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ORIGINAL ARTICLE

Adverse Biochemical and Physiological Effects of Metformin in Diabetic Type-2 Patients, A Comparative Clinical Study

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ABSTRACT

Task: The aims and objectives of present study were to highlight the efficacy and adverse side effects of metformin in patients with diabetes type-2 and this study was conducted from December 2021to May 2022 in different medical and diabetic centers of Pakistan.

Materials and methods:

Subjects: 700 male and female subjects were selected for this study.

Division of individuals: 100 normal individuals were in Control group, further 600 individuals were divided into three different groups. In group-X, 200 diabetic type-2, patients were taking 2000 mg/day metformin and in group-Y, 200 diabetic type-2, patients were taking 1500 mg/day metformin while in group-Z, 200 diabetic type-2, patients were taking 500 mg/day metformin respectively.

Parameters: Fasting and random serum glucose levels, blood lactic acid levels, serum creatinine levels, myoglobin blood levels and blood hemoglobin levels.

Analysis: Microlab and Spectrophotometry kit, regent method were used for the measurement of different parameters.

Bio-statistical presentation: All collected raw data were interoperated bio-statistically through the application of SPSS version 2000, in which all parameters were described with the application of standard mean deviation and significant ($p<0.05$) regression.

Results: In this study Fasting and random serum glucose levels, serum creatinine levels, blood lactic acid levels, myoglobin blood levels and blood hemoglobin levels of males and females in Control group, Group-X, Group=Y and Group-Z were (80.1±0.01, 139.2±0.02, 0.2±0.01, 9.2±0.03, 39.2±0.00, 14.1±0.02) (80.1±0.01, 140.2±0.02, 0.1±0.01, 10.2±0.03, 39.2±0.00, 12.1±0.01), (120.1±0.05, 269.2±0.01, 2.2±0.01, 19.1±0.01, 73.2±0.00, 12.1±0.01) (110.1±0.01, 270.2±0.01, 3.2±0.01, 18.1±0.01, 72.2±0.00, 11.1±0.02), (110.1±0.00, 239.2±0.00, 1.2±0.01, 21.1±0.01, 60.2±0.00, 11.1±0.01)(106.1±0.01, 275.2±0.01, 1.2±0.01, 19.1±0.01, 59.2±0.00, 12.1±0.00) ,(100.1±0.00, 198.2±0.00, 1.1±0.01, 18.1±0.01,52.2±0.00,12.1±0.00) (110.1±0.00, 239.1±0.00, 1.2±0.01, 17.1±0.00, 51.2±0.00, 12.1±0.00) measured respectively. A remarkable significant ($p<0.05$) were seen in between the variables of each group.

Conclusion: Metformin considered as a safe drug for diabetic type-2 patients but it has some very severe side effects, it may cause lactic acidosis, protein breakdown, skeletal muscular atrophy and striking loss of muscle etc. Long life its use can develop myocardial infarction.

INTRODUCTION

Diabetes mellitus may be divided into many different classes such as type 1 diabetes, type 2 diabetes, gestational diabetes mellitus and stress induced diabetes caused by reactive oxygen species [1]. Many researcher concluded by considering different studies that 95% type 2 diabetes is indicated in the population and majority of them basic cause is oxidative stress. Diabetes mellitus is a condition in which the body does not generate enough or utilize insulin as it should, leading to abnormally high blood glucose levels. [18] Cells become less responsive to the effects of insulin when biological system has type 2 diabetes, and pancreas is unable to produce enough insulin to overcome this resistance. Although the exact cause of this is unknown, it is thought that both hereditary and environmental factors contribute to the onset of type 2 diabetes. Type 2 diabetes is highly associated with being overweight, but not all people with type 2 are obese [2].

Metformin hydrochloride, or N, N-dimethylbiguanide is a compound extracted from medicinal plant i.e. Galega officinalies but now it is also synthesis synthetically on large scale [17]. Different studies stated that metformin has an efficacy to reduce the hyperglycemic conditions of the biological system in the cases where insulin cannot response. This compound recommended to the diabetic patients where their carbohydrate rich diet do not metabolized completely in the cells through the process of glycolysis and citric acid cycle [3]. Although it has been used in clinical practice for 60 years, its molecular mechanisms of action are still hotly contested because it was proven to be a safe and effective medication before thorough mechanistic research were feasible [16]. The medicine metformin is a complicated one with numerous molecular processes and sites of action. Metformin physiologically affects the liver to reduce glucose synthesis, either directly or indirectly, and the stomach to enhance glucose absorption, raise GLP-1, and change the microbiome [4].

Metformin causes number of adverse side effects some of them are mild and some are very serious. On long term uses metformin reduces weight and weaken the muscles of the body. Lactic acidosis is the most severe adverse effect of metformin, despite its rarity [15]. The accumulation of metformin in human body might result in lactic acidosis, a rare but serious issue and metformin associated lactic acidosis has a mortality incidence of between 30 and 50 percent [5]. Regular intake of metformin may reduce the levels of cobalamin in human body which may cause anemia. Metformin may develop hypoglycemic condition in case of low diet, use of alcoholic and stress [4]. When kidneys could not receive enough blood from heart circulation this may increase the risk of developing lactic acidosis by obstructing kidney function to remove metformin from body. Cardiac muscles are also received weakness because of long use of metformin [14].

MATERIALS AND METHODS

Study Design: 700 male and female subjects were selected for this study and divided them into four different groups regarding metformin dosage.

Division of Individuals: 100 normal individuals were in Control group, further 600 individuals were divided into three different groups. In group-X, 200 diabetic type-2, patients were taking 2000 mg/day metformin and in group-Y, 200 diabetic type-2, patients were taking 1500 mg/day metformin while in group-Z, 200 diabetic type-2, patients were taking 500 mg/day metformin respectively.

Parameters: Fasting and random serum glucose levels, blood lactic acid levels, serum creatinine levels, myoglobin blood levels and blood hemoglobin levels.
Analysis: Microlab and Spectrophotometry kit, regent method were used for the measurement of different parameters.
Bio-statistical presentation: All collected raw data were interoperated bio-statistically through the application of SPSS version 2000, in which all parameters were described with the application of standard mean deviation and significant ($p<0.05$) regression.

RESULTS

Group-Control, Normal individual

Normal male n= 60 Age=35-50 years			
Parameters	Units	Mean ±SD	P<0.05
Fasting glucose levels	mg/dL	80.1±0.01	0.01
Random glucose levels	mg/dL	139.2±0.02	0.02
Creatinine levels	mg/dL	0.2±0.01	0.01
Lactic acid levels	mg/dL	9.2±0.03	0.03
Myoglobin levels.	ng/mL	39.2±0.00	0.00
Hemoglobin levels.	g/dL	14.1±0.02	0.02

Normal female n= 40 Age=35-50 years			
Parameters	Units	Mean ±SD	P<0.05
Fasting glucose levels	mg/dL	80.1±0.01	0.01
Random glucose levels	mg/dL	140.2±0.02	0.02
Creatinine levels	mg/dL	0.1±0.01	0.01
Lactic acid levels	mg/dL	10.2±0.03	0.03
Myoglobin levels.	ng/mL	39.2±0.00	0.00
Hemoglobin levels.	g/dL	12.1±0.01	0.01

Group-X, Diabetic type-2 individual taking 2000mg/day oral metformin

Diabetic type-2 individual male n= 50 Age=35-50 years			
Parameters	Units	Mean ±SD	P<0.05
Fasting glucose levels	mg/dL	120.1±0.05	0.05
Random glucose levels	mg/dL	269.2±0.01	0.01
Creatinine levels	mg/dL	2.2±0.01	0.01
Lactic acid levels	mg/dL	19.1±0.01	0.01
Myoglobin levels.	ng/mL	73.2±0.00	0.00
Hemoglobin levels.	g/dL	12.1±0.01	0.01

Diabetic type-2 individual female n= 50 Age=35-50 years			
Parameters	Units	Mean ±SD	P<0.05
Fasting glucose levels	mg/dL	110.1±0.01	0.01
Random glucose levels	mg/dL	270.2±0.01	0.01
Creatinine levels	mg/dL	3.2±0.01	0.01
Lactic acid levels	mg/dL	18.1±0.01	0.03
Myoglobin levels.	ng/mL	72.2±0.00	0.00
Hemoglobin levels.	g/dL	11.1±0.02	0.02

Group-Y, Diabetic type-2 individual taking 1500mg/day oral metformin

Diabetic type-2 individual male n= 50 Age=35-50 years			
Parameters	Units	Mean ±SD	P<0.05
Fasting glucose levels	mg/dL	110.1±0.00	0.00
Random glucose levels	mg/dL	239.2±0.00	0.00
Creatinine levels	mg/dL	1.2±0.01	0.01
Lactic acid levels	mg/dL	21.1±0.01	0.01
Myoglobin levels.	ng/mL	60.2±0.00	0.00
Hemoglobin levels.	g/dL	11.1±0.01	0.01

Diabetic type-2 individual female n= 50 Age=35-50 years			
Parameters	Units	Mean ±SD	P<0.05
Fasting glucose levels	mg/dL	106.1±0.01	0.01
Random glucose levels	mg/dL	275.2±0.01	0.01
Creatinine levels	mg/dL	1.2±0.01	0.01
Lactic acid levels	mg/dL	19.1±0.01	0.03
Myoglobin levels.	ng/mL	59.2±0.00	0.00
Hemoglobin levels.	g/dL	12.1±0.00	0.00

Group-Z, Diabetic type-2 individual taking 500mg/day oral metformin

Diabetic type-2 individual male n= 50 Age=35-50 years			
Parameters	Units	Mean ±SD	P<0.05
Fasting glucose levels	mg/dL	100.1±0.00	0.00
Random glucose levels	mg/dL	198.2±0.00	0.00
Creatinine levels	mg/dL	1.1±0.01	0.01
Lactic acid levels	mg/dL	18.1±0.01	0.01
Myoglobin levels.	ng/mL	52.2±0.00	0.00
Hemoglobin levels.	g/dL	12.1±0.00	0.00

Diabetic type-2 individual female n= 50 Age=35-50 years			
Parameters	Units	Mean ±SD	P<0.05
Fasting glucose levels	mg/dL	110.1±0.00	0.00
Random glucose levels	mg/dL	239.1±0.00	0.00
Creatinine levels	mg/dL	1.2±0.01	0.01
Lactic acid levels	mg/dL	17.1±0.00	0.00
Myoglobin levels.	ng/mL	51.2±0.00	0.00
Hemoglobin levels.	g/dL	12.1±0.00	0.00

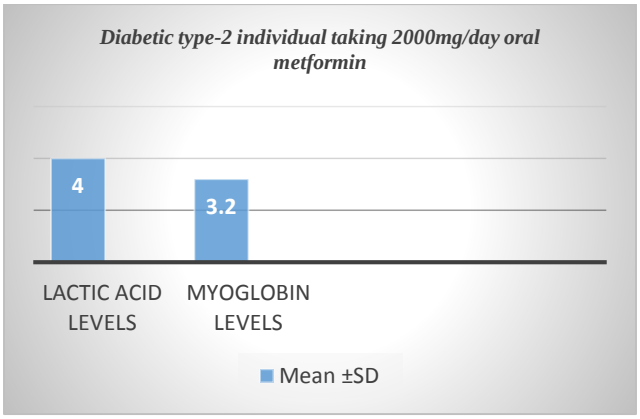
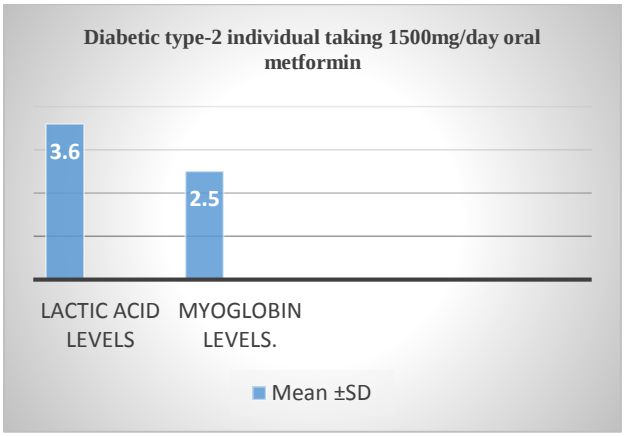


Figure-1:



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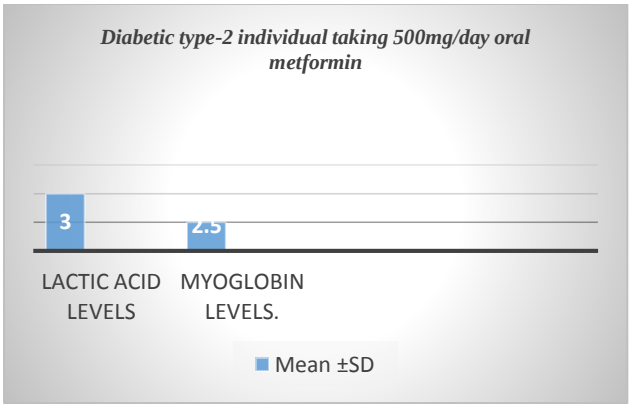

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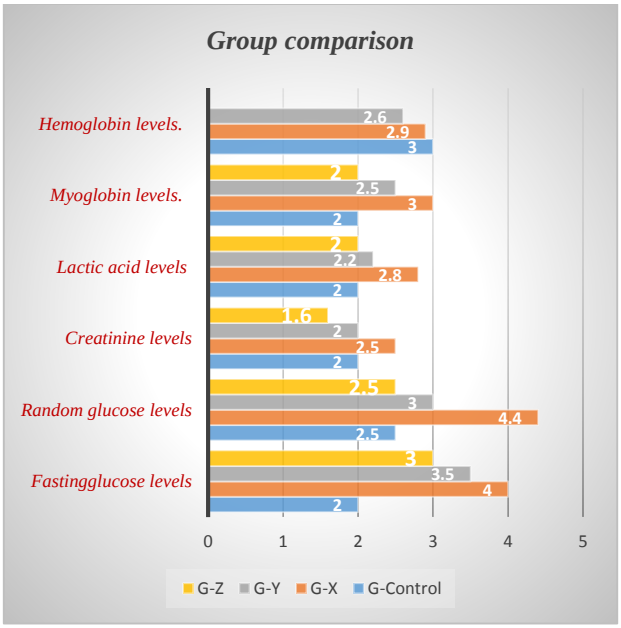

Figure-:

In this study Fasting and random serum glucose levels, serum creatinine levels, blood lactic acid levels, myoglobin blood levels and blood hemoglobin levels of males and females in Control group, Group-X, Group=Y and Group-Z were (80.1±0.01, 139.2±0.02, 0.2±0.01, 9.2±0.03, 39.2±0.00, 14.1±0.02) (80.1±0.01, 140.2±0.02, 0.1±0.01, 10.2±0.03, 39.2±0.00, 12.1±0.01), (120.1±0.05, 269.2±0.01, 2.2±0.01, 19.1±0.01, 73.2±0.00, 12.1±0.01) (110.1±0.01, 270.2±0.01, 3.2±0.01, 18.1±0.01, 72.2±0.00, 11.1±0.02), (110.1±0.00, 239.2±0.00, 1.2±0.01, 21.1±0.01, 60.2±0.00, 11.1±0.01)(106.1±0.01, 275.2±0.01, 1.2±0.01, 19.1±0.01, 59.2±0.00, 12.1±0.00) ,(100.1±0.00, 198.2±0.00, 1.1±0.01, 18.1±0.01,52.2±0.00,12.1±0.00) (110.1±0.00, 239.1±0.00, 1.2±0.01, 17.1±0.00, 51.2±0.00, 12.1±0.00) measured respectively. A remarkable significant ($p<0.05$) were seen in between the variables of each group. Comparatively all biomarkers are represented graphically in figure-4 while significant ($p<0.05$) changes in blood lactic acid levels, myoglobin blood levels of Group-x, Group-Y and Group-Z were represented in figure-1,figure-2 and figure-3.

DISCUSSION

Metformin considered as a safe drug for diabetic type-2 patients but it has some very severe side effects [6]. Despite the fact that metformin has emerged as a top medication for the treatment of type 2 diabetes mellitus, some people may not be given it because of the possibility of developing lactic acidosis. By blocking mitochondrial respiration, mostly in the liver, metformin and other medicines in the biguanide class raise plasma lactate levels in a way depending on plasma concentration [7]. Along with other medications in the biguanide class, metformin raises plasma lactate levels primarily in the liver and in a plasma concentration-dependent manner. A blood pH of less than 7.35 and an arterial blood lactate level of more than 5 mmol/L are indicators of metformin-associated lactic acidosis (MALA) [14]. By preventing lactate from being removed in the liver and muscles at the level of the mitochondrial respiratory chain complex, where lactate is oxidatively digested, it causes lactate levels to rise. Plasma lactate concentrations are typically less than 2 mmol/L with therapeutic dosages of metformin. It is eliminated unaltered through the kidneys [13].

Despite research suggesting that metformin may aid in weight loss, the medication is not a panacea. According to one extensive research According to a Reliable Source, metformin weight loss usually happens over the course of one to two years. Additionally, each person experiences weight loss differently [12]. In both insulin sensitive and insulin resistant overweight and obese patients, metformin is a potent weight-reduction medication that works well in a naturalistic outpatient context. Insulin, the hormone that enables tissues throughout the body to absorb glucose from the bloodstream, has a reduced ability to activate cells in patients with diabetes [7]. Treatment with metformin reduces muscular function by controlling myostatin in skeletal muscle cells via the AMPK-FoxO3a-HDAC6 axis. It is clearer that metformin has a muscle-wasting impact, suggesting that more intricate processes may be at play in metformin-mediated muscular dysfunction. When the rate of protein synthesis is greater than the rate of protein breakdown, skeletal muscular atrophy, a striking loss of muscle, results. This condition is defined by a decrease in the size and protein content of muscle fibers [8].

Although metformin has historically been considered contraindicated in patients with chronic kidney disease (CKD), recommendations have recently been loosened to allow medication if the glomerular filtration rate (GFR) is more than 30 mL/min. The perceived risk of lactic acidosis is the key issue (LA) [9]. Epidemiological data indicates that this fear is exaggerated. Patients on metformin do not have an elevated risk. Weight loss is one of the therapeutic outcomes of metformin that are advantageous to patients and are not dependent on glucose decrease. The introduction of metformin therapy to more advanced stages of CKD may have therapeutic advantages that outweigh any potential concerns, it is hypothesized [8].

It's time to reevaluate the current contraindication for CKD patients, as it was with heart failure. There is no reason to think that CKD patients, whose risk of cardiovascular disease is significantly raised, would not experience the same cardiovascular benefits as diabetic people who are otherwise healthy. Preventing intoxication is the main issue with metformin treatment in CKD patients [10]. Heart failure risk can be raised by many ant-hyperglycemic medications. The first-line medication for type 2 diabetes, metformin, is thought to both lower the risk of and improve the clinical course of heart failure. Twenty to twenty-five percent of patients taking metformin are thought to have heart failure [9]. In the current study the results are very similar and correlated with the previous studies by different researchers. The findings of present study indicated that fasting and random serum glucose levels, serum creatinine levels, blood lactic acid levels, myoglobin blood levels and blood hemoglobin levels of males and females in Control group, Group-X, Group=Y and Group-Z were presented a significant ($p<0.05$) variation of such parameters with the oral dosage of metformin in diabetic type-2 patients. Further research is required on this topic for public awareness.

REFERENCES

1. Cheen AJ, Paquot N. Metformin revisited: A critical review of the benefit-risk balance in at-risk patients with type 2 diabetes. Diabetes Metab. 2013;39:179–90.
2. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: An update. Ann Intern Med. 2012;137:25–33.
3. Hundal RS, Inzucchi SE. Metformin: New understandings, new uses. Drugs. 2003;63:1879–94.
4. Scarpello JH, Howlett HC. Metformin therapy and clinical uses. Diab Vasc Dis Res. 2018;5:157–67.
5. Rafieian-Kopaei M, Baradaran A. Combination of metformin with other antioxidants may increase its renoprotective efficacy. J Ren Inj Prev. 2013;2:35–6
6. Seo-Mayer PW, Thulin G, Zhang L, Alves DS, Ardito T, Kashgarian M, et al. Preactivation of AMPK by metformin may ameliorate the epithelial cell damage caused by renal ischemia. Am J Physiol Renal Physiol. 2011;301:F1346–57.
7. Sung JY, Choi HC. Metformin-induced AMP-activated protein kinase activation regulates phenylephrine-mediated contraction of rat aorta. Biochem Biophys Res Commun. 2012;421:599–604.
8. Rosen P, Wiernsperger NF. Metformin delays the manifestation of diabetes and vascular dysfunction in Goto-Kakizaki rats by reduction

of mitochondrial oxidative stress. Diabetes Metab Res Rev. 2016;22:323–30.
9. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:854–65.
10. Nasri H. On the occasion of the world diabetes day2013; Diabetes education and prevention; a nephrology point of view. J Ren Inj Prev. 2013;2:31–2.
11. Tertti K, Ekblad U, Vahlberg T, Rönnemaa T. Comparison of metformin and insulin in the treatment of gestational diabetes: A retrospective, case-control study. Rev Diabet Stud. 2018;5:95–101.
12. Balani J, Hyer SL, Rodin DA, Shehata H. Pregnancy outcomes in women with gestational diabetes treated with metformin or insulin: A case-control study. Diabet Med. 2019;26:798–802.
13. Cheung NW. The management of gestational diabetes. Vasc Health Risk Manag. 2009;5:153–64.
14. Kidson W. Polycystic ovary syndrome: A new direction in treatment. Med J Aust. 1998;169:537–40.
15. National Collaborating Centre for Women's and Children's Health. Fertility: Assessment and treatment for people with fertility problems. London: Royal College of Obstetricians and Gynaecologists. 2020;97:58–9.
16. Balen A. Royal college of Obstetricians and Gynaecologists. Metformin therapy for the management of infertility in women with polycystic ovary syndrome. ;2018 Dec;:12–3.
17. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JM. New users of metformin are at low risk of incident cancer: A cohort study among people with type 2 diabetes. Diabetes Care. 2009;32:1620–5.
18. Esteghamati A, Eskandari D, Mirmiranpour H, Noshad S, Mousavizadeh M, Hedayati M, et al. Effects of metformin on markers of oxidative stress and antioxidant reserve in patients with newly diagnosed type 2 diabetes: A randomized clinical trial. Clin Nutr. 2013;32:179–85.