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THE EFFECT OF METFORMIN AND GLIMEPIRIDE ON PLATELET COUNT AND INDICES AMONG DIABETIC PATIENTS WERE ATTENDING JABER ABU ALIZ DIABETIC CENTER IN KHARTOUM STATE

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Abstract

Background: Diabetes mellitus (DM) is a global pandemic, Platelets have crucial role in accelerated atherosclerosis and thrombosis which characterize DM.

Aim: The aim of the study was to detect the effect of two major oral hypoglycemic drugs (Metformin and Glimepiride) on platelet count and indices{ MPV (Mean platelet volume), PLCR (platelet large cell ratio),PDW (platelet distribution width)}.Beside, to studythe effects of variation induration of the drug, dose of drug, HbA1C level and associated complications.

Material and methods: A case control study was performed 146subjects 50 were using metformin, 46 were using Glimepiride in addition to 50 apparently healthy non-diabetic matching for age and sex subjects have been tested as control group.

EDTA anti-coagulated venous blood samples has been taken from eachsubject , platelet count and indices were measured using automatic blood counter (Sysmex KX-21N) and HbA1C was Measured using Ichroma II . Statistics was performed by SPSS (version 22).

Results: The results showed that both types of treatment (Metformin, Glimepiride)have reduced the platelets indices but the reduction in Glimepiride was insignificant except in PDW when comparedwith controls. Also both treatments have no effect on platelet count and there was insignificant variation between different doses of metformin and Glimepiride.Glimepiride diabetic patients from 15 to 20 yearshave increased platelet count in contrast to patients whom used glimepiride for less than 15 years.there was increased platelet count and decreased platelet indices in patients with foot ulcers whom using glimepiride than patients without complications. Also increased platelet indices in patients with HbA1C level less than 6% in contrast to those with HbA1C more than 7%.

Conclusion: It is concluded that both types of drugsreduce platelet indices. Glimepiride have a good prognostic effect on the Pro-thrombotic state and accelerated atherosclerosis which is associated with type 2 study population because the platelet indices were insignificant compared withcontrols.

Keywords: Diabetes Mellitus, Metformin, Glimepiride, platelet count and indices

Introduction

DM is a chronic disease characterized by increased blood glucose level[(1).] Approximately 90-95% of diabetic patients are type 2 DM which is caused by insulin resistance [(2)]. Chronic complications of DM are vascular or nonvascular. Vascular complications are further subdivided into macrovascular (coronary artery disease, peripheral vascular disease, and cerebrovascular disease) or microvascular (retinopathy, neuropathy, and nephropathy)[(2,3)].

Automated blood counters rapidly measure Platelet count and indices (MPV, PDW, and P-LCR) which are features of platelet activation. MPV determine the platelet volume and reported by analyzing the platelet distribution curve, PDW is an indicator for variation in the platelet size and it is calculated at 20% relative height in platelet size distribution curve. P-LCR is discriminate of the circulating

larger platelets (> 12 fL), which is measured by fixed discriminator at12 fL and reported as percentage [4].

The platelets have important roles in normal homeostasis and atherosclerosis process [3, 5]. MPV is increased in patients at a high risk for athero-thrombotic diseases [6]. DM has been considered as a 'prothrombotic state' with increased in thrombocytes reactivity [7, 8]. MPV is increased in patients with type 2 DM [9] Researchers also found that PDW and PLCR were all increased in diabetic patients. PDW was increased in those withcomplications in contrast to those without microvascular complications of DM [8]. An increased MPV is a risk marker for platelet activation [6].

However, whether oral hypoglycemic drugs (Metformin and Glimepiride) can effectively prevent thrombosis or reduce Microvascular and Macrovascular complications or not there is no published study on the effect of diabetes mellitus hypoglycemic drugs on platelets count and indices among Sudanese population.

This study was conducted to explore the effect of diabetes mellitus treatments (Metformin and Glimepiride) on platelet count and indices (MPV, PLCR, PDW).Beside the effect of dose and duration of the drug used , associated complications, HbA1C level were also explored.

Materials and Methods

A case control study was carried out on a group of 146Sudanese subjects 50 diagnosed with Type 2 diabetes and they were under Metformin and 46 wereunder Glimepiride treatment who attended Jaber Abu Aliz Diabetic Center in Khartoum State during the period of 6 months from March to September 2020 .An age, and sex-matched control group consisting of 50 apparentlyhealthy control were also tested . Excluding Non-Sudanese ,Subjects with renal failure, cancer, hepatic ,malaria infected or treated patients in last 7days, hematological disorders, pregnancy and a history of drug used affect platelets count or indices (aspirin, warfarin, heparin, statin, anticoagulant medications) and those younger than 18 years were excluded from the study.

Approvals have been taken from Khartoum State Ministry of Health Research Department, and verbalconsent has been taken from each participant volunteer. The samples have collected from participants under COVID 19 outbreak Precautions by administered written questionnaire.

On 5 ml EDTA anti coagulated venous blood sample, platelet count and indices were measured by automatic blood counter (Sysmex KX-21N) for type2 DM patients and controls, and also HbA1Cwas measured by I chroma II for DM patient's blood samples.

Statisticalanalysis was performed by statistical package for the social sciences (SPSS) version 22, independent sample t-test for comparisons between two groups, differences based on patient characteristic measurements were analyzed by one-way analysis of variance (ANOVA) for more than two groups. The findings were mean ± standard mean ageof 56.4 years oldtaking diffferent dosesdeviation. And the P-value <0.05 was considered statistically significant.

Result

DM patients under Metformin hypoglycemic drug and DM patients under Glimepiride were categorized into groups according to diabetes chronic complications, dose per day, duration of Metformin or Glimepiride used and the level of Hb A1C.

patients using Metforminwere26 females and 24 males with mean age of 55.4years old,22% of them were use 500 mg and 78% taking 850 mg Metformin.Patients onGlimepiride were27 females and 19 males and 27 females with (2mg=17.3%, 3mg=10.9%, 4mg=65.2%, 5mg=6.6%).

drugs durations were divided in to less than 5, 5-10 ,< 10-15, <15-20 and more than 20 years their percentages were [Metformin=(30%, 36%, 12%, 14%, 8 %), Glimepiride=(44%, 39%, 9%, 7%, 2%)],respectively.According to the presence of associated complications in Metformin's and Glimepiride's study populations 10% and 4%, were with retinopathy , 20% and 40% with foot ulcer and patients with no detected complications were 70%, 56 %, respectively.

DM Patients with HbA1C less than 6% were 15% , 6-7%, were 16% and more than 7% were 69%.

The mean , standard deviation and P-value of the measured platelet count and indices of the Metformin and Glimepiride study population compared to the control group are shown in table (1)and(2)respetviely. Glimepiride and Metformin were population were compared in table (3)

Table 1: Comparison in platelet count and indices between Metforminstudy subjects and control group

Parameters	Mean Metformin ± SD	Mean Non diabetes ± SD	p.value
Platelet count(x10^9/ l)	319.2±138.6	280.1±77.7	.087
MPV (fl)	9±.83	9.7±.86	.000
PDW (fl)	10±1.2	11.8±1.6	.000
P-LCR (%)	17.8±6.5	22.9±6.4	.000

p. value <0.05 is considered significant SD=standard deviation

Table 2: Comparison in platelet count and indices between Glimepiride study subjects and control group

Parameters	Mean Glimepiride ± SD	Mean Non diabetes ± SD	p.value
Platelet count(x10^9/ l)	298±114	280.1±77.7	.378
MPV (fl)	9.4±.93	9.7±.86	.153
PDW (fl)	11±1.9	11.8±1.6	.028
P-LCR (%)	20.7±7.2	22.9±6.4	.117

Table 3: Comparison in platelet count and indices between Glimepiride and Metforminstudy population

Parameters	Mean Metformin ± SD	Mean Glimepiride ± SD	p.value
Platelet count(x10^9/ l)	319.2±138.6	298±114	.423
MPV (fl)	9±.83	9.4±.93	.044
PDW (fl)	10±1.2	11±1.9	.004
P-LCR (%)	17.8±6.5	20.7±7.2	.039

Table 4: Comparisons between platelet count and platelet indices in DM patientsusing Metformin as oral hypoglycemic drug according to complications, dose, Metformin using duration and hba1c groups.

Characteristic	Groups	N (Number of subjects)	Mean Platelet count (x 10^9/ l) ±S.D	Mean MPV (fl) ±S.D	Mean PDW(fl) ±S.D	Mean P-LCR (%) ±S.D
Complications						
	Eye	5	222.8±55.7	9.66±.38	10.54±.75	22.14±2.8
	Foot	10	437.6±238.4	8.7±.92	9.47±1.3	14.97±7.3
	No complication	35	299.14±79.8	9.06±.82	10.7±1.9	17.97±6.3
	p.value		.050	.107	.171	.123
Dose (day)						
	500mg	40	309.87±136.4	8.98±.7	10.38±1.8	17.14±5.9
	850mg	10	352.27±147.7	9.28±1.1	10.48±1.9	20.09±8.1
	p.value		.376	.297	.452	.184
Metformin's duration (years)						
	less than 5	15	267.2±66.5	8.99±.82	10.5±1.8	17.28±6.9
	5 to 10	18	315.78±111.8	9.17±.98	10.4±2	18.71±6.9
	>10 to 15	6	433.83±245	9.02±.95	10.2±1.6	16.52±8.3
	>15 to 20	7	295.57±121.7	8.96±.45	10.5±1.5	17.69±3.5
	more than 20	4	399±207	8.95±.86	10.1±1.7	17.6±6.7
	p.value		.330	.967	.993	957
Hb A1c (%)						
	less than 6%	8	385.76±244.9	9.24±.82	10.3±1.4	18.9±6
	6 to 7 %	9	273.5±57.6	9.3±.6	10.6±1.6	20±4.8
	More than 7%	33	316.8±118.4	8.9±.89	10.4±1.9	16.8±6.9
	p.value		.414	.365	.912	.343

Table 5: Comparison between platelet count and platelet indices in DM patients using Glimepiride as oral hypoglycemic drug according to complications, dose, Glimepiride using duration and HbA1C groups.

Characteristic	Groups	N	Mean Platelet count ($x\ 10^9$/ l) ±S.D	Mean MPV(fl) ±S.D	Mean PDW(fl) ±S.D	Mean P-LCR (%) ±S.D
Complications	Foot	18	351.7±141.15	8.9±.87	9.97±1.4	17.2±5.9
	No complication	28	269.4±79.67	9.7±.89	11.6±2	22.6±7.4
	p.value		.034	.007	.006	.014
Dose (day)						
	2mg	8	266.38±107.7	9.8±1	11.7±2.3	24.25±8.46
	3mg	4	273.8±112	9.2±.95	10.16±1.5	18.5±6.9
	4mg	31	318.2±117.5	9.3±.96	10.8±1.98	19.6±7.16
	5mg	3	258±110.1	9.5±.23	11.7±1.35	22.4±2.78
	p.value		.559	.548	.468	.377
Glimepiride's duration (years)						
	less than 5	19	285.7±84.9	9.3±.85	10.6±1.5	19.4±6.4
	5 to 10	18	298.3±110.2	9.4±1.16	11.4±2.6	21.5±9
	>10 to 15	4	247.3±16.7	9.6±.52	10.8±.68	21.1±3.1
	>15 to 20	5	488.7±242.3	9±.46	10.4±1.2	17.6±4
	p.value		.021	.880	.408	.746
Hb A1c (%)						
	less than 6%	7	222.7±65.9	10.2±1.1	12.8±2.4	27.7±8.8
	6 to 7%	4	305.8±70.9	9.5±1	10.9±1.8	20.5±7.7
	More than 7%	35	315.4±120.4	9.2±.84	10.6±1.7	19±6.1
	p.value		.145	.034	.016	.012

Statistically insignificance difference was detected on platelet count in patients used Metformin, Glimepiride in contrast to controls. Both drugs have reduced platelet indices (MPV, PLCR, PDW) when compared with the control group but platelet indices were much more reduced in patients usingMetformin than those takingGlimepiride as oral hypoglycemic drug as shown in (Table 1, 2, 3).

There was insignificant difference in platelet count and indices among those usingMetformin in term of dose, drug duration, associated complications and HbA1C level as shown in (Table 4). But among those usingGlimepiride as oral hypoglycemic drug, there was increased platelet count and decreased platelet indices in patients withfoot ulcers than patients without complications. Also increased platelet indicesin patients with HbA1C level less than 6% in contrast to those with HbA1C more than 7%.

Glimepiride diabetic patients from 15 to 20 yearshave increased platelet count (488.7) than patients used Glimepiride less than 15 years (247.3), less than 10 years (298.3) and less than 5 years (285.7). There was insignificant difference in term of dose inGlimepiride users as shown in (Table 5).

Discussion

A patient with DM has accelerated atherosclerosis [10, 11]. The interference effects of oral hypoglycemic drugs (Metformin, Glimepiride) on the platelet count and indices are very important because platelets have direct impact in the pro thrombotic condition which characterizes patients with DM. Platelets of DM patients are characterized by problems in regulation of several signaling pathways leading to the acceleration of adhesion, activation and aggregation [11]. Thus, Platelet count, MPV, P-LCR and PDW were measured as a marker of production rate and platelet activation.

Both Metformin and Glimepiride have been found to have anti-thrombotic effect. Metformin has more anti thrombotic effect than Glimepiride. Patients used Metformin have reduced platelet indices when compared with Glimepiride and non-diabetic population.

These findings were supported by Dib et al. their study showed that the diabetic complications may increase MPV in DM patients and Metformin decreased the MPV Regardless of glucose lowering effect of the Metformin. These findings may provide a further explanation for the anti atherogenic effect of metformin [12]. Dolasık et al.

also reported decreased MPV values in Metformin hypoglycemic drug group. Increased MPV appears to have a crucial role at the beginning of atherosclerosis development. This may help to understand the anti atherogenic effect of Metformin [13]. Also, Papazafiropoulou et al. demonstrated Metformin, sulfonylureas (Glimepiride) can reduce the cardiovascular risk in type 2 Diabetes Mellitus DM by exert a favorable effect on platelet function [14].

The mechanism that Metformin inhibits the platelet activation is described by Xin et al., they found Metformin prevent platelet activation by inhibiting extracellular mitochondrial DNA (mtDNA) release [15].

Regarding Glimepiride mechanism of preventing thrombosis is reported by Yukio et al. they found that cyclooxygenase pathway is inhibited by Glimepiride, while the activities of 12-lipoxygenase and phospholipase A2 were unaffected thus, prevent the formation of thromboxane A2 from Arachidonic acid metabolism of human platelets .The main function of thromboxane A2 is platelet activation and aggregation [16]. we compared different DM Patients groups using Glimepiride and Metformin according to (dose, associated complications,duration of drug used, Hb A1C level), stable anti thrombotic effect was found among Metformin users because there were no significant differences in platelet count and indices (MPV, P-LCR and PDW) in term of above prescribed variables in contrast of Glimepiride which has variable a favorable anti thrombosis effect.

Mardia et al. found a high platelet count, PDW and PCT levels in DM patients with diabetic foot ulcers in contrast to DM patients without diabetic foot ulcers. It indicates that platelets are activated and increased its ability for aggregation [17]. In our findings Patients with diabetic foot using glimepiride showed high anti thrombotic effect with relatively increased platelet count and deceased indices than patients without complications. These results may explain that Glimepiride is not a drug of choice during diabetic foot complications when compared to Metformin because regardless the high platelet counts, platelet inactivation is insufficient.

BackSterner et al. found that increased platelet count is a common finding in DM patients with nephropathy [18]. The in vivo generation of advanced glycation end products (AGEs) in the kidney is time dependent reported by Soulis et al.[19]. they supported our finding regarding increased platelet count in DM patients used Glimepiride for more than 15 to 20 years.

Our results showed that platelet indices were decreased in patients with HbA1C more than 7% and increased in the patients with HbA1C less than 6%. Singer et al. they found that Long termed uncontrolled DM type2 patients even after Intensive glycemic control didn't seem to have decreased platelet activation which characterized DM [20] .Kodiatte et al. Reported that DM Patients have MPV positively correlated with HbA1c [21] which is contradicted with our findings because we have patient's glycemic control history just for the last 3 months not for entire drug using period which is a limitation in our study.

Conclusion

Platelet indices were reduced among an oral hypoglycemic drug study group (Metformin and Glimepiride) Metformin has stronger anti-prothrombotic effect than Glimepiride,and patients with diabetic foot ulcer under glimepiride showed stronger anti-prothrombotic effect than patients without diabetic foot complication.Thus,Glimepiride have a good prognostic effect on the Pro-thrombotic state and accelerated atherosclerosis which is associated with type 2 study population than Metformin because the platelet indices were insignificant compared with controls.However, these results need further case control trails.

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References

1. Kerner W, Brückel J. Definition, classification and diagnosis of diabetes mellitus. *Experimental and clinical endocrinology & diabetes*. 2014 Jul;122(07):384-6.
2. Cdc.gov [internet].Atlanta: *Centers for Disease control and prevention* [updated 2019 May 30;cited 2020 December 9].Available from: https://www.cdc.gov/diabetes/basics/type2.html
3. Tripathi BK, Srivastava AK. Diabetes mellitus complications and therapeutics. *Medical science monitor*. 2006 Jul 1;12(7):130-47.
4. Budak YU, Polat M, Huysal K. The use of platelet indices, plateletcrit, mean platelet volume and platelet distribution width in emergency non-traumatic abdominal surgery: a

systematic review .*Biochemiamedica*. 2016 Jun 15;26(2):178-93.

5. Zuberi BF, Akhtar N, Afsar S. Comparison of mean platelet volume in patients with diabetes mellitus, impaired fasting glucose and non-diabetic subjects. *Singapore medical journal*. 2008 Feb 1;49(2):114.
6. Park Y, Schoene N, Harris WJP. Mean platelet volume as an indicator of platelet activation: methodological issues.*Platelets*. 2002;13(5-6):301-6.
7. Jindal S, Gupta S, Gupta R, Kakkar A, Singh HV, Gupta K, Singh S. Platelet indices in diabetes mellitus: indicators of diabetic microvascular complications. *Hematology.* 2011 Mar 1;16(2):86-9.
8. Schneider DJJDc. Factors contributing to increased platelet reactivity in people with diabetes.*Diabetes Care*. 2009;32(4):525-7.
9. Şahpaz F, Ulutaş KJDTD. Assessment of mean platelet volume in type 2 diabetics receiving insulin or oral antidiabetic agents.*Journal of Clinical and Experimental Investigations.*2015;42(4):399-403.
10. Goraya TY, Leibson CL, Palumbo PJ, Weston SA, Killian JM, Pfeifer EA, Jacobsen SJ, Frye RL, Roger VL. Coronary atherosclerosis in diabetes mellitus: a population-based autopsy study. *Journal of the American College of Cardiology*. 2002 Sep 4;40(5):946-53.
11. Ferreiro JL, Gómez-Hospital JA, Angiolillo DJ. Platelet abnormalities in diabetes mellitus.*Diabetes and vascular disease research.* 2010 Oct;7(4):251-9.
12. Dib S, Makhous R. The Effect of Metformin on Mean Platelet Volume. *Research Journal of Pharmacy and Technology*. 2020;13(5):2329-34.
13. Dolasık I, Sener SY, Celebı K, Aydın ZM, Korkmaz U, Canturk Z. The effect of metformin on mean platelet volume in dıabetıc patients.*Platelets*. 2013;24(2):118-21.
14. Papazafiropoulou A, Papanas N, Pappas S, Maltezos E, Mikhailidis DP. Effects of oral hypoglycemic agents on platelet function. *Journal of diabetes and its complications*. 2015 Aug 1;29(6):846-51
15. Xin G, Wei Z, Ji C, Zheng H, Gu J, Ma L, Huang W, Morris-Natschke SL, Yeh JL, Zhang R, Qin C. Metformin uniquely prevents thrombosis by inhibiting platelet activation and mtDNA release. *Scientific reports*. 2016 Nov 2;6:36222.
16. Yukio O, Yutaka Y, Shoji K. Effects of oral hypoglycaemic agents on platelet functions. *Biochemical pharmacology*. 1992 Aug 18;44(4):687-91.
17. Mardia AI, Gatot D, Lindarto D. Comparison platelet indices in diabetic patients with and without diabetic foot ulcer. *InIOP Conference Series: Earth and Environmental Science* 2018 Mar 1 (Vol. 125, No. 1, p. 012134). IOP Publishing.
18. BackSterner G, Carlson J, Ekberg G. Raised platelet levels in diabetes mellitus complicated with nephropathy. *Journal of internal medicine.* 1998 Dec;244(6):437-41.
19. Soulis T, Cooper ME, Vranes D, Bucala R, Jerums G. Effects of aminoguanidine in preventing experimental diabetic nephropathy are related to the duration of treatment. *Kidney international*. 1996 Aug 1;50(2):627-34.
20. Singer J, Snir AW, Leshem-Lev D, Rigler M, Kornowski R, Lev EI. Effect of intensive glycemic control on platelet reactivity in patients with long-standing uncontrolled diabetes.*Thrombosis research*. 2014 Jul 1;134(1):121-4.
21. Kodiatte TA, Manikyam UK, Rao SB, Jagadish TM, Reddy M, Lingaiah HK, Lakshmaiah V. Mean platelet volume in type 2 diabetes mellitus. *Journal of laboratory physicians*. 2012Jan;4(1):5.