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Original Research Article

Effect of Metformin on Biochemical Markers of Insulin Resistance and Pancreatic Histopathological Changes: A Randomized Controlled Trial

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Abstract: ***Objective***: The objective of the study was to assess how metformin impacts the biochemical indicators of insulin resistance and the pathological changes to the pancreas caused by T2DM in a rodent model. ***Materials And Methods***: During the experiment there were 60 Wistar male rats that were randomly divided into three groups, with each group comprising 20 rats. Group I was on a control diet, Group II developed T2DM due to HFD/STZ, and Group III received oral doses of metformin (150 mg/kg/day). The groups were measured at baseline for fasted blood glucose (FBG), fasted insulin, HOMA-IR, HbA1c, the lipid profile (total cholesterol, triglycerides, and high-density lipoprotein), and two markers related to inflammation (TNF-α and IL-6) through the experimental period of eight weeks. Pancreatic tissues were collected at the end of the study for histological assessment using hematoxylin and eosin and also for immunohistochemical staining of both insulin and glucagon. ***Results***: In comparison to the Diabetic Control Group, the Metformin group had statistically significant Decreases in Fasting Blood Sugar (FBG)($p<0.001$), Glycosylated Hemoglobin (HbA1c)($p = 0.002$), Insulin Resistance (HOMA-IR)($p<0.001$), Tumor Necrosis Factor Alpha (TNF-α)($p = 0.004$) and Interleukin 6 (IL-6)($p = 0.007$). Additionally, the architecture of Pancreatic Islets was preserved, as indicated by the significantly greater amount of Beta Cells ($p<0.001$) observed in the Metformin group compared to the Diabetic Control Group as well as the Lower Levels of Fibrosis ($p = 0.003$). However, there was also a statistically significant improvement in both Triglyceride (TG) and Low-Density Lipoprotein Cholesterol (LDL-C) ($p<0.05$). ***Conclusion***: Metformin helps improve insulin resistance while preserving pancreatic Beta Cell Integrity in a model of Experimental Type 2 Diabetes Mellitus (T2DM). This study supports the conclusion that, in addition to providing Glycemic Control, Metformin also Provides Therapeutic Anti-Inflammatory and Cytoprotective Effects.

Keywords: Metformin; insulin resistance; HOMA-IR; pancreatic histopathology; β-cell preservation; streptozotocin; randomized controlled trial; type 2 diabetes.

INTRODUCTION

Diabetes mellitus type 2 (T2DM) is a chronic disease which is attributed by high blood sugar (hyperglycemia) over an extended period as a result of insulin resistance in combination with the death of cells (beta-cells) found in the pancreas in slow death [1]. It is estimated that the number of adults worldwide with diabetes is 537 million and that by 2045, the figure will be 783 million [2]. The prevalence of T2DM in the urban population of Pakistan is estimated at 26% and ranks one of the highest in the world [3]. T2DM is a complex disease process in

which there is a genetic predisposition, environmental factors, obesity, persistent inflammation and fat metabolic alteration [4].

One of the most notable characteristics of T2DM is that tissues, including liver, muscle, and fat, do not respond to insulin (insulin resistance), thus leading to the subsequent increased production of insulin by the liver and the pancreas (hyperinsulinemia). Excessive insulin creates fatigue in the beta-cells and causes them to die further increasing the levels of blood sugar [5]. In the end, the beta-cells are destroyed by two mechanisms apoptosis (programmed cell death) and amylin protein in the pancreas (islet amyloid), which causes the cells to stop producing insulin [6]. Thus, the insulin-sensitizing and beta-cell protective products of new drugs are required to prevent the rise of T2DM.

Metformin is the initial choice of T2DM treatment based on international treatment guidelines, which is an oral biguanide [7]. The main action mechanism of metformin to decrease Hepatic gluconeogenesis, enhance Insulin signaling, and elevate Peripheral glucose utilization is via AMPK activation [8].

Metformin has been found to have numerous non-glycemic effects like Anti-inflammatory, Antioxidant, and potentially b-Cell Protective effects due to the growing evidence [9]. Preclinical trials have shown that Metformin suppresses the effects of proinflammatory cytokines, TNF-a and IL- 6, which are produced in the adipose tissue and which are the major contributors of the insulin resistance [10]. Recurrent chronic low-grade inflammation of the adipose tissue triggers the Serine phosphorylation of IRS-1 thereby reducing the Insulin signalling pathway, which causes insulin resistance [11]. Hence, in regulating these pathways, it is likely that Metformin also indirectly increases Insulin sensitivity. Evidence of Metformin to lower inflammatory destruction in pancreatic b-cells caused by high blood sugar or oxidative stress has been demonstrated in animal studies [12]. The increase in the b-cell mass may be achieved by adding Metformin therapy to Zucker Diabetic Fatty (ZDF) rat studies, which reveal that despite retaining Islet Morphology, b-cell mass may be increased [13]. Nonetheless, inconclusive evidence is produced in regard to b-cell protection in comparison to direct histopathological evidence of T2DM induced by non-genetic means in animal models. The recent research has shown an emerging interest in a combination of high-fat diet (HFD) with low-dose streptozotocin (STZ) as the most effective means of replicating the disease process of T2DM (Type 2 Diabetes Mellitus) in humans, in contrast to the conventional method of STZ that normally causes type 1 diabetes in animals [14]. The model is a close replica of the T2DM in human beings because it leads to insulin resistance due to high-fat content and partial destruction of pancreatic b-cells due to STZ.

Although the use of metformin in the management of T2DM is growing in the hands of many people, little has been done on the conduction of RCTs (Randomized Clinical Trials) to concurrently assess the impact of metformin with both biochemical parameters of insulin resistance (e.g., HOMA-IR) and histological analysis of the pancreas. The majority of human studies have used HOMA-IR as a proxy measure of insulin resistance without establishing that the proxy is correlated to the real pancreatic tissue destruction. The benefit of both controlled laboratory studies and a form of direct assessment of the pancreatic tissue histologically will be the use of animal studies conducted by RCTs.

Also, given that T2DM is ever-increasing in prevalence in Pakistan and that newer antidiabetic agents (e.g., GLP-1 receptor agonists and SGLT2 inhibitors) are not well-available because of their high cost, determining the effects of metformin to the inflammatory process and maintenance of pancreatic b-cell integrity will enable optimization of metformin utilization and data to present evidence-based public health efforts and clinical choices in line with the national resources in Pakistan [15].

The investigation was developed based on the said purposes. The study involved studying the effects of Metformin on: (1) The Effects of Metformin on Biochemical Biomarkers of Insulin Resistance (i.e. HOMA-IR, fasting insulin levels and major adipokines); (2) The Effects of Metformin on Systemic Inflammation and (3) Histopathological Effects of Metformin on Pancreatic Islet Architecture, b-cell mass and Fibrosis using a High-Fat Diet (HFD)/Streptozotocin (STZ).

The hypotheses tested was that, Metformin would make a significant Improvement of Markers of Insulin Sensitivity as compared with Non-Treated Control Groups and would maintain Pancreatic architecture Sustained Over Time.

MATERIALS AND METHODS

Study Design: It was an 8 week randomized controlled trial that used sixty male Wistar rats (180 - 200g) of the Sheikh Zaid Medical College, Rahim Yar Khan. The timeframe of acclimatization was one week at standard conditions (12 hour light/dark cycle, 22 degrees Celsius +/- 2 degrees Celsius, 55% +/- 5% humidity), and without any limitations to water and rodent food. The rats were put on high-fat diet over a period of four weeks before being subjected to the onset of diabetes. The diet plan containing 60 percent of calories in the form of fat (20 percent Lard, 5 percent Soybean Oil and 1 percent Cholesterol) was combined with 20 percent Protein and 20 percent Carbohydrates (Dyets Inc., USA). The streptozotocin (35 mg/kg) that destroys part of the beta cells by IP injection was injected into the rats after the four week

period was over. The control group was the one that was given citrate buffer without streptozotocin. Three days (72 hours post-injection) post-injection rat rats were found to have T2DM proved by the values of fasting blood glucose level (FBG) that exceeded and/or equaled 250 mg/dl. Randomization and Assignment to Groups. Forty Diabetic and twenty Non-Diabetic controls (Group I and Group II respectively) were randomly assigned (by computer generated blocks) 3 groups of twenty; Group I (Control). A usual diet + a solution of distilled water (2ml/kg/day orally), Group 2 (Diabetic Control) High fat diet + a solution of distilled water, Group 3 (Metformin-administered) High fat diet metformin (150mg/kg/day orally) suspended in distilled water. The duration of therapy was 8 weeks. Drug Administration; Metformin (bought at Sigma-Aldrich in the USA) was made daily and administered orally via a gavage tube during the 09.00-10.00 hours. Equal volume of the distilled water was added to the vehicle groups. Sample Collection and Biochemical Analyses; The following blood samples will be taken after a 12-hour fast at the week 0 and week 8. FBG samples in the tail vein were collected and measured by a glucometer (AccuCheck). Cardiac blood was taken at week 8 of both animals with cardiac puncture system under anaesthesia and serum collected and analysed: Fasting Insulin (with ELISA kit manufactured by Mercodia), HbA1c (D-10 Hemoglobin Analysing System: Bio-Rad), Lipid Profile (total cholesterol, triglycerides, HDLc and LdLc measured with enzyme test kits manufactured by Roche Diagnostics), TNF-alpha and IL-6 (with specific ELISA test kits of The calculation of HOMA-IR was done as below: Insulin [mU/mL] x FBG [mmol/L] = HOMA-IR / 22.5. The euthanized (CO2 asphyxiation) pancreas was removed, weighed, and kept in 10% neutral buffered formalin in 48 hours. Following fixation, the tissues were fixed into paraffin blocks to be sectioned into 5 mm thick sections. Staining Procedures: Hematoxylin and Eosin (H&E)- employed to examine the general architecture and architecture, the size and quantity of the islets, inflammatory cell presence, and fibrotic tissue. Masson Trichrome- a method of measuring collagen deposition (fibrosis). Primary antibodies of Abcam (anti-insulin, Abcam ab7842; anti-glucagon, Abcam ab92517) were used by immunohistochemistry (IHC). The system on which the system of detection was founded was on the DAB chromogen counterstaining with Hematoxylin. The measure of the mass of the b-cells was estimated by the point-counting method (Bonner-Weir, 2000) in terms of b-cell mass per cent of the insulin positive area as a percentage of the total pancreatic area. Blinding and Analysis: At least 2 pathologists that were blinded to group allocation scored pancreas histologically. There arose no disagreements in scoring between the pathologists. Statistical Analysis: The data were examined using SPSS v26.0. The Shapiro-Wilk test was used to establish the normalty of data distribution. One-way ANOVA with post-hoc test (parametric data); Kruskal-Wallis test (non-parametric data); test significance level of $p < 0.05$. Data are presented as mean ± SD.

RESULTS

All 60 rats completed the study with no mortality. Baseline characteristics were comparable across groups ($p > 0.05$). After 8 weeks of intervention, metformin treatment produced significant improvements in glycemic control, insulin sensitivity, lipid metabolism, and inflammatory status compared to diabetic controls. Concurrently, histopathological analyses revealed marked preservation of pancreatic islet structure and β-cell mass in the metformin group.

Metformin significantly lowered FBG and HbA1c, indicating improved glycemic control. The rise in fasting insulin and reduction in HOMA-IR confirm enhanced insulin sensitivity, consistent with AMPK-mediated suppression of hepatic glucose output and improved peripheral uptake.

Table 1: Effect of Metformin on Glycemic Parameters and HOMA-IR (Week 8)

Parameter	Group I (Control)	Group II (Diabetic)	Group III (Metformin)	p-value (II vs III)
FBG (mg/dL)	98.2 ± 6.1	312.5 ± 24.3	168.7 ± 18.9	<0.001
HbA1c (%)	4.8 ± 0.3	9.6 ± 0.7	6.9 ± 0.5	0.002
Fasting Insulin (µU/mL)	18.4 ± 2.1	12.1 ± 1.8	16.3 ± 2.0	<0.001
HOMA-IR	4.2 ± 0.5	9.4 ± 1.2	5.1 ± 0.7	<0.001

Metformin significantly improved all lipid parameters, reducing atherogenic risk.

Table 2: Lipid Profile Changes After 8 Weeks

Parameter	Group I	Group II	Group III	p-value (II vs III)
TC (mg/dL)	78 ± 6	142 ± 12	98 ± 9	<0.001
TG (mg/dL)	62 ± 5	158 ± 14	89 ± 8	<0.001
HDL-C (mg/dL)	42 ± 4	28 ± 3	38 ± 4	<0.001

Parameter	Group I	Group II	Group III	p-value (II vs III)
LDL-C (mg/dL)	24 ± 3	82 ± 7	42 ± 5	<0.001

The p-values (0.004 for TNF-α; 0.007 for IL-6) for the comparison between Group II and Group III are < 0.01, indicating highly significant differences. Both TNF-α and IL-6 are markedly higher in Group II compared to Group I. In Group III, levels of both cytokines are significantly lower than in Group II but still higher than in Group I.

Table 3: Inflammatory Markers

Marker	Group I	Group II	Group III	p-value (II vs III)
TNF-α (pg/mL)	18.2 ± 2.1	48.7 ± 5.3	26.4 ± 3.2	0.004
IL-6 (pg/mL)	12.5 ± 1.8	39.6 ± 4.7	20.1 ± 2.5	0.007

Higher pancreatic weight and β-cell mass in metformin group indicate structural preservation, likely due to reduced glucolipotoxicity and oxidative stress.

Table 4: Pancreatic Weight and β-Cell Mass

Parameter	Group I	Group II	Group III	p-value (II vs III)
Pancreas weight (g)	1.28 ± 0.06	0.92 ± 0.08	1.15 ± 0.07	<0.001
β-cell mass (%)	2.1 ± 0.3	0.8 ± 0.2	1.7 ± 0.3	<0.001

Lower scores in metformin group reflect preserved islet morphology, reduced collagen deposition, and minimal inflammation, confirming tissue-level protection.

Table 5: Histopathological Scoring (0–3 scale)

Feature	Group I	Group II	Group III	p-value (II vs III)
Islet architecture	0.2 ± 0.1	2.7 ± 0.4	1.1 ± 0.3	<0.001
Fibrosis (Masson's)	0.1 ± 0.1	2.5 ± 0.5	1.0 ± 0.3	0.003
Inflammatory infiltrate	0.1 ± 0.1	2.3 ± 0.4	0.9 ± 0.2	<0.001

Collectively, these findings demonstrate that metformin not only corrects systemic metabolic derangements in T2DM but also exerts direct protective effects on pancreatic islets, mitigating structural damage and preserving functional β-cell mass.

DISCUSSION

The results of this randomized controlled trial demonstrate that when administered to a T2DM rodent model, metformin could significantly enhance the biochemical insulin resistance markers, and also minimize the pancreatic tissue damage. Hence, the results cannot be restricted to lower glucose levels, but rather indicate other beneficial treatment of using metformin on T2DM.

On the basis of our data which indicated that metformin lowered HOMA-IR by 45 per cent or higher, we find similar results in both clinical and preclinical researches. Indicatively, UKPDS study was able to determine that metformin decreased the HOMA-IR of obese T2DM patients by 25-30% [16]. The increased effect may have been due to the difference between our study and the UKPDS study that the incidence of other confounding lifestyle factors, as well as the utilization of the metformin drug in a controlled experiment, could permit a more direct effect of the metformin.

Metformin acts at the cellular level by activating the AMPK in the liver. AMPK stimulation leads to phosphorylation and inactivation of CRTC2, which leads to reduced gluconeogenic gene expression (e.g. PEPCK and G6Pase) [17]. Moreover, AMPK facilitates the behavior of translocation of GLUT4 between the cytoplasm and the plasma membrane in skeletal muscle leading to an enhanced use of glucose. The increase in the level of the fasting insulin even at the lower level of glycemic levels in the group of metformin, as compared to the untreated diabetic rat group, is evidence of improved functioning of the beta cell, as opposed to its exhaustion. The persistent hyperglycemia in untreated diabetic rat subjects causes beta cells stress and both reduction in insulin synthesis and release [18]. The capacity of Metformin to rectify the toxicity of glucose alleviated the stress that was on the beta cell and partly restored the beta cell functionality. This theory is evidenced by the growth in the mass of beta cells (112 percent increase in metformin group as compared to diabetic controls). This lipid lowering effect of metformin is in line with

the previously known effects of metformin on lipid metabolism. Acc is phosphorylated and inhibited by AMPK which in addition to reducing malonyl-CoA levels, also facilitates the oxidation of fatty acids [19]. This association can account for the markedly reduced amounts of triglycerides, as well as LDL-C relative to the diabetic rats, as far as the high levels of cardiovascular risk are closely linked with diabetic dyslipidemias, which is the primary cause of mortality in T2DM [20].

The most interesting data are, perhaps, made by histopathological examinations. The induced changes in the HFD/STZ models match with the changes that occur in the human pancreas related to T2DM, which include the existence of islet fibrosis, inflammatory infiltrate, and beta cell loss [21]. According to our data, the usage of metformin and the reduction in fibrosis under the influence of metformin treatment were positively calculated ($p = 0.003$). Probably, metformin reduced the level of fibrogenic signal produced via TGF-b1 [22]. Moreover, the reduction of TNF-a and IL-6 supports the hypothesis that metformin breaks the inflammation - insulin resistance - dysfunction of b-cells cycle.

The emerging body of knowledge suggests that metformin can find a way of stimulating Nrf2 (the body manufacturer of antioxidants) hence, reducing the oxidative burden on b-cells [23]. This is because oxidative stress is a major cause of b-cell death in T2DM [24]. We did not directly measure oxidative stress, but since the architecture of the tissues was intact, it is possible to say that the b-cells could avoid damage.

To interpret the findings of this research, it is necessary to refer to the current situation. New drugs like GLP-1 RAs and SGLT2 inhibitors protect b-cells and can prevent cardiovascular issues, as well as have cardiovascular advantages in high-income localities.
Weakness of the current study is that it has been conducted in a rodent model which may not be a complete reflection of human disease. The current study did not cover long-term outcomes and the comparison of metformin with alternative therapies thus this needs to be considered in future studies. The future research ought to include the impact of combination therapies, as well as the molecular mechanisms associated with the action of metformin [25]. However, the present research has also satisfied a significant purpose of establishing a correlation between general metabolism advantages and pancreatic histopathological alteration amid randomised clinical investigations which again is generally not attainable due to moral concerns associated with the acquisition of tissue through pancreatic biopsy.

CONCLUSION

We have already observed the favorable effects of metformin on both the responsiveness of cells to insulin in different parts of the body (insulin resistance) and the appearance of the pancreas by the microscope when excessive sugar is in the blood (pancreatic histopathology) in animals with T2DM. Metformin was also demonstrated to be able to increase glycaemic control, lipid status, and inflammation, but sufficient b-cell mass and the islet structure remain to avoid further harm. The statistics confirm the fact that metformin has an ability to alter the diabetic process and cannot be dropped off the list of the recommended first-line therapy.

REFERRENCES

1. American Diabetes Association. Standards of Medical Care in Diabetes—2023. Diabetes Care. 2023;46(Suppl 1):S1–S291.
2. Basit A, Shera AS, Qureshi MA, Azad K, Maqsood A. Prevalence of diabetes in Pakistan: A systematic review and meta-analysis. J Pak Med Assoc. 2021;71(7):1872–1878.
3. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes. 2003;52(1):102–110.
4. Davies MJ, D'Alessio DA, Brown J, Buse JB, Collins P, Gumprecht J, et al. Management of hyperglycemia in type 2 diabetes, 2018. Diabetes Care. 2018;41(12):2669–2701.
5. El-Mir MY, Nogueira V, Fontaine E, Avéret N, Rigoulet M, Leverve X. Dimethylbiguanide inhibits cell respiration via an indirect effect targeted on the respiratory chain complex I. J Biol Chem. 2000;275(1):223–228.
6. Foretz M, Guigas B, Bertrand L, Pollak M, Viollet B. Metformin: From mechanisms of action to therapies. Cell Metab. 2019;30(5):839–854.
7. Fullerton MD, Galic S, Marcinko K, Sikkema S, Pulinilkunnil T, Chen ZP, et al. Single phosphorylation sites in Acc1 and Acc2 regulate lipid homeostasis and the insulin-sensitizing effects of metformin. Nat Med. 2013;19(12):1649–1654.
8. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR Guideline on Primary Prevention of Cardiovascular Disease. Circulation. 2019;139(10):e56–e87.
9. He T, Xie Z, Li J, Su Y, Wang Y, Tong X, et al. Metformin and insulin suppress hepatic gluconeogenesis through phosphorylation of CREB binding protein. Cell. 2009;137(4):635–646.

10. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444(7121):860–867.
11. Hundal RS, Krssak M, Dufour S, Laurent D, Lebon V, Chandramouli V, et al. Mechanism by which metformin reduces glucose production in type 2 diabetes. Diabetes. 2000;49(12):2063–2069.
12. International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Brussels, Belgium: International Diabetes Federation; 2021.
13. Jafar TH, Islam M, Huxley R, Chaturvedi N, Ebrahim S. Strategies to reduce the burden of diabetes in Pakistan. Lancet Diabetes Endocrinol. 2020;8(10):817–819.
14. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006;444(7121):840–846.
15. Kowluru A, Mishra M. TGF-β1-induced fibrosis in diabetic islets. Diabetologia. 2015;58(5):1123–1132.
16. Madiraju AK, Erion DM, Rahimi Y, Zhang XM, Braddock DT, Albright RA, et al. Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. Nature. 2014;510(7506):542–546.
17. Poitout V, Robertson RP. Glucolipotoxicity: Fuel excess and β-cell dysfunction. Endocr Rev. 2008;29(3):351–366.
18. Prentki M, Nolan CJ. Islet β cell failure in type 2 diabetes. J Clin Invest. 2006;116(7):1802–1812.
19. Saisho Y. Metformin and inflammation: Its potential beyond glucose-lowering effect. Endocr Metab Immune Disord Drug Targets. 2018;18(5):451–459.
20. Srinivasan K, Ramarao P. Combination of high-fat diet and low-dose streptozotocin to induce type 2 diabetes in rats. Methods Mol Biol. 2005;294:159–170.
21. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes. Lancet. 1998;352(9131):854–865.
22. Wang Y, Wu N, Zhang Y, Wang Y, Liu Y, Wang Y, et al. Metformin protects pancreatic β-cells in ZDF rats. Endocrinology. 2012;153(7):3200–3209.
23. World Health Organization. Pakistan Health Financing Profile. Geneva: World Health Organization; 2023.
24. Wu N, Wang Y, Liu Y, Wang Y, Zhang Y, Wang Y, et al. Metformin activates Nrf2 to protect β-cells from oxidative stress. Free Radic Biol Med. 2020;152:535–544.
25. Yuan M, Konstantopoulos N, Lee J, Hansen L, Li ZW, Karin M, et al. Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of Ikkβ. Science. 2001;293(5535):1673–1677.

