Original Article

Serum total bilirubin is a risk factor of metabolic syndrome and its components in obese Egyptians

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Abstract

Background/Aim: The link between serum total bilirubin and metabolic syndrome and its components has been previously proposed. However, it is unknown whether total bilirubin is a risk factor of metabolic syndrome and its components in obese Egyptians. Therefore, this study was conducted to clarify the association of total bilirubin levels with metabolic syndrome and its components in obese Egyptians.

Methods: A total of 200 adults with obesity were enrolled in this study. Obese participants were evaluated for metabolic syndrome; there were 92 obese participants with metabolic syndrome and 108 obese participants without metabolic syndrome. Anthropometric measurements, fasting blood glucose (FBG), fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), HOMA-β (%), lipid profile, uric acid, alanine aminotransferase, aspartate aminotransferase, and serum total bilirubin were assessed.

Results: Total bilirubin was significantly lower in obese participants with metabolic syndrome than in those without metabolic syndrome. Compared with middle bilirubin tertile, high and low bilirubin tertiles were independently associated with metabolic syndrome. Regarding metabolic syndrome components, a significant positive association between low bilirubin tertile and hypertension was found independent of the all studied confounding factors, whereas the association of total bilirubin level with waist circumference (WC), FBG, high-density lipoprotein cholesterol, and triglycerides was dependent on body mass index (BMI), HOMA-IR, and high sensitive C-reactive protein (hs-CRP).

Conclusion: Total bilirubin is an independent risk factor of metabolic syndrome in obese Egyptians. We have found an independent association between high bilirubin level and reduced risk of metabolic syndrome, whereas low bilirubin level was associated with increased risk of metabolic syndrome. Bilirubin is also independently associated with hypertension, but its association with other components of metabolic syndrome is mainly dependent on BMI, HOMA-IR, and hs-CRP.

Key words: Bilirubin, obesity, metabolic syndrome

Background

Metabolic syndrome is a clustering of metabolic disorders including obesity, hypertension, hyperglycemia, and dyslipidemia.[1] Chronic inflammation, insulin resistance, and oxidative stress[2-4] are implicated as contributing factors of metabolic syndrome. The prevalence of metabolic syndrome is dramatically increasing worldwide because of urbanization, increased energy intake, obesity, and sedentary lifestyle. In adult populations, the prevalence of metabolic syndrome is approximately 20–30% depending on ethnicity, gender, age, and diagnostic criteria.[5,6] Of importance, metabolic syndrome is strongly associated with type 2 diabetes, cardiovascular, and fatty liver diseases.[7-9]

Bilirubin, the end product of normal heme catabolism, has long been considered as a harmful waste product to the central nervous system.[10] Bilirubin serves as a traditional marker of hepatobiliary disorders.[11] However, recent researchers have identified bilirubin as a strong antioxidant, anti-inflammatory, and immune-regulatory product[12,13]; it is a physiological modulator of oxidative stress and chronic inflammation in metabolic syndrome.[14,15] Therefore, mild hyperbilirubinemia is associated with improved cardiometabolic outcomes.[16] In patients with Gilbert syndrome, mild hyperbilirubinemia is negatively associated with body mass index (BMI), hip circumference, and serum lipids.[17]

Although many studies demonstrated an inverse association between total bilirubin and metabolic syndrome,[18-20] others

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found that total bilirubin was not a risk factor of metabolic syndrome.[19] The conflicting results may be related to genetic background; bilirubin is a highly heritable product;[21] lifestyle and eating habits. Limited data from Egypt are currently available; therefore, this study was conducted to clarify the relationship between serum total bilirubin levels and the metabolic syndrome and its components in obese Egyptians.

Methods

A total of 200 adults with obesity (BMI>30 kg/m^2) were enrolled in this cross-sectional study. They were consecutively recruited from the Obesity Clinic at Mansoura Specialized Medical Hospital, Mansoura University, Egypt. All participants signed informed consent, and the study was approved by the local ethics committee, Mansoura University Faculty of Medicine. Obese participants were evaluated for metabolic syndrome; there were 92 obese participants with metabolic syndrome and 108 obese participants without metabolic syndrome. Diagnosis of metabolic syndrome was based on the National Cholesterol Education Program's Adult Treatment Panel III (NCEP: ATP III); metabolic syndrome was defined when 3 or more of the following 5 criteria were met: waist circumference (WC) >102 cm in women or >88 cm in men, triglycerides (TGs) >150 mg/dL, high-density lipoprotein cholesterol (HDL-C) <50 mg/dL in women and <40 mg/dL in men, blood pressure ≥135/85 mmHg and/or antihypertensive medication use, and fasting blood glucose (FBG) ≥ 100 mg/dL.[22]

All participants were subjected to a thorough medical history and clinical examination. Systolic and diastolic blood pressures (SBP and DBP) and anthropometric measurements including BMI and WC were obtained using standardized techniques. Exclusion criteria were smoking; chronic liver disease; hepatitis B or C virus infections; hepatic or renal failure; connective tissue disorders; malignancy; pregnancy; history of hepatotoxic drugs; women taking birth control pills or hormone replacement therapy; and participants taking insulin sensitizers, steroids, and antioxidant supplements. Participants with serum total bilirubin exceeding 2 mg/dL or alanine aminotransferase (ALT) exceeding 100 IU/L were also excluded.

Laboratory assay

FBG was assessed with an automated chemistry analyzer (Cobas C311) using commercial kits supplied by Roche Diagnostics Germany. Fasting insulin was assayed using a solid-phase enzyme-linked immunosorbent assay supplied by BIOS kits. Homeostasis model assessment of insulin resistance (HOMA-IR) was done with the following formula: HOMA-IR= [fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5].[23] Homeostatic model assessment of beta cell % (HOMA-β), a marker of basal insulin secretion of pancreatic β-cells, was performed with the following formula: HOMA-β cell % = (360 × fasting insulin in μU/L)/(fasting glucose in mg/dL−63).[23] Total cholesterol (TC), TGs, and HDL-C were estimated with an automated chemistry analyzer (Cobas C311) using commercial kits supplied by Roche Diagnostics Germany. Low-density lipoprotein cholesterol (LDL-C) was assessed according to the Friedewald formula.[24] Assessment of total bilirubin, ALT, aspartate aminotransferase (AST), serum creatinine, and uric acid was performed with an automated chemistry analyzer (Cobas C311) using commercial kits supplied by Roche Diagnostics Germany.

Statistical analysis

Data entry and analysis were performed using the SPSS statistical package (version 20, SPSS Inc., Chicago, IL). The continuous data were expressed as M±SD, whereas categorical data were expressed as numbers and percentage. The Student t test and χ^2 test were conducted to compare continuous and categorical data, respectively. The study population was reclassified according to the percentiles of serum total bilirubin into 3 groups: low bilirubin tertile <33.3% percentile, middle bilirubin tertile from 33.3 to 66.7% percentile, and high bilirubin tertile >66.7% percentile. The associations of total bilirubin tertiles with metabolic syndrome and its components were determined by logistic regression analysis models using middle bilirubin tertile as a reference category. Prediction of metabolic syndrome using the total bilirubin was done using the receiver operating characteristic (ROC) curve. The best cutoff point was chosen according to the Youden index. Area under the curve (AUC), sensitivity, specificity, and positive and negative predictive values were assessed. $P \leq .05$ was considered to be significant.

Results

Obese adults with metabolic syndrome had significantly higher levels of SBP, DBP, BMI, WC, FBG, fasting insulin, HOMA-IR, TGs, uric acid, and hs-CRP than did obese participants without metabolic syndrome. HOMA-B and HDL-C were significantly lower in obese participants with metabolic syndrome than in those without metabolic syndrome. Total bilirubin was significantly lower in obese participants with metabolic syndrome compared with those without metabolic syndrome (P-value <.001) (Table 1).

Compared with middle bilirubin tertile, high and low bilirubin tertiles were significantly associated with metabolic syndrome independent of age, gender, BMI, HOMA-IR, and hs-CRP. High bilirubin tertile was associated with reduced risk of metabolic syndrome, whereas low bilirubin tertile was associated with increased risk of metabolic syndrome (Table 2).

Table 3 presents the association between total bilirubin and components of metabolic syndrome. Compared with middle bilirubin tertile, there was a significant negative association between high bilirubin tertile and high WC (defined as WC ≥ 102 cm in women and ≥88 cm in men) after adjustment for age, gender, HOMA-IR, and hs-CRP, but not BMI. However, there was no significant association between low bilirubin tertile and high WC.

A significant positive association between low bilirubin tertile and hypertension (defined as SBP ≥130 mmHg and/or DBP ≥85 mmHg or antihypertensive medication use) was found after adjustment for age, gender, BMI, HOMA-IR, and hs-CRP. However, there was no significant association between high bilirubin tertile and hypertension.

A significant positive association between low bilirubin tertile and high FBG (≥100 mg/dL) was found after adjustment for age, gender, BMI, and hs-CRP, but not HOMA-IR. By contrast, there was no significant association between high bilirubin tertile and high FBG.

Low and high bilirubin tertiles were significantly associated with hypertriglyceridemia (≥150 mg/dL) after adjustment for age and gender. The positive association between low bilirubin tertile and hypertriglyceridemia was found to be dependent on HOMA-IR, whereas the negative association between high bilirubin tertile

Table 1

Study participant characteristics.

Characteristics	Obese participants with metabolic syndrome (n=92)	Obese participants without metabolic syndrome (n=108)	P
Age (y)	38.65 ± 9.82	36.64 ± 8.69	.128
Male gender, n (%)	15 (16.3)	20 (18.5)	.681
SBP (mmHg)	135.07 ± 14.94	119.41 ± 10.68	<.001*
DBP (mmHg)	87.04 ± 9.58	74.94 ± 9.04	<.001*
Hypertension n (%)	67 (72.8)	23 (21.03)	<.001*
WC (cm)	114.68 ± 15.38	96.77 ± 10.85	<.001*
BMI (kg/m^2)	34.82 ± 2.62	33.95 ± 1.86	.007*
FBG (mg/dL)	91.36 ± 12.63	83.76 ± 9.53	<.001*
High FBG n (%)	22 (23.9)	10 (9.3)	.005*
Fasting insulin (IU/L)	12.80 ± 4.12	9.43 ± 3.32	<.001*
HOMA-IR	2.84 ± 0.87	1.94 ± 0.70	<.001*
HOMA-β	141.36 ± 42.67	181.46 ± 59.45	<.001*
ALT (IU/L)	27.11 ± 7.31	26.94 ± 9.33	.891
AST (IU/L)	34.32 ± 7.49	32.52 ± 9.17	.135
ALT/AST ratio	0.83 ± 0.21	0.78 ± 0.16	.085
Serum creatinine (mg/dL)	0.89 ± 0.19	0.92 ± 0.20	.288
Serum uric acid (mg/dL)	8.20 ± 1.93	5.76 ± 1.83	<.001*
TC (mg/dL)	196.16 ± 30.61	191.57 ± 25.33	.248
TGs (mg/dL)	189.25 ± 40.35	128.85 ± 30.50	<.001*
Hypertriglyceridemia (mg/dL) n (%)	77 (83.7)	24 (22.2)	<.001*
LDL-C (mg/dL)	116.56 ± 30.36	109.83 ± 27.58	.102
HDL-C (mg/dL)	41.75 ± 6.34	58.22 ± 11.08	<.001*
Low HDL-C (mg/dL) n (%)	85 (92.4)	17 (15.7)	<.001*
hs-CRP (mg/dL)	1.18 ± 0.32	0.9 ± 0.28	<.001*
Total bilirubin (mg/dL)	0.70 ± 0.13	0.85 ± 0.10	<.001*
Bilirubin tertile n (%)			<.001*
Low	29 (31.5)	38 (35.2)	
Middle	50 (54.3)	11 (10.2)	
High	13 (14.1)	59 (54.6)	

Data are expressed as M±SD, numbers or percentages.

* *P* is significant if ≤.05

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of beta cell function; hs-CRP, high sensitive C-reactive protein; high FBG: FBG ≥100 mg/dL; hypertriglyceridemia, TGs >150 mg/dL; LDL-C, low-density lipoprotein cholesterol; low HDL-C, HDL <40 mg/dL in men and <50 mg/dL in women; SBP, systolic blood pressure; TC, total cholesterol; TGs, triglycerides; WC, waist circumference. The high bilirubin group includes participants with serum bilirubin ≥50% percentile.

and hypertriglyceridemia was found to be dependent on BMI, HOMA-IR, and hs-CRP.

Significant associations of low and high bilirubin tertiles with low HDL-C (<40 mg/dL in men and <50 mg/dL in women) were found after adjustment for age, gender, BMI, and hs-CRP, but not HOMA-IR.

Serum total bilirubin levels at ≤ 0.735 mg/dl predicted metabolic syndrome in obese participants with 59% sensitivity, 86% specificity, AUC (95% CI) 0.803 (0.744:0.862), and *P* < .001 (Fig. 1).

Table 2

Association between total bilirubin and metabolic syndrome.

Models	Bilirubin tertiles	OR (95% CI)	P
Model 1	Low tertile	5.956 (2.644:13.418)	<.001*
	High tertile	0.289 (0.134:0.624)	.002*
Model 2	Low tertile	7.963 (3.254:19.489)	<.001*
	High tertile	0.266 (0.120:0.589)	.001*
Model 3	Low tertile	9.041 (3.584:22.805)	<.001*
	High tertile	0.329 (0.143:0.761)	.009*
Model 4	Low tertile	3.480 (1.292:9.376)	.014*
	High tertile	0.193 (0.080:0.466)	<.001*
Model 5	Low tertile	9.053 (3.568:22.971)	<.001*
	High tertile	0.363 (0.158:0.837)	.017*

* *P* is significant if ≤0.05

Model 1: no adjustment; Model 2: adjusted for age and gender; Model 3: adjusted for age, gender, and BMI; Model 4: adjusted for age, gender, and HOMA-IR; Model 5: adjusted for age, gender, and hs-CRP. Middle bilirubin tertile was the reference category for all models. OR, odds ratio; CI, confidence interval.

Discussion

In this study, obese participants with metabolic syndrome had significantly higher serum total bilirubin levels than those without metabolic syndrome. In obese participants, the bilirubin level at ≤0.735 mg/dl predicted metabolic syndrome with a higher positive predictive value compared with the negative predictive value; therefore, serum bilirubin could be used as a marker for identification of metabolic syndrome. The potential role of bilirubin as an early biomarker of metabolic syndrome was previously proposed by Jenko-Praznikar et al.[25] They reported that the mean total bilirubin values were decreased with increasing numbers of metabolic syndrome components.

Obesity-induced metabolic syndrome remains a global epidemic. However, data on the total bilirubin as a predictor of metabolic syndrome in obese Egyptians are limited. In this study, total bilirubin was an independent risk factor of metabolic syndrome in obese participants. Of interest, both high and low bilirubin tertiles were independently associated with metabolic syndrome where high bilirubin levels reduced the risk of metabolic syndrome and low bilirubin levels increased the risk of metabolic syndrome. Accordingly, a recent meta-analysis revealed that the elevated bilirubin levels could lower the risk of

Table 3

Association between total bilirubin and components of the metabolic syndrome.

Models	Bilirubin tertiles	OR (95% CI)	*P*
Association between total bilirubin and high WC			
Model 1	Low tertile	1.616 (0.708–3.688)	.254
	High tertile	0.283 (0.139–0.574)	<.001*
Model 2	Low tertile	1.292 (0.551–3.033)	.556
	High tertile	0.233 (0.110–0.495)	<.001*
Model 3	Low tertile	1.308 (0.554–3.089)	.540
	High tertile	0.473 (0.155–1.447)	.190
Model 4	Low tertile	0.514 (0.189–1.393)	.191
	High tertile	0.189 (0.085–0.421)	<.001*
Model 5	Low tertile	1.307 (0.553–3.093)	.542
	High tertile	0.260 (0.121–0.561)	.001*
Association between total bilirubin and hypertension			
Model 1	Low tertile	4.725 (2.220–10.057)	<.001*
	High tertile	0.646 (0.316–1.321)	.231
Model 2	Low tertile	4.112 (1.845–9.165)	.001*
	High tertile	0.511 (0.234–1.116)	.092
Model 3	Low tertile	4.239 (1.884–9.537)	<.001*
	High tertile	0.567 (0.249–1.291)	.176
Model 4	Low tertile	2.891 (1.186–7.050)	.020*
	High tertile	0.490 (0.222–1.081)	.077
Model 5	Low tertile	4.192 (1.866–9.419)	<.001*
	High tertile	0.595 (0.265–1.339)	.210
Association between total bilirubin and high FBG			
Model 1	Low tertile	3.048 (1.157–8.029)	.024*
	High tertile	1.224 (0.429–3.496)	.705
Model 2	Low tertile	2.995 (1.120–8.010)	.029*
	High tertile	1.195 (0.417–3.423)	.739
Model 3	Low tertile	3.023 (1.129–8.095)	.028*
	High tertile	1.259 (0.425–3.736)	.678
Model 4	Low tertile	2.113 (0.698–6.395)	.186
	High tertile	1.159 (0.403–3.334)	.785
Model 5	Low tertile	3.101 (1.150–8.368)	.025*
	High tertile	1.422 (0.478–4.228)	.527
Association between total bilirubin and hypertriglyceridemia			
Model 1	Low tertile	3.354 (1.577–7.133)	.002*
	High tertile	0.513 (0.258–1.023)	.058*
Model 2	Low tertile	2.978 (1.380–6.429)	.005*
	High tertile	0.472 (0.233–0.955)	.037*
Model 3	Low tertile	3.639 (1.612–8.217)	.002*
	High tertile	0.691 (0.323–1.477)	.340
Model 4	Low tertile	1.596 (0.677–3.763)	.285
	High tertile	0.567 (0.269–1.195)	.136
Model 5	Low tertile	3.286 (1.464–7.377)	.004*
	High tertile	0.655 (0.309–1.388)	.269
Association between total bilirubin and low HDL-C			
Model 1	Low tertile	5.181 (2.475–10.869)	<.001*
	High tertile	0.483 (0.226–1.033)	.050*
Model 2	Low tertile	5.618 (2.584–12.195)	<.001*
	High tertile	0.225 (0.085–0.601)	.003*
Model 3	Low tertile	4.001 (1.776–9.009)	.001*
	High tertile	0.164 (0.058–0.460)	.001*
Model 4	Low tertile	2.364 (0.983–5.682)	.055
	High tertile	0.495 (0.209–1.171)	.109
Model 5	Low tertile	4.545 (2.028–10.204)	<.001*
	High tertile	0.208 (0.076–0.568)	.002*

* *P* is significant if ≤.05.
Model 1: no adjustment; Model 2: adjusted for age and gender; Model 3: adjusted for age, gender, and BMI; Model 4: adjusted for age, gender, and HOMA-IR; Model 5: adjusted for age, gender, and hs-CRP. Middle bilirubin tertile was the reference category for all models.
CI, confidence interval; high FBG, FBG ≥100 mg/dL; high WC, WC >102 cm in women or >88 cm in men; hypertension, SBP ≥130 mmHg or DBP ≥85 or taking antihypertensive medication; Hypertriglyceridemia, TGs >150 mg/dL; low HDL-C, HDL <40 mg/dL in men and <50 mg/dL in women; OR, odds ratio. The high bilirubin group includes participants with serum bilirubin ≥50% percentile.

metabolic syndrome.[26] Moreover, Shiraishi et al found an association between total bilirubin and the risk of incident metabolic syndrome in a cohort of middle-aged Japanese patients without metabolic syndrome.[27] The association of modestly elevated bilirubin levels with better insulin sensitivity and decreased risk of metabolic syndrome independent of BMI was
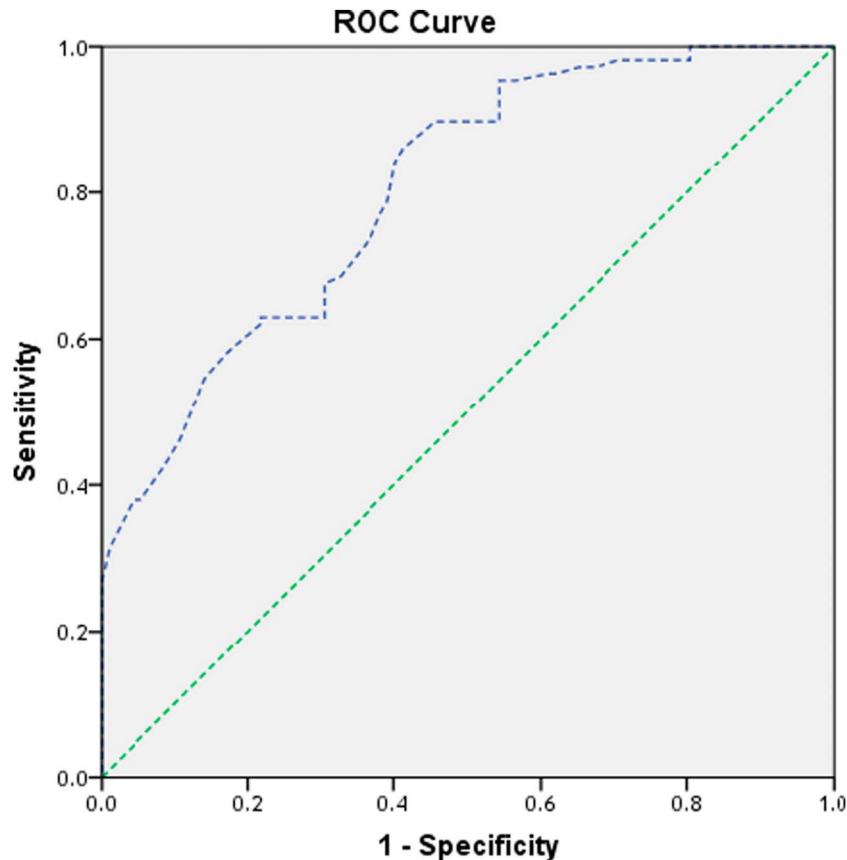
Figure 1. ROC curve analysis of the predictive value of total bilirubin for metabolic syndrome in obese subjects.

also reported by others.[20,28] These findings highlight the possible role of bilirubin in prevention of metabolic syndrome.[29]

Indeed, the inverse association between bilirubin and metabolic syndrome was also demonstrated in a recent meta-analysis of 7 cross-sectional studies; an inverse association between odds ratios of bilirubin levels and metabolic syndrome in fully adjusted models was found.[30] However, they found no significant association with prospective evidence, but the number of such studies was limited. By contrast, Pei et al showed that the GGT and ALT were the best predictors of future metabolic syndrome in healthy elderly men and women, respectively; however bilirubin was not considered as a confounding factor of metabolic syndrome.[31] These conflicting results can be explained by differences in the study populations, e.g. ethnicity, gender, different distributions of age, comorbidities, and study methodologies.

In this study, total bilirubin was associated with all components of metabolic syndrome. A significant positive association between low bilirubin tertile and hypertension was found independent of all confounding factors, whereas the association between total bilirubin and WC was dependent on BMI and the associations of total bilirubin with FBG, TGs, and HDL-C were dependent on HOMA-IR.

Compared with middle bilirubin tertile, there was a significant association between high bilirubin tertile and high WC after adjustment for confounding factors; however, this association was dependent on BMI. There was no significant association between low bilirubin tertiles and high WC. In line with this, there

is considerable evidence supporting the association between low bilirubin levels and obesity.[25,32,33] Hyperbilirubinemia protects against the development of obesity[34,35] as it reduces visceral obesity and IR through suppression of inflammatory cytokines. Bilirubin directly activates peroxisome proliferator-activated receptor alpha (PPARα), which increases target genes to reduce adiposity and decreased de novo lipogenic enzymes.[35] In addition, the reduced bilirubin levels in adiposity state may be due to its increased consumption to compensate for increased oxidative stress.[36] Obesity-induced systemic inflammation and oxidative stress are closely involved in the pathogenesis of metabolic syndrome.[37] Therefore, the decreased total bilirubin may reflect inflammatory and oxidative stress states as previously discussed.

The association between total bilirubin and insulin sensitivity state could be explained by: Bilirubin improves insulin sensitivity at least in part by suppressing endoplasmic reticulum stress and chronic inflammation in adipose tissue and the liver.[38] Bilirubin improves insulin sensitivity through regulation of cholesterol metabolism, adipokines, and PPARɣ.[39] Intracellular bilirubin inhibits NADPH oxidase activity,[40] the enzyme responsible for increased oxidative stress production from hypertrophied insulin resistant adipocytes.[41,42]

In line with our findings, Kunutsor et al found a significant relationship between total bilirubin levels and risk of hypertension.[43] Low total bilirubin promotes the development of hypertension, whereas high bilirubin levels promote normalized BP, blood glucose, and lipid levels.[44] Bilirubin may prevent

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hypertension through decreasing glucose and lipid accumulation and/or obesity development.[34] However, hypertension can occur in hypobilirubinemia independent of diabetes, dyslipidemia, and obesity.[45] Bilirubin inhibits vascular smooth muscle cell proliferation, in addition to its antioxidant and anti-inflammatory effects.[46]

Wallner et al have previously proposed the underlying mechanism behind the association between bilirubin and plasma lipids.[47] In Gilbert syndrome, mild hyperbilirubinemia is associated with reduced circulating TC, LDL-C, triacylglycerol, and elevated HDL/LDL ratio.[48-51] An inverse association between Ox-LDL, TGs, and serum bilirubin is also reported in young obese participants.[52,53] In turn, HDL-C induces heme oxygenase-1 (HO-1), which mediates reduction of reactive oxidative stress and LDL-C levels.[54-56] Indeed, bilirubin activates PPARα[34] and its associated pathways that promote β-oxidation of fatty acids and decrease fatty acid synthesis.[57] On the contrary, familial hypercholesterolemia exhibits lower bilirubin levels with increased systemic inflammation, consequent atherosclerosis,[58] and hypertension.[43]

Conclusion

Total bilirubin is an independent risk factor of metabolic syndrome in obese Egyptians. We have found an independent association between high bilirubin level and reduced risk of metabolic syndrome, whereas low bilirubin level is associated with increased risk of metabolic syndrome. Regarding metabolic syndrome components, bilirubin is independently associated with hypertension but its association with other components of metabolic syndrome is mainly dependent on BMI, HOMA-IR, and hs-CRP.

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