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Original Article

Lower serum bilirubin concentration in patients with migraine

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Abstract: Background: Bilirubin has been seen as a toxic waste product since it is product of heme metabolism. It's the latest in a series of studies showed that the concentration of serum bilirubin is associated with various diseases such as multiple sclerosis, hypertension and cardiovascular diseases (CVD). However, no study to investigate the association between serum bilirubin and migraine, thus, our aim is to investigate the association between serum bilirubin and migraine. Methods: Serum samples were collected from 120 patients with migraine and 128 healthy individuals, serum total bilirubin (Tbil), serum direct bilirubin (Dbil) and serum indirect bilirubin (Ibil) concentration were measured to this study. Results: Tbil, Dbil and Ibil concentration were significantly lower in patients with migraine than healthy controls. Tbil, Dbil and Ibil concentration also were lower in patients with migraine compared with healthy controls when serum bilirubin concentration further was grouped by gender. Conclusions: We found evidence that lower serum bilirubin in patients with migraine, serum bilirubin may be useful markers to estimate neurogenic inflammation in patients with migraine.

Keywords: Serum bilirubin, migraine, neurogenic inflammation

Introduction

Migraine is one of the most common neurological diseases seen in middle-aged or older, which leads to conspicuous frustration and sufferance in patients with migraine. There are approximately 12-15% adults who suffered from migraine in the European and American countries [1]. Accumulating data have showed that migraine patients has a risk of cardiovascular diseases (CVD) [2], a large of research in clinical practice have confirmed that migraine causes cerebrovascular accident symptomatology and may, although rarely, play a remarkable role of trigger for migrainous infarction [3]. It is clear that we should clinically pay close attention to patients with migraine.

Bilirubin has been seen as a toxic waste product since it is product of heme metabolism. However, recent studies have demonstrated that bilirubin possess cytoprotective and strong antioxidant properties [4, 5]. In addition, Vtvicka V et al [6] indicated that bilirubin contributes to influence the expression of Fc receptors in macrophages, which indicates underlying immunomodulatory properties of bilirubin [7]. Of note, bilirubin can reduce production of interleukin-2 in human lymphocytes [8]. Obviously, bilirubin may be an important antioxidant and anti-inflammatory agent. It has been recently shown that serum total bilirubin level can be used to stratify arterial stiffness in patients with coronary artery disease [9]. Moreover, serum bilirubin is associated with glomerular filtration rate, and lower serum bilirubin is considered to be a potential risk factor to determine reduction of kidney function in the general population [10]. Meanwhile, Fuhua Peng and Mehmet Demir et al [11, 12] investigated an association between serum bilirubin and multiple sclerosis (MS), hypertension, and found that MS and hypertension are specifically associated with serum bilirubin. However, in the previous study, no study to investigate the relationship between serum bilirubin and migraine, therefore, the aim of our study is to investigate the association between serum bilirubin concentration and migraine.

Table 1. Serum bilirubin concentration in patients with migraine and healthy controls

	Migraine groups n=120	Healthy controls n=128	*P*-value
Gender (male/Female) [n]	20/100	31/97	0.159
Age [years]	52.65±13.49	53.45±12.47	0.688
Total bilirubin [μmol/L]	9.80±3.90	15.89±5.64	<0.001
Direct bilirubin [μmol/L]	3.35±1.66	4.13±1.33	<0.001
Indirect bilirubin [μmol/L]	6.40±3.37	11.77±5.02	<0.001

Methods and patients

Serum samples were collected from 120 patients with migraine and 128 healthy individuals. Fasting blood was used to measure serum total bilirubin (Tbil) concentration (normal range: 5.5-27.5 mmol/L), serum direct bilirubin (Dbil) concentration (normal range: 0-8.6 mmol/L) and serum indirect bilirubin (Ibil) concentration (normal range: 5.5-18.9 mmol/L). The diagnosis of all migraineurs was made on the basis of international criteria [13]. Individuals with following diseases and/or situations were excluded in our study: cardia-cerebrovascular diseases, hypertension, diabetes, presence of known chronic liver and kidney diseases, infectious diseases, malignant tumor, metabolic syndrome and other diseases that may influence the measure of serum Tbil concentration. The normal range for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) is 9-50 U/L and 15 -40 U/L, respectively. Hence, individuals with abnormal ALT and AST concentration were also excluded in this study. Tbil, Dbil, Ibil, ALT and AST concentration were measured using Roche 8000 automatic biochemical analyzer.

Statistical analysis

The data were showed as means ± SD. We recruited appropriate healthy individuals matching with age and gender of patients with migraine to avoid the effects from gender and age for the measure of serum bilirubin concentration. Difference of measurement data was compared between the two groups using the Student's t test and Mann-Whitney U test in accordance with whether the data were normally distributed using the Kolmogorov-Smirnov test. X^2 test was also used to compare the difference of enumeration data between migraine patients and healthy controls. The data used SPSS16.0 (SPSS Inc, Chicago, IL, USA) statistical software for statistical analysis. P<0.05 was determined as significant.

Results

In patients with migraine, the average serum concentration of Tbil, Dbil and Ibil was 15.89 mmol/L, 4.13 mmol/L, and 11.77 mmol/L, respectively. Tbil, Dbil and Ibil concentration were significantly lower in patients with migraine than healthy controls, as shown in **Table 1**. Tbil, Dbil and Ibil concentration further were grouped by gender in that serum bilirubin concentration main depend on gender although gender was matched between migraine groups and healthy controls, our results showed that Tbil, Dbil and Ibil concentration were also lower in patients with migraine compared with healthy controls, as shown in **Figures 1**-**3**.

Discussion

The level of serum bilirubin is asoociated with various diseases such as MS, hypertension, and CVD [11, 12, 14]. In the present study, we observed lower Tbil, Dbil and Ibil in patients with migraine compared with healthy controls, and found that Tbil, Dbil and Ibil concentration were significantly lower in patients with migraine after those who were stratified by gender.

It has been recently highlighted that serum bilirubin concentration was a significant protector in patients with atherosclerosis [15]. Several lines of evidence attest that the level of serum bilirubin is negative correlation with several adverse factors in patients with coronary artery disease such as smoking, obesity, diabetes and metabolic syndrome [16, 17]. Recently, a prospective study based on 2784 individuals without chronic kidney diseases as a baseline in Japan found that lower serum bilirubin level may be taken into consideration as a potential risk factor of reduction of kidney function [10]. The results of our investigation showed that lower Tbil, Dbil and Ibil concentration in patients with migraine compared with healthy individuals. These founding, in fact, is attribute to strong cytoprotective and antioxidant properties of bilirubin, that it can inhibit oxidative stress and has much stronger antioxidant prop-

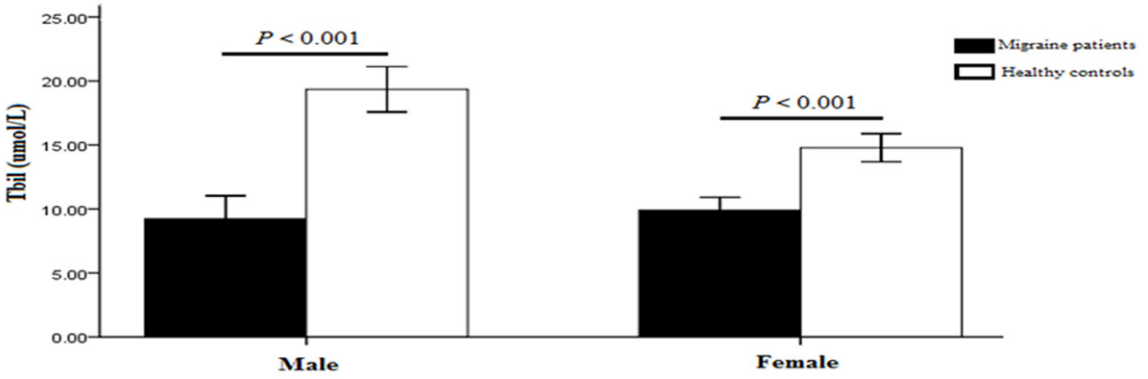

Figure 1. Serum total bilirubin (Tbil) concentration in male and female patients with migraine indicating decreased concentrations in patients with migraine.

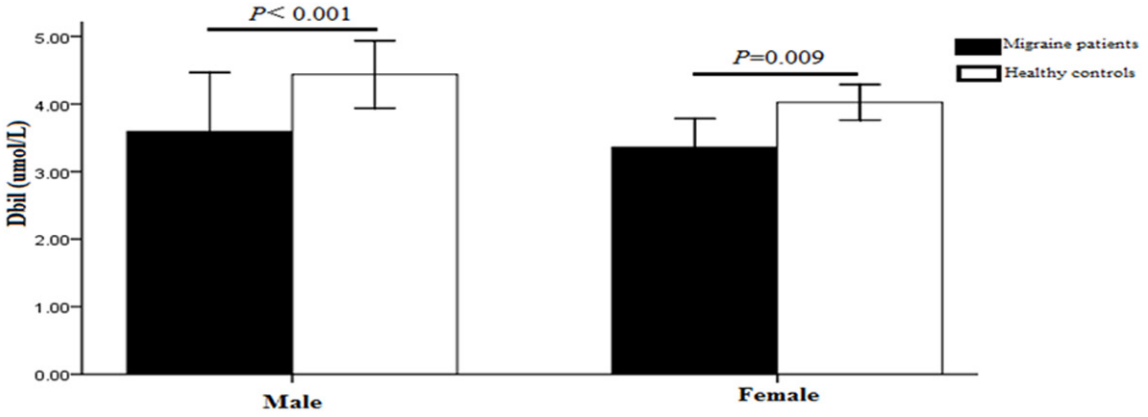

Figure 2. Serum direct bilirubin (Dbil) concentration in male and female patients with migraine indicating decreased concentrations in patients with migraine.

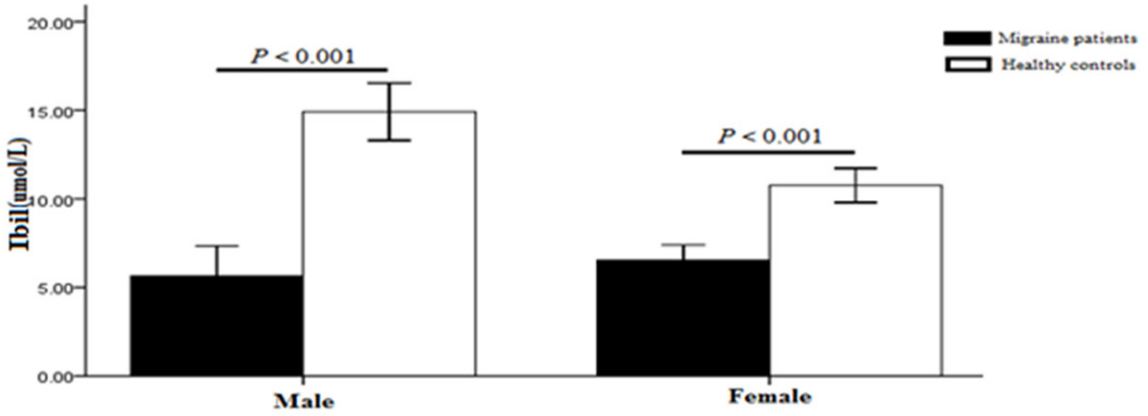

Figure 3. Serum indirect bilirubin (Ibil) concentration in male and female patients with migraine indicating decreased concentrations in patients with migraine.

erties than other antioxidants such as catalase and vitamin E [4, 5]. Importantly, bilirubin is an important endogenous antioxidant and has anti-inflammatory properties, which suppress-

es reactive Oxygen Species (ROS) activity [11, 18, 19]. It has been well documented that the association between migraine and stroke, CVD and atherosclerosis was reported in previous studies [20, 21], revealing neurogenic inflammation and oxidative stress may be a crucial participant in the pathogenesis of migraine [22, 23]. Indeed, several large studies have shown that inflammation plays a significantly role in the pathogenesis of migraine, wherein largely pro-inflammatory cytokines are released and involved in sensitization of nerve endings during migraine [24]. In clinical practice, anti-inflammatory agents also has been considered to be effective medications for patients with migraine [25], obviously, existence of neurogenic inflammation and high oxidative stress during migraine may lead to the lower serum bilirubin concentration.

We are aware, however, that there may be several limitations in this study. First, these findings were limited by small samples, and the present findings should be further replicated in future studies with larger samples. In additional, our study, as a cross-sectional study, serum bilirubin level should be further observed after undergoing anti-inflammation therapy. However, we found evidence that lower serum bilirubin in patients with migraine, serum bilirubin may be a useful marker to estimate neurogenic inflammation in patients with migraine.

Disclosure of conflict of interest

None.

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