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A Comparative Study of Metformin and/or Glimepiride on Non-Migrant South Indian Middle-Aged Type 2 Diabetes Mellitus Patients

Raveendran Prakash¹, Ramamoorthy Senthilkumar^{1*} and Mahalingam Gunasekaran²

¹PG and Research Department of Biochemistry, Thanthai Periyar Government Arts and Science College (Autonomous) (Affiliated to Bharathidasan University), Tiruchirappalli – 620 024, Tamil Nadu, India

²Director, Dravidian Speciality Hospital, Pattukottai, Thanjavur District, Tamil Nadu, India

*Corresponding Author

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Abstract: This study aimed to evaluate the effectiveness of metformin and/or glimepiride in delaying the onset of Type 2 diabetes mellitus (T2DM) in non-migrant South Indian population. The present study comprised of 526 participants, including 260 males and 266 females in the middle age group ranging from 39 to 57, who were continuously monitored for up to 96 months. Anthropometric, hematological, and biochemical parameters were assessed during the treatment with metformin and/or glimepiride in T2DM patients. Age and BMI are widely recognized risk factors contributing to the severity of T2DM. Our findings revealed that both metformin and glimepiride, as well as their combination therapy led to significant reductions in BMI compared to the untreated group. Metformin exhibited profound effectiveness in male patients, while the combination therapy demonstrated remarkable glycaemic control in female patients. Regarding blood glucose and HbA1c levels, male patients receiving metformin experienced significant improvements, whereas there were reductions observed in female patients while receiving glimepiride alone. The results of BMI and Age of drug-treated T2DM group positively correlated with levels of blood glucose and compared to prediabetic group. Notably, metformin alone resulted in a slight non-significant reduction in HDL levels compared to other treatments. Female patients receiving glimepiride showed effective glycaemic control and delayed the progression of T2DM from prediabetes which can be attributed to their consistent medication adherence and lifestyle choices as opposed to the male group. These results underscore the importance of gender-specific considerations in diabetes management.

Keywords: Insulin Resistance, BMI, Diabetic drugs, Diet, HbA1C, Metformin, Glimepiride, Diabetes mellitus

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Introduction

According to the report of the International Diabetic Federation in 2013, the total global adult

diabetic population comprised 382 million individuals, with 198 million males and 184

million females. This population falls within the age range of 40 to 59 years, and it is anticipated that this figure will exceed 592 million by 2035. Currently, the count of individuals grappling with diabetes mellitus has already exceeded 500 million, with an additional 175 million cases remaining undiagnosed (Kharroubi, 2015). In developing countries, individuals between the ages of 35 and 64 are commonly the demographic most impacted by diabetes mellitus (Tabish, 2007).

In India, the consumption of meals with high carbohydrate content has been identified as a factor leading to hyperinsulinemia and insulin resistance (Borkman *et al.*, 1991). Previous research by Misra and Vikram (2004) highlighted a higher carbohydrate content in Asian meals (45%) in comparison to European meals (25%). Asian Indians and non-migrants in India consume more carbohydrates (67%) than other countries, especially at lunchtime. This dietary pattern is significant in the context of insulin resistance-related diseases, which exhibit global variations. The Indian population is recognized for its susceptibility to insulin resistance and metabolic imbalances (Maurya and Bal, 2010).

The rise in insulin resistance disorders encompasses conditions such as hypertension, diabetes mellitus, and obesity, contributing significantly to cardiovascular diseases (Borkman *et al.*, 1991). Insulin resistance signifies alterations in the biological effects of insulin on carbohydrates, lipids, and protein metabolism, as well as other metabolic actions in the tissues (McClenaghan, 2005). While an ideal carbohydrate (simple sugars) diet has not proven effective in preventing or treating insulin resistance, modern dietary practices favouring complex carbohydrates are suggested to be more beneficial. However, there is a postulation that such an approach may result in glycaemic responses even more pronounced than those observed with simple sugars. Despite numerous reviews, only some have reported the influence of dietary nutrients on insulin resistance and

cardiovascular risk factors in Indians. The treatment of insulin resistance often involves drugs such as biguanides and sulfonylurea. The increasing prevalence of Type 2 Diabetes Mellitus (T2DM) in various migrant Indian populations has been previously studied, and it is associated with rapid shifts in lifestyle and dietary habits (Misra *et al.*, 2007).

The American Diabetes Association and the European Association recommended metformin as the drug for Diabetes mellitus (Davies *et al.*, 2018). Derived from the plant *Galega officinalis*, metformin is a biguanide derivative renowned for its anti-hyperglycaemic effects (Bailey, 2017). Metformin effectively reduces blood glucose levels when used medicinally in individuals with T2DM without inducing hypoglycaemia (Sanchez-Rangel and Inzucchi, 2017). Metformin has been a cornerstone in the management of Type 2 Diabetes Mellitus (T2DM) for over six decades (Foretz *et al.*, 2014). The glimepiride, an FDA-approved drug, is a second-generation sulfonylurea that controls blood glucose levels in T2DM patients (Basit *et al.*, 2012). The combination of Metformin and Glimepiride is frequently utilized in the treatment of T2DM patients to attain their desired HbA1c levels, particularly in patients without atherosclerotic cardiovascular diseases (Sahay *et al.*, 2020).

However, there exists insufficient data on the impact of antidiabetic drugs when non-migrant South Indian Type 2 Diabetes Mellitus (T2DM) patients adhere to a modern South Indian carbohydrate diet. Additionally, research on the relationships between metformin and/or glimepiride with insulin resistance needs to be conducted within the non-migrant population in South India. Therefore, this current study was aimed to address these gaps by investigating how metformin and/or glimepiride impact insulin resistance in both male and female T2DM patients among non-migrant South Indians.

Materials and Methods

Study population:

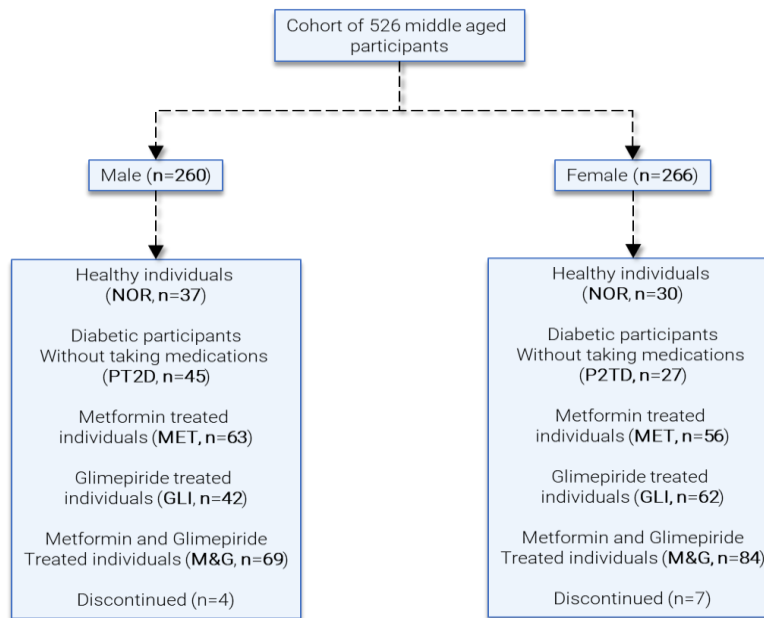


Fig. 1: Distribution of the study participants.

A total of 526 samples from Type 2 Diabetes Mellitus (T2DM) patients were collected from Dravidian Specialty Hospital in Pattukottai, Tamil Nadu, India, following ethical guidelines established by the Institute Ethical Committee for Human Research at Bharathidasan University. These guidelines align with national ethical standards for biomedical and health research involving human participants, as outlined 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).

In this study, 4 male patients and 7 female patients were excluded due to the severity of other complications caused by diabetes mellitus. The baseline characteristics of the remaining participants are provided in Tables 1, 2, and 3.

The study population was classified into five groups:

Group 1: Normal (NOR)

Group 2: Untreated Pre-Type 2 Diabetes Mellitus group (PT2D)

Group 3: Diabetes patients treated with Metformin (MET)

Group 4: Diabetes patients treated with Glimepiride (GLI)

Group 5: Combination of both Metformin and Glimepiride (M&G)

Patients treated with medications were monitored continuously. The distribution of the cohort is given in Figure 1.

Biochemical analysis:

From each participant, 5 ml of blood was collected via venipuncture. Blood samples were collected in EDTA tubes (for whole blood) and red tubes (for serum). Demographics and clinical data, including age, sex, diabetes duration, medical history, education, occupation, height, weight, BMI, heartbeat rate, diastolic blood pressure, and systolic blood pressure, were obtained from the patients. Throughout the study, blood parameters were analyzed every three months during regular medical check-ups at the hospital. All biochemical parameters were assessed using TURBOCHEM 100 fully automated analyzers, covering HbA1c (Immune Turbidimetric Method), fasting blood glucose (God-Pod method), total cholesterol (Chod-Pod Method), triglyceride (Gpo method), and Hdl-C

(Polymer Detergent Method). A complete blood count (CBC), including hemoglobin, total WBC count, platelet count, polymorphs, hematocrit, lymphocytes, and eosinophil, was examined using a MEDONIC fully automated analyzer. The erythrocyte sedimentation rate was determined through the Westergren method.

Statistical Analysis:

For statistical analysis, one-way ANOVA and Tukey's multiple comparisons were used to compare the data from multiple experimental groups. Two-way ANOVA (mixed model) was used to compare the mean differences between row (treatment options) and column factors (Gender). All the reports of p-values less than $p < 0.05$, $p < 0.001$, and $p < 0.0001$ were considered to be statistical significance. All data entries and statistical analysis were performed by using Graph Pad Prism.

Results and Discussion

Age and gender disparities in onset and treatment response of T2DM:

Age has emerged as a significant risk factor in the development and progression of T2DM consistent with prior research findings. Notably, this study revealed variations in the onset of T2DM between male and female participants, with females experiencing earlier onset in this cohort. Metformin is a preferable drug for middle-aged males, and metformin and/or glimepiride drugs are very effective in middle-aged females. Furthermore, the severity of T2DM was observed to increase with age, leading to the prescription of combination therapies for relatively older patients (Table 1).

The study revealed that alterations in different anthropological parameters under the specified treatment conditions significantly varied based on gender. The results of the two-way ANOVA highlighted substantial variations in responses across diverse treatment options and a noteworthy divergence in response patterns between genders.

Effect of metformin and/or glimepiride treatment on BMI in male and female patients with T2DM:

Both male and female patients with T2DM exhibited significantly higher Body Mass Index (BMI) compared to nondiabetic individuals. Treatment with metformin and/or glimepiride resulted in a notable reduction in BMI (Fig. 2). In males, metformin treatment significantly lowered BMI to 25.12 ± 3.53 ($p < 0.0001$), glimepiride also notably reduced BMI to 24.61 ± 2.49 ($p < 0.0001$), and the combination of both medications (M&G) led to a reduction in BMI to 23.97 ± 3.86 ($p < 0.0001$). Among females, all three treatment options significantly reduced BMI (MET - 26.31 ± 3.41 ($p < 0.0001$), GLI - 24.92 ± 3.22 ($p < 0.0001$), and M&G - 25.63 ± 2.48 ($p < 0.0001$) (Fig. 2).

Gender-specific cardiovascular dynamics in T2DM onset and treatment:

The onset of T2DM correlated with a notable increase in heart rate. In male participants, PT2DM resulted in an elevated heart rate of 81.6 ± 6.90 ($p < 0.0001$) compared to the NOR group (72.81 ± 3.14 bpm), and a similar observation was noted in female participants (PT2D - 83.40 ± 12.89 , NOR - 80.26 ± 10.73). MET treatment significantly increased heart rate (91.50 ± 8.63 , $p < 0.0001$) compared to the GLI and M&G groups. However, in both males and females, the GLI and M&G groups showed no significant change in heart rate, as indicated in Figure 3. Additionally, the administration of MET and/or GLI did not result in significant changes in blood pressure.

Age is the most prominent risk factor among patients with T2DM and cardiovascular diseases (CVD) (Savji *et al.*, 2013). Numerous studies have explored the connection between age and various long-term difficulties in individuals with T2DM. Several of these studies exhibit significant variations in methodological rigor and population characteristics leading to varying and inconclusive outcomes. For instance, some studies suggest a correlation between younger age and an increased risk of additional

Table 1: Basal Characteristics of study participants

Gender	MALE					FEMALE				
Group	NOR (n=37)	PT2D (n=45)	MET (n=63)	GLI (n=42)	M&G (n=69)	NOR (n=30)	PT2D (n=27)	MET (n=56)	GLI(n=62)	M&G(n=84)
AGE (years)	39.73±8.91	41.62±8.51 ^{ns}	48.04±9.29 ^{b,a}	47.16±5.60 ^{a,ns}	49.59±9.84 ^{c,y}	43.03±9.97	36.18±12.57 ^{ns}	44.06±4.53 ^{ns,x}	53.51±10.59 ^{c, z}	47.11±10.54 ^{ns,z}
BMI (kg/m ²)	23.13±3.65	28.2±2.9	25.12±3.53 ^z	24.61±2.49 ^z	23.97±3.86 ^z	24.33±2.27	29.94±3.36	26.31±3.41 ^z	24.92±3.22 ^z	25.63±2.48 ^z
HR (beats/min)	72.81±3.14	81.6±6.90 ^c	91.50±8.63 ^{c,z}	81.85±6.07 ^{c,ns}	86.03±9.52 ^{c, ns}	80.26±10.73	83.40±12.89 ^{ns}	84.07±5.99 ^{ns,ns}	87.91±8.02 ^{b,ns}	92.27±7.22 ^{c,z}
SBP (mmHg)	113.78±12.09	129.68±19.37 ^a	119.74±18.2 ^{ns}	121.19±20.97 ^{ns}	122.5±8.8 ^{ns}	118.66±13.82	125.55±13.40 ^{ns}	132±15.37 ^a	117.87±18.02 ^{ns}	128.5±19.35 ^{ns}
DBP (mmHg)	80±8.81	84.04±11.64	77.44±12.44	78.23±10.09	83.88±11.33	80.73±8.46	85.92±5.72	81.5±9.21	77.25±11.89	80.12±13.26
GLU (F)(mg/dl)	83.32±11.44	278.64±43.98 ^c	192.0±47.37 ^{c,z}	241.02±39.55 ^{c,z}	202.9±32.53 ^{c,z}	94.63±8.31	292.40±21.63 ^c	216±29 ^{c,z}	214.12±23.53 ^{c,z}	206±33 ^{c,z}
HbA1c (%)	5.70±0.75	8.61±0.80 ^c	7.68±0.87 ^{c,z}	8.32±0.79 ^{c,ns}	8.11±0.68 ^{c,x}	5.61±0.68	8.42±0.43 ^c	7.90±0.74 ^{c,ns}	7.76±0.72 ^{c,y}	7.81±0.71 ^c

Comparisons were made between the Normal (NOR) group and the untreated PT2D, MET, GLI, and M&G groups (a = p < 0.05, b = p < 0.001, c = p < 0.0001, ns = non-significant). Additionally, comparisons were conducted between the untreated PT2D group and the MET, GLI, and M&G 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.

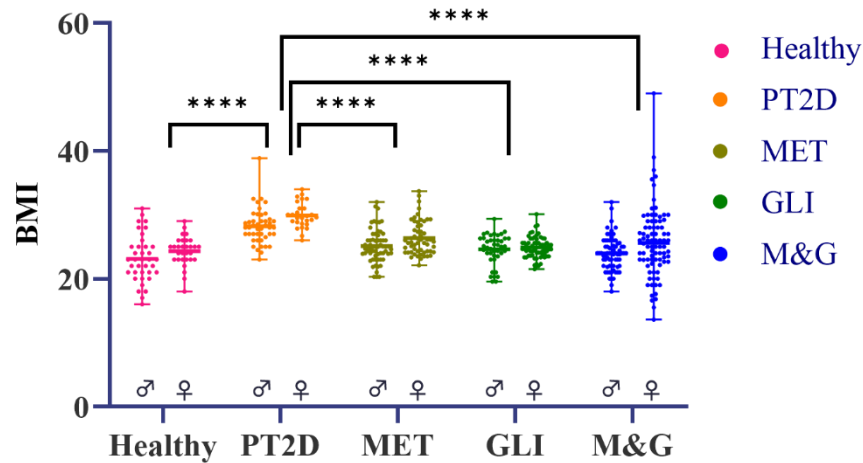


Fig. 2: Analyzing BMI levels in male and female participants across different Groups: Normal (NOR), Untreated T2DM (PT2D), Metformin (MET) Treatment, Glimepiride (GLI) Treatment, and Metformin-Glimepiride (M&G) Treatment. Notably, BMI levels showed a significant reduction in MET, GLI, and M&G groups compared to untreated diabetic patients' data is summarized as mean $\pm$ SD****($p < 0.0001$). (♂-Male, ♀-Female).

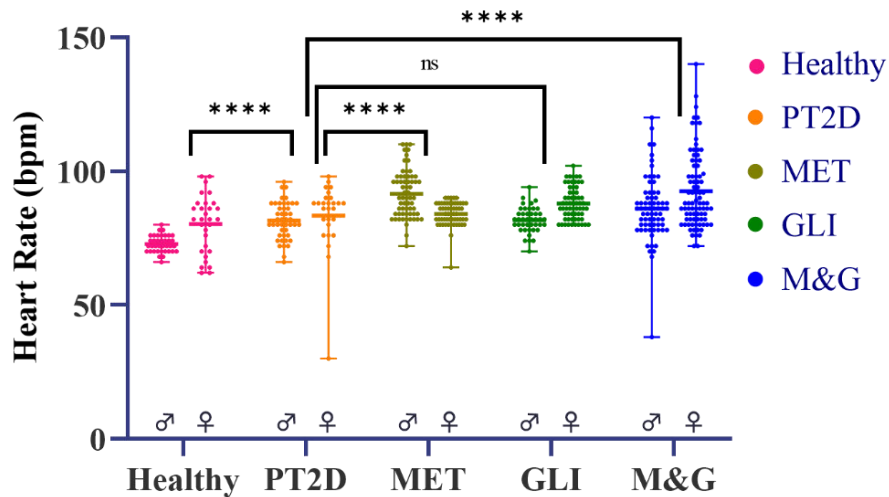


Fig. 3: Comparison of heart rate levels in both male and female participants among specified treatment groups. Heart rate levels were significantly reduced in MET, and M&G groups when compared to untreated diabetic patients and not significantly changed in GLI. ****- $p < 0.0001$, ns- $p > 0.05$.

complications, especially in the context of CVD (Song and Hardisty, 2009; Yeung *et al.*, 2014; Song, 2016).

This study revealed elevated cholesterol levels and a potential risk of CVD in South Indian middle-aged (between 48 and 57) male patients with T2DM treated with M&G, and MET alone. Prior research indicated that individuals diagnosed with T2DM at an early age face a

higher susceptibility to the early onset of CVD (Nanayakkara *et al.*, 2020).

In this study, the BMI levels demonstrated a notable increase in the group treated with metformin compared to the group treated with glimepiride (GLI). Based on previous studies, (Bramante *et al.*, 2019; Low *et al.*, 2019) this study also affirms that BMI is an important factor to diagnose the efficacy of antidiabetic drugs

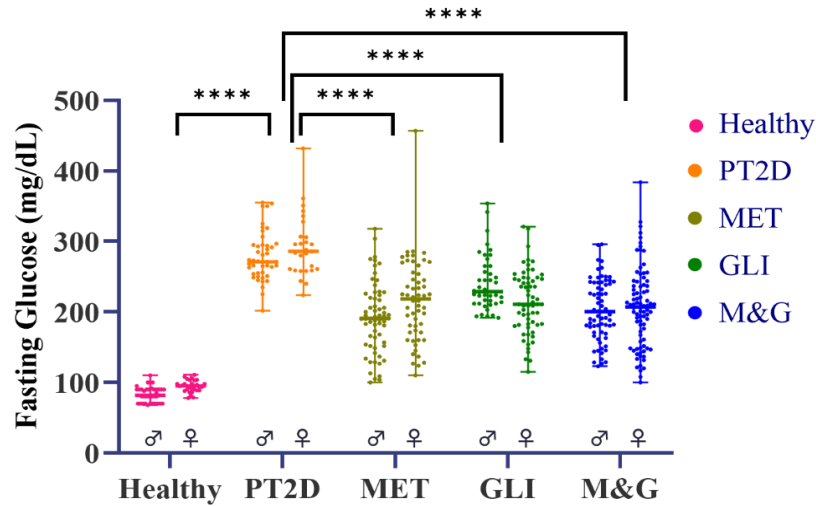


Fig. 4: An assessment of fasting glucose levels in both male and female participants across designated treatment groups revealed a significant increase in MET, GLI, and M&G groups compared to untreated diabetic patients ($p < 0.0001$).

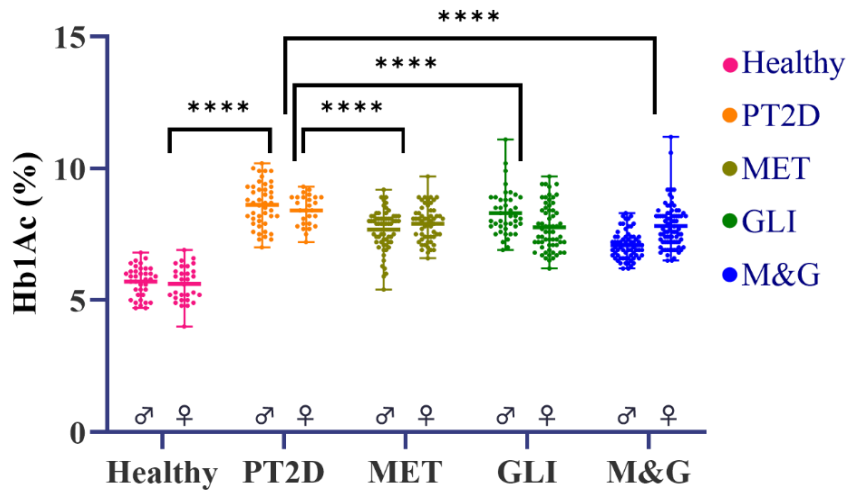


Fig. 5: Analysis of HbA1c levels in both male and female participants across the mentioned treatment groups revealed a significant increase in MET, GLI, and M&G groups compared to untreated diabetic patients ($p < 0.0001$).

However, a combination of metformin and glimepiride is frequently associated with weight gain and hypoglycaemic events (Verma *et al.*, 2000; Martín-Timón, 2014).

Another study highlights a strong correlation between BMI and the elevated occurrence of hypertension among Filipinos residing in the United States and the Philippines (Palaniappan *et al.*, 2010). The non-migrant Asian Indian populations showed the high intake of dietary

carbohydrates and other diets influences the development of insulin resistance. Insulin resistance may contribute to developing T2DM and hypertension by increasing the activity of sympathetic, renal sodium retention, and vascular smooth muscle tone and proliferation. The blood glucose levels exhibited a significant reduction in groups treated with MET and/or GLI patients' groups. These results are same as aforesaid statement of Ferrannini *et al.* (2008). In

particular, glimepiride had shown to enhance glucose transport and exert various additional effects outside of the pancreas, affecting muscle and fat cells (Müller *et al.*, 1995). The results of the study showed their potential efficacy in achieving glycaemic control and managing type 2 diabetes in South Indian males and females.

Efficacy of metformin and/or glimepiride treatments on glucose control and HbA1c levels:

MET treatment effectively lowered fasting blood glucose levels in male patients, registering at 192.0 ± 47.37 ($p < 0.0001$), in contrast to GLI at 241.02 ± 39.55 ($p < 0.0001$). Among female participants, GLI demonstrated a significant reduction in glucose levels, reaching 214.12 ± 23.53 ($p < 0.0001$), compared to MET at 216 ± 29 ($p < 0.0001$) (Fig. 4). M&G exhibited commendable glycemic control, showcasing levels of 206 ± 33 ($p < 0.0001$). Notably, GLI treatment brought about a substantial decrease in HbA1c levels. In male patients, MET at 7.68 ± 0.87 ($p < 0.0001$) proved more effective in HbA1c control compared to GLI at 8.32 ± 0.79 ($p < 0.0001$) and M&G at 8.11 ± 0.68 ($p < 0.0001$) (Fig. 5). Among female participants, GLI at 7.76 ± 0.72 ($p < 0.0001$) exhibited greater efficacy than MET at 7.90 ± 0.74 ($p < 0.0001$) and M&G at 7.81 ± 0.71 ($p < 0.0001$).

Another significant finding of the present study showed that the HbA1c levels in males were align closely with those reported in previous reports (Jeon and Oh, 2011; Gautam *et al.*, 2015). Metformin interacts with α -dicarbonyl intermediates, advanced glycation end-products (AGEs) are biosynthesised. Metformin plays a critical role in neutralizing and inhibiting AGE formation (Beisswenger and Ruggiero-Lopez, 2003). Notably, our study demonstrated that metformin treatment in type 2 diabetic male patients resulted in a significant reduction in dicarbonyl intermediates, highlighting the drug's effectiveness in countering this pathological process but not in females (Beisswenger *et al.*, 1999).

In females, HbA1c levels were reduced by the glimepiride-alone treatment. This is one of the important findings to prove that it delays the progression of T2DM in females. These finding underscore the multifaceted benefits of metformin in managing the complexities of T2DM. Particularly its capacity to form harmful by-products and counteract the effects of deleterious substances. It is essential to note that glycated hemoglobin (HbA1c) serves as a fundamental protein biomarker. The HbA1c offers valuable insights into the average glucose levels over a 3-month period and serves as a key diagnostic marker for T2DM (ESC, 2013).

Examining the impact of metformin and/or glimepiride treatments on lipid profiles:

In contrast to other factors, metformin treatment resulted in an increase in blood cholesterol levels at 203.39 ± 52.09 ($p < 0.0001$) compared to the untreated, GLI, and M&G groups in both males and females (Table 2; Fig. 6). GLI exhibited exceptional control over triglyceride levels at 167.64 ± 63.98 ($p < 0.0259$) in comparison to MET at 175.47 ± 77.49 ($p < 0.003$) and M&G at 190.5 ± 148.7 ($p < 0.0001$) in males, but not in females (MET- 197.74 ± 105.77 , $p = 0.02$; GLI- 136.13 ± 49.98 , $p = 0.06$; M&G- 159.6 ± 94.83 , $p = 0.26$) (Fig. 7). HDL levels exhibited a slight reduction in the MET group compared to the GLI and M&G groups in males, although this difference did not reach statistical significance (MET- 33.47 ± 5.44 , $p = 0.012$). Additionally, no significant difference was observed in female participants (MET- 39.92 ± 10.11 , $p > 0.999$) (Fig. 8).

Finally, the deviations in HDL-Cholesterol levels among all groups exhibited parallel values to the findings of Zang *et al.* (2015). This response of HDL-Cholesterol to metformin may be influenced by racial and ethnic factors. It also emphasizes the importance of considering these factors when interpreting the effects of metformin treatment. The combination of Metformin treatment with South Indian diet yields modest enhancements in the lipid profile. It results in marginal reductions in LDL cholesterol

Table 2: Comparison of lipid profile levels

Gender	Male					Female				
Group	NOR (n=37)	PT2D (n=45)	MET (n=63)	GLI (n=42)	M&G (n=69)	NOR (n=30)	PT2D (n=27)	MET (n=56)	GLI(n=62)	M&G (n=84)
CHO (mg/dl)	168.45±29.38	181.86±24.79 ^{ns}	203.39±52.09 ^c	183.76±33.57 ^{ns}	191±32.01 ^a	178.23±32.17	203.03±48.76 ^{ns}	207±36.83 ^a	199.77±52.08 ^{ns}	194.9±38.65 ^{ns}
TGL (mg/dl)	103.35±12.51	201.08±75.17 ^c	175.47±77.49 ^a	167.64±63.98 ^a	190.5±48.7 ^c	135.66±31.61	186.66±25.76 ^{ns}	197.74±105.77 ^a	136.13±49.98 ^{ns}	159.6±94.83 ^{ns}
HDL (mg/dl)	39.11±6.02	34.06±5.11 ^{ns}	33.47±5.44 ^a	35.28±11.13 ^{ns}	37.56±11.18 ^{ns}	38.67±5.03	34.34±4.79 ^{ns}	39.92±10.11 ^{ns}	39.87±10.53 ^{ns}	41.13±14.25 ^{ns}
LDL	112.07±29.99	108.02±28.94 ^{ns}	140.58±32.96 ^a	129.21±24.48 ^{ns}	116.5±36.49 ^{ns}	115.78±29.17	130.19±45.56 ^{ns}	122.36±117.02 ^{ns}	117.02±40.10 ^{ns}	121.8±36.75 ^{ns}
VLDL	20.67±2.50	40.21±15.03	35.74±14.13	33.66±12.80	38.1±19.81	27.13±6.30	37.33±5.15	39.75±3.62	27.07±21.96	32.61±19.37
NON-HDL	132.74±30.06	148.24±26.67	172.98±47.12	152.88±43.53	154.9±33.19	142.91±29.52	167.53±46.26	168.81±48.39	160.74±57.47	154.7±42.13
R1 (CHO/HDL)	4.30±1.41	5.56±1.42	5.70±1.97	5.61±1.62	5.33±1.39	4.68±1.18	5.88±1.49	5.53±3.68	5.22±1.49	5.05±1.50
R2 (TGL/HDL)	3.04±0.81	6.15±2.47	5.25±2.41	5.39±2.87	5.56±3.05	3.98±1.14	5.49±1.37	5.53±3.68	4.59±3.68	3.83±3.30

Comparisons were conducted between the Normal (NOR) group and the untreated PT2D, MET, GLI, and M&G 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 MET, GLI, and M&G groups (x = p < 0.05, y = p < 0.001, z = p < 0.0001, ns = non-significant).

CHO-Cholesterol; TGL-Triglycerides; HDL-High density lipoprotein; LDL- Low density lipoprotein; VLDL- Very low-density lipoprotein; NON-HDL- non high-density lipoprotein, R1-(CHO/HDL), R2-(TGL/HDL).

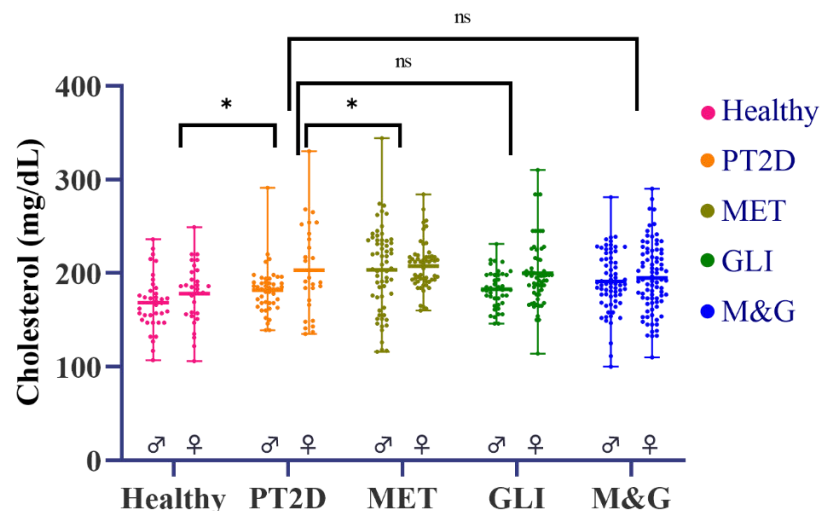


Fig. 6: An evaluation of cholesterol levels in both male and female participants within the mentioned treatment groups demonstrated a significant difference in the MET group, while no significant variation was observed in the other treatment groups compared to untreated diabetic patients (* $p < 0.05$, ns- $p > 0.05$).

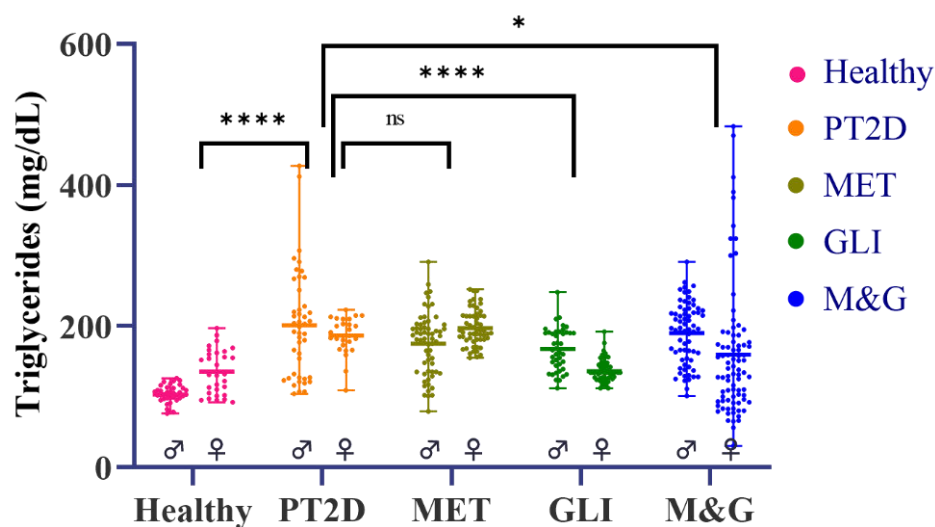


Fig. 7: An analysis of triglyceride levels was conducted in both male and female participants within the mentioned treatment groups. TGL levels exhibited significant differences in the GLI and M&G groups compared to untreated diabetic patients, whereas the MET group showed no significant alterations (* $p < 0.05$, **** $p < 0.0001$, ns- $p > 0.05$).

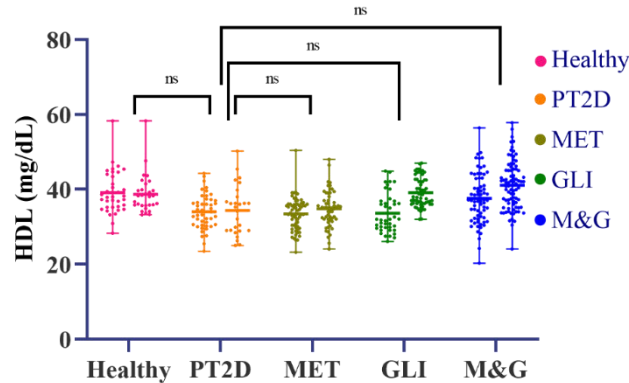


Fig. 8: Analysis of HDL level was carried out in both male and female participants across the specified treatment groups. The results indicated that there were no significant differences in HDL levels among the treatment groups ($p>0.05$).

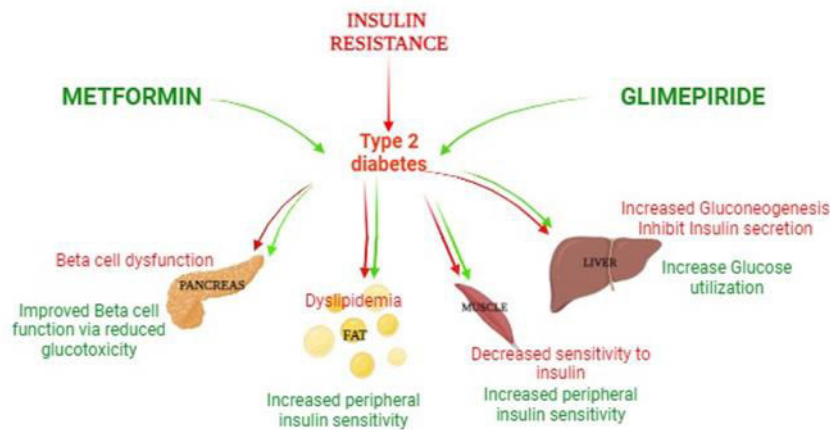


Fig. 9: Illustration of the therapeutic impact of metformin and glimepiride in treating complications associated with type 2 diabetes.

and triglycerides. The minimal impact on HDL cholesterol level show consistency with earlier findings (Saenz *et al.*, 2015; Pavithran *et al.*, 2020).

Evaluation of blood lipids and hematological Parameters:

R1 (CHO/HDL) and R2 (TGL/HDL) exhibited no change in all treatment groups. Levels of LDL, VLDL, and non-HDL were also unaffected (Table 3). In male participants, MET treatment resulted

in lower haemoglobin levels at 13.03 ± 2.02 ($p<0.0001$), while no significant change was observed in female groups. Other blood parameters, including WBC, platelet count, haematocrit, polymorph, lymphocyte, eosinophil count, and ESR, remained unaffected across all treatment groups.

A meta-analysis indicated that metformin had no significant impact on systolic blood pressure, diastolic blood pressure, WBC, platelets, and ESR

Table 3: Comparison of Haematological parameters

Gender	Male					Female				
Group	NOR(n=37)	PT2D(n=45)	MET(n=63)	GLI(n=42)	M&G(n=69)	NOR(n=30)	PT2D(n=27)	MET(n=56)	GLI(n=62)	M&G (n=84)
Hemoglobin (g/dl)	14.82±1.15	14.79±1.39 ^{ns}	13.03±2.02 ^{c,z}	14.02±1.38 ^{ns,ns}	13.67±1.52 ^{a,x}	11.76±1.60	12.38±1.26 ^{ns}	11.34±1.28 ^{ns,ns}	11.48±1.05 ^{ns,ns}	11.73±1.30 ^{ns,ns}
WBC (cells/cumm)	7343.24±1704	7908.88±1276	6954±1862	8136±1398	7453±1813	8656.66±1259.	8737.03±2205.	9351.08±2788	8854.53±1358.	8537±1991
Platelets (lakhs/cumm)	2.06±0.46	2.15±0.42	2.15±0.48	1.87±0.32	2.29±0.69	2.37±0.80	2.28±0.54	2.78±0.89	2.45±0.88	2.72±.17
Haematocrit %	40.21±3.04	39.64±3.82	41.34±5.09	38.14±4.01	39.17±7.88	38.04±3.95	36.29±3.89	35.69±9.22	34.45±3.66	33.81±5.12
Polymorph %	62.48±9.63	61.91±7.41	62.18±9.78	66.75±9.96	65.38±7.99	63.86±9.59	62.29±8.58	63.74±13.83	63.19±11.87	64.7±9.5
Lymphocyte %	31.32±10.02	31.08±6.94	29.76±10.46	26.64±10.77	27.89±8.12	29.86±8.94	32.29±7.64	29.29±9.19	31.17±10.93	27.72±8.73
Eosinophil %	6.89±1.17	6.73±1.30	8.05±4.63	6.60±2.03	6.37±2.28	6.4±1.0	6.18±0.86	6.28±4.02	5.57±2.37	7.64±4.01
ESR(mm/1h)	9.37±3.72	11.24±4.63	10.75±4.81	12.09±3.3	9.19±4.03	8.03±2.24	9.23±4.27	10.2±3.31	9.52±2.82	8.86±2.94

Analyses were performed to assess differences between the Normal (NOR) group and the untreated PT2D, MET, GLI, and M&G groups, with significance levels marked as a = p < 0.05, b = p < 0.001, c = p < 0.0001, and ns indicating non-significant findings. Moreover, specific comparisons were executed exclusively within the untreated PT2D group. WBC, White Blood Cells; ESR, Erythrocyte Sedimentation Rate. Normal compared to untreated PT2D, MET, GLI, M&G (a=p<0.05, b=p<0.001, c=p<0.0001, ns-non-significant.),

in individuals with T2DM in both male and female South Indian populations. However, a separate meta-analysis reported an average reduction in systolic blood pressure and obesity (Zhou *et al.*, 2017).

Based on the results, our study highlights the substantial influence of metformin and glimepiride on various physiological and metabolic parameters in South Indian males and females with T2DM. These findings emphasize the potential of tailored antidiabetic therapies to address the complex interplay of insulin resistance, glycaemic control, and cardiovascular risk factors. The MET and/or GLI treatment shows more effective management and prevention of T2DM and associated complications in South Indian males and females.

Conclusion

In summary, our findings indicated that non-migrant South Indian middle-aged individuals, both males and females, tend to follow a high-carbohydrate diet, significantly impacting insulin resistance. Our study revealed that the use of metformin and/or glimepiride effectively mitigates insulin resistance in this population. Notably, glimepiride alone showed promise in delaying the progression from prediabetes to Type 2 diabetes among South Indian middle-aged females, while metformin alone effectively manages Type 2 diabetes in South Indian middle-aged males. Furthermore, the combination therapy of metformin and glimepiride acted as a preventive measure against insulin resistance in middle-aged South Indian males. This study provided valuable insights into how diet and medication interact to influence insulin resistance. Further investigation is necessary to explore the intricacies of this relationship more comprehensively.

Understanding how these interventions affect different demographic groups is crucial for tailoring effective diabetes management strategies. This study sets the stage for

developing more personalized approaches to tackle Type 2 diabetes, taking into account factors such as dietary habits, medication effectiveness, and demographic characteristics.

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