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Review

Association of circulating total bilirubin with the metabolic syndrome and type 2 diabetes: A systematic review and meta-analysis of observational evidence

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Abstract

Objective. – Emerging evidence suggests that bilirubin levels might be associated with the metabolic syndrome (MetS) and type 2 diabetes (T2D), although the nature of the association remains unclear.

Design. – This systematic review and meta-analysis investigated the relationship between total plasma bilirubin and the risk of MetS and T2D.

Data sources. – Relevant studies were identified using five databases (Embase, Medline [Ovid], Web of Science, PubMed, Cochrane Central and Google Scholar), with the last search done on 21 October 2015. Study references were checked and authors contacted to identify additional studies.

Study selection. – Randomized controlled trials, and cohort, case-control and cross-sectional studies of adults examining the association between blood bilirubin levels and MetS and T2D were included, irrespective of language and date of publication. Abstract and full-text selection was done by two independent reviewers, with a third reviewer available in case of disagreement.

Data extraction. – Data were extracted by two independent reviewers using a predesigned data collection form.

Main outcomes and measures. – MetS and T2D.

Methods. – Summary estimates were obtained by random-effects meta-analysis.

Results. – Of the 2313 searched references, 16 observational studies (11 cross-sectional, two prospective, one that was both cross-sectional and prospective, two retrospective and one national survey) met our inclusion criteria. Overall, data were available for 175,911 non-overlapping participants, including 7414 MetS cases and 9406 T2D cases. In the meta-analysis of seven cross-sectional studies, the pooled odds ratio (95% confidence interval) for MetS in a comparison of extreme tertiles of serum bilirubin levels was 0.70 (95% CI: 0.62, 0.78), whereas no significant association was found for the pooled estimated relative risk between two prospective studies (0.57, 95% CI: 0.11, 2.94). The corresponding estimate was 0.77 (95% CI: 0.67, 0.87) for T2D from four cross-sectional studies.

Conclusion. – The available evidence, mainly from cross-sectional studies, supports an inverse association of bilirubin levels with adverse metabolic outcomes. Large-scale prospective studies are now needed to establish whether bilirubin levels may be useful in the prevention of MetS and T2D.

Keywords: Bilirubin; Meta-analysis; Metabolic syndrome; Systematic review; Type 2 diabetes

1. Introduction

The metabolic syndrome (MetS) is characterized by a constellation of disorders, including high blood pressure, dyslipidaemia, hyperglycaemia and abdominal obesity, and has consistently been shown to be strongly associated with type 2 diabetes (T2D) [1,2] and cardiovascular disease [1,3]. MetS and T2D share the same risk factors, including a family history of diabetes [4–6]. However, the pathogenesis of T2D is still not fully established and appears to involve multiple factors.

Serum circulating total bilirubin, a breakdown product of normal heme catabolism, is useful for assessing liver function, and

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several epidemiological studies have suggested inverse associations with MetS [7,8] and T2D [9] and its complications [10]. Experimental studies show that bilirubin may antagonize oxidative stress by acting as an antioxidant and cytoprotectant, with a role in scavenging excess reactive oxygen species [11–14]. Nevertheless, uncertainties remain as to the magnitude and constancy of the association. Furthermore, some studies were conducted in populations at high vascular risk or with comorbidities such as Gilbert syndrome and chronic kidney disease [15–19]. An earlier review by Vitek [20] in 2012 provided detailed information on the experimental and clinical evidence of the link between heme catabolic pathways and cardiometabolic outcomes. However, the extent to which plasma bilirubin levels are associated with the risk of MetS and T2D was not quantitatively addressed. Given the ongoing debate over the potential value of total bilirubin levels as a biomarker and therapeutic target for both MetS and T2D [21–23], a comprehensive assessment of the association of baseline total bilirubin levels with MetS and T2D risk is clearly needed. Therefore, the present systematic review and meta-analysis was conducted to determine the association of bilirubin levels with the risk of MetS and T2D.

2. Material and methods

2.1. Literature search

The present review was conducted using a predefined protocol, and reported in accordance with the PRISMA [24] and MOOSE [25] guidelines (Appendix A; see supplementary material associated with this article online). Five databases (Embase, Medline, Web of Science, PubMed, Cochrane Central and Google Scholar) were searched to identify the relevant published studies. The last search was conducted on 21 October 2015. The aim was to find studies that examined the association between circulating bilirubin levels and MetS and T2D in adults ($\geq$ 18 years of age). Terms related to bilirubin (such as "hyperbilirubin") were combined with key terms related to these outcomes (such as "syndrome X" and "diabetes mellitus"); no language restriction was applied. The full search strategy for all of the databases is provided in Appendix A (see supplementary material associated with this article online). Reference lists of the selected studies and experts were also used to identify further studies.

2.2. Study selection and inclusion criteria

Included were randomized controlled clinical trials and cohort, case-control and cross-sectional studies that examined the association between bilirubin levels in blood (total bilirubin, direct or indirect bilirubin levels) and MetS and T2D. Two independent reviewers screened the retrieved titles and abstracts, and selected the eligible studies. Discrepancies between the two reviewers were resolved through consensus and discussion with a third independent reviewer when necessary. Finally, the full texts of studies that satisfied all selection criteria were retrieved.

2.3. Data extraction

This was carried out by two reviewers independently and according to a predesigned form, including study design, study name, publication date, geographical location, population source, time of baseline survey, sample population, sample source (plasma/serum), sample nature (fresh or frozen and storage temperature), assay type, case definition, sample size, number of outcome events, mean age at baseline, gender, summary statistics (using a standardized abstraction form) and degree of adjustment for potential confounders. Adjustments were classified as: "+" when risk estimates were adjusted for age and gender; "++" when further adjusted for potential risk factors such as blood pressure, body mass index (BMI), family history of diabetes and alcohol consumption; and "+++" when additionally adjusted for inflammatory markers such as C-reactive protein (CRP) and liver enzymes. Also extracted were the estimates reported with the greatest degree of adjustment. If risk estimates were not available in the published reports, the authors were contacted to obtain further data.

2.4. Quality assessment

Bias within each individual study was evaluated by two independent reviewers using the validated Newcastle–Ottawa Scale (NOS), a semi-quantitative scale designed to evaluate the quality of cohort studies [26]. Study quality was judged on the selection criteria for participants, comparability of cases and controls, and exposure and outcome assessments. The NOS assigns a maximum of 4 points for selection, 2 points for comparability and 3 points for outcome, with 9 points reflecting the highest study quality. For cross-sectional studies, quality was evaluated using the NOS modified for cross-sectional studies [27], which was further modified for the purposes of our review question, with a maximum of 8 points reflecting the highest study quality. Overall, a score $\geq$ 5 indicated adequate quality for inclusion in the present review.

2.5. Outcome assessment and statistical methods

To uniformly evaluate the effects of the top vs bottom tertiles of baseline distribution of bilirubin levels in all studies, previously described methods to transform relative risk (or risk ratio [RR]) estimates were used [28], which were often differentially reported (for example, per unit change, per 1 standard deviation [SD] change, or comparing quartiles or tertiles). In brief, log RRs were transformed by assuming a normal distribution, with comparisons between extreme tertiles considered 2.18 times the log RR for each 1 SD increase in exposure (or 2.18/2.54 times the log RR for a comparison of extreme quartiles of exposure). The standard error (SE) of the log RR was calculated using published confidence intervals (CIs), all standardized in the same way. Hazard ratios and odds ratios (ORs) were assumed to approximate the same measure as the RRs [29].

Analyses were done using random-effects models calculated from the logarithm of the RR and corresponding 95% CI of each

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