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The Correlation Between Plasma Bilirubin Concentrations and Glomerular Filtration Rate and Creatinine in Type 2 Diabetes with Renal Damage

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ABSTRACT

Background: Diabetic nephropathy is one of the causes of chronic kidney disease with a very complex mechanism, in which oxidative stress plays an important role and bilirubin acts as an effective antioxidant, protecting cells from damage caused by oxidative stress. **Objective:** The aim of the study was to investigate the relationship between plasma bilirubin concentration with glomerular filtration rate and creatinine in patients with type 2 diabetes with renal damage. **Methods:** Total amount of 60 patients with type 2 diabetes with renal damage. Study design was descriptive. **Results:** Mean age 64.1±4.76. The rate of decreased glomerular filtration rate was 86.7% and increased albuminuria accounted for 96.7%. The concentration of total bilirubin in plasma decreased correspondingly to the decrease in glomerular filtration rate. The concentration of total, free and conjugated bilirubin was negatively correlated with creatinine concentration (r=-0.48), (r=-0.37), (r=-0.34) and positively correlated with glomerular filtration rate (r=0.54), (r=0.45), (r=0.41) with p<0.05). The area under the curve (AUC) of total bilirubin concentration was 0.7, lower than the area under the curve (AUC) of creatinine concentration 0.8, uric acid 0.74. **Conclusion:** Plasma bilirubin concentration is inversely correlated with creatinine concentration and positively correlated with glomerular filtration rate.

Keywords: glomerular filtration rate, diabetic nephropathy, creatinine, total bilirubin.

1. BACKGROUND

Diabetic nephropathy is one of the causes of chronic kidney disease, with the fastest increasing morbidity and mortality (1). It is the result of long-term exposure to hyperglycemia, leading to progressive changes in renal structure and function.

The initial development of diabetic nephropathy has no clinical manifestations and when albuminuria is detected, the lesions are often in an advanced stage, leading to rapid deterioration of renal function to end-stage renal disease (2).

The progression of diabetic nephropathy can be prevented or significantly slowed if detected and treated at an early stage. And albuminuria and glomerular filtration rate (GFR) are both well-established diagnostic/prognostic biomarkers of this disease (3).

The disease is characterized by persistent albuminuria and progressive decline in glomerular filtration rate (GFR) (4). The pathogenesis of diabetic nephropathy is complex, in which oxidative stress plays an important role (5-7). As a metabolite of hemoglobin, bilirubin acts as a potent antioxidant, protecting cells from oxidative stress-induced damage through interactions with the processes mentioned above (8).

In addition, bilirubin modulates mitochondrial function; specifically, it improves respiratory chain function, increases ATP production, and enhances cellular energy supply (9). Furthermore, bilirubin reduces inflammation by inhibiting the activation of inflammatory cells and the release of inflammatory mediators, achieved through the regulation of related signaling pathways (9, 10).

2. OBJECTIVE

The aim of the study was to describe the relationship between plasma bilirubin concentration and glomerular filtration rate and creatinine in patients with type 2 Diabetes mellitus and kidney damage.

3. MATERIAL AND METHODS

Subjects of the study

Selection criteria for the group of patients with type 2 diabetes mellitus and kidney damage was:

- Patients diagnosed with type 2 diabetes mellitus and kidney damage are determined when there is at least 1 of 3 signs:
  - Positive microalbuminuria: MAU (+).
  - Proteinuria/24 hours (+) or positive macroalbuminuria
  - Glomerular filtration rate < 60 ml/min (estimated based on creatinine)

Exclusion criteria

- Patients with acute infections, malignancies, liver failure, gout, alcoholism.
- Currently taking drugs that change the concentration of total bilirubin in the blood plasma such as diuretics, cyclosporine.

Time and location of the study

- Time: From June 2020 to June 2021.
- Location: Central Endocrinology Hospital.

Methods

Research design: this is cross-sectional study.

Sample size was convenient, purposeful. During the study period, 60 patients was included in the study who met the criteria for inclusion in the study were collected.

Data processing

Data were entered and processed using medical statistical methods on SPSS 25.0 software. Linear regression correlation between data was displayed using coefficient r.

Ethical issues in research

The study was approved by the Ethics Council of Thai Nguyen University of Medicine and Pharmacy and the Scientific Council of the Central Endocrinology Hospital.

4. RESULTS

Results of the study shown by Tables 1-3 and Figures 1-3..

As shown in Table 1, average age 64.1±4.76. Mean creatinine was 111.81±3.71 (µmol/l). The rate of decreased glomerular filtration r 86.7% and increased albuminuria was 96.7%.

As shown in Table 2, The average total bilirul centration in men is 8.69±3.6µmol/l. Total pla irubin concentration decreased correspondingl decrease in glomerular filtration rate, the differe statistically significant with p<0.05.

Total bilirubin concentration is negatively co with plasma creatinine concentration (r=-0.48) a itively correlated with glomerular filtration rate with p<0.05).

General characteristics		Number (n=60)	Percentage (%)
Age	< 60	41	68.3
	≥ 60	19	31.7
	Average	64.1±4.76	
Gender	Male	29	48.3
	Female	31	51.7
Average blood pressure	Systolic	132.88±14.9	
	Diastolic	77.83±8.65	
Creatinin (µmol/l)	Average	111.81±3.71	
Glomerular filtration rate (ml/min/1.73 m²)	Normal	8	13.3
	Decreased	52	86.7
Albumin (mg/l)	Normal	2	3.3
	Increased	13	96.7

Table 1. General characteristics of the study subjects

Characteristics		Total plasma bilirubin (± SD) (µmol/l)	p
Gender	Male	8.69± 3.6	>0.05
	Female	8.65 ± 4.03	
	Average	8.85±4.89	
Glomerular filtration rate (ml/min/1.73 m²)	60-89	13.00±4.02	<0.05
	45-59	11.08±3.69	
	30-44	9.54±3.69	
	15-29	9.00±4.38	
	< 15	7.23±3.2	

Table 2. Relationship between total bilirubin concentration and glomerular filtration rate

Indirect bilirubin concentration is negatively correlated with plasma creatinine concentration (r=-0.37) and positively correlated with glomerular filtration rate (r=0.45) with p<0.05).

Direct bilirubin concentration is negatively correlated with plasma creatinine concentration (r=-0.34) and positively correlated with glomerular filtration rate (r=0.41)

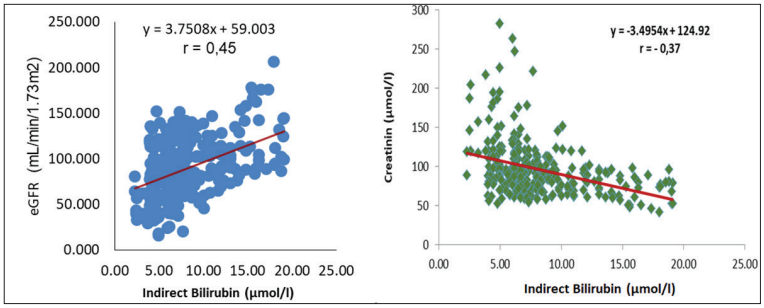

Figure 1. Correlation between total bilirubin concentration with creatinine concentration and glomerular filtration rate

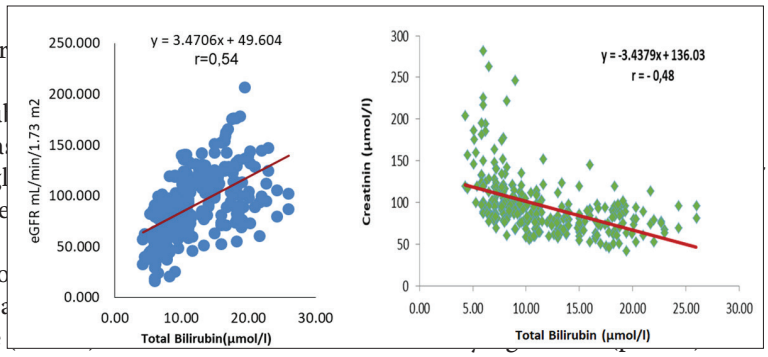

Figure 2. Correlation between free bilirubin concentration with creatinine concentration and glomerular filtration rate

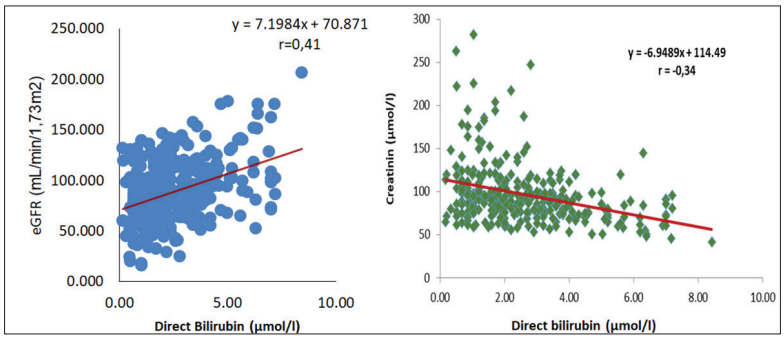

Figure 3. Correlation between Direct bilirubin concentration with creatinine concentration and glomerular filtration rate

Variable	General		Male		Female	
	AUC	p	AUC	p	AUC	p
Creatinin(µmol/l)	0.80	0.000	0.84	0.000	0.88	0.000
Acid uric (µmol/l)	0.74	0.000	0.76	0.000	0.75	0.001
Urê (mmol/l)	0.65	0.003	0.69	0.002	0.56	0.453
Total bilirubin (µmol/l)	0.7	0.001	0.73	0.039	0.69	0.010

Table 3. Area under the ROC curve of some factors related to kidney damage in patients with type 2 diabetes

5. DISCUSSION

The study was conducted on 60 patients with type 2 diabetes with kidney damage and the average age of the study subjects was 64.1±4.76 years old. This age group is a risk factor for metabolic syndrome and insulin resistance. Diabetes is the stage of clinical manifestation of hyperglycemia in the natural course of insulin resistance. Type 2 diabetes progresses silently, the disease is often detected late when complications have occurred. The age of onset of type 2 diabetes is usually from 40 - 50 years old, after about 5 -15 years, kidney complications will appear, so the age above or below 60 is the most common for complications, including kidney complications. Increased urinary albumin excretion, decreased estimated glomerular filtration rate (eGFR) or the presence of other signs of kidney disease are diagnostic features of chronic kidney disease. The study results showed that the rate of decreased GFR was 86.7% and increased albuminuria was 96.7%.

In the study by Jian-Min name 2023, the mean age was 62 [52-71] years; 52.96% were male4. In the entire group, no significant association was observed between STB concentration and DKD in any logistic regression model ($p > 0.05$). Subgroup analysis showed that, in men with diabetes in the United States, serum bilirubin concentration > 11.98 µmol/L was associated with a nearly 30% lower risk of diabetic nephropathy compared with serum bilirubin concentration ≤ 8.55 µmol/L4.

The total plasma bilirubin concentration decreased correspondingly to the decrease in glomerular filtration rate, the difference was statistically significant with $p<0.05$. The results of the study also showed that the total bilirubin concentration was negatively correlated with the plasma creatinine concentration (r=-0.48) and positively correlated with the glomerular filtration rate (r=0.54) with $p<0.05$) (Figure 1). Free bilirubin concentration was negatively correlated with plasma creatinine concentration (r=-0.37) and positively correlated with glomerular filtration rate (r=0.45) with $p<0.05$) (Figure 2) and conjugated bilirubin concentration was negatively correlated with plasma creatinine concentration (r=-0.34) and positively correlated with glomerular filtration rate (r=0.41) with $p<0.05$ (Figure 3).

Yucheng Wu's study (2019) found that plasma bilirubin concentration was inversely correlated with the presence of severe renal disease in the glomerular, interstitial, and tubular regions in Chinese patients diagnosed by biopsy. The study also showed that patients with lower serum bilirubin concentrations may have poorer renal function, which is associated with a higher risk of progression to chronic kidney disease, independent of the effects of age, sex, diabetes duration, anemia, blood glucose, and hypertension, but not eGFR (hazard ratio, 0.406; 95% confidence interval, 0.074 to 2.225; P = 0.299) (11).

Shin and colleagues also showed that increased serum total bilirubin concentrations were associated with increased eGFR and decreased albuminuria in nondiabetic and diabetic Korean adults (12).

Shulei Fan (2019): Among 1070 patients, 429 had IgA nephropathy (IgAN), 641 did not have IgAN. Serum uric acid levels were correlated with eGFR ($r = - 0.418$, $p < 0.001$), Cr ($r = 0.391$, $p < 0.001$), urea ($r = 0.410$, $p < 0.001$), 24-u-pro ($r = 0.077$, $p = 0.022$). Multivariate logistic regression analysis showed that after adjusting for Cr, age, and blood pressure, HUA was a risk factor for segmental glomerulosclerosis (OR = 1.800, 95% CI: 1.309-2.477) and tubular atrophy/interstitial fibrosis (OR = 1.802, 95% CI: 1.005-3.232) (13).

Recent studies have shown that bilirubin has a novel function as a metabolic hormone that regulates the transcription of nuclear receptor 14-regulated genes. Higher bilirubin concentrations within the physiological range may have beneficial effects on the kidney (14). Bilirubin can bind directly to PPARα and increase transcriptional activity. Stec et al. (15) showed that global PPARα gene knockout mice had a reduced genetic response to bilirubin treatment, especially to hepatic fibroblast growth factor-21, a well-characterized PPARα target gene. Although bilirubin may have an unknown role in activating other pathways, PPARα has been shown to be a protein that binds bilirubin directly as a ligand agonist. Recent studies have shown that bilirubin binds selectively only to PPARα and does not interact with PPARγ or PPARδ (16). Therefore, it is speculated that the specific mechanism by which higher bilirubin concentrations slow disease progression is related to the hormonal properties of bilirubin. Although the results obtained in this clinical study cannot directly reveal the intrinsic mechanism by which bilirubin as a hormone exerts a protective effect, they suggest that with a gradual increase in total bilirubin concentrations within the physiological range over time, it may slow disease progression, having a positive effect on the above mecha-

nisms. The use of multivariate binary logistic regression models showed that serum bilirubin concentrations (%/year) exhibited a significant correlation with the slope of eGFR.

Furthermore, ROC curve analysis showed a cut-off value of -6.729%/year for serum bilirubin concentration (%/year) with a sensitivity of 0.75 and a specificity of 0.603, in diagnosing eGFR decline >-5.48%/year (17). The area under the curve (AUC) of total plasma bilirubin concentration was 0.7 (male: 0.73; female: 0.69), lower than the area under the curve (AUC) of creatinine concentration 0.8 (male: 0.84; female: 0.88), uric acid 0.74 (male: 0.76; female: 0.75), urea 0.65 (male: 0.69; female: 0.56), the difference was statistically significant ($p<0.05$). The area under the curve (AUC) of total plasma bilirubin was smaller than the AUC of plasma creatinine and uric acid, but larger than the AUC of plasma urea. The difference was statistically significant ($p<0.05$). This difference showed that the sensitivity and specificity of total bilirubin is also a good biomarker contributing to the detection of early kidney damage.

6. CONCLUSION

The concentration of total plasma bilirubin decreased correspondingly to the decrease in glomerular filtration rate. The concentrations of total, free and conjugated bilirubin were inversely correlated with the concentration of plasma creatinine and positively correlated with the glomerular filtration rate with $p<0.05$. The area under the curve (AUC) of total plasma bilirubin was smaller than the AUC of plasma creatinine and uric acid, but larger than the AUC of plasma urea.

- **Data Availability**: Data are available upon request. Please contact the respective authors for further information.
- **Author's contribution**: Pham Thi Thuy contributed to sample collection, biomedical data compilation, analysis and review, Hoang Thi Ngoc Tram manuscript writing, contributed to study design, Vu Thi Thu Hang contributed to biomedical data compilation and analysis, Nguyen Tien Dung was the project leader. All authors read and approved the final manuscript.
- **Conflict of interest**: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.
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