ORIGINAL ARTICLE

Are total bilirubin and high-sensitivity C-reactive protein independently associated with Type 2 diabetes mellitus in postmenopausal women?

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Background: Various studies have reported contradictory results regarding the relationship of total bilirubin and high-sensitivity C-reactive protein levels (hsCRP) with diabetes mellitus Type 2 (DM2). Therefore, we aimed to examine which one of them could be more convenient for the estimation of DM2 risk in postmenopausal women. **Materials and Methods:** A total of 150 healthy postmenopausal women (mean age 57[53–60] years) and 79 postmenopausal women with DM2 (mean age 66 [61–71] years) were enrolled in cross-sectional study. Examinees were recruited consecutively in the study during their regular check-up visit in the Primary Health Care Center in Podgorica, Montenegro, in a period from October 2012 to May 2016. Anthropometric measurements, biochemical parameters, and blood pressure were obtained. Multivariable logistic regression analysis was used to find the independent predictors for DM2 development in postmenopausal women. **Results:** Age, waist circumference, and total bilirubin were the independent predictors for DM2 development in postmenopausal women (odds ratio [OR] =1.224, 95% confidence interval [CI] [1.117–1.341], $P < 0.001$; OR = 1.137, [95% CI = 1.036–1.215], $P < 0.001$, and OR = 0.727, [95% CI = 0.611–0.866], $P < 0.001$, respectively), whereas hsCRP lost its independent predictive role (OR = 1.155, [95% CI = 0.854–1.560], $P = 0.349$). **Conclusion:** Unlike hsCRP, total bilirubin independently correlated with DM2 in postmenopausal women.

Key words: Diabetes, inflammation, postmenopausal, total bilirubin

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INTRODUCTION

Postmenopausal women are at increased cardiometabolic risk as compared with women in reproductive age,[1] mainly due to hormonal changes which might lead to increase in visceral fat, resulting in insulin resistance occurrence.

Obesity is regarded as a state of inflammation and oxidative stress with compromised antioxidant defense.[2] The enlarged visceral adipose tissue represents the milieu of increased production of reactive oxygen species (ROS) and proinflammatory adipokines and cytokines.[2-4] The above mechanisms together have been reported in modulating insulin signaling pathways and thus aggravating insulin resistance and inducing cardiometabolic disorders.[1,2]

Mildly elevated levels of total bilirubin (i.e., above physiological level) are regarded to have protective properties, acting like an anti-oxidant and anti-inflammatory molecule due to its ability to scavenge ROS and to suppress the oxidation of lipids and lipoproteins.[2] In line with this, many studies conducted so far reported the beneficial role of moderately high bilirubin in cardiometabolic disorders, like in metabolic syndrome (MetS),[5-7] diabetes mellitus Type 2 (DM2),[8,9] as well as cardiovascular disease (CVD).[10,11]

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Contradictory to the above hypothesis, various other group of studies have questioned the association of lower total bilirubin with MetS,[12-14] DM2,[15,16] and CVD.[17,18]

In addition, *in vitro* investigations have reported that bilirubin may act as a pro-oxidant in endothelial cells that were exposed to glucose[19,20] thus further making confusion of anti-oxidant properties of this biomarker.

On the other hand, inflammation as measured with high-sensitivity C-reactive protein (hsCRP) was not associated with increased risk of incident DM2,[21] while some others have shown its association with DM2 in women, but not in men.[22]

On the basis of the various contradictory results reported regarding the relationship of total bilirubin and hsCRP with DM2, we aimed to examine which one of them could be more convenient for estimation of DM2 risk in the cohort of postmenopausal women.

MATERIALS AND METHODS

Study population

The examined groups comprised 150 healthy postmenopausal women (mean age 57 [range 53–60] years) and 79 postmenopausal women with DM2 (mean age 66 [range 61–71] years) who volunteered to participate in the study. Examinees were recruited consecutively in the study during their regular check-up visit in the Primary Health Care Center in Podgorica, Montenegro, in a period from October 2012 to May 2016. Women were considered to be postmenopausal if reported the absence of menstrual bleeding for >1 year. Medical history and clinical examinations were obtained on the same day.

Inclusion criteria for the control group were as follows: healthy postmenopausal women not receiving hormone replacement therapy or any other medication in the past 6 months, as well as nonsmokers. In addition, all women who had fasting glucose ≥5.6 mmol/L, but ≤6.9 mmol/L, were asked to undergo a 2-h oral glucose tolerance test. Women with fasting glucose ≥7.0 mmol/L or with 2-h postload glucose ≥11.1 mmol/L were excluded from the control study group but were included in the case group with DM2.[1,23,24]

The methods and assays used to include postmenopausal women with DM2 have been described in detail elsewhere.[23,24] Exclusion criteria for all postmenopausal women that participated in the study were: Type 1 DM, hypo- or hyperthyroidism, liver disease other than hepatic steatosis, ethanol consumption >20 g/day, acute inflammatory disease, hsCRP >10 mg/L, malignant diseases, as well as participants who were unwilling to enter the study.[23,24]

All postmenopausal women with DM2 used oral antihyperglycemic therapy (100%), whereas 11.4% of them were on insulin therapy, also. A total of 44.3% and 81% of the women with DM2 were on hypolipidemic drugs and antihypertensive medications, respectively.

Written informed consent was obtained from all examined participants. The Ethical Committee of Primary Health Care Center in Podgorica, Montenegro, approved the study protocol and the research was carried out in compliance with the Declaration of Helsinki.

Anthropometric measurements

All participants underwent basic anthropometric measurements, such as body height (cm), body weight (kg), and waist circumference (WC) (cm). Body mass index (BMI) was calculated, as described previously.[1]

Biochemical analyses

The blood samples for determining biochemical parameters were obtained as described elsewhere.[23,24]

Serum levels of glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), triglycerides (TG), uric acid, creatinine, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase , and gamma-glutamyl transferase (GGT), were measured as described previously,[23,24] using the standardized enzymatic procedure (Roche Cobas 400, Mannheim, Germany). hsCRP levels were determined using a nephelometric assay (Behring Nephelometer Analyzer, Marburg, Germany).

Blood pressure was measured, and the glomerular filtration rate was estimated using creatinine in the Modification of Diet in Renal Disease Study equation ($eGFR_{MDRD}$), as described elsewhere.[1,23]

Statistical analysis

Results are expressed as arithmetic mean (standard deviation) for normally distributed variables, as geometric mean and 95% confidence interval (CI) for the mean for *log*-normally distributed variables and as median (interquartile range) for skewed distributed variables. Differences in continuous variables between postmenopausal women with and without DM2 were tested using Student's *t*-test for normally and *log*-normally distributed variables and Mann–Whitney test for skewed distributed variables. Chi-square test was used for testing differences in categorical variables. The association between variables was assessed using Spearman's nonparametric

correlation analysis. Using univariable and multivariable logistic regression analysis, we tested the risk for diabetes development in postmenopausal women. Multivariable adjustment was made for all continuous variables, which were statistically different between postmenopausal women with and without DM2, and which were correlated with DM2, (e.g., model included years of age, BMI, WC, HDL-c, TG, creatinine, bilirubin, and hsCRP). Variables in the logistic regression analysis were presented as odds ratio (OR) and 95% CI. Receiver operating characteristic (ROC) curve analysis was used to discriminate postmenopausal women with DM2 from non-DM2 women and to examine the diagnostic performance of each clinical parameter, which was statistically different between the groups. The area under the ROC curve (AUC) between 0.5 and 0.7 could suggest that diagnostic test has low accuracy, between 0.7 and 0.8 diagnostic test has satisfactory accuracy, between 0.8 and 0.9 diagnostic test has good accuracy and AUC higher than 0.9 suggested the excellent accuracy of the diagnostic test. A value of $P < 0.05$ was considered as statistically significant. All statistical calculations were performed using the Statistical Package for Social Sciences (SPSS) - PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The demographic characteristics of postmenopausal women with and without DM2 are presented in Table 1. Postmenopausal women with DM2 were significantly older, had greater BMI, WC, and longer menopause duration than women without DM2 ($P < 0.001$, respectively). DBP was lower in diabetic women ($P = 0.010$). The prevalence of smokers, antihypertensive and hypolipidemic therapies usages were higher among DM2 than non-DM2 patients ($P < 0.001$, respectively), since non-DM2 women were not smokers, nor did they use any medicament therapy, as described in methods section.

The DM2 group had lower TC and LDL-c concentrations than controls ($P < 0.001$, respectively). Furthermore, the patients had lower HDL-c concentration but higher concentrations of TG than the control group ($P < 0.001$, respectively). Lower total bilirubin concentration was determined in DM2 patients than in controls ($P < 0.001$). Glucose, uric acid, creatinine, hsCRP concentrations, and GGT activities were higher ($P < 0.001$, respectively), but eGFR was lower in patients with DM2 than in controls ($P < 0.001$).

Spearman's correlation analysis indicated statistically significant negative correlations between total bilirubin and variables such as age, menopause duration, BMI, WC, SBP, TG, glucose, creatinine, hsCRP, and positive correlations between total bilirubin and HDL-c, AST, $eGFR_{MDRD}$. HsCRP correlated positively with age, menopause duration, BMI, WC, SBP, DBP, TG, glucose, GGT, uric acid, and creatinine. Negative correlations were determined between hsCRP and HDL-c, as well as between hsCRP and $eGFR_{MDRD}$ [Table 2].

Table 1: Demographic characteristics, laboratory, and clinical parameters of postmenopausal women

	Control group	Diabetic group	*P*
n	150	79	
Age (years)	57 (53-60)	66 (61-71)	<0.001
BMI (kg/m²)*	26.1 (25.4-26.8)	30.5 (29.4-31.6)	<0.001
WC (cm)**	89 (79-99)	105 (98-112)	<0.001
SBP (mmHg)	130±25	135±16	0.087
DBP (mmHg)	84±14	79±10	0.010
Smoking habits (smoker/nonsmoker)	0/150	12/67	<0.001
Hipolipidemic drugs (yes/no)	0/150	35/44	<0.001
Antihypertensives (yes/no)	0/150	64/15	<0.001
Antihyperglycemics (yes/no)	0/150	79/0	<0.001
Insulin (yes/no)	0/150	9/70	<0.001
Menopause duration (years)	4 (2-9)	13 (8-18)	<0.001
TC (mmol/L)	6.47±1.05	5.71±1.13	<0.001
HDL-C (mmol/L)	1.69±0.42	1.31±0.30	<0.001
LDL-C (mmol/L)	4.31±1.02	3.47±1.00	<0.001
TG (mmol/L)*	1.29 (1.20-1.39)	1.89 (1.71-2.09)	<0.001
Glucose (mmol/L)**	5.2 (5.0-5.7)	7.1 (6.5-8.5)	<0.001
Total bilirubin (μmol/L)**	7.5 (6.2-10.2)	5.3 (4.1-7.1)	<0.001
AST (U/L)**	18 (16-21)	18 (16-22)	0.325
ALT (U/L)**	18 (14-23)	19 (15-25)	0.521
GGT (U/L)**	12 (9-15)	17 (13-23)	<0.001
Uric acid (μmol/L)	262±65	302±86	<0.001
Creatinine (μmol/L)**	55 (50-61)	68 (57-77)	<0.001
$eGFR_{MDRD}$ (mL/min/1.73 m²)**	101 (96-104)	74 (63-93)	<0.001
hsCRP (mg/L)*	0.98 (0.83-1.16)	2.10 (1.72-2.56)	<0.001

Data are presented as arithmetic mean±SD and compared with Student's *t*-test. **Log*-normal distributed data are presented as geometric mean (95% CI) and compared with Student's *t*-test after logarithmic transformation; **Skewed distributed data are presented as median (IQR) and compared with Mann–Whitney test. IQR=Interquartile range; CI=Confidence interval; BMI=Body mass index; WC=Waist circumference; TC=Total cholesterol; HDL-C=High-density lipoprotein cholesterol; LDL-C=Low-density lipoprotein cholesterol; TG=Triglycerides; AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; GGT=Gamma-glutamyl transferase; $eGFR_{MDRD}$=Estimated glomerular filtration rate; hsCRP=High-sensitivity C-reactive protein; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; SD=Standard deviation

To assess the effects of variables on diabetes occurrence, we used univariable logistic regression analysis [Table 3]. Age, BMI, WC, HDL-c, TG, creatinine, total bilirubin, and hsCRP showed significant OR in univariable logistic regression [Table 3]. As age rose for 1 year, WC for 1 cm, BMI for 1 kg/m², and hsCRP for 1 mg/L, odds for DM2 development in postmenopausal women increased for 28%, 13%, 23%, and 34.7%, respectively. Odds for DM2

Table 2: Associations between total bilirubin and high-sensitivity C-reactive protein with other clinical parameters

	Total bilirubin (μmol/L)	hsCRP (mg/L)
Age (years)	−0.232**	0.175**
Menopause duration (years)	−0.230**	0.330**
BMI (kg/m^2)	−0.162*	0.512**
WC (cm)	−0.251**	0.546**
SBP (mmHg)	−0.190**	0.318**
DBP (mmHg)	−0.032	0.170*
TC (mmol/L)	0.075	−0.075
HDL-C (mmol/L)	0.341**	−0.299**
LDL-C (mmol/L)	0.044	−0.046
TG (mmol/L)	−0.360**	0.204**
Glucose (mmol/L)	−0.312**	0.256**
Total bilirubin (μmol/L)	-	−0.111
AST (IU/L)	0.146*	−0.062
ALT (IU/L)	0.078	0.038
GGT (IU/L)	−0.077	0.286**
Uric acid (μmol/L)	−0.038	0.384**
Creatinine (μmol/L)	−0.162*	0.191**
$eGFR_{MDRD}$ (mL/min/1.73 m^2)	0.211**	−0.182*
hsCRP (mg/L)	−0.111	-

Data are presented as correlation coefficient (ρ). *P<0.05; **P<0.01. BMI=Body mass index; WC=Waist circumference; TC=Total cholesterol; HDL-C=High-density lipoprotein cholesterol; LDL-C=Low-density lipoprotein cholesterol; TG=Triglycerides; AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; GGT=Gamma-glutamyl transferase; $eGFR_{MDRD}$=Estimated glomerular filtration rate; hsCRP=High-sensitivity C-reactive protein; SBP=Systolic blood pressure; DBP=Diastolic blood pressure

Table 3: Univariable and multivariable logistic regression analysis for the associations of clinical parameters and diabetes mellitus Type 2 development in postmenopausal women

Predictors	Unadjusted OR (95% CI)	P	Nagelkerke (R^2)
Age (years)	1.280 (1.198-1.368)	<0.001	0.473
WC (cm)	1.130 (1.094-1.174)	<0.001	0.440
BMI (kg/m^2)	1.230 (1.144-1.320)	<0.001	0.232
HDL-C (mmol/L)	0.047 (0.017-0.129)	<0.001	0.279
TG (mmol/L)	2.600 (1.764-3.807)	<0.001	0.170
Creatinine (μmol/L)	1.138 (1.093-1.174)	<0.001	0.365
Total bilirubin (μmol/L)	0.735 (0.645-0.837)	<0.001	0.185
hsCRP (mg/L)	1.347 (1.176-1.544)	<0.001	0.122
Model	**Adjusted OR (95% CI)**	**P**	**Nagelkerke (R^2)**
Age (years)	1.224 (1.117-1.341)	<0.001	0.725
WC (cm)	1.137 (1.036-1.215)	<0.001	
Total bilirubin (μmol/L)	0.727 (0.611-0.866)	<0.001	
hsCRP (mg/L)	1.155 (0.854-1.560)	0.349	

Model=Age, WC, BMI, HDL-C, TG, creatinine, total bilirubin, hsCRP; BMI=Body mass index; WC=Waist circumference; HDL-C=High-density lipoprotein cholesterol; TG=Triglycerides; hsCRP=High-sensitivity C-reactive protein; OR=Odds ratio; CI=Confidence intervals

development were 2.6 times higher when TG concentration increased for 1 mmol/L. Increase in HDL-c by 1 mmol/L reduced the odds for DM2 development by 95.3%. Furthermore, increase in total bilirubin concentration by 1 μmol/L reduced the odds for DM2 development by 26.5%. Nagelkerke R^2 showed that age, BMI, WC, HDL-c, TG, creatinine, total bilirubin, and hsCRP could explain the contributory role of the variables in developing DM2 by 47.3%, 44%, 23.2%, 27.9%, 17.0%, 36.5%, 18.5%, and 12.2%, respectively. Further, multivariable logistic regression analysis was performed to determine independent factors associated with the risk for DM2 development in postmenopausal women [Table 3]. All predictors tested in univariable analysis entered in the Model and were tested by multivariable analysis.

In multivariable logistic regression analysis, age and WC were shown to be the independent predictors for DM2 development (model OR = 1.224, P < 0.001 and OR = 1.137, P < 0.001, respectively). As age increased for 1 year and WC for 1 cm, odds for DM2 occurrence got higher for 22.4% and 13.7%, respectively. Total bilirubin was also shown to be the independent predictor of DM2 development (model OR = 0.727, P < 0.001). Increase in total bilirubin by 1 μmol/L reduced the odds for DM2 development by 27.3%. On the other hand, hsCRP lost its independent predictive role (model OR = 1.155, P = 0.349). According to Nagelkerke R^2, the model could explain the contributory role of the variables in developing DM2 by even 72.5%.

To determine the potential benefit of the single parameter to discriminate postmenopausal women that had DM2 from those who did not have it, ROC analysis was used [Table 4]. The single parameter discriminatory abilities for BMI, WC, HDL-c, TG, creatinine, total bilirubin, hsCRP (all AUCs between 0.7 and 0.8) could suggest satisfactory accuracy for each diagnostic tool. The cutoff for total bilirubin was 7.35 μmol/L. AUC for age and WC were between 0.8 and 0.9 (0.845 for both) and suggested good accuracy for each diagnostic tool to discriminate postmenopausal women who had DM2 from those who did not have it. We also investigated the potential benefit of traditional risk factors used as a single parameter but afterward put in the model to test its accuracy as a diagnostic procedure. The calculated AUC for the model (AUC = 0.956) indicated that this diagnostic procedure had an excellent accuracy [Figure 1]. Furthermore, this diagnostic procedure had high sensitivity (93.7%), suggesting its potential usage as a screening tool in population of postmenopausal women to detect DM2 in those who really had it.

DISCUSSION

Although contradictory results exist in literature when concerning the protective role of total bilirubin in cardiometabolic diseases, the current study reported

Table 4: Receiver operating characteristic analysis for single parameter discriminatory abilities regarding diabetes mellitus Type 2 development in postmenopausal women

Predictors	AUC (95% CI)	SE	Sensitivity (%)	Specificity (%)	*P*
Age (years)	0.845 (0.791-0.889)	0.030	79.9	80.0	<0.001
WC (cm)	0.845 (0.792-0.890)	0.025	91.1	62.7	<0.001
BMI (kg/m^2)	0.748 (0.687-0.803)	0.032	73.4	65.3	<0.001
HDL-C (mmol/L)	0.767 (0.707-0.820)	0.031	82.3	61.3	<0.001
TG (mmol/L)	0.729 (0.667-0.786)	0.035	75.9	66	<0.001
Creatinine (μmol/L)	0.781 (0.721-0.832)	0.036	59.5	94.7	<0.001
Total bilirubin (μmol/L)	0.760 (0.691-0.829)	0.035	55.7	87.3	<0.001
hsCRP (mg/L)	0.767 (0.707-0.820)	0.031	83.3	61.3	<0.001

BMI=Body mass index; WC=Waist circumference; HDL-C=High density lipoprotein cholesterol; TG=Triglycerides; hsCRP=High-sensitivity C-reactive protein; ROC=Receiver operating characteristic; AUC=Area under the ROC curve; CI=Confidence interval; SE=Standard error

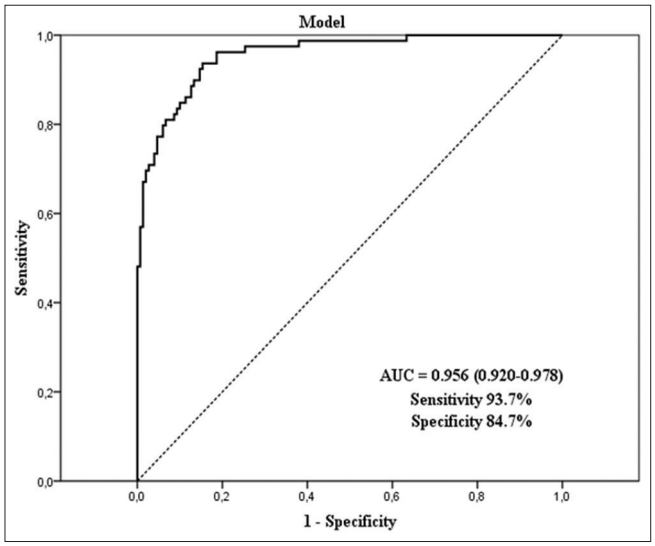

Figure 1: Receiver operating characteristic curve for models discriminative ability for diabetes mellitus Type 2 development in postmenopausal women. Model: Age, waist circumference, body mass index, high density lipoprotein cholesterol, triglycerides, total bilirubin, high-sensitivity C-reactive protein, creatinine

lower levels of serum total bilirubin in postmenopausal women with DM2, compared to nondiabetic counterparts. In addition, high inflammation (as measured with hsCRP) correlated positively, whereas total bilirubin correlated negatively with unfavorable cardiometabolic risk factors in examined cohort of postmenopausal women. However, in multivariable logistic regression analysis advanced age, higher WC, and lower serum total bilirubin levels were shown to be the independent predictors for DM2 development. On the other hand, hsCRP lost its independent predictive role for DM2 development.

Our results are contrary to the study conducted by Thorand *et al.*,[22] which reported the association of hsCRP with incident DM2 in women. On the other hand, our results are in agreement with recent study showing that hsCRP was not associated with increased risk of incident DM2[21] when stratified by baseline glycated hemoglobin (HbA1c) levels. Namely Pan *et al.*[21] confirmed the positive relationship between CRP and DM2 only among those participants who had already had high HbA1c levels (i.e., undiagnosed diabetes), but not in those having low HbA1c levels (i.e., incident diabetes), suggesting that high CRP levels might be rather hyperglycemia by-product, instead of its direct contribution to the development of incident DM2.

As far as total bilirubin levels are concerned, our results are in line with previous findings[6,8,9] that confirmed the association of total bilirubin with DM2. In addition, in longitudinal study that comprised nearly 6000 Korean men, low serum total bilirubin level was shown to provide additional information for predicting future development of DM2 in healthy individuals.[25]

Abbasi *et al.*[9] performed the Mendelian randomization in a prospective cohort of nearly 3400 participants free of DM2 at baseline, and confirmed the causal link between bilirubin level and risk of DM2, thus supporting its protective role in diabetes.

Anti-inflammatory and antioxidant properties of bilirubin may be explained by its ability to scavenge ROS by inhibiting the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, showing that in cultured vascular endothelial and mesangial cells, bilirubin significantly inhibited NADPH-dependent superoxide production in high glucose-induced production of ROS.[26]

On the contrary, there are many studies which questioned the role of this biomarker in DM2. Yeh *et al.*[16] found bilirubin levels to be even higher in the group with DM2, compared with the healthy control group, and also indicated that total bilirubin does not correlate with predictors of cardiovascular risk in the population with DM2. In line with this, Wang *et al.*[15] did not show the association between serum total bilirubin levels and incident DM2 in the adult population. Similar results that also rejected the hypothesis of independent relationship between serum total bilirubin levels and incident DM2 were shown in a longitudinal study during 6-year follow-up[27] that comprised >2000 participants who were normoglycemic at baseline, where

no significant association with prediabetes was shown. Furthermore, the gender difference in response to oxidative stress caused by glycemic variability might be an important underlying factor when evaluating the protective role of total bilirubin[28] in DM2. In a longitudinal study during 5-year follow-up,[29] no association between baseline total bilirubin and incident MetS in males, but a significant inverse association in females has been reported. However, after adjustment for insulin resistance, this inverse association in females became nonsignificant.[29] In another study, the bilirubin level within the physiological range was shown to be the independent predictor for glycemic variability only in females with DM2.[28] In line with this, bilirubin levels were independently correlated with thiobarbituric acid reactive substances (marker of oxidative stress) in women, but not in men, thus suggesting that bilirubin was a poor indicator for oxidative stress in men.[30] Studies have also reported insufficient anti-oxidant defense mechanisms in men as compared to women.[28] In addition, women have a higher percentage of body fat than men,[22] presuming that obesity-related inflammation and oxidative stress could have a greater influence on insulin resistance and DM2 development in women than in men.

Cross-sectional design and relatively small sample-size of postmenopausal women are the limitations of our study. Therefore, longitudinal studies with large sample size are needed to confirm our results. Nevertheless, our results show that in addition to traditional risk factors (e.g., BMI, WC, HDL-c, TG, creatinine), including serum total bilirubin and hsCRP indicates an excellent accuracy (AUC = 0.956) of this diagnostic procedure. Furthermore, high sensitivity (93.7%) of this diagnostic procedure suggests its potential usage as a screening tool in postmenopausal women with DM2 to distinguish them from those who do not have DM2.

CONCLUSION

Lower total bilirubin independently correlated with DM2 in postmenopausal women, in addition to advanced age and higher WC. On the other hand, hsCRP did not independently correlate with DM2, suggesting that total bilirubin may be a more reliable biomarker than hsCRP when estimating risk for DM2 development. However, including both total bilirubin and hsCRP, in addition to traditional risk factors (e.g., BMI, WC, HDL-c, TG, creatinine), may be useful screening test in predicting women at risk for DM2. Moreover, it is important to note that all of these parameters are cost-effective and can be easily measured.

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Conflicts of interest

There are no conflicts of interest.

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