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Patients with Gilbert syndrome and type 2 diabetes have lower prevalence of microvascular complications

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ABSTRACT

Objective: Accumulating clinical evidence indicates an inverse relationship between oxidative stress and unconjugated hyperbilirubinemia. This study aimed to compare the prevalence of diabetes microvascular complications in patients with Gilbert syndrome and type 2 diabetes mellitus (T2D).

Methods: A total of 1200 electronic records with T2D were reviewed. From them, 50 patients with Gilbert syndrome (cases [indirect bilirubin ≥1.2 mg/dl without evidence of hemolysis or liver disease]) and 50 controls (T2D without hyperbilirubinemia) were included. Linear and logistic regression models were performed to evaluate the independent association between indirect hyperbilirubinemia with microvascular complications related with T2D.

Results: Both case and control group had the same proportion of gender (female = 20 [40 %]) and diabetes duration (14.0 ± 6.5 years) and similar mean of age (60 ± 9.6 and 60 ± 9.2 years, respectively, $p = 0.91$). The median of unconjugated bilirubin of case and control group was 1.4 (1.2–1.6) vs. 0.4 (0.2–0.6) mg/dl ($p < 0.001$), respectively. Patients with elevated unconjugated bilirubin had less urine albumin-creatinine ratio compared with control group (8.5 [4.3–23] vs. 80 [8–408] mg/g, $p < 0.001$), and lower rate of diabetes microvascular complications and metabolic syndrome. After adjustment for BMI, age, HbA1c, blood pressure, triglycerides, and the metabolic syndrome, the lineal regression analysis showed that unconjugated bilirubin protects against microalbuminuria in T2D patients (β = −414.11, 95 % CI [-747.9, −80.3], p = 0.006. Also, unconjugated hyperbilirubinemia was independently associated with a better glomerular filtration rate (GFR) (β = 9.87, 95 % CI [1.5, 18.3], P = 0.02).

Conclusions: Patients with Gilbert syndrome and T2D had a lower prevalence of diabetes microvascular complications.

1. Introduction

It has been more than 25 years since serum bilirubin has been negatively correlated with coronary artery disease [1]. Since then, increasing evidence supports the finding of this negative relationship between lower bilirubin levels and higher risk for cardiovascular disease (CVD) including stroke, coronary and peripheral atherosclerotic disease [2–4].

Serum levels of bilirubin are governed by the crucial enzymes: heme oxygenase (HO), biliverdin reductase, and bilirubin uridine diphosphate-glucuronosyltranferase (UGT1A1). The formation of bilirubin is controlled by both HO and biliverdin reductase while the clearance of bilirubin by the liver and bile are modulated by UGT1A1 [5]. Observations based predominantly on in vitro studies and animal models suggest that HO-1 have a protective role in the development of atherosclerosis [2,6–10]. In addition, anti-atherosclerotic properties of biliverdin and bilirubin are also reported [11–13]. In human studies, increasing amount of research on bilirubin as a protective factor for CVD are being reported and further characterized. Inhibition of low density lipoprotein cholesterol (LDL-cholesterol) [12,13] and scavenge oxygen radicals [11] and the hampering of oxidative stress [14,15] are some of the few studied mechanism of the antioxidant and anti-inflammatory properties of the bilirubin. Additionally, anti-proliferative properties [16–18] and total serum antioxidant capacity [15,19] are other

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beneficial aspect of bilirubin in human.

The relationship of Gilbert syndrome with type 2 diabetes and the prevalence of microvascular complications is limited [20]. The goal of our study was to compare the prevalence of diabetes microvascular complications in patients with Gilbert syndrome and type 2 diabetes mellitus (T2D).

2. Methods

The study protocol was approved by the Local Ethics Review Committee and followed the ethical guidelines of the Declaration of Helsinki.

2.1. Study participants

The clinical records of all patients with T2D treated in the Diabetes Outpatient Clinic at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, a tertiary referral center in Mexico City were evaluated. We included patients with Gilbert syndrome (cases) which were matched by diabetes duration and age (±3 years) (controls). Gilbert syndrome was determined on the presence of serum unconjugated bilirubin ≥1.2 mg/dL and ≥75 % of total bilirubin level for ≥3 months in the absence of any liver disease and/or hemolysis [21,22].

2.2. Anthropometric and biochemical measurements

Age, sex, type and duration of diabetes mellitus, body mass index (BMI [calculated as the weight in kilograms divided by the squared height in centimeters]), were collected from the clinical record. Metabolic parameters including uric acid, creatinine, lipid profile (total cholesterol, high density cholesterol [HDL-C] and triglycerides), apolipoprotein B (Apo B), and hepatic enzymes (AST, ALT) were measured with colorimetric assays (Unicel DxC 600 Synchron Clinical System Beckman Coulter). Low density cholesterol (LDL-C) as calculated using the Martin's formula [23]. Glycosylated hemoglobin (HbA1c) concentration was assessed by HPLC (Variant II Turbo, Bio-Rad). Glomerular filtration rate (eGFR) was estimated using the Cockroft-Gault equation and the urinary creatinine to albumin ratio (UACR) was also calculated.

2.3. Diabetes microvascular complications and metabolic syndrome

Diabetes complications (nephropathy, retinopathy, peripheral and/or neuropathy) were defined according to the American Diabetes Associations diagnostic criteria [24]. Diabetic retinopathy was considered with a previous diagnosis by a certified Ophthalmologist which were split by proliferative and non-proliferative diabetic retinopathy. Nephropathy was defined as the presence of either albuminuria (UACR >30 mg/g), eGFR ≤60 mL/min/1.73 m^2, the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers for proteinuria. Albuminuria was considered as UACR >30 mg/g. Further renal status were divided in moderately increased albuminuria (ACR 30–300 mg/24h) and severely increased albuminuria (ACR >300mg/24h). Diabetic neuropathy was considered with positive nerve conduction velocity study and/or the use of any first-line agents for the pharmacological management of neuropathic pain [25]. The modified National Cholesterol Education Program Adult Treatment Panel III (ATP III) criteria were used for diagnosing metabolic syndrome, using abdominal circumference cutoffs for Latin-American population [26].

2.4. Statistical analysis

Data are presented as mean ± SD or median and interquartile range, as appropriate. Distribution of categorical variables is reported as frequencies and percentages and was compared between groups using chi-squared tests. To evaluate intergroup differences, we used student's t-test or Mann–Whitney *U* test, where appropriate. Two-sided $P < 0.05$ was considered significant. The association between unconjugated hyperbilirubinemia and the presence of retinopathy, neuropathy and metabolic syndrome were assessed using a stepwise multiparametric logistic regression models adjusted with confounder variables. The results are presented as odds ratios (OR) and 95 % confidence intervals (CI). Statistical analyses were conducted using SPSS v25.0.

3. Results

3.1. Clinical and biochemical characteristics of the study cohort

Among 1200 records of patients with T2D, 50 subjects had Gilbert syndrome (case group) which was compared to 50 subjects without Gilbert syndrome (control group). Both case and control group had the same proportion of gender (20 [40 %]) and diabetes duration (14.0 ± 6.5 years) and similar mean of age (60 ± 9.6 and 60 ± 9.2, respectively, $p = 0.91$). Among the control group, systolic blood pressure, creatinine and microalbuminuria were significantly higher than the case group. Body weight and diastolic blood pressure had a higher tendency in control group compared to case group. Others clinical and biochemical baseline characteristics are shown in Table 1.

3.2. Diabetes microvascular complications and metabolic syndrome

Compared to the case group, control group had a higher frequency of microvascular complications including nephropathy with albuminuria, neuropathy and retinopathy. Also, the frequency of MS was higher in the group without Gilbert syndrome (Table 2). A significant correlation was identified between albuminuria and unconjugated bilirubin of the case group ($R^2 = 0.086$, $p = 0.003$) (Fig. 1).

3.3. Simple linear and logistic-regression analyses

Parameters estimated from the simple linear and logistic regression analyses between explanatory variables and albuminuria, eGFR, retinopathy and MS are reported in Tables 3 and 4. In the simple linear regression analyses, an inverse association existed between unconjugated bilirubin and albuminuria (β = −414.11, 95 % CI [-747.9, −80.3], P = 0.006), whereas a direct association was observed between eGFR and albuminuria (β = 9.87, 95 % CI [1.5, 18.3], P = 0.02). In addition,

Table 1
Comparison of the baseline characteristics of the studied cohort.

Variable	Case group (n = 50)	Control group (n = 50)	p
Female	20 (40.0)	20 (40.0)	0.20
Age, years	60 ± 9.6	60 ± 9.2	0.91
BMI, kg/m^2	27.8 ± 5.16	28.9 ± 5.17	0.26
Diabetes duration, years	14 ± 6.5	14 ± 6.5	0.98
Blood pressure	124.9 ± 18	132.7 ± 14	**0.01**
Systolic	75.5 ± 11	79 ± 8.8	0.08
Diastolic			
Total bilirubin, mg/dl	1.6 (1.4–1.8)	0.5 (0.42–0.7)	**<0.001**
Unconjugated bilirubin, mg/dl	1.4 (1.2–1.6)	0.4 (0.2–0.6)	**<0.001**
Glucose, mg/dl	137 (107–168)	147 (123–195)	0.21
HbA1c, %	8.4 ± 1.8	8.9 ± 1.8	0.19
Creatinine, mg/dl	0.7 (0.6–0.9)	0.9 (0.7–1.3)	0.03
Total cholesterol, mg/dl	179 ± 37	185 ± 34	0.35
Triglycerides, mg/dl	140 (108–186)	172 (111–231)	0.12
HDL-C, mg/dL	45 ± 29	41 ± 24	0.14
LDL-C, mg/dl	105 ± 29	111 ± 24	0.28
AST, UI/L	17 [13–22]	21 [18–31]	0.59
ALT, UI/L	22 [17–34]	21.5 [17–31]	0.72
eGFR, mL/min/1.73m^2	94 ± 26	87 ± 40	0.32
UACR, mg/g	8.5 (4.3–23)	80 (8–408)	**<0.001**

Data expressed as frequencies (%), mean (SD) or median (IQR), as appropriate. BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C. low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-creatine ratio.

Table 2
Prevalence of diabetic complications and metabolic syndrome.

Diabetic complications	Case group (n = 50)	Control group (n = 50)	p
Nephropathy	13 [26]	34 (68)	**<0.001**
Albuminuria	10 [20]	32 (64)	**<0.001**
Moderately increased albuminuria	6 [12]	18 [36]	**<0.001**
Severely increased albuminuria	3 [6]	7 [14]	**<0.001**
Neuropathy	16 [32]	26 (52)	0.04
Retinopathy	9 [19]	20 (52)	**<0.001**
Non-proliferative	3 [6]	4 [11]	0.03
Proliferative			
MS	26 (52)	43 (86)	**<0.001**

Data expressed as absolute and relative frequencies (%). MS, metabolic syndrome.

age and BMI had an inverse and direct association with eGFR, ($\beta = -1.43$, 95 % CI [-2.0, −0.80], $P < 0.001$) and ($\beta = 2.80$, 95 % CI [1.70, 3.90], $P < 0.001$), respectively. In the logistic regression model, unconjugated bilirubin were significant independent protectors of both retinopathy and MS, (OR = 0.24, 95 % CI [0.084–0.66], $P < 0.001$) and (OR = 0.21, 95 % CI [0.056–0.80], P = 0.024), respectively. On the other hand, SBP was a significant predictor of MS (OR = 1.11, 95 % CI [1.03–1.19], $P < 0.001$).

4. Discussion

We found that a significant lower rate of microvascular complications and MS were present in patients with Gilbert syndrome and T2D. Also, a significant inverse relationship between unconjugated bilirubin and albuminuria, retinopathy and MS were found; while a direct association between unconjugated bilirubin and eGDR was reported. The lower level of systolic blood pressure we observed in patients with Gilbert syndrome is in keeping with the findings of Inoguchi et al. [20]. However, contrary to their findings, we did not find a significant difference in LDL, total cholesterol and triglyceride between both groups.

The role of oxidative stress in the pathogenesis in diabetic complications is well-established [27]. Gastrointestinal complications of diabetes include diabetic gastroparesis and usually occurs in patients with more than 5 years of disease which can result in high glycemic variability [28,29]. Accordingly, these oscillating glucose concentrations results in endothelial damage that contributes to the microvascular diabetes complications [30]. Interestingly, high glycemic variability may contribute to the so-called metabolic memory through the increased chromatin remodeling [31,32]. All these knowledges support that oxidative stress play a noxious role between the etiology of the microvascular complications and its continuation. It is highly likely that elevated unconjugated bilirubin interferes these aforementioned mechanisms [33]. In addition, physiological levels of serum total bilirubin hinder vascular endothelial activation resulting from oxidative stress [34,35].

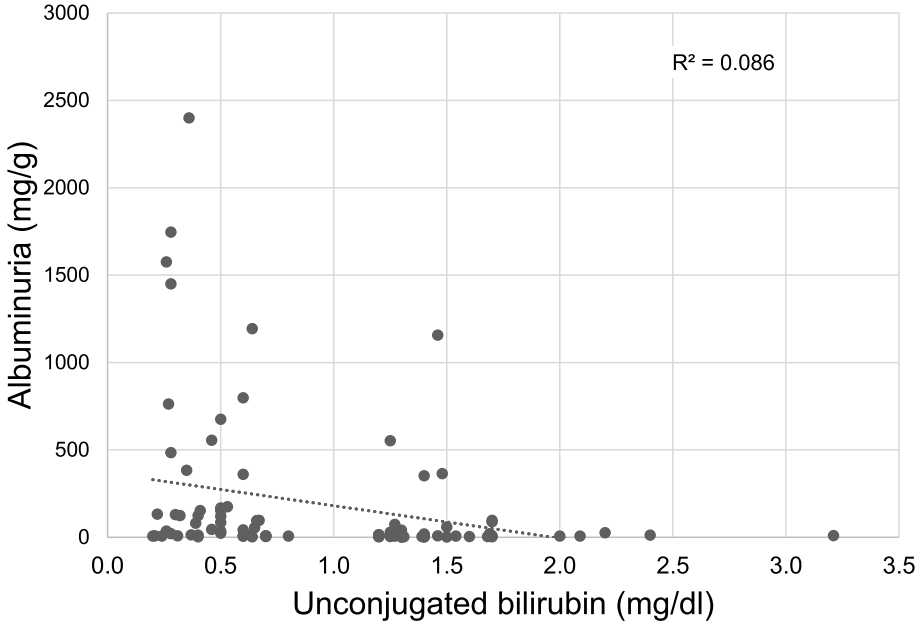

Fig. 1. Correlation between albuminuria (mg/g) and unconjugated bilirubin (mg/dL).

Table 3
Simple linear regression analyses of albuminuria and estimated glomerular filtration rate.

	Albuminuria			Estimated glomerular filtration rate		
Independent Variable	P Value	95 % CI	β	P Value	95 % CI	β
Age	0.372	−35.2, 13.3	−10.95	**<0.001**	**−2.0, -0.8**	**−1.43**
HbA1c	0.984	−110.9, 108.7	−1.13	0.080	−0.3, 5.2	2.47
BMI	0.423	−59.1, 25.0	−17.03	**<0.001**	**1.7, 3.9**	**2.80**
SBP	0.465	−10.1, 21.9	5.90	0.374	−0.6, 0.2	−0.18
DBP	0.924	−23.2, 25.5	1.17	0.202	−0.2, 1.0	0.40
Triglycerides	0.553	−1.7, 3.2	0.74	0.952	−0.06, 0.06	0.002
Unconjugated bilirubin	**0.016**	**−747.9, -80.3**	**−414.11**	**0.022**	**1.5, 18.3**	**9.87**
MS	0.423	−59.1, 25.0	−71.90	0.444	−8.9, 20.2	5.62

CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MS, metabolic syndrome.

Table 4
Logistic-regression analysis for retinopathy and metabolic syndrome.

	Retinopathy			MS		
Independent Variable	P Value	OR (95 % CI)	β	P Value	OR (95 % CI)	β
Age	0.795	0.99 (0.92–1.06)	-.0009	0.225	0.95 (0.88–1.03)	- 0.048
HbA1c	0.085	1.28 (0.97–1.68)	0.24	0.831	1.03 (0.75–1.44)	0.035
BMI	0.815	0.99 (0.88–1.11)	−0.014	0.359	1.07 (0.93–1.24)	0.69
SBP	0.348	1.02 (0.98–1.05)	0.017	**<0.001**	**1.11 (1.03–1.19)**	**0.104**
DBP	0.444	0.98 (0.92–1.04)	−0.023	0.301	1.04 (0.96–1.12)	0.040
Unconjugated bilirubin	**0.006**	**0.24 (0.084–0.66)**	**−1.45**	**0.024**	**0.21 (0.056–0.80)**	**- 1.50**
EGFR	0.157	0.98 (0.96–1.01)	−0.016	0.288	1.02 (0.99–1.05)	0.016

MS, metabolic syndrome; OR: odd ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR: estimated glomerular filtration rate.

Data derived from the National Health and Nutrition Examination Survey (NHANES) suggests that total bilirubin was associated with a 26 % reduction of MS [36]. Numerous component of MS including hyperglycemia, dyslipidemia, and obesity are inversely associated with serum level of bilirubin in T2D [37]. Mechanistic published data indicate that serum bilirubin is involved on the lipid metabolism [38], modulation of various transcription factor including peroxisome proliferator-activated receptors (PPARs) [39], sterol regulatory element-binding protein-1 (SREBP-1) [40], and inhibition of inflammatory mediators [41].

In animal studies, diabetic hyperbilirubinemic rats had significantly less albuminuria compared to the diabetic non-hyperbilirubinemic rats [42]. More importantly, mesangial expansion, which is a distinct feature of diabetic nephropathy, did not develop in the diabetic hyperbilirubinemic rats. Also, biliverdin-treated diabetic rodents were protected against both albuminuria and renal mesangial expansion [42]. The benefit seen in T2D rodent models treated with biliverdin could be explain by the increased levels of intracellular bilirubin since biliverdin is converted to bilirubin by the biliverdin reductase [43]. As previously stated, the increment of antioxidant capacity by hyperbilirubinemia may explain the beneficial effects [42]. In agreement with various clinical studies [44–46], individuals with higher serum levels of bilirubin had a lower prevalence of diabetic nephropathy and albuminuria. However, we did not observe significant difference in the eGFR between both groups as Fukui et al. reported [45]. Although the pathophysiological significance of bilirubin in diabetic nephropathy is not fully elucidated, suggested underlying mechanism include downregulation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase components and decreased expression of transforming growth factor beta (TGF-β) and fibronectin [42]. The above data support the anti-oxidative, anti-adipogenic and anti-inflammatory role of the indirect bilirubin which prompt a possible exploration of the bilirubin and its metabolites as part of their pathogenic role and possible therapeutic applications for microvascular complications of type 2 diabetes.

Limitations of this study includes its retrospective design and a relatively small number of patients. Furthermore, some selection bias may be present inherent in observational studies. We try to reduce such bias, however, doing an exhaustive search of cases in our clinical records as described above. We acknowledge that the relatively short duration of diabetes could somewhat explain the low frequency of diabetic complications in the case group. However, the fact that there was a significant difference in their frequencies after compared groups with same diabetes duration strengthen our conclusions.

5. Conclusion

Patients with Gilbert syndrome and T2D had a lower prevalence of diabetes microvascular complications and metabolic syndrome. We believe our study results open interesting pathogenic roles and possible therapeutic applications for microvascular complications of type 2 diabetes.

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CRediT authorship contribution statement

Ana Cecilia Uribe-Weichers: made the conception and design of the study, analysis and interpretation of data, the acquisition of data. **Francisco J. Gómez-Pérez:** made the conception and design of the study. **César Ernesto Lam-Chung:** Writing – original draft, drafted the article. All authors revised the paper critically for important intellectual content, and agreed the final approval of the version to be submitted. **Daniel Cuevas-Ramos:** Writing – original draft, made the conception and design of the study, analysis and interpretation of data, drafted the article.

Declaration of competing interest

The authors have nothing to declare.

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