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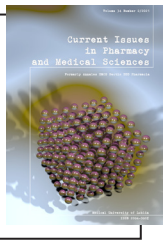

Treatment modality, diabetic control and blood homeostasis in type 2 diabetes mellitus patients in Basra

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ABSTRACT

This study is aimed at investigating the relationship between treatment modality, glycemic control and blood homeostasis as represented by prothrombin time (PT) and activated thromboplastin time (APTT) in T2DM patients. Sixty-four type 2 diabetic patients (40 males and 24 females) on metformin or insulin or both for not less than six months of ages between 20 and 75 years were selected during their visit to Diabetes Endocrine and Metabolism Centers in two General Hospitals in Basra. Socioeconomic characteristics and treatment plans were recorded. Glycated haemoglobin (HbA1c), lipid profiles and hematological parameters measured in blood samples were taken. Lower mean HbA1c ($p = 0.0383$) was found in patients on metformin alone, higher percentage of hemoglobin was found in patients on insulin treatment, and higher levels of LDL ($P = 0.0018$) and HDL ($P = 0.0241$) in patients on metformin and insulin. Treatment manner had no effect on mean PT or APTT, however, there was a significant inverse correlation of PT with LDL ($P = 0.0042$), and a direct correlation of APTT with HbA1c ($p = 0.0209$) and an inverse correlation of APTT with platelets count ($P = 0.0324$) in patients on insulin treatment. In addition, there was a significant direct correlation of APTT with triglycerides (TG) ($P = 0.0069$) in patients on metformin treatment. In conclusion, lower mean of HbA1c was found only in patients receiving metformin drug alone, higher Hb percentage were found in patients treated with insulin alone, higher LDL and higher HDL levels were found in patients treated with both metformin and insulin for at least six months. Treatment manner had no effect on mean PT or APTT and further studies are needed to bring about understanding of diabetic control and blood homeostasis.

INTRODUCTION

Worldwide, about 5.0 million people died from diabetes mellitus (DM) in 2015. This corresponds to one death every six seconds [1]. Thrombosis is the main cause of death in patients with DM, indeed, around two thirds of all diabetic patients eventually die from thrombotic diseases [2].

In Iraq, a high rate of incidence of diabetes has been documented. T2DM includes a broad variety of elevated glucose level conditions because of insulin resistance. Comparative deficiencies of insulin secretion and hepatic insulin resistance cause an elevation of gluconeogenesis and a reduction of glycogen synthesis [3]. T2DM is associated with enhanced triglycerides (TG), low-density lipoprotein cholesterol (LDL), C-reactive protein (CRP) and plasminogen activator inhibitor-1 (PAI-1) levels. In addition, it is accompanied by low high-density lipoprotein cholesterol (HDL) levels [4].

Metformin is an insulin sensitizer belonging to the biguanide class of drugs. It increases the sensitivity of liver and peripheral tissues to insulin and reduces hepatic glucose production. It is commonly used as the first-line treatment for T2DM patients, as previous study has stated that metformin reduces diabetes-associated thrombotic complications [5]. However, whether metformin can prevent thrombosis effectively is unknown – nor is its possible mechanism of action. In addition, whether metformin is effective against thrombosis in both diabetic and non-diabetic individuals is not known.

This study was carried out to estimate the possible effect of long-term use of Metformin or insulin or both on glycemic control and blood homeostasis as represented by prothrombin time (PT) and activated thromboplastin time

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(APTT) in T2DM patients – as APTT and PT, as well as platelet counts are hematological indicators for patient coagulation states [6].

SUBJECTS AND METHODS

This study was conducted during the period from February to May 2019. Sixty-four type 2 diabetic patients (40 males and 24 females) on metformin or insulin or both for not less than six months and between ages between 20 and 75 years were selected during their visit to the Diabetes Endocrine and Metabolism Centers in two General Hospitals in Basra.

The patients were placed into three groups. The first group (M) consisted of 20 patients on metformin therapy, the second group (MI) consisted of 25 patients on metformin and insulin therapy and the third group (I) was of patients undergoing insulin therapy alone. Patients were excluded from the study if they were type 1 diabetic patients or if they have any cognitive problems. Socioeconomic characteristics and treatment plans were documented. Fasting blood samples were obtained to determine glycated haemoglobin (HbA1c) and lipids profile. In addition, hematological tests (PT, APTT, INR, Hb (%) and platelets count) were undertaken. Here, HbA1c level of 7% or less indicates sufficient glycemic control, while HbA1c level of more than 7% demonstrates a reduced glycemic control – as stated within the American Diabetic Association guidelines [7].

Laboratory investigations

Glycated hemoglobin (HbA1C) was measured by means of D-10 Dual Program (Bio-Rad Laboratories, Inc., Hercules, CA 94547, 220-020, California; USA). The D-10 Dual Program is based on chromatographic separation of the analytes by ion exchange (HPLC). Patient serum lipid profile (cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL) and high-density lipoprotein cholesterol (HDL) levels) were determined by applying enzymatic methods (Dimension Vista 1500T Intelligent Lab System from Siemens Company-Germany) at the laboratory of biochemistry. PT and APTT were assayed through standard clotting methods by using a BIOLABO Kit (France), according to company instructions.

Statistical analysis

Statistical analysis was performed by means of GraphPad Prism software (version 7.0, GraphPad Software, Inc., San Diego, CA). Descriptive statistics such as mean ± standard deviation (SD), were established for all evaluated parameters. ANOVA (and non-parametric analysis) was applied to perform comparison between groups. Pearson's correlation coefficients were used to estimate the associations between variables. Here, p values of less than 0.05 were considered as significantly different.

RESULTS

Sixty-four type 2 diabetic patients (40 males and 24 females) of ages between 20 and 75 years, on metformin or insulin or both for not less than six months were included in this study. Lower mean HbA1c (p=0.0383) was found in the group M patients (on metformin treatment at least six months). In this group, the dose of metformin ranged between 500 to 1000 mg/day. Higher Hb (%) was found in group I patients (on insulin treatment at least six months). Higher LDL (P=0.0018) and higher HDL (P=0.0241) levels were noted in the MI group patients (on metformin and insulin treatments at least six months) (Table 1).

Table 1. Measured haematological and biochemical tests (Mean ± STDEV) of type 2 DM patients in long-term treatment with: metformin only (group M), metformin and insulin (group MI) and Insulin only (group I)

Variables	Groups (Mean ± SD)			P value
	M (n=20)	MI (n=25)	I (n=19)	
Age (years)	54.2±7.4	57.4±9.9	50.9±18.3	0.2349
Sex (M/F)	6/14	11/14	7/12	
HbA1C (%)	8.1±1.5	9.2±1.7	9.2±1.4	0.0383*
PT (sec)	14.8±1.7	14.5±1.7	15.7±1.3	0.0677
PTT (sec)	37.2±7.0	33.0±6.5	33.7±4.5	0.0669
INR	1.1±0.2	1.05±0.07	1.06±0.1	0.4288
Hb (%)	12.1±1.6	12.4±1.5	13.3±1.0	0.0264*
Platelets count	285.8±68.8	261.9±88.5	294.9±65.2	0.3323
Cholesterol	5.5±1.1	5.3±1.2	5.6±1.5	0.7249
Triglycerides	3.0±1.5	3.3±2.1	3.6±2.2	0.6372
LDL	1.5±0.7	1.9±0.6	1.3±0.1	0.0018**
HDL	1.3±0.3	2.4±2.3	1.4±0.3	0.0241*

HbA1c: glycated haemoglobin; PT: prothrombin time; PTT: partial thromboplastin time; INR: international normalized ratio; Hb: haemoglobin; LDL: low density lipoprotein; HDL: high density lipoprotein.*, ** Statistically significant values (significance P <0.05) (significance P<0.05)

Treatment manner had no effect on mean PT or APTT, however, there was a significant inverse correlation of PT with LDL (P=0.0042), direct correlation of APTT with HbA1c (p=0.0209) and inverse correlation of APTT with platelets counts (P=0.0324) in the third group of patients (on insulin treatment at least six months). In addition, there was a significant direct correlation of APTT with TG (P=0.0069) in the first group (M) of patients (Table 2).

Table 2. Correlations between PT and PTT with HbA1c, lipid profile and hematologic parameters in type 2 DM patients in long term treatment with: metformin only (group M), metformin and insulin (group MI) and Insulin only (group I)

	PT			APTT		
	M (n=20)	MI (n=25)	I (n=19)	M (n=20)	MI (n=25)	I (n=19)
HbA1c	r=-0.05158 p=0.8290	r=-0.2667 p=0.1975	r=0.09842 p=0.6885	r=0.4158 p=0.0683	r=-0.102 p=0.6275	r=0.5253 p=0.0209*
Hb	r=-0.06573 p=0.7831	r=0.05202 p=0.8049	r=-0.06543 p=0.7901	r=0.1436 p=0.5459	r=0.1245 p=0.5532	r=0.4282 p=0.0674
Platelets	r=-0.1018 p=0.6692	r=0.06154 p=0.7701	r=0.1807 p=0.4592	r=0.2566 p=0.2747	r=0.2814 p=0.1730	r=-0.492 p=0.0324*
Cholesterol	r=-0.2506 p=0.2865	r=0.00264 p=0.9900	r=0.2823 p=0.2416	r=0.05481 p=0.8185	r=-0.1857 p=0.3741	r=-0.1205 p=0.6231
TG	r=0.1096 p=0.6455	r=-0.04515 p=0.8303	r=0.05924 p=0.8096	r=0.5833 p=0.0069*	r=-0.4464 p=0.8322	r=-0.1268 p=0.6050
LDL	r=0.2167 p=0.3568	r=-0.1893 p= 0.3648	r=-0.6254 p=0.0042*	r=-0.1379 p=0.5620	r=0.01125 p=0.9574	r=-0.2115 p=0.3847
HDL	r=0.1881 p=0.4271	r=-0.1386 p=0.5089	r=0.1648 p=0.5003	r=-0.2644 p=0.2599	r=0.08819 p=0.6751	r=-0.2746 p=0.2552

HbA1c: glycated haemoglobin; PT: prothrombin time; PTT: partial thromboplastin time; Hb: haemoglobin; TG: Triglycerides; LDL: low density lipoprotein; HDL: high density lipoprotein. *Statistically significant values

DISCUSSION

This study was designed to investigate the association between treatment modality, glycemic control and blood homeostasis as represented by prothrombin time (PT) and activated thromboplastin time (APTT) in T2DM Iraqi patients receiving metformin or insulin or both. Diabetes mellitus is associated with many complications. Hyperglycemia, increased blood pressure, oxidative stress, dyslipidemia and inflammation are all features of T2DM, and are risk factors in the development of vascular complications [8-11]. Diabetes control helps to decrease the risk of these complications.

Most of the diabetic patients involved in this study were glycemic uncontrolled regardless of which drug treatment used. This study discovered that lower mean of glycated hemoglobin (HbA1c) was more common in patients receiving metformin drug alone, when compared with patients on metformin with insulin or on insulin alone, however, the mean HbA1c was 8.1, which is still higher than the normal HbA1c values, and the dose of metformin ranged between 500 to 1000 mg/day.The results also revealed higher Hb (%) in patients treated with insulin alone, this result is consistent with a previous study on insulin that noted that insulin analogs alleviate the decline of haemoglobin in diabetic patients with impaired renal function [12].

Furthermore, higher LDL and higher HDL levels was found in patients treated with a combination of metformin and insulin for at least six months, when compared to patients treated with metformin alone or insulin alone. This finding, to the best of our knowledge, is novel.Treatment manner had no effect on mean PT or APTT; however, there was a significant inverse correlation of PT with LDL, direct correlation of APTT with HbA1c and inverse correlation of APTT with platelets counts in patients treated with insulin for at least six months. In addition, there was a significant direct correlation of APTT with TG in patients treated with metformin for at least six months. These findings are consistent with a recent study on the impact of glycemic control on lipid metabolism and coagulation in pregestational (PGDM) and gestational (GDM) diabetes women treated with insulin; they concluded that poor glycemic control influences both lipid profile and the coagulation of blood [13].

Moreover, we found it notable that different types, dosage forms and duration of metformin, insulin and combined drugs used, in addition to the variety of the populations evaluated may determine the effects on hemostasis. Thus, it would be motivating to extend research to non-diabetic patients using metformin, such as patients with polycystic ovary syndrome [14] or patients with obesity [15], to investigate the effect of metformin on blood homeostasis in non-diabetic patients.

CONCLUSION

Lower mean of HbA1c was found in patients receiving metformin drug alone, higher Hb (%) was noted in patients treated with insulin alone, higher LDL and higher HDL levels was indicated in patients treated with both metformin and insulin for at least six months. Treatment manner had no effect on mean PT or APTT, and further studies are needed to understand the connection between diabetic control and blood homeostasis.

AUTHOR'S CONTRIBUTION

None.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

No data used to support this study is available.

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