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Cardio Metabolic Outcomes of Glimepiride with Metformin Combinations Therapy in Diabetes-Associated Cardiovascular Disease

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Abstract: This study aimed to assess the efficacy of different potencies of Glimepiride with Metformin (M&G CVD) combinations in managing cardiovascular disease in patients with Type 2 Diabetes Mellitus (T2DM). The current investigation involved a cohort of 256 subjects, encompassing 140 males and 116 females within the mid-age bracket spanning from 40 to 63 years, who underwent continuous monitoring over a duration of 9 years. Throughout the study period, anthropometric, hematological, and biochemical parameters were systematically evaluated in individuals with normal, untreated Type 2 diabetes, CVD Cardiovascular Disease, receiving treatment with a combination of metformin with glimepiride induced CVD (M&G CVD). Body Mass Index (BMI) emerges as a pivotal risk factor influencing the severity of cardiovascular disease in Type 2 Diabetes Mellitus (T2DM). Our study revealed significant BMI reductions in patients treated with metformin with glimepiride for cardiovascular disease (M&G CVD) compared to untreated counterparts. Noteworthy distinctions in systolic blood pressure were observed between T2DM patients and male/female. metformin with glimepiride CVD groups. Further analyses demonstrated substantial differences in both genders, emphasizing the effectiveness of combined therapy in managing BMI and blood pressure. These findings provide comprehensive insights into the potential of metformin plus glimepiride for mitigating T2DM-induced cardiovascular complications. Our study highlights the pivotal role of Body Mass Index (BMI) as a key determinant influencing cardiovascular disease severity in Type 2 Diabetes Mellitus (T2DM) patients. Notably, individuals receiving metformin with glimepiride for cardiovascular disease (M&G CVD) exhibited significant BMI reductions compared to untreated counterparts. Distinct differences in systolic blood pressure between T2DM and male/female M&G CVD groups underscore the therapeutic potential of combined therapy, offering valuable insights for a holistic approach to managing T2DM-induced cardiovascular complications.

Keywords: Glimepiride, Metformin, Type 2 Diabetes Mellitus, Cardiovascular Disease, Body Mass Index, Blood Pressure

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Introduction

In recent decades, the intersection of Type 2 Diabetes Mellitus (T2DM) and cardiovascular disease has emerged as a critical area of research, given the escalating global prevalence of both conditions. According to the International Diabetes Federation (IDF), diabetes impacts 8.8% of the adult population, with a marginally higher prevalence in men (9.6%) than in women (9.0%). Current global statistics reveal that 463 million individuals presently live with diabetes. Projections indicate a significant increase in these numbers, reaching an estimated 700 million people with diabetes by the year 2045. (International Diabetes Federation. IDF Diabetes Atlas. 9th ed. Brussels, Belgium: International Diabetes Federation; 2019). The prevalence of diabetes in India has experienced a gradual increase from 7.1% in 2009 to 8.9% in 2019. Notably, India holds the second position globally, following China, in the diabetes epidemic, with 77 million individuals affected. Among this population, 12.1 million are aged over 65 years, and projections suggest an increase to 27.5 million by the year 2045. Furthermore, it is estimated that approximately 57% of adults with diabetes in India remain undiagnosed, constituting around 43.9 million individuals. These findings underscore the need for comprehensive strategies to address the evolving landscape of diabetes in the country (Pradeepa and Mohan, 2021). Cardiovascular-related deaths represent 44% of the mortality rate in individuals diagnosed with type 1 diabetes mellitus (DM) and account for 52% of deaths in those with type 2 DM. Moreover, type 2 DM is linked to a two to six times higher risk of mortality associated with cardiovascular causes (Morrish *et al.*, 1977). Type 2 diabetes mellitus significantly heightens the risk of cardiovascular disease (CVD). The correlation between obesity, hypertension, and dyslipidemia further compounds the risk, leading to a clustering of metabolic and cardiovascular risk factors in individuals with obesity, particularly those at high risk (González-Muniesa *et al.,* 2017). The contemporary pairing of glimepiride, a modern sulfonylurea, with metformin is extensively recommended for proficient regulation of blood glucose levels. This combination is favoured for its ability to address both insulin secretion disorder and insulin resistance. In India, various potencies of the glimepiride and metformin fixed-dose combination are accessible and commonly prescribed by primary care physicians and specialists alike (Sahay *et al.,* 2020). Initiating combination therapy with glimepiride with metformin in the early stages could yield the advantage of a lasting effect by achieving prompt glucose control. This proactive approach helps prevent the development of a detrimental glycemic memory associated with both macrovascular complications (Kim *et al.,* 2014). It's noteworthy that hypertension significantly amplifies the risk of cardiovascular disease (CVD) (Pasquale *et al.*, 2018).

Metformin with glimepiride, commonly prescribed medications for managing diabetes. Metformin, known for its blood sugar-lowering effects, has demonstrated cardiovascular benefits by improving lipid profiles and reducing the risk of cardiovascular events in diabetic patients. Glimepiride aids in insulin secretion, contributing to glycemic control. This study aims to evaluate the effects of both standalone therapy and combination therapy involving metformin with glimepiride in patients with Type 2 Diabetes Mellitus experiencing cardiovascular dysfunctions. Through a comprehensive exploration of these treatment modalities, we aspire to contribute valuable insights towards optimizing diabetes management and mitigating associated cardiovascular risks.

Materials and Methods

Study Population:

A total of 256 patient samples were collected from Dravidian Specialty Hospital in Pattukottai, Tamilnadu, India, following ethical guidelines outlined by the Institute Ethical Committee for Human Research at Bharathidasan University. These guidelines adhere to national ethical standards for biomedical and health research involving human participants, as established by

the ICMR, Government of India. Ethical clearance for this study was obtained from the institution (IEC Ref. No. BDU/IEC/2020/03, dated 24th June 2020). Twelve male patients and five female patients were excluded from the study due to the severity of complications caused by diabetes mellitus.

The study population was categorized into: (1) Normal group (male 37, female 30); (2) Untreated pre-type 2 diabetes mellitus (T2DM) group (male 45, female 27); (30 Cardiovascular disease (CVD) group (male 25, female 35); (4) Combination of both metformin with glimepiride with CVD (M&G CVD) group (male 33, female 24). Patients treated with medications were monitored for 9 years.

Biochemical Analysis:

From each participant, 5 ml of blood was collected through venipuncture, with samples collected in both EDTA tubes (for whole blood) and red tubes (for serum collection). Collected demographic/clinical data included age, sex, diabetes duration, medical history, education, occupation, height, weight, BMI, heart rate, diastolic blood pressure, and systolic blood pressure. Blood parameters were analyzed every three months during regular medical check-ups at the hospital. Biochemical assays, including HbA1c (Immune Turbidimetric Method), fasting blood glucose (God-Pod method), total cholesterol (Chod-Pod Method), triglyceride (Gpo method), Hdl-C (Polymer Detergent Method), TURBOCHEM 100 fully automated analyzers. and a complete blood count (CBC) were conducted using a MEDONIC fully automated analyser. Erythrocyte sedimentation rate was determined using the Westergren method, CVD, M&G CVD Patient diagnosed test CK-MB (Immunoinhibition Method), TROP-I, ECG (Electrocardiogram), echocardiogram.

Statistical Analysis:

For statistical analysis, One-way ANOVA and Tukey's multiple comparisons were employed to compare data from multiple experimental groups. A reported p-value less than $p<0.0001$ and $p<0.001$ was considered statistically significant. Data entries and statistical analyses were performed using Graph Pad Prism.

Results and Discussion

In this study, we delved into the intricate relationship between Type 2 Diabetes Mellitus (T2DM), cardiovascular health, and the impact of metformin with glimepiride combination therapy (Fig. 1). The results presented a nuanced perspective on the interplay of these variables, revealing both anticipated and unexpected outcomes that warrant thorough consideration. Age emerged as a pivotal factor influencing the onset, management, and prognosis of T2DM and its associated comorbidities, particularly cardio-vascular diseases. The cohort highlighted the significance of additional treatment measures required for managing diabetes in older age groups, as this demographic is more susceptible to T2DM-associated cardiovascular diseases and morbidities. Several studies have pointed out that age seems to play a crucial role in determining the severity of diabetic complications, with individuals facing potentially greater risks in some cases. Early-onset diabetes appears to be a significant risk factor for multiple adverse health outcomes in older adults, highlighting the importance of early diagnosis and intervention.

The timing of type 2 diabetes diagnosis significantly influences the risk of future complications, with younger individuals potentially requiring more aggressive management strategies (Nanayakkara *et al*., 2020; Cigolle *et al*., 2022). Remarkably, our study observed an earlier onset of T2DM in female participants compared to their male counterparts, attributed to the gender-specific nature of healthcare-seeking behavior and diagnosis. Contrarily, symptoms of cardiovascular dysfunctions surfaced earlier in men than in females. Also gender specific effectiveness also addressed by several studies and more studies reveal that glimepiride with metformin both are

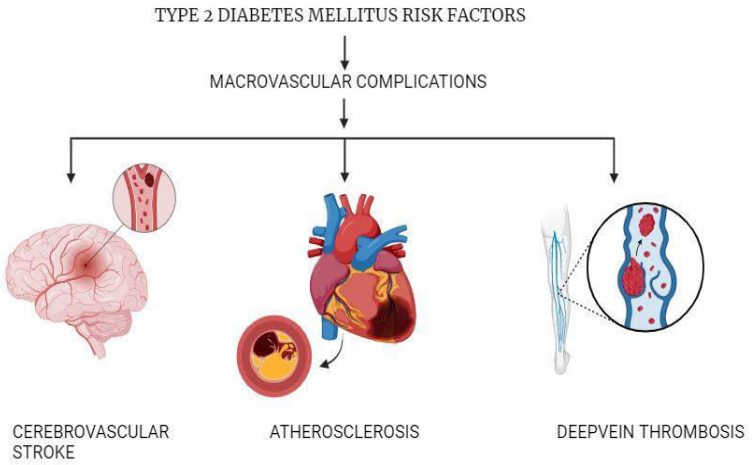

Fig. 1: Effects of combining metformin with glimepiride in addressing Macrovascular complications linked to type 2 diabetes and cardiovascular disease.

more effective in women than men. Our studies results also comply with those findings (Raparelli *et al*., 2020).

Body Mass Index (*BMI*):

BMI, a crucial prognostic indicator for Type 2 Diabetes Mellitus (T2DM) and cardiovascular-related mortality, demonstrated a noteworthy reduction in individuals undergoing metformin with glimepiride combination therapy, evident in both male (26.2±1.8; p<0.005) and female (27.2±3.53; p<0.03) participants. However, no significant changes were observed in individuals with PT2D male (28.2±2.3; p<0.0001), female (29.94±3.36 p<0.006) and CVD male (27.2±2.3; p<0.0001) female 27.98±3.80; p 0.0001) groups, maintaining higher levels compared to healthy individuals (Fig. 2).

Heart Rate:

Elevated heart rates were observed in both PT2D male (81.6±6.90; p<0.0001) female (83.40±12.89; ns) and CVD male (92.96±11; p<0.0001) female (90.45±9.17; p=0.002) groups. Notably, the combination of metformin with glimepiride exhibited efficacy in reducing elevated heart rates in male patients (89.75±10.12; p< 0.0001) but no significant reduction was noted in females (94.25±12.17; p<0.0001) (Fig. 3).

Blood Pressure:

Surprisingly, metformin with glimepiride combination therapy led to increased systolic blood pressure levels in the treatment group male (146.66 ±22.03; p=0.0006) female (141.25±20.06; ns) contrary to previous findings. This unexpected result may reflect unique characteristics of this cohort (Fig. 4). Similar effects were observed in diastolic pressure male (92.36 ±12.5; ns) female 91.66±13.7; ns).

Glucose:

In patients with CVD only, blood glucose levels were lower -- male (153±28; p<0.0001). female (139.1±28.13; p<0.0001) compared to the PT2D group male (278.64±43.98; p<0.0001). female (292.40±21.63; ns). Metformin with glimepiride combination therapy effectively regulated blood glucose levels in male patients (224±32.05; p<0.0001) however, no significant reduction was observed in female patients (262.03±46.08; p<0.0001).

HbA1c:

HbA1c levels, indicative of future diabetes management, saw a significant reduction with metformin with glimepiride therapy in both male (7.02 ± 2.3; p=0.0006) and female (8.03 ± 0.08;

Table 1: Biochemical analysis of Glimepiride with Metformin Combinations Therapy in Diabetes

	MALE					FEMAE				
Parameters	**NOR n(37)**	**PT2D (n45)**	**CVD n(25)**	**M&G CVD n(33)**	**Sign**	**NOR n(30)**	**PT2D n(27)**	**CVD n(35)**	**M&G CVD n(24)**	**Sign**
AGE (years)	39.73 ± 8.91	41.62 ± 8.51	51.84 ±7.51	60.87 ±9.13	****	43.03 ± 9.97	36.18 ± 12.57	57 ±9.25	63.33 ±11.18	****
BMI (kg/m2)	23.13 ±3.65	28.2^{C} ±2.3	$27.2^{Z,x}$ ±2.3	$26.2^{C,ns}$ ±1.8	****	24.33 ±2.27	$29.94^{a,}$ ±3.36	$27.98^{b,ns}$ ±3.80	$27.42^{c,x}$ ±3.53	****
HR (beats/min)	72.81 ±3.14	$81.6^{c,}$ ±6.90	$92.96^{c,z}$ ±11	$89.75^{c,x}$ ±10.12	****	80.26 ±10.73	$83.40^{ns,}$ ±12.89	$90.45^{a,ns}$ ±9.17	$94.25^{c,x}$ ±12.17	****
SBP (mmHg)	113.78 ±12.09	$129.68^{b,}$ ±19.37	$138^{c,ns}$ ±15.7	$146.66^{c,y}$ ±22.03	****	118.66 ±13.82	125.55^{ns} ±13.40	$136.28^{a,ns}$ ±21.43	$141.25^{c,x}$ ±20.06	****
DBP (mmHg)	80 ±8.81	84.04^{ns} ±11.64	$88^{a,ns}$ 10	$92.36^{c,x}$ 12.5	****	80.73 ±8.46	85.92^{ns} ±5.72	$89.42^{b,ns}$ ±7.25	$91.66^{b,ns}$ ±13.7	****
GLU.,(F) (mg/dl)	83.32 ±11.44	$278.64^{c,z}$ ±43.98	$153^{c,z}$ 28	$224^{c,z}$ 32.05	****	94.63 ±8.31	292.40^{ns} ±21.63	$139.11^{c,z}$ ±28.13	$262.03^{c,z}$ ±46.08	****
HbA1c (%)	5.70 ±0.75	$8.61^{c,}$ ±0.80	$6.2^{ns,z}$ ±1.32	$7.02^{a,z}$ ±2. 3	****	5.61 ±0.68	8.42^{c} ±0.43	$5.71^{ns,z}$ .0.61	$8.03^{c,x}$ ±0.81	****
UREA(mg/dl)	25.64 ±5.84	30.51 ±11.13	36.16 ±9.33	43.84 ±7.30	****	23.73 ±5.58	26.62 ±7.8	35.20 ±8.17	40.22 ±13.51	****
Creatinine(mg /dl)	0.99 ±0.20	$1.02^{ns,}$ ±0.30	$1.18^{a,ns}$ ±0.29	$1.22^{a,x}$ ±0.21	***	0.86 ±0.19	$0.88^{ns,}$ ±0..6	$1.14^{ns,ns}$ ±0.41	$1.20^{a,ns}$ ±0.56	**
CRP(mg/l)	5.41 2.58	$13.89^{c,z}$ 5.33	$24.48^{c,z}$ 6.69	$33.90^{c,z}$ 7.98	****	10.30 1.66	$19.33^{c,}$ 4.36	$28.64^{c,z}$ 8.92	$35.89^{c,z}$ 7.29	****
CHO,(mg/dl)	168.45 ±29.38	181.86 ±24.79	209.4 ±26.12	233.72 ±38.63	****	178.23 ±32.17	203.03 ±28.76	226.54 ±31.65	216.08 ±25.55	****
TGL(mg/dl)	103.35 ±12.51	201.08^{c} ±75.17	$236.57^{c,ns}$ ±89.28	$280.57^{c,z}$ ±107.22	****	135.66 ±31.61	186.66^{c} ±25.76	$196.94^{c,ns}$ ±38.12	$234.25^{c,y}$ ±43.12	****
HDL(mg/dl)	39.11 ±6.02	$34.06^{b,}$ ±5.11	$29.68^{c,x}$ ±6.39	$31.13^{c,ns}$ ±5.08	****	38.67 ±5.03	34.34^{a} ±4.79	$30^{c,x}$ ±6.21	$29.77^{c,x}$ ±8.06	****
LDL	112.07 ±29.99	108.02^{ns} ±28.94	$132.52^{a,x}$ ±17.8	$145.94^{c,z}$ ±32.10	****	115.78 ±29.17	$130.19^{ns,}$ ±45.56	$157.16^{c,x}$ ±22.19	$139.46^{a,ns}$ ±11.25	****
VLDL	20.67 ±2.50	40.21^{c} ±15.03	$47.2^{c,x}$ ±8.92	$56.5^{c,z}$ ±6.14	****	27.13 ±6.30	37.33^{c} ±5.15	$39.3^{c,ns}$ ±3.25	$46.85^{c,z}$ ±6.24	****
NON HDL	132.74 ±30.06	148.24 ±26.67	179.72 ±19.2	202.44 ±23.8	****	142.91 ±29.52	167.53 ±46.26	196.54 ±25.44	186.31 ±17.49	****
R1(cho/hdl)	4.30 ±1.41	5.56 ±1.42	7.63 ±1.49	7.50 ±1.13	****	4.68 ±1.18	5.88 ±1.49	755 ±2.03	725 ±1.89	****
R2(tgl/hdl)	3.04 ±0.81	6.15 ±2.47	7.97 ±1.06	8.96 ±3.02	****	3.98 ±1.14	5.49 ±1.37	6.56 ±2.67	7.86 ±3.60	****
Hemoglobin (g/dl)	14.82 ±1.15	$14.79^{ns,}$ ±1.39	$13.15^{a,y}$ ±1.87	$12.88^{c,z}$ ±2.04	****	11.76 ±1.60	$12.38^{ns,}$ ±1.26	$10.42^{a,z}$ ±1.25	$11.09^{ns,x}$ ±1.70	****
WBC (cells/cu mm)	7343.24 ±1704	$7908.88^{ns,}$ ±1276.5	$9412^{a,x}$ ±2186.7	$11621^{c,z}$ ±2847	****	8656.66 ±1259.0	8737.03 ns, ±2205.2	$10378.5^{a,x}$ ±3016	$12477^{c,z}$ ±2851	****
Platelets(lakhs /cu mm)	2.06 ±0.46	2.15^{ns} ±0.42	$2.45^{a,ns}$ ±0.40	$2.67^{c,x}$ ±0.82	****	2.37 ±0.80	2.28^{ns} ±0.54	$2.15^{ns,ns}$ ±0.42	$2.45^{ns,ns}$ ±0.83	
Haematocrit%	40.21 ±3.04	39.64 ±3.82	36.32 ±4.52	34.72 ±4.41	****	38.04 ±3.95	36.29 ±3.89	36.32 ±4.52	34.72 ±4.41	*
Polymorph %	62.48 ±9.63	61,91 ±7.41	67.88 ±11.02	71.36 ±10.96	****	63.86 ±9.59	62.29 ±8.58	67.88 ±11.02	73.86 ±9.82	**
Lymphocyte %	31.32 ±10.02	31.08 ±6.94	25.12 ±9.54	28.66 ±11.72	*	29.86 ±8.94	32.29 ±7.64	25.12 ±9.54	29.92 ±11.72	*
Eosinophil%	6.89 ±1.17	6.73 ±1.30	6.44 ±1.35	5.42 ±1.43	****	6.4 ±1.0	6.18 ±0.86	5.55 ±1.22	5.25 ±1.39	***
ESR (mm/1h)	9.37 ±3.72	11.24 ±4.63	19.24 ±3.6	28.27 ±6.4	****	8.03 ±2.24	9.23 ±4.27	25.25 ±5.82	36.75 ±7.14	****

(NOR) Normal, (PT2D) untreated diabetes, (CVD) Cardiovascular Disease, (M&G CVD) metformin with glimepiride induced CVD groups (a =p <0.05, b=p < 0.001, c = p < 0.0001, ns = non-significant). Additionally, comparisons were made between the untreated PT2D group and the CVD M&G CVD groups (x = p <0.05, y = p < 0.001, z = p< 0.0001, ns = non-significant). HR, Heart rate. BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HbA1c, Glycated haemoglobin; GLU (F), Fasting glucose; CRP, *c-reactive protein*, CHO, Cholesterol, TGL, Triglycerides; HDL-C High –density lipoprotein cholesterol: LDL, Low- Density Lipoprotein; VLDL, Very Low- Density lipoprotein: NONHDL, Non high –Density Lipoprotein cholesterol R1(T CHO/HDL), R2(TGL/HDL) WBC, White Blood Cells: ESR, Erythrocyte Sedimentation Rate

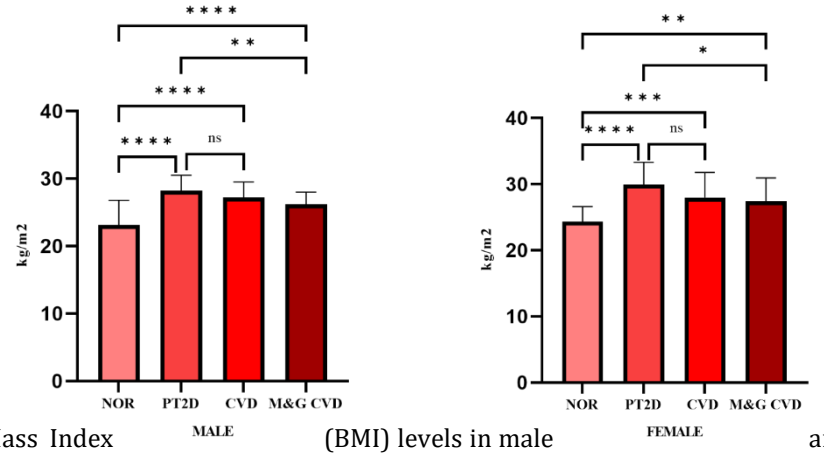

Fig. 2: Body Mass Index (BMI) levels in male and female participants across diverse cohorts. (NOR Normal, PT2D untreated Pre T2DM, CVD Cardio vascular disease, M&G CVD Metformin with Glimepiride Cardiovascular disease) BMI levels were significantly reduced in CVD, and M&G groups when compared to untreated diabetic patients. The data is summarized as mean ± SD**** (p<0.0001). mean ± SD*** (p<0.001), mean ± SD**(p<0.005), mean ± SD*(p<0.05), ns-not significant.

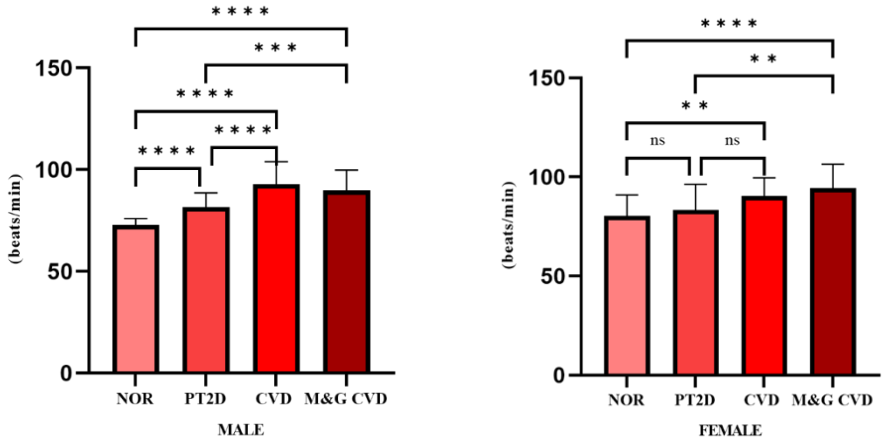

Fig. 3: Comparative analysis of heart rate levels in males and females. The data is summarized as mean ± SD**** (p<0.0001) mean ± SD***(p<0.001), mean ± SD**(p<0.005 mean ± SD*(p<0.05), ns-not significant.

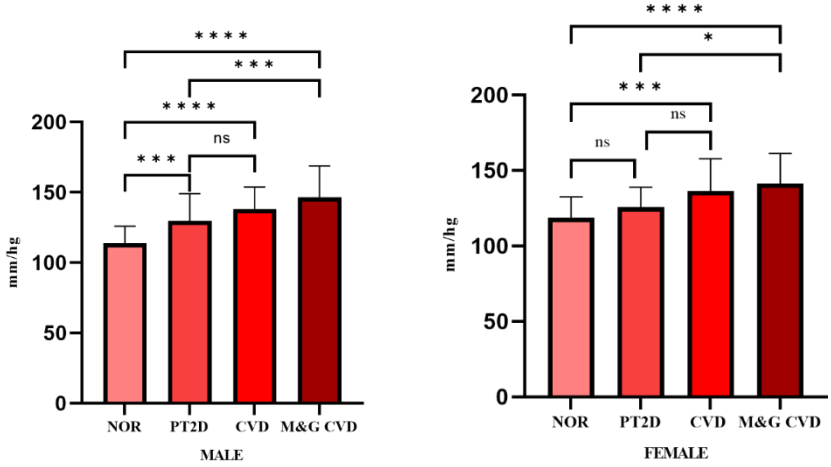

Fig. 4: Comparative analysis of systolic blood pressure levels in males and females. The data is summarized as mean ± SD**** (p<0.0001). mean ± SD***(p<0.001), mean ± SD*(p<0.05), ns-not significant.

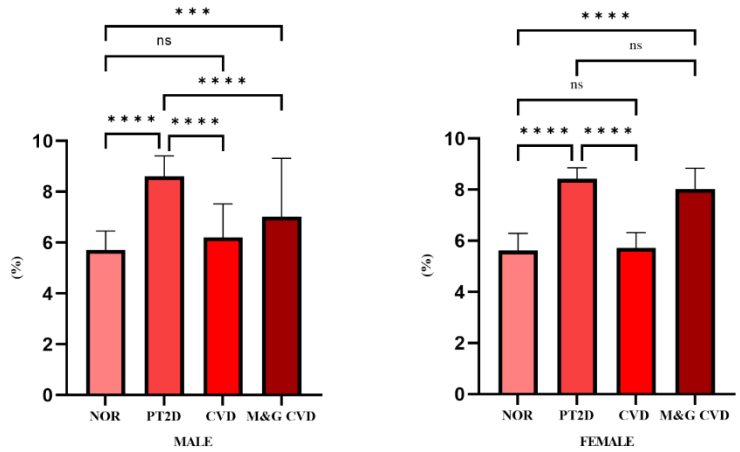

Fig. 5: Presents a visual representation illustrating the comparison of HbA1c levels between male and female cohorts. The data is summarized as mean ± SD**** ($p<0.0001$). mean ± SD***($p<0.001$), mean ± SD*($p<0.05$), ns-not significant.

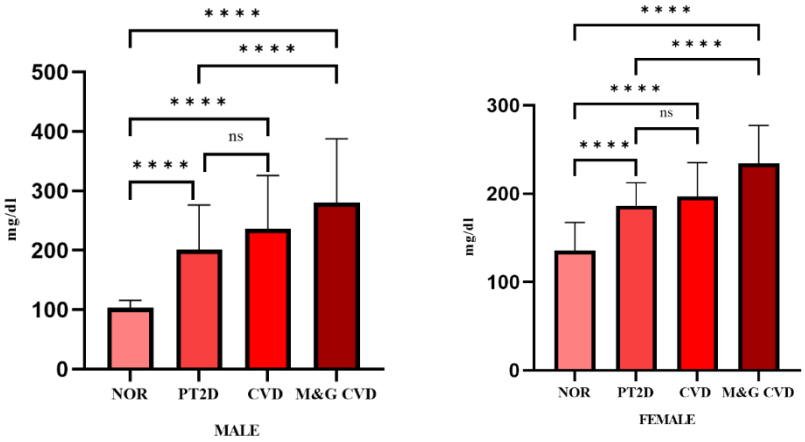

Fig. 6: Showcases a visual representation of Triglyceride levels in both male and female cohorts for comparative analysis. The data is summarized as mean ± SD.****($p<0.0001$), ns-not significant.

$p<0.0001$) participants. In CVD patients, no significant increase was found -- male (6.2 ±1.32; ns) female (5.71±0.61; ns) maintaining levels comparable to healthy individuals (Fig. 5).

Creatinine:

Creatinine levels significantly increased in both PT2D male (1.02±0.30; ns), female (0.88±0.6; ns) and CVD male (1.18±0.29; p=0.02) female (1.14±0.41; ns) groups compared to normal individuals male. But, metformin with glimepiride therapy failed to decrease creatinine levels in both male (1.22±0.21; p=0.004) and female 1.20±0.56;p=0.03) patients.

Lipid Profile:

An escalation in cardiovascular disease CVD, M&G CVD among both male and female patients was evident. Triglyceride comparing patients (PT2D) to combined male and female M&G CVD patients showed a significant difference in both males (280.57 ± 107.22, $p < 0.0001$) and females (234.25 ± 43.12, $p < 0.0001$). However, when assessing CVD combined M&G CVD male non significant (Fig. 6).

Significant differences were observed in VLDL, LDL, and HDL levels among PT2D, CVD, and M&G CVD groups compared to normal healthy

individuals. Notably, in female patients, the M&G CVD group exhibited a slight reduction in LDL (139.46±11.25; p=0.02) and HDL (29.77± 8.06; p<0.0001) levels compared to the CVD group LDL (157.16±22.19; p< 0.0001), HDL (30 ± 6.21;p<0.0001). Conversely, in male patients, the M&G CVD group showed markedly elevated LDL (145.94±32.10; p<0.0001) and HDL (31.1±5.08; p<0.0001) levels compared to both the CVD in LDL (132.52±17.8; p=0.03), HDL (29.68±6.69; p<0.0001) and normal.

Hemoglobin:

Hemoglobin levels showed non-significant differences between normal male (14.82±1.15), female (11.76±1.60), PT2D male (14.79±1.39; ns), and female (12.38±1.26; ns) groups. In the CVD group male (13.15±1.87; p<0.001), female (10.42±1.25; ns) a slight reduction in hemoglobin levels was noted compared to the normal group, with a significant decrease observed in both male (12.88±2.04; p<0.0001) and female (11.09±1.70; p<0.02) patients in the M&G CVD group.

WBC and ESR:

WBC levels were significantly increased in the CVD group compared to normal and PT2D groups, with further elevation observed in the M&G CVD group. ESR levels demonstrated a significant elevation in PT2D and CVD groups, with a further increase observed in M&G CVD patients, consistently observed in both male and female participants. These comprehensive findings contribute valuable insights into the interplay between diabetes, cardiovascular health, and the impact of metformin with glimepiride therapy, shedding light on both expected and unexpected outcomes within this specific cohort.

Body Mass Index (BMI) emerged as a valuable predictor for treatment trajectories in both T2DM and cardiovascular dysfunctions. Higher BMI participants exhibited greater resistance to insulin and other diabetic treatments, indicating a challenge in achieving optimal blood glucose levels. Moreover, elevated BMI proved indicative of a higher probability of developing cardiovascular dysfunctions and unresponsive-ness to T2DM treatment regimens. Encouragingly, the metformin with glimepiride combination demonstrated success in reducing BMI in the treatment groups (Bombelli *et al.*, 2011).

A meta-analysis of 743 patients with type 2 diabetes treated with metformin and atypical antipsychotics reported a significant reduction in BMI and insulin resistance (Seifarth *et al.*, 2013). Another study observed that metformin use was associated with a small but sustained decrease in body weight over 10 years in individuals with type 2 diabetes (Yerevanian and Soukas, 2019; Aleidi *et al.*, 2021).

Unexpectedly, metformin demonstrated an increase in blood pressure levels, challenging previous findings. This anomaly might be attributed to the irregular and high-spice diet prevalent among South Indian populations. Despite this unexpected result, metformin reaffirmed its longstanding role as a cardiovascular protector in T2DM, displaying cardioprotective properties in our study agreeable with previous findings. Lowering heart rate, achieved through combination therapy, emerged as beneficial in reducing T2DM-associated cardiovascular comorbidities (Azimova *et al.*, 2014)

The combination therapy not only effectively managed glucose levels but also significantly improved them. HbA1c, a predictor of future glycemic levels, witnessed a notable reduction with the metformin with glimepiride combination, suggesting a potential role in mitigating T2DM-associated comorbidities. Metformin primarily works by decreasing hepatic glucose production and increasing insulin sensitivity in the muscles. Glimepiride stimulates the pancreas to release more insulin, directly lowering blood sugar levels. The combination of these mechanisms provides a comprehensive approach to glycemic control, addressing both insulin production and insulin utilization (Kim *et*

al., 2014; Paczkowska *et al*., 2021). This combination therapy appears to be well-tolerated, with side effects like hypoglycemia usually manageable through dose adjustments or dietary modifications (Kim *et al*., 2014; Park *et al*., 2014; Sahay *et al.*, 2020). However, our study noted an unfavorable alteration in the lipid profile with the combination therapy. Although higher lipid profiles are indicative of cardiovascular dysfunctions, the metformin with glimepiride combination failed to reduce increased LDL and VLDL levels in T2DM patients. Consequently, prescribing additional drugs that favorably alter lipid levels alongside the combination therapy is recommended (Mondol *et al.*, 2020; Anchit *et al.*, 2023; Elsayed *et al*., 2023). It demonstrated significant improvements in both glycemic control and lipid profiles, highlighting the potential benefit of adding lipid-lowering medication. Standards of Medical Care in Diabetes (2023) emphasize the importance of managing dyslipidemia in T2DM patients. It recommends lowering LDL cholesterol and managing other lipids like VLDL to reduce cardiovascular risks.

Moreover, an increase in WBC levels observed in both PT2D and the treatment group may be attributed to T2DM-associated inflammation conditions. However, the combination therapy did not exert a favorable effect in reducing the elevated WBC levels. This underscores the need for further exploration and potential adjunct interventions to address inflammation in T2DM patients (Okdahl *et al.,* 2022). A meta-analysis by Wang *et al.* (2018) found a significant association between increased total WBC count and T2DM. This suggests that WBC levels could serve as a potential marker for inflammation and disease progression in diabetic patients (Wang *et al.*, 2022).

Several studies evaluated the effect of metformin-glimepiride combination on inflammatory markers in T2DM patients. While it showed improvements in glycemic control, there was no significant reduction in C-reactive protein (CRP), a marker of inflammation. This aligns with our observation of unaltered WBC levels (Karbalaee-Hasani *et al.*, 2021).

Conclusion

In conclusion, our study navigates the intricate landscape of T2DM, cardiovascular health, and the impacts of metformin with glimepiride combination therapy. While yielding valuable insights, our findings also prompt the consideration of tailored interventions and the exploration of additional therapeutic avenues to address the multifaceted challenges posed by these interconnected health concerns.

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