best of our knowledge, no prospective community-based cohort study has examined the effects of bilirubin on new-onset T2DM in an Asian population. Given the inconsistent results and lack of data from previous studies, the impact of serum bilirubin on new-onset T2DM in Korean adults, and in participants with impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) at baseline, has been investigated in the present study.

Methods

Study population

Data from the Korean Genome and Epidemiology Study (KoGES), a general population-based prospective cohort study, was used to assess environmental and lifestyle determinants of the prevalence and incidence of chronic degenerative disorders, such as hypertension, diabetes, osteoporosis and CVD. The KoGES invited all adults in the rural and urban areas of Ansung and Ansan, respectively, in South Korea, where demographic shifts are infrequent and the population can be followed over the long-term, to participate in the study. Detailed information on the design and aims of the KoGES can be found elsewhere [19]. In brief, the baseline survey, conducted from 2001 to 2002, included 10,038 adults (5018 men and 5020 women) 40 to 69 years of age. Study participants were invited to attend follow-up visits twice a year, and data from the baseline visit in 2013 to the sixth examination in 2014 has been used in the present study. All study participants were again invited to participate in the follow-up survey. Of the original 10,038 participants, 641 had T2DM at baseline and 431 refused to participate (and so had missing data and were excluded). In addition, a further 188 were excluded due to excessive alcohol consumption ($>$ 135 g/week for men, $>$ 90 g/week for women). Those with abnormal liver enzyme levels of aspartate aminotransferase (AST) or alanine aminotransferase (ALT), defined as $\geq$ 2.5 times above the upper limit of normal (n = 90), were also excluded, while participants with total bilirubin levels $>$ 2.0 mg/dL (n = 38) were excluded to eliminate those who might potentially have Gilbert syndrome. Thus, the final sample size for the present analysis was 8650 (4015 men and 4635 women) without T2DM at baseline (Fig. S1; see supplementary material associated with this article online). The study protocol was approved by the Institutional Review Board of Yonsei University College of Medicine, and all participants gave their written informed consent to participate in the present survey.

Data collection

At baseline and on follow-up examination, all study participants completed a standardized medical history and lifestyle questionnaire, and underwent a comprehensive health examination according to standard procedures. Body weight and height were measured with participants wearing light indoor clothing and no shoes. Blood pressure was measured from the right arm, after a rest for at least 5 min in a quiet room, using a standard mercury sphygmomanometer (Baumanometer, W.A. Baum Co. Inc., Copiague, NY, USA). With each subject seated, an appropriately sized cuff, chosen according to mid-arm circumference, was applied snugly around the upper right arm at heart level. Two measurements were taken 5-min apart, and the mean of the two measurements was used for analyses. Smoking status was determined based on self-reports: non-smokers were defined as those who had smoked $<$ 100 cigarettes ($<$ 5 packs of cigarettes) in their lifetime; while current smokers were those who had smoked $\geq$ 100 cigarettes in their lifetime and reported 'currently smoking' in the questionnaire. An alcohol habit was defined as having $>$ 20 g of drinks on any given day. CVD status was collected from the self-reported questionnaire, with participants answering either 'yes' or 'no' to whether they were diagnosed with any of the following diseases: coronary artery disease; myocardial infarction; and stroke. Due to a lack of information on menopausal status, women were divided into two groups based on age (cut-off at 50 years) as a way to roughly divide women into pre- and postmenopausal. A venous blood sample was drawn after a fast of $\geq$ 12 h or overnight. Fasting glucose was determined using a glucose-oxidase-based assay. Serum concentrations of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides (TG) were determined using enzymatic methods (ADVIA 1650 chemistry system, Bayer, Leverkusen, Germany). High-sensitivity C-reactive protein (hsCRP) was measured using a turbidimetric assay method (Denka Seiken Co., Ltd., Tokyo, Japan) validated against the Dade Behring method. Details of the study design and procedures have been described elsewhere [19].

Definition of T2DM, IGT and IFG

The study endpoint of this follow-up survey was new-onset T2DM, using diagnostic criteria based on WHO criteria [20]: 8-h fasting plasma glucose (FPG) $\geq$ 7.0 mmol/L (126 mg/dL); HbA_{1c} level $\geq$ 6.5%; and/or 2-h plasma glucose level $\geq$ 11.1 mmol/L (200 mg/dL) during a 75-g oral glucose tolerance test (OGTT). Those who reported currently taking hypoglycaemic medications at follow-up were also considered to have new-onset T2DM. Impaired glucose tolerance (IGT) was defined as a glucose level of 7.8 mmol/L (140 mg/dL) to 11.0 mmol/L (199 mg/dL) during a 2-h plasma glucose test after ingestion of a 75-g oral glucose load, and IFG was defined as an FBG level of 6.1 mmol/L (110 mg/dL) to 6.9 mmol/L (125 mg/dL).

Statistical analysis

All analyses were performed using SAS version 9.2 software (SAS Institute, Cary, NC, USA). P values $<$ 0.05 were considered statistically significant. Baseline characteristics of the study population related to new-onset T2DM were compared using an independent t-test or Mann–Whitney U-test for continuous variables, and the Chi^2 test for categorical variables. Continuous variables with normal distributions were expressed as means $\pm$ s-standard deviation (SD), whereas TG, AST, ALT, HbA_{1c} and hsCRP levels were markedly skewed and therefore expressed as medians (25th, 75th percentiles). The study population was divided into Qs of serum bilirubin levels, with cut-off points at 0.46, 0.61 and 0.82 mg/dL for men and 0.35, 0.47 and 0.61 mg/dL for women. Their basic characteristics according to bilirubin levels were compared using one-way analysis of variance, or Kruskal–Wallis test for continuous variables and Chi^2 test for categorical variables. To determine the

Please cite this article in press as: Kwon Y-J, et al. Total serum bilirubin and 8-year incident type 2 diabetes mellitus: The Korean Genome and Epidemiology Study. Diabetes Metab (2017), http://dx.doi.org/10.1016/j.diabet.2017.07.004