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Clinical Efficacy and Safety of Metformin in Prediabetics

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ABSTRACT

Background: Prediabetes is defined as a state of abnormal glucose homeostasis, HbA1c 5.7% to 6.4% and fasting blood glucose 100 mg/dl to 125mg/dl. Mainstay of treatment in prediabetes is lifestyle changes. However if not controlled pharmacotherapy is added. Metformin HCL is a biguanide drug.
Objectives: To evaluate clinical efficacy of metformin HCl with lifestyle modifications and to assess the adverse effects, safety profile and cost effectiveness of metformin in pre-diabetics.
Materials and Methods: This randomized controlled clinical trial (RCT) was conducted at diabetic clinics of National Medical Centre and Bay View Hospital Karachi. Individual study duration was 3 months. This randomized controlled clinical trial (RCT) is registered at clinicaltrials.gov, bearing NCT number. Males and females, 17-40 years of age, were included. Metformin HCl was given 500 mg orally BD for 12 weeks alongwith lifestyle modification. Anthropometric parameters were evaluated at baseline week 6 and week 12. Metabolic parameters and safety profile parameters were evaluated at baseline and week 12. Adverse effects were assessed at 6 and week 12 whereas cost effectiveness at the end of study.
Results: Majority of participants were in age group 32 to 40 years. Weight, HBA1c, FBS were highly significantly reduced, HDL was significantly increased. Metformin was found to be safe. No adverse effects were reported.
Conclusion: Metformin is clinically effectively reduced weight, improved FBG and HbA1c in prediabetics. Metformin was safe for the dose and duration used and devoid of adverse effects in prediabetics. Metformin is very cost effective.
Keywords: FBG, HbA1c, HCL, Lifestyle changes, Metformin HCL, Pre-diabetes, Weight.

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INTRODUCTION

Prediabetes indicates transitional phase of dysglycemia from normoglycemia towards diabetes. Consequently this term "prediabetes" has been utilized for identification of individuals having a risk of acquiring diabetes, following prediabetes. This is also correlated to elevated cardio-metabolic risk factors as well as poor outcomes.[1] Prediabetes can cause type II diabetes amongst 25% of individuals as part of a time span from three to five years. Consequently, a higher proportion inclusive of seventy percent of individuals having prediabetes if unchecked, become diabetics after a certain period of time. Hence prediabetes merely constitutes a transition in between appropriate blood glucose level, as well as diabetes mellitus(DM), yet correction is by implementing on lifestyle modification regimen (ADA, 2019).[2]

One of the major risk factor associated with it is obesity.[2] Visceral obesity increases likelihood to have prediabetes. Waist circumference constitutes conventional marker indicating visceral obesity and escalated chance of prediabetes.[3]

Prediabetes is prevalent in Asian countries based individuals. These include Chinese, Saudi Arabians, Malaysians at differing rates including 35.7%, 6.8%, as well as 22.6%, respectively. Prediabetes prevalence in Thai adults is 5.4%.[4]

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The International Diabetes Federation, has reported prevalence of diabetes in Pakistan being 26.7% in the year 2022. Based on this the overall cases were nearly 33,000,000. As per World Health Organization (WHO), The documented data on prevalence of pre-diabetes in Pakistan is scarce. The documented data on prevalence of pre-diabetes in Pakistan is scarce. Prevalence of prediabetes has been reported in adult population in Pakistan as nearly 10.91%.[5]

The diagnosis of prediabetes has its basis being World Health Organization (WHO) as well as American Diabetes Association (ADA) yardsticks. Impaired glucose tolerance as well as HbA1c have been proposed as diagnostic criteria by WHO as well as ADA, HbA1c 5.7 -6.4% as well as fasting plasma glucose 5.6-6.9 mmol/L (100-125 mg/dL) are the cut off values for prediabetes. Defect in insulin secretion leads to insulin sensitive tissues incapacitated in connection with response to insulin. The molecular mechanisms on which synthesis as well as release of insulin, along with insulin response in tissues is based, require tight regulation as insulin activity precisely catches with metabolic demand.[6]

In the individuals having a high risk of acquiring diabetes, various trials have exhibited efficacious role of drugs that lower glucose as well as weight, in diminishing the number of new cases of diabetes, including metformin, acarbose, thiazolidinediones, glucagon-like peptide 1 (GLP1) agonists as well as weight lowering drugs. Based on certainty of diabetes having the potential of leading to micro as well as macrovascular sizeable effort directed towards preventing is considered important in order to lower chances of long-standing complications.[7]

The non-pharmacological treatment of prediabetes includes life style changes which are inclusive of regular physical activity, weight loss and dietary measures. In individuals having pre-diabetes, ardent screening as well as expeditious lifestyle modification have highly efficacious role to evade type 2 diabetes mellitus or to reverse pre-diabetes.[7] In accordance with American College of Sports Medicine (ACSM) as well as ADA guidelines150 minutes per week should be spent in moderate to powerfully intense aerobic activity. The recommended exercises include, walking, jogging, running and cycling. Aerobic exercise enhances insulin sensitivity as well asvascular function along with improved aerobic fitness and diminishedbody fat.[8] Specific diet recommendations for prediabetics include, adhering to whole grains, nuts, legumes, vegetables. Furthermore, prediabetics are also adviced, strict avoidance of refined carbohydrates (CHO), red meat, processed meat as well as sugar-sweetened beverages. Furthermore High antioxidant consumption peculiarly as fruits as well as vegetables, is linked to preventing progression of prediabetes to type 2 diabetes mellitus.[9]

The ADA as well as NICE guidelines approve therapeutically using metformin in order to prevent diabetes, within specific spheres. Data from the studies DPP as well as Diabetes Prevention Program Outcomes Study (DPPOS) support the IDF guidelines, regarding metformin having preventive role amongst individuals at risk of acquiring diabetes.[10]

Metformin use in prediabetes is linked to improvement in control of glycemic indices as well as diminished longstanding complications. Metforminh as exhibited high efficacy in lowering progression of prediabetes to diabetes as part of the Diabetes Prevention Program study.[11]

The pharmacokinetics of metformin are sufficiently specified. Metformin is orally available at an average of 50% bioavailability. As strongly evidenced, metformin is distributed within tissues as well as deep compartments, inclusive of red blood cells. Metformin clearance is done solely by kidneys. Amongst patients having deficiently functional kidney, metformin renal clearance is lowered.[12]

Metformin due to its manifold pharmacodynamic actions, has become anavenue of interest within multifarious areas, inclusive of preventing type 2 diabetes. Metformin diminishes hepatic gluconeogenesis, elevates peripheral insulin sensitivity within insulin sensitive tissues. These include muscle, adipose tissue. This is also followed by elevated peripheral glucose utilization. Metformin is highly efficaciously lowers hepatic glucose yield via slight halting of mitochondrial respiratory-chain complex. Consequently, energy status of cell enhances activation of adenosine monophosphate-activated protein kinase (AMPK), that eventually incites adenosine triphosphate (ATP) forming catabolic pathways simultaneously halting ATP-consuming anabolic pathways. Hence leading to maintenance of cellular energy stores.[13]

Prediabetic is globally a grave problem, due to it's propensity to proceed to type II diabetes mellitus, if left unchecked. Proper and timely diagnosis pitched with appropriate management in prediabetics can prevent or delay the onset of type II diabetes. Exploration of effective and cost effective conservative and or drug treatment options are the dire need at our national level. Consequently, this study is aimed at evaluating role of metformin in curing prediabetes and consequently preventing it's progression to diabetics.

MATERIALS AND METHODS

This study was a randomized, open label, prospective, clinical trial registered at Clinicaltrials.gov with NCT number NCT05759442. Study was commenced after approval from Bahria University Health Sciences Campus, Ethical Review Committe (ERC) vide letter number ERC123/2022 dated 19/12/2022.

The study was conducted after approval from research review committee Bahria University Health Sciences Campus Karachi. Following which the study received approval by the Ethical Review Committee Bahria University Health Sciences Campus Karachi. Recruitment began in December 2022. Written informed consent form for 17 to 18 year old participants was parental consent form whereas for 18 to 40 years old participants consent form was the subject consent form for over 18 years old individuals.

Screening of patients followed by enrolment in the study was done from Diabetic Clinics, National Medical Center Karachi and Bay View Hospital Karachi.

The sample size came out to be 25. Sampling technique was non probability purposive sampling.

The inclusion criteria included, males and females 17-40 years of age. adolescents with BMI exceeding ≥85th percentile as overweight and obese ≥95th BMI percentile, adults overweight & Obese (WHO Asian BMI criteria),[9] FBS (100-125 mg/dl) and HBA1c 5.7% to 6.4%.[9] Exclusion criteria included, concomitant medical problems as established diabetes, hepatic or renal insufficiencies hypertension etc, known allergy or intolerance to metformin.

Total duration of study was 6 months from 19th December 2022 to 19th June 2023 and individual study period was 12 weeks.

Twenty five diagnosed prediabetic patients after screening without any other co-morbid illness were included in the study. The intervention included tablet

metformin HCl 500 mg per oral twice daily for 12 weeks along with life style changes including diet and exercise. Escalation dose therapy strategy was followed for one week.

All study participants were required to fill subject evaluation form.

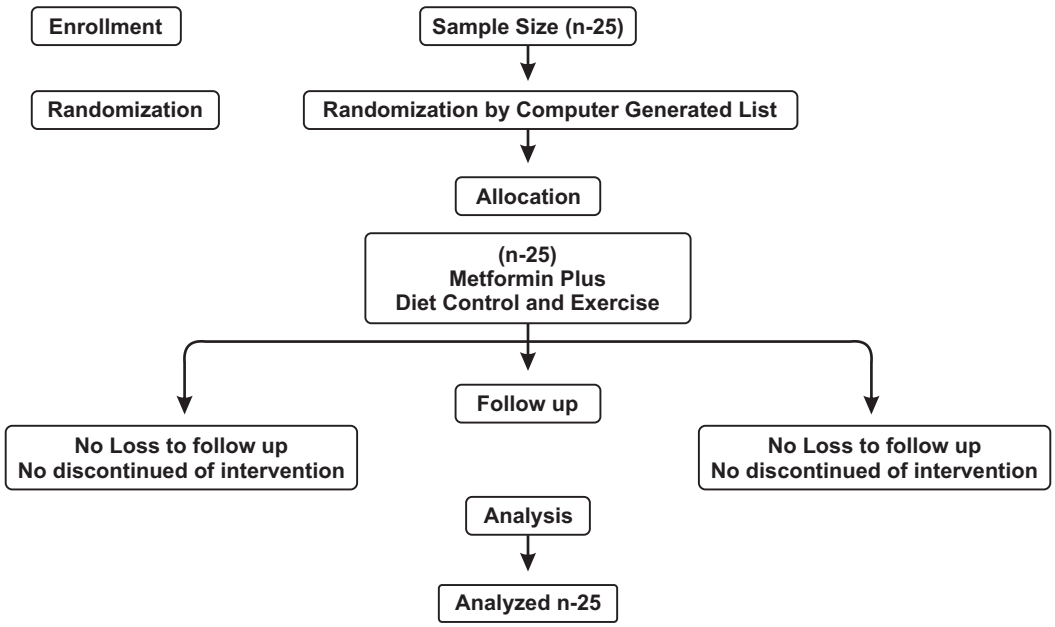
Anthropometric parameters including weight, height, BMI, waist circumference, waist hip ratio, neck circumference were assessed at baseline, week 6 and week 12. Metabolic parameters including glycemic indices as well as lipid profile and safety profile parameters were only assessed at baseline and week 12.

SPSS version 25 was used for statistical analysis. Descriptive statistics were mean and standard deviation for quantitative variables and frequencies and percentages for qualitative variables. Data was found to be non-parametric and tests including Man Whitney U test, Friedman test and Wilcoxon signed rank test, were utilized in this study. P value cut off was <0.05.

RESULTS

In this study 17-24 year old age group study participants were 5(20%),25-31 years were 8(32%) and 32-40 were 12(48%) as shown in Figure 01.

At baseline HbA1C was12.62.It reduced to 7.70 at week 12.The result was statistically highly significant exhibiting effect of metformin on HbA1C. Fasing blood sugar at baseline week 1 was 13.48 and at week 12 it was 1.50. The result was statistically highly significant, showing effect of metformin on FBS. Mean ranks of glycemic indices are as shown in figure 02.



CONSORT Flow Chart

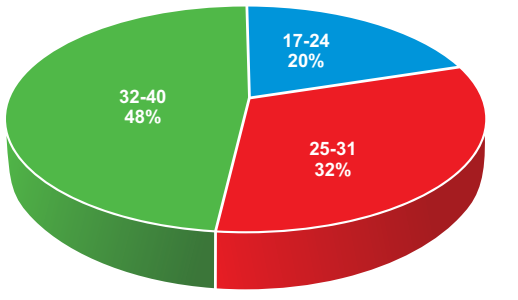


Figure 01.

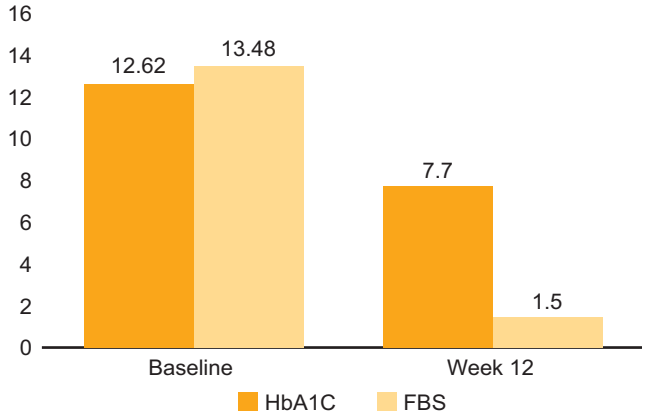


Figure 2 : Mean ranks ofHbA1C and fasting blood sugar (FBS) at baseline and week 12

Mean ranks of baseline anthropometric parameters were as shown in Table 01.

Table 01. Anthropometric Parameters, N= 25

Parameters	Baseline	Week 6	Week 12	P-value
Weight (kg)	2.98	2.96	2.91	0.0001*
BMI (kg/m2)	2.20	2.16	1.64	0.03*
Waist circumference (cm)	2.56	2.12	1.32	0.012*
Hip circumference (cm)	2.60	2.344	2.32	0.156
Waist to Hip Ratio	2.32	2.25	2.21	0.378
Neck Circumference (cm)	2.49	2.40	2.48	0.459

The mean rank for baseline weight of participants was 2.98, yet it reduced to 2.96, 2.91 in week 6 and week 12 respectively. The difference in mean ranks in weight from baseline to week 12 was statistically significant. BMI at baseline was mean rank 2.20 and it lowered to 2.16 in week 6, whereas it reduced to 1.64 in week 12. The lowering in mean rank for BMI was statistically significant. The waist circumference of study participants at baseline had mean rank 2.56 but lowered to 2.12 and 1.32 respectively in week 6 and week 12. The results were statistically significant. The mean rank for hip circumference of participants having received metformin lowered from 2.60 to 2.34, baseline to week 6 respectively. However it further lowered to 2.32in week 12. The lowering of mean rank for hip circumference in group A was statistically non-significant. The waist hip ratio of participants lowered from 2.32 at baseline to 2.25 at week 6 and 2.21at week 12. Neck circumference of participants was mean rank2.49 at baseline,2.40 week 6 and at week 12 being 2.48. There was no effect on neck circumference as depicted by results being non-significant statistically.

The mean rank for total cholesterol level was 1.52 at baseline and lowered to 1.48 at week 12. The mean rank for triglyceride at baseline was 1.62 and lowered to 1.38. The mean rank for HDL at baseline was 1.02 and increased to 1.98 at 12th week. The result was statistically highly significant. The mean rank for LDL at baseline was 1.68 and lowered to 1.32 at 12th week. The mean rank for VLDL at baseline was 3.33and lowered to 2.50 at week 12. Mean ranks of lipid profile are shown in figure 03.

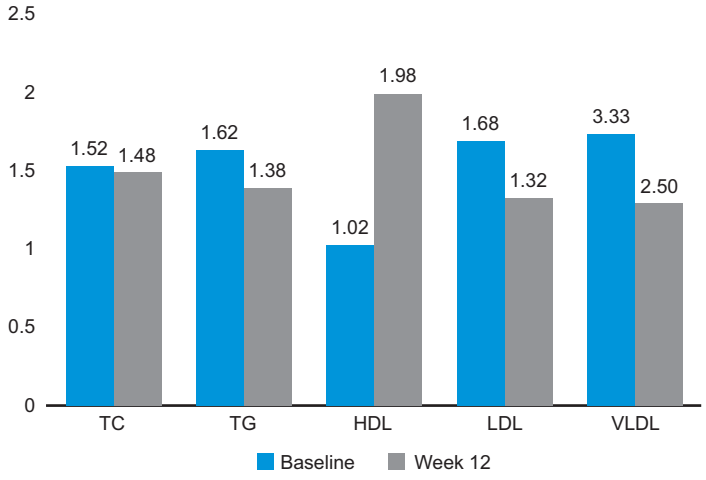


Figure 03. Mean ranks of lipid profile at baseline and week 12

Safety profile is as shown in table 02.

Table 02. Safety Profile, N=25

Parameters	Week 1 (N=25)	Week 12 (N=25)	P-value
CBC			
Hemoglobin g/dl	1.60	1.40	0.275
SGOT units/L	12.82	11.25	0.927
Creatinine mg/dl	13.39	12.50	0.501

As shown in table 02, metformin did not significantly derange the safety parameters hemoglobin, SGOT and creatinine.

There were no adverse effects reported or observed in any of the study participant. In any of the participant, the adverse effects of metformin including nausea, vomiting, diarrhoea and any other were not observed. Metformin was found to be very cost effective.

DISCUSSION

Age group 17-24 was 5(20%), age group 25-31was 8(32%) and age group 32-40 was 12 (48%). Majority of study participants fell in 32 to 40 years group.

In this study parameters related to anthropometric indices incorporating, weight, body mass index, waist circumference, hip circumference, waist to hip ratio as well as neck circumference were assessed at baseline, week 6 and week.

In our study weight of prediabetes patients taking metformin significantly decreased from baseline to week 12. Metformin also had significant effect on BMI & waist circumference from baseline to week 12. Hip circumference, waist to hip ratio and neck circumference were non-significantly reduced in our study.

Our study revealed that metformin treatment in a dose of 500 mg BD produced significant reduction in weight, BMI and in waist circumference. Our finding has been synchronous with study of Kujawska Łuczak et al, 2016 wherein three months duration metformin use in dose of 500 mg twice a day for 12 weeks resulted in significantly reduced weight, BMI and waist circumference. According to this study lowering of 4.2 % weight from baseline led to metformin induced adiponectin secretion indicating weight loss due to metformin. We have observed weight reduction by 3.96% that is equivalent to 4% and is coinciding with the study of Kujawska Łuczak et al, 2016.[12] Weight reduction by metformin within three months duration is similar to study by Qudah et al.[13] Metformin induced changes in anthropometric parameters inclusive of weight, BMI and waist circumference reduction in our study differed from study by Jensterle et al, in which metformin dose was 1000 mg twice per day but a combination of metformin with other drugs was considered superior to metformin alone for weight loss in PCOS without lifestyle changes.[13]

Similar to study by, Farhadian et al, 2020, our study revealed non-significant reduction regarding effect of metformin on hip circumference.[14] Contrary to our findings, in study by Safiah et al., weight, BMI were non-significantly reduced in prediabetics.[23] The reason for non-significant reduction in weight, BMI and waist circumference could be inclusion of diagnosed dyslipidemic patients in their study even though they used 2250 mg of metformin for 12 months.[14]

In this study metformin lowered HbA1c from baseline to week 12. The level of FBS was also reduced by metformin at end of week 12 highly significantly. These findings corroborated with study by, Izadi et al.[15]

Synchronous with our study, the findings of, Glechner et al revealed that metformin coupled to lifestyle changes culminated in prevention of progression of prediabetes to type 2 diabetes mellitus in prediabetes.[16]

The study also strongly differed from study by Ko et al, 2015 wherein metformin was given at a dose similar to our study but significant decline in HbA1C and fasting blood sugar, took a longer duration of 6 months and probably also due to existence of excessive oxidative stress in cancer patient.[17]

There was non-significant reduction in all parameters of lipid profile with the exception of HDL. This could be speculated to connection into significant results with longer than 12 weeks of study.

Our findings are coinciding with study by (Sauriasari et al.,2022) wherein similar results were obtained in connection with lowered total cholesterol, triglycerides, low density lipoprotein, very low density lipoprotein lowering as well as high density lipoprotein elevation.[18] The non-significant reduction in total cholesterol in response to metformin was in contrast to the study by of Basit et al., 2020 etc.[19] As metformin has effect of lowering possibilities of cardiovascular diseases, hence these additionally significant cardio-protective effects of metformin going beyond improvement in glycemic indices, are much less prominent in prediabetics as evident from our study. However, it is documented that in established diabetics the metabolic profile improving effect of metformin is more prevalent Wasif et al.[20] Furthermore, it may be predicted that metformin may produce significant results if used for more than three months duration in the prediabetics.

Present study revealed significant elevation in HDL levels following metformin usage in prediabetic patients, similar to study by, Hend et al. Our findings are contradictory to study by Lin et al.,2018 that showed HDL elevation only after 12 months as opposed to 12 weeks.

Coinciding with study by Luo et al, in our study metformin did not have efficacious role in lowering triglycerides in 12 weeks.[21] Contrary to this study a significant reduction in triglycerides by metformin was revealed in study done by Hu et al,2020 in diabetes.[22] The study by Hu et al also indicated a novel interface in connection with metformin use between cholesterol as well as glucose regulation via a novel linkage between ChREBP as well as PCSK9 regulation. The finding of novel pathway via study by Hu et al.,2020, warrants elucidation into furthermore similar molecular

mechanisms underlying metformin effect on cholesterol levels.

Contrary to our study, the study by Koc et al ,2022 showed improvement in prediabetes being strongly linked to improvement in all lipids in pre-diabetic patients after receiving metformin treatment for a period of 9 months.[23]

The effect of metformin on safety profile was assessed in this study. The safety profile was inclusive of complete blood count (CBC) test, serum SGOT and serum creatinine evaluation. There was no effect of metformin as indicating damage to liver and kidney. There was non-significant reduction effect of metformin on these parameters indicating that it is safe for use at the dose of 500 mg twice daily for a period of 12 weeks in pre-diabetics. Contrary to our study by Alvarez et al.,2023 has exhibited possibility of lactic acidosis in diabetics[24]. Synchronous with our study Gabriel et al,. 2023 exhibited lack of effect in connection estimated glomerular filtration rate.[25]

CONCLUSION

Metformin along with life style changes reduced weight, BMI waist circumference, HBA1c, FBG, lipid parameters and increased HDL. Metformin is found to be safe, cost effective and without any adverse effects.

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Ethical Consideration

This study was approved by Institutional Review Board of Bahria University Health Sciences Campus, Karachi, Pakistan.

Funding

There is no role of any funding agency in this study.

Conflict of Interest

Authors declared no conflict of interest.

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DATA SHARING STATEMENT: The data that support the findings of this study are available on request from the corresponding author. The data is not publicly available due to privacy or ethical restrictions.

AUTHORS' CONTRIBUTION

The following authors fulfill authorship criteria as per ICMJE guidelines;

Junejo S:	Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.
Karim N:	Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.
Jafri MSA:	Analysis and interpretation of data, drafting the manuscript, final approval, agreed to be accountable for all the work.
Razzak MA:	Analysis and interpretation of data, critical revision, final approval, agreed to be accountable for all the work.

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