The effects of metformin versus glibenclamide on complete blood picture in type 2 diabetic patients

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Abstract

To assess the effects of metformin and glibenclamide each one alone on complete blood picture (CBP) in type 2 diabetic patients. A case control study. This study was conducted during the period from 1/5/2011 to 31/1/2012 in Ibn Sina hospital in Mosul city. CBP were measured in patients suffering from type 2 diabetes mellitus. Group 1: 21 patients on metformin therapy (850-1500mg/day), group 2: 23 patients on glibenclamide therapy (5-10mg/day), also 22 apparently healthy volunteers were taken as the control group. Blood samples were taken from the three groups and analyzed for full blood count including red blood cells count (RBCs) ,white blood cell count (WBCs), and platelet count, hemoglobin (Hb) , mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and hematocrit (PCV). WBC count was higher in group 2 than that in group 1 and control group. The other parameters of complete blood picture in group 1 and 2 showed no significant differences compared with the control group. Metformin and glibenclamide have no significant effect on CBP except for the effect metformin which decreases WBC and platelet level which are already elevated in type 2 DM , but remain within the normal range. Such effect could not be seen in glibenclamide group.
Keywords: CBP, type 2 diabetes mellitus , metformin, glibenclamide.

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الخلاصة

أهداف البحث : لدراسة تأثير عقار الميتفورمين وعقار الكلايبينكلاميد كل عقار لوحده على صورة الدم الكاملة في المرضى المصابين بداء السكري النم ط الثاني. **تصميم الدراسة** : دراسة عينية مقارنة. الطرق المتبعة والأشخاص : أجريت هذه الدراسة بين الفترة   من 1 أيار 2011 ولغاية 31 كانون الثاني 2012 في مستشفى ابن سينا في مدينة الموصل. تم قياس صورة الدم الكاملة لمجاميع المرضى المصابين بداء السكري النمط الثاني : المجموعة الأولى من 21 مريض تحت علاج الميتفورمين   (850-1500 ملغم / اليوم)، المجموعة الثانية من 23 مريض تحت علاج الكلايبينكلاميد (5-10 ملغم/ اليوم) و مجموعة الضبط 22 من الأصحاء غير السكريين . وأخذت عينة دم من المجاميع الثلاثة وتم تحليل الدم وحساب العدد الكلي ل لدم والذي شمل عدد كريات الدم الحمراء وعدد كريات الدم البيضاء والصفيحات الدموية وخضاب الدم وحجم الكريات الدموية ومعدل خضاب الكريات الدموية ومعدل تركيز خضاب الكريات الدموية وهيماتوكرت الدم. **النتائج**: كان عدد كريات الدم البيضاء أكثر في المجموعة الثانية منه في المجموعة الاولى ومجموعة السيطرة. ولم تتغير معنويا بقية القياسات للعدد الكامل للدم   للمجموعة الاولى والثانية مقارنة بمجموعة السيطرة. **الاستنتاج**: عقار الميتفورمين وعقار الكلايبينكلاميد معنويا ليس له تاثير على صورة الدم الكاملة ماعدا تاثير عقار الميتفورمين الذي يقلل اعداد كريات الدم البيضاء وخضاب الدم الذي هو يزيد عند مرضى السكري النمط الثاني لكن تبقى ضمن المعدل الطبيعي وهذا التاثير غير موجود لدى عقار الكلايبينكلاميد.

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Introduction

Diabetes mellitus (DM) is a group of metabolic disorders which consider carbohydrate metabolism and especially glucose is underutilized, producing hyperglycemia resulting from a defect in insulin secretion, insulin action, or both (1, 2). Type 2 diabetes, arises as a result of β cell failure combined with concomitant insulin resistance (3). Glibenclamide is a second generation sulfonylurea used in the treatment of type 2 diabetes (4). Sulphonylureas stimulate insulin secretion by interacting with specific receptors on the β cells surface (5). The frequency of adverse effects of glibenclamide is low, and the other effects are usually mild and reversible on withdrawal of the drug. The most common adverse effect is hypoglycemia (5), this may be profound and long lasting occasionally leading to permanent neurological damage or death (6). Other rare adverse effects are hematological (a granulocytes and hemolytic anemia) (7) and weight gain (5).

Metformin is a biguanide , which represents one of the oldest oral hypoglycemic agents used in the management of type 2 diabetes mellitus (8). The blood glucose-lowering actions of metformin result primarily from an amelioration of insulin resistance, mainly in liver and muscle, with a lesser effect in adipose tissue (9). Modest reductions in body weight often observed with metformin are associated with redistribution of fat from visceral depots to subcutaneous depots, which carry lesser cardiovascular (CV) risk (10, 11, 12, 13).   Metformin is considered one of the safest oral hypoglycemic agents. It reduces insulin resistance but does not promote insulin

secretion from β cells, and thus it is not associated with increased risk of hypoglycemia (13, 14). Minor untoward effect of metformin is lowering the levels of vitamin B12 and folate due to impaired gastrointestinal absorption and this effect has been documented with long term metformin therapy, but clinically these effects are insignificant and do not cause anemia (15).   The effects of metformin and glibenclamide on complete blood picture (CBP) are not fully studied in human. Diabetes is a chronic illness that requires continuing medical care and patient self-management education to prevent acute and to reduce the risk of long-term complications (16). The most common agents used for the treatment of DM are metformin and glibenclamide therefore, this study was done to see whether these drugs affects CBP or not.

Materials and methods

This study was conducted from 1/5/2011 to 31/1/2012 in Al-Wafa Clinic for Treatment and Researches of Diabetes Mellitus in Ibn Sina Hospital in Mosul City. Forty four patients enrolled in this study were divided into two groups. The first group involved 21 type 2 diabetic patients (9 males and 12 females), their ages ranged between (52±5.55 and 44.8±10.7) respectively on regular treatment with metformin in doses ranged between 850-1500mg/day. The second group involved 23 type 2 diabetic patients (15 males and 8 females), their ages ranged between (51.8±5.09 and 52.2±7.7) respectively on regular treatment with glibenclamide in doses ranged between 5-10 mg /day. The control group included 22 apparently healthy volunteers, who had no chronic disease and did not received

any chronic medications. It consist of (13 males and 9 females), their ages ranged between (45.5±7.5 and 48.89±6.6) respectively. The study design was case – control study and patients were excluded if they had a history of any other diseases or those taking anti-diabetic drugs other than glibenclamide or metformin. Three milliliters of blood samples were collected from each individual (patients and controls) and all blood sample were transferred to EDTA tubes. The hematological parameters were measured by hematology auto analyzer (HORIBA ABX Coulter Counter , France, 9070T87726). Complete blood pictures parameters measured in this study included: red blood cells count (RBCs) ,white blood cell count (WBCs), Platelet count, hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and hematocrit (PCV). Data are presented as mean±SD. and paired t test was used for comparing the means of these groups (17). The level of significance was at $p<0.05$.

Results

The ages of the three groups (control group, metformin group and glibenclamide group) is shown in table 1. No significant differences was found between the three groups. Tables 2 shows a comparison between complete blood picture parameter of control group, metformin group and glibenclamide group.

Table (1):-. The ages of the studied groups

Characteristic	Control group N=22	Metformin group N=21	Glibenclamide group N=23
Age (yr)	47.5±7.1	46.52±4.14	51.52±6.65

Table (2):- Complete blood picture of control group metformin group and glibenclamide group.

Hematological parameter	Control group N=25	Metformin group N=21	Glibenclamide group N=23
RBCs (10^{12}/L)	5.21±0.69	4.79±0.63	4.93±0.51
WBCs (10^9/L)	7.15±1.21	7.56±1.6	9.17±3.13*
Hb (g/dL)	14.44±2.12	14.05±2.34	14.53±1.7
Platelet (10^9/L)	234.1±58.8	232.4±59.4	254.5±84.5*

MCV (fL)	81.01±8.34	81.56±7.97	83.79±3.65
MCH (pg)	27.69±3.9	28.29±3.94	29.44±2.1
MCHC (g/dL)	34.1±1.79	34.58±2.06	35.12±1.43
PCV (%)	42.58±5.42	40.15±5.93	41.3±4.32

Significantly different from the respect control group * p value < 0.05

Discussion

Some studies on animals showed increased platelet aggregation and increased fibrinogen levels in diabetes (18). Diabetes also affects the erythrocytes causing an increase in the MCV (19). These increases were prevented by metform in treatment (20). The age distribution in the three tested groups was chosen to be similar in order to exclude any effect that may affect on the CBP parameters (table 1). In this study, the results showed that there were no significant differences in all CBP parameters (except WBC and platelet) in the three tested groups (table 2), this is in agreement with other similar studies (21, 22, 23). The results also showed that there was a significant increase in WBC in glibenclamide group with no such effect in metformin group as compared with control (table 2) , this may be due to DM which may increase WBC and metformin decreases these elevations but glibenclamide has no such effect (20). Also elevated WBC count , even within the normal range, is associated with both macro- and microvascular complications in type 2 diabetes (24, 25, 26). Arnon (27) showed that there was decreased   WBC after metformin treatment which returned to the normal range after discontinuation of metformin therapy. However the inter-individual variation   and   environment   are contributing factors (28). In addition , changes in environmental temperatures were associated with changes in WBC count (29, 30). Platelet level showed no changes in metformin group, but little elevation could be seen in glibenclamide group as compared with control group but still within the normal ranges (table 2). Again this effect could be due to the metformin ability to decrease the platelet count. This is in agreement with many studies (31, 32) observed that the level of   platelet   was   decreased   after metformin treatment. This effect may be due to other antithrombotic mechanisms of metformin include stabilization of reduced aggregation of platelet.

Conclusion

In   conclusion   ,   metformin   and glibenclamide have no significant effect on CBP except metformin which decreases WBC and platelet   levels. These are already increased in type 2 DM , but remain within the normal range. Such effect could not be seen with glibenclamide.   The   periodical examination   of   metformin   and glibenclamide type 2 diabetic treated patients for CBP is necessary because elevation   in   some   parameters   are associated with complication of disease.

References

1. Bastaki S. Diabetes mellitus and its treatment. Int J Diabetes & Metabolism 2005;13: 111-134.
2. Dipirio J.T., Talbert R.L., Yee G.C., Wells B.G. Pharmacotherapy: A path physiologic approach, 6th ed., Mc. Graw Hill Medical publishing division, 1999. 1333-1364.
3. DeFronzo RA, Bonadonna RC and Ferannini E. Pathogenesis of NIDDM: a balanced overview. Diabetes Care 1992; 15: 318-368.
4. Yap WS. Review of management of type 2 diabetes mellitus. J Clin Pharm Ther 1998; 23(6): 457-65 .
5. Williams G. Management of the non insulin dependant diabetes mellitus. Lancet 1994; 343 : 95-100.
6. Podolsky S, Krall LP, Bradley RF. Treatment of diabetes with oral hypoglycemic agents. In Clinical diabetes : modern management . Podolsky S (ed) . Appleton Century of Crofts , New York 1980: 131-172.
7. Cantrill JA. Diabetes Mellitus . In: clinical pharmacy and therapeutics. Walker R , Edwards C (eds) . 2nd edition , Churchill Living stone , London 1999: 633-652.
8. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2006; 49:1711–21.
9. Giannarelli R, Aragona M, Coppelli A, et al. Reducing insulin resistance with metformin: the evidence today. Diabetes Metab 2003; 29:6S28-6S35.
10. Saenz A, Fernandez-Esteban I, Mataix A, et al. Metformin monotherapy for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2005; 3:CD002966.
11. Golay A. Metformin and body weight. Int J Obes 2008; 32:61-72.
12. Scarpello JHB, Howlett HCS. Metformin monotherapy and clinical uses. Diabetes Vasc Dis Res. 2008 ; 5:157–67.
13. Papanas N, Maltezos E. Oral antidiabetic agents: anti-atherosclerotic properties beyond glucose lowering? Curr Pharm Des. 2009; 15:3179–92.
14. Blonde L, Dailey GE, Jabbour SA, et al. Gastrointestinal tolerability of extended-release metformin tablets compared to immediate release metformin tablets: results of a retrospective cohort study. Curr Med Res Opin. 2004; 20:565–72.
15. Bailey CJ, Turner RC. Metformin. New Engl J Med. 1996; 334:574–9.
16. American Diabetes Association. Standards of medical care for patients with diabetes mellitus, Diabetes Care 2003 ; 26: S33–S50.
17. Petrie A. Lecture Notes on Medical Statistics. Black Well Sciientific Publications, Oxford. 1978.
18. Litile, H. L. The role of abnormal hemorrheo-dynamics in the pathogenesis of diabetic retinopathy. Transactions of the Ophthalmological Society 1976 ; 74: 573.
19. Kowluru R, Bitensky M W, kowluru A, et al. Reversible sodium pump defect and swelling in the diabetic rat erythrocyte: Effects on filterability and implications for microangiopathy. Proceedings of the

National Academy of Sciences of the USA 1989; 86: 3327-3331.

20. Michelle Mc Guire and Mary Macdermott. The influence of streptozotocin diabetes and metformin on erythrocyte volume and on the membrane potential and the contractile characteristics of the extensor longus and soleus muscles in rats . Experimental Physiology : 1999 ; 84: 1051- 1058.

21. Koan-Day Lin, Jen-Der Lin, Jyuhn-Huarng Juang, et al. Metformin-Induced Hemolysis with Jaundice. N Engl J Med 1998 ; 339:1860-1861.

22. Kashyap A S, Shekhar Kashyap. Haemolytic anaemia due to metformin. Postgrad *Med J* 2000; 76:125–126.

23. Yngen M, Ostenson CG, Hjemdahl P, et al. Meal-induced platelet activation in Type 2 diabetes mellitus: effects of treatment with repaglinide and glibenclamide. Diabet Med. 2006 Feb; 23(2):134-40.

24. Targher G, Seidell JC, Tonoli M, etal. The white blood cell count: its relationship to plasma insulin and other cardiovascular risk factors in healthy male individuals. J Intern Med 1996; 239:435–441.

25. Noto D, Barbagallo CM, Cavera G, et al. Leukocyte count, diabetes mellitus and age are strong predictors of stroke in a rural population in southern Italy: an 8-year follow-up. Atherosclerosis 2001; 157:225–231.

26. Peter C. Tong, Ka-Fai Lee, et al. White Blood Cell Count Is Associated With Macro- and Microvascular Complications in Chinese Patients With Type 2 Diabetes. Diabetic care 2004; 27: 216- 222.

27. Arnon Blum , Wisam Ghaben , Guy Slonimsky, et al . Metformin-Induced Hemolytic Anemia. IMAJ 2011; 13: 444–445.

28. Ross DW, Ayscue LH, Watson j, et al. Stability of hematological parameters in healthy subjects. Am J Pathol 1988 ; 90: 262-267.

29. Cross MC, Radomski MW, Vanhelder WP, et al. Endurance exercise with and without a thermal clamp: effects on leukocytes and leukocytes subsets. J Appl Physiol 1996 ; 81 (2): 822-829

30. Brenner IK, Castellani JW, Gabaree C, et al. Immune changes in humans during cold exposure : effects of prior heating and exercise . J Appl Physiol 1999; 87(2): 699- 710.

31. Gargiulo P, Caccese D, Pignatelli P, et al. Metformin decreases platelet superoxide anion production in diabetic patients. Diabetes Metab Res Rev. 2002; 18(2):156-9.

32. Standeven KF, Ariens RA, Whitaker P, et al. The effect of dimethylbiguanide on thrombin activity, FXIII activation, fibrin polymerization, and fibrin clot formation. Diabetes 2002 ; 51:189-97.