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CLOPIDOGREL AND LIVER INJURY IN DIABETIC PATIENTS

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ABSTRACT

Inhibition of platelet activation with antiplatelet therapy is central to the management of acute coronary syndromes (ACS), especially in cases where percutaneous coronary intervention (PCI) is performed. Clopidogrel is a second-generation thienopyridine that selectively inhibits the adenosine diphosphate (ADP) P2Y12 receptor. The present study was aimed to compare the effect of clopidogrel on hepatic function in the presence or absence of diabetic. sixty patients with coronary artery disease and twenty control subject were included in this study. All patients received a dose of 75 mg/day of clopidogrel. Of whom thirty patients were diabetic and other thirty patients were non-diabetic. Liver function tests were measured and studied for patients and control. Liver function tests in diabetic and non-diabetic coronary disease patients showed high significant elevation ($P<0.001$) in mean serum total alkaline phosphatase and gamma-glutamyl transferase and significant elevation ($P< 0.05$) in mean serum direct bilirubin compared with control mean. Whereas insignificant elevation ($P>0.05$) appeared in mean serum total bilirubin, alanine aminotransferase, aspartate aminotransferase, and total protein in relation to control mean. In conclusion, diabetes is not associated with an increased incidence and severity of clopidogrel induced liver injury.

KEYWORDS: Clopidogrel; diabetic; liver function tests.

1. INTRODUCTION

Antiplatelet agents are the main stay of treatment to prevent and manage athero- thrombotic events.[1] Furthermore, new antiplatelet regimens overcoming many limitations of standard-dose clopidogrel were proven to further improve clinical outcomes.[2]

Clopidogrel is an oral pro-drug converted after intestinal absorption and liver passage into an irreversible inhibitor of the $P2Y_{12}$ adenosine–diphosphate platelet receptor. Whereas over 10 Million patients are currently under treatment with clopidogrel, Response to clopidogrel is highly variable and often delayed, thus requiring increased loading doses.[3]

1.1 Patients and Methods

Sixty patients, (30 females, 30 males) their ages ranging from (45-65) year, with coronary heart disease diabetic and non-diabetic. In addition to 20 control subject (10 females, 10 males) aged (40-60) year recruited from Ibn-Albitar Center for Cardiac Surgery.

Diagnoses are made based on clinical symptoms and biochemical tests. Patients with liver disease, renal failure and heart failure have been excludd. Blood samples are aspirated to measure serum levels of liver function tests by Photometric Colorimetric test.

All serum samples were obtained after receiving patients' informed consent and followed a standardized protocol. Results are shown as mean ± SD with 95% confidence interval (CI) and *P* values of 0<0.05 were regarded to be statistical significant. All statistical analyses were performed using SPSS version 16.0.

1.1.1 RESULT

The current results of liver biochemical tests showed high significant increases ($P<0.001$) in mean serum levels of alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) and significant increase ($P< 0.05$) in mean serum level of direct bilirubin for diabetic and non-diabetic patients compared with control mean.

Whereas insignificant changes ($P > 0.05$) were appeared in mean serum levels of total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total protein for diabetic and non-diabetic patients in relation to control mean.

Moreover, insignificant differences ($P > 0.05$) were clarified in mean liver function tests between diabetic and non-diabetic patients as shown in (Table 1; Figure 1 and 2).

Table -1: Liver enzymes and biochemical characteristics for the studied groups.

	Control	***N***on-***D***iabetic patients	***D***iabetic patients	***P-value***		
				ND *vs.* C	**D *vs.* C**	**D *vs.* ND**
-number	20	30	30			
-Serum total bilirubin (mg/dl)	0.85 ±0.3	0.9 ±0.45	0.95 ±0.65	NS	NS	NS
-serum direct bilirubin (mg/dl)	0.21 ±0.11	0.36 ±0.28	0.41 ±0.35	S	S	NS
-serum ALT (IU/L)	32.8 ±3.8	34.23 ±2.05	34.7 ±1.78	NS	NS	NS
-serum AST (IU/L)	32.5 ±3.5	34.42 ±2.3	33.67 ±2.5	NS	NS	NS
-serum ALP (IU/L)	76.7 ±20.3	168.78 ±37.6	175.2 ±40.3	HS	HS	NS
-serum GGT (IU/L)	28.7 ±15.8	46.14 ±21.8	44.36 ±20.07	HS	HS	NS
-serum total protein (g/dl)	6.8 ±1.5	7.28 ±0.77	7.03 ±0.86	NS	NS	NS

NS=Non-Significant differences (*P>0.05*); S=Significant differences (*P<0.05*); HS=high Significant differences (*P<0.001*); ND=non-diabetic; D=diabetic; C=control; *vs.*=versus.

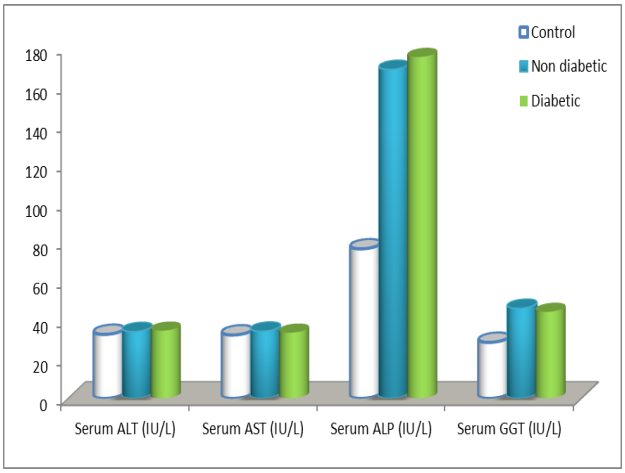

Figure -1: The mean serum levels of ALT, AST, ALP and GGT for control, non-diabetic and diabetic patients

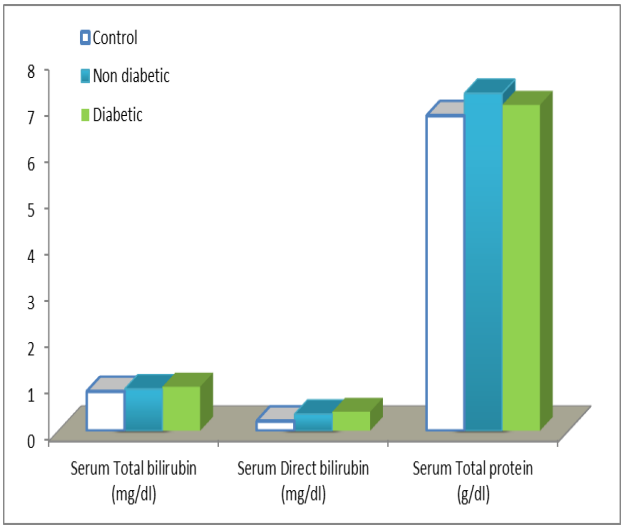

Figure -2: The mean serum levels of total bilirubin, direct bilirubin and total protein for control, non-diabetic and diabetic patients.

1.1.2 DISCUSSION

Platelet activation and aggregation play a central role in atherothrombotic vascular disease.[4] Platelets are exposed to the sub-endothelial matrix at the sites of athero-sclerotic plaque rupture, allowing adhesion to matrix proteins including collagen and von Willebrand factor Activation of the platelets by these interactions results in release of adenosine 5′-diphosphate (ADP) which can induce secondary platelet activation and aggregation through ADP-induced platelet activation via the G-protein linked $P2Y_{12}$ and $P2Y_1$ receptors, further amplifying and propagating platelet activation induced by the primary activators.[5]

Activated platelets are recruited to sites of coronary plaque rupture forming aggregates that may lead to platelet-rich thrombi, vascular occlusion, tissue ischemia and necrosis in what is collectively known as acute coronary syndrome.[6]

A number of studies have demonstrated the effectiveness of the thieno- pyridines, a class of $P2Y_{12}$ ADP receptor antagonists, of which the most commonly used is clopidogrel, in improving clinical outcomes in patients with ACS and those undergoing percutaneous coronary intervention.[7]

Clopidogrel is a prodrug which, following oral administration, is metabolized to an active metabolite that binds to and irreversibly antagonizes the platelet Gi-linked $P2Y_{12}$ class of ADP receptors.[8] Clopidogrel is currently the thienopyridine of choice due to its more favorable safety profile compared with the first approved thienopyridine, ticlopidine. However, there are reported limitations of clopidogrel therapy, namely variability in antiplatelet effects and a relatively slow on set of action.[9]

Epidemiological and animals studies suggested that

diabetes is associated with an increased incidence of acute liver failure and severity of drug induced liver injury.[11]

In a prospective study of Chalasani, *et al*., in 2008, diabetes mellitus was reported to be an independent risk factor for severe drug induced liver injury[10], these finding consistent with the result of current study at which an insignificant differences in mean serum levels of liver function biomarkers were clarified between diabetic and non-diabetic patients with coronary artery disease and taking clopidogrel therapy.

1.1.3 CONCLUSION

Diabetes is not associated with an increase incidence and severity of clopidogrel induced liver injury.

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