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# DIFFERENCES OF LIVER FUNCTION TESTS IN TYPE 2 DIABETES MELLITUS PATIENTS WITH AND WITHOUT CORONARY ARTERY DISEASE

Hendra Saputra<sup>1</sup>, Burhanuddin Nasution<sup>1</sup>, Santi Syafril<sup>2</sup>

<sup>1</sup>Department of Clinical Pathology, Faculty of Medicine, North Sumatera University/Adam Malik Hospital, Medan, Indonesia. E-mail: [h.saputra12@gmail.com](mailto:h.saputra12@gmail.com) <sup>2</sup>Department of Internal Medicine, Faculty of Medicine, North Sumatera University/Adam Malik Hospital, Medan, Indonesia

## ABSTRACT

One of the macroangiopathic complications of Diabetes Mellitus (DM) is Coronary Arterial Disease (CAD). Several studies showed that the liver was one of the organs involved in the pathological development of diabetes. The aim of this study was to find the differences of liver function in type 2 DM patients with CAD and without CAD. This was an analytical observational study with cross-sectional design. Forty-four type 2 DM patients with and without CAD at the Adam Malik Hospital Medan who came during June - August 2016 were studied for liver function (total bilirubin, direct bilirubin, AST and ALT). In this study, the average values of total bilirubin and direct bilirubin level in patients with CAD were found to be lower than without CAD. Statistically a significant difference revealed a total bilirubin ( $p < 0.001$ ) and direct bilirubin ( $p = 0.001$ ) in type 2 DM patients with and without CAD. There was a significant difference in liver function tests in DM type 2 patients with, and without coronary arterial disease, these data suggested that total bilirubin and direct bilirubin levels in type 2 DM patients with CAD were found lower than those without CAD.

**Key words:** Type 2 diabetes mellitus, coronary arterial disease, liver function

## INTRODUCTION

Diabetes mellitus is a group of carbohydrate metabolism disorders. Under this condition, glucose will undergo over production and become underutilized causing hyperglycemia due to insulin secretion disorder, insulin inactivity or both.<sup>1</sup>

In 2013, the International Diabetes Foundation (IDF) stated that 3,82 million patients lived with DM worldwide. Diabetes mellitus cases is estimated to be increased to 5.92 million. In 2035, 1.75 million people out of 3,82 million people with DM will be undiagnosed making them prone to progress into complications.<sup>2</sup>

The prevalence of DM patients in Indonesia is in the seventh rank, after India, USA, China, India, Brazil, and Mexico. The World Health Organization predicted that DM patients in Indonesia will increase from 8.4 million in 2000 to 21.3 million in 2030.<sup>3</sup>

Diabetes mellitus is followed by acute and chronic complications. Acute complications consist of Diabetic Ketoacidosis (DKA), Hyperglycemic Hyperosmolar State (HHS) and hypoglycemia. Chronic complications are divided into microangiopathy and neuropathy. Microangiopathy complications comprised cardiovascular disorders e.g. coronary heart disease, cerebrovascular disorder, peripheral blood vessel disorder.<sup>4</sup> A WHO international survey showed that the prevalence of coronary heart disease and DM was 26-35%, with females and elderly having a higher prevalence and wide heterogeneity.<sup>5</sup>

Many researchers reported the liver function involvement in DM development, but no further research showed which enzyme played the best DM progression marker.<sup>6</sup>

This research aimed to know the difference of liver enzyme examination in serum, specifically total bilirubin, direct bilirubin, AST and ALT in DM type 2 patients with and without CHD.<sup>7</sup>

## METHODS

This was an observational analytical research with cross-sectional design comprising 44 type 2 DM patients with and without CHD who received treatment at the Adam Malik Hospital, Medan since June until August 2016 and who met the inclusion criterias. The 44 type 2 DM patients were grouped into 22 patients diagnosed as type 2 DM with CHD and 22 patients diagnosed as type 2 DM without CHD.

The ethical clearance for this research was approved by the medical research committee, Medical Faculty of USU at the Adam Malik Hospital, Medan. Written informed consents were obtained. History, physical examination were done and the results were reported in the research status. Blood was obtained by Venoject as much as 5 mL and put in a citric acid anticoagulant tube. The blood was centrifugated at 3,000 rpm for 10 minutes to obtain the serum. Total bilirubin, direct bilirubin, ALT and AST examinations were performed by automated photometry method ARCHITECT Plus analyzer.

Data analysis was performed to evaluate the characteristics of type 2 DM patients with and without CHD. The characteristic differences of type 2 DM with, and without CHD were presented in tables and description. The differences of liver functions in type 2 DM patient with and without CHD were analyzed by unpaired-T test if the data distribution was normal. The Mann-Whitney U test was used if the data distribution was non-normally distributed. P-value <0.05 was considered to be statistically significant. The data analysis was done by SPSS program.

## RESULT AND DISCUSSION

The 44 patients with type 2 DM participating in this study ranged from 37 until 86 years old. Study participants were grouped into 2 groups i.e. 22 patients diagnosed as type 2 DM with CHD and 22 patients diagnosed as type 2 DM without CHD. Most the study participants were males (30 patients).

**Table 1.** Subject characteristics based on the age and sex

Characteristics	Type 2DM		P value
	Without CHD	With CHD	
n (person)	22	22	
Sex			
Male (person) %	16 (72.7%)	14 (63.6%)	0.216
Female (person) %	6 (27.3%)	8 (36.4%)	
Age			
mean±SD (years)	61.91±9.081	60.32±11.370	0.603
HbA1c	8.05	8.35	
median(min-max) (%)	(6.1-13.6)	(6.5-10.9)	0.851

The differences were statistically significant if the p-value was <0.05 the differential test was performed by unpaired t-test.

Table 1 showed that the mean age of the type 2 DM patients without CHD was 61.91±9.081 years old. That mean age was older than patients with CHD who had a mean value of age as 60.32±11.370 years old. No significant difference of the age between the two groups was found. The gender data of the two groups showed no statistically significance difference with p-value <0.216.

Total and direct bilirubin median value in type 2 DM patients with CHD was higher compared to type 2 DM patients without CHD. Statistical analysis results showed that

the total and direct bilirubin levels in type 2 DM patients with without CHD group with p-value of p<0.001 and p<0.001 respectively. However, there was no statistically significant difference in AST and ALT parameters between the two groups with p-value 0.832 for AST and 0.088 for ALT.

Diabetes mellitus can cause some complications, such as liver function disorders. There were obvious correlations between diabetes and liver injury. The liver plays a pivotal role in carbohydrate balance regulation. This regulation causes that the liver function of patients with metabolic disorder especially DM, are more susceptible to be disturbed. Hepatocellular glycogen accumulations cause hepatomegaly, and liver enzyme disorder in uncontrolled DM.<sup>8</sup>

In hyperglycemic condition, there is intracellular glycogen accumulation in the hepatocytes that cause glycogen synthesis increase. This accumulation causes aminotransferase to increase with or without alkaline phosphatase increase. Those disorders and the hepatomegaly condition can become normal again if the glucose level has been controlled.

In the past, bilirubin was only considered as the end product of heme catabolism. Nowadays, bilirubin has been known as an endogenous antioxidant and anti-inflammation. There have been many researches who reported that the increase of bilirubin was associated with a decrease of CHD risk. Billirubin effectively holds lipid and lipoprotein oxidations, also against plaque, and arteriosclerosis formations.<sup>9</sup>

In addition, bilirubin protects lipid against oxidation more effectively compared to other hydrophilic antioxidants such as glutathione. Bilirubin has been demonstrated to be 30 times better in preventing Low Density Lipoprotein (LDL) than the vitamin E analogue, trolox which is a lipid soluble antioxidant. The most important is that serum total bilirubin acts as the main antioxidant in plasma. The latest study reported that total bilirubin in serum had anti-inflammation effects.<sup>10</sup>

Serum total bilirubin was first reported to be correlated with CHD in 1994. A low level of serum total bilirubin was associated with an increased CHD risk, while a high normal level was associated with a decreased CHD risk. Serum total bilirubin concentration inversely associated with CHD severity both in males and females.<sup>11</sup>

Another research involving 398 males and 239 females reported that serum total bilirubin was closely related with

**Table 2.** The subject differences based on laboratory examination results

Characteristics	Type 2 DM		p value
	With CHD	Without CHD	
n (person)	12	12	
Total bilirubin (mg/dL)			
{median(min-max)}	0.65(0.5-1.0)	0.3(0.1-0.7)	<0.001^
Direct bilirubin (mg/dL)			
{median(min-max)}	0.2(0.2-0.7)	0.1(0.1-0.4)	<0.001^
AST(IU)			
(median(min-max))	21.5(15-53)	22(10-48)	0.823^
ALT (IU)			
(median(min-max))	26(12-85)	21.5(8-53)	0.088^

Statistically difference if the p-value was < 0.05, the differential study used Mann-Whitney U test.

Coronary Artery Calcification (CAC). Serum total bilirubin 1  $\mu\text{mol/L}$  increase would decrease 14% CAC score  $>4.00$  after addition of other few main risk factors.<sup>12</sup>

This recent study showed that total and direct bilirubin levels in type 2 DM patients with CHD were higher compared to patients with type 2 DM without CHD. Statistical analysis result showed significant differences between type 2 DM patients with and without CHD in total bilirubin (p-value  $<0.001$ ), but no significant differences in ALT and AST in both groups with a p-value of 0.823 and 0.088, respectively.

Ramesh's study reported total protein, albumin, globulin, ALT, AST, total bilirubin and direct bilirubin as predictors of CHD in type 2 DM. Fifty patients out of 100 patients were type 2 DM with CHD and the rest were type 2 DM without CHD. There were significant differences between those two groups in total bilirubin, direct bilirubin, indirect bilirubin, total protein, albumin, ALT, AST and HbA1c. This research showed that a decrease of serum bilirubin could increase CHD risk in type 2 DM patients and also a reverse correlation between HbA1c and bilirubin.<sup>13</sup>

Schwertner *et al.* reported that plasma bilirubin concentration had a inverse correlation with CHD. Hopkin *et al.* also reported that the bilirubin level in CHD patients was lower compared to normal subjects, which showed that the bilirubin level was low in type 2 DM patient with CHD compared to DM2 without CHD.<sup>14</sup>

## CONCLUSION AND SUGGESTION

This present study revealed that total bilirubin and direct bilirubin levels were statistically significantly lower in type 2 DM patients with CHD compared to type 2 DM patient without CHD. However, ALT and AST levels showed no significant difference in type 2 DM with and without CHD.

A further research with a larger sample number, longer research time and stricter selection is needed, so that the research results can be more representative.

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