Original Article

# Association of FTO Gene Variant (rs9939609) with Antidiabetic Drug Response in Patients with Type 2 Diabetes Mellitus (T2DM)

Mazhar Hussain, Asif Hussain, Haroon Aziz, Asim Elahi, Abid Hussain, & Syed Abdullah Faiz

**ABSTRACT**

***Objective:*** Our earlier work demonstrated that the FTO gene variant rs9939609 not only predicts cardiovascular disease risk but also has a strong association with diabetes-related micro-and macrovascular complications. In this study, we evaluated the therapeutic response to antidiabetic drugs in individuals with type 2 diabetes mellitus (T2DM), stratified by their FTO rs9939609 genotypes.

***Methodology:*** After obtaining ethical approval, this three-month prospective cohort study was conducted at Sheikh Zayed Medical College & Hospital, Rahim Yar Khan. A total of 140 T2DM patients with and without cardiovascular disease (CVD) were enrolled. All participants, of either gender and taking antidiabetic medications were followed for a period of three months. The therapeutic response was evaluated based on glycemic control, primarily through changes in HbA1c levels.

***Results:*** In our study, 66% of participants were male and 34% were female. Non-responders had a significantly longer duration of type 2 diabetes mellitus (T2DM), with a mean duration of 7.6 years compared to 6.2 years in responders ($p = 0.002$). Based on their therapeutic response, 76 (54.3%) patients were classified as responders while 64 (45.7%) were classified as non-responders. Statistical analysis showed no significant difference between responders and non-responders in genotype distribution ($p = 0.404$) or allele frequencies ($p = 0.500$). Furthermore, when assessing the association between the FTO gene rs9939609 genotypes and response to different classes of antidiabetic medications, no significant differences in genotype or allele frequencies were observed between the two groups ($p > 0.05$).

***Conclusion:*** Our study revealed no significant association between treatment response and the FTO rs9939609 genotypes or alleles. However, individuals with the AA genotype and risk allele (A) exhibited substantially higher levels of HbA1c and fasting blood glucose (FBG) as compared to other genotypes.

**KEYWORDS**: Antidiabetic Drugs, FTO gene, HbA1c, Responder, T2DM

## INTRODUCTION

Diabetes mellitus affects an estimated 537 million people globally as of 2021, with numbers expected to rise to 783 million by 2045, reflecting a 59% increase in prevalence. About 90% of cases are type 2 diabetes, and three-quarters live in low- and middle-income countries (LMICs), where most undiagnosed cases also occur. Urban areas have a higher prevalence than rural. In 2021, diabetes-related complications caused approximately 6.7 million deaths worldwide.[1,2]

According to the International Diabetes Federation (IDF) Diabetes Atlas (2021), Pakistan has 33 million people living with diabetes, with a prevalence rate of 30.8%, the highest in adults globally. It ranks third in total diabetes cases after China and India. Without preventive measures, the diabetic population is expected to reach 62.2

**Mazhar Hussain,**[1] *MBBS, M.Phil, PhD*
Professor
**Asif Hussain,**[2] *MBBS, M.Phil*
Additional Principal Medical Officer
**Haroon Aziz,**[3] *MBBS, M.Phil*
Demonstrator
**Asim Elahi,**[4] *MBBS, MD, FACP*
Program Director
**Abid Hussain,**[5] *MBBS, MCPS, FCPS*
Professor
**Syed Abdullah Faiz,**[6] *MBBS, FCPS*
Senior Registrar
[1-3,5-6]Sheikh Zayed Medical College, Rahim Yar Khan, PAK.
[4]Harlingen Medical Center, Harlingen Texas, USA.

***Correspondence***
**Dr. Mazhar Hussain**
mazharhussain214@gmail.com

million by 2045. In 2021, around 396,000 deaths in Pakistan were attributed to diabetes and its complications.[3,4]

Diabetes management involves lifestyle changes, risk factor control, insulin, and antidiabetic medications. Type 1 diabetes mellitus (T1DM) requires lifelong insulin, while type 2 diabetes mellitus (T2DM) typically starts with oral agents like metformin and sodium–glucose cotransporter-2 (SGLT2) inhibitors, especially in overweight patients. Additional drugs, including dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor (GLP-1) agonists, sulfonylureas, thiazolidinediones (TZDs) may be added if adequate glycemic control cannot be achieved.[5] Insulin therapy is initiated when oral therapy fails. Managing weight, blood pressure, and lipids is essential to prevent complications. Several drug classes have proven benefits in reducing diabetes-related comorbidities.[6]

The fat mass & obesity associated (FTO) gene, initially identified through genome-wide association studies (GWAS), was first reported as an obesity-susceptible gene. Subsequent studies have demonstrated a strong association between the FTO gene and several CVD risk factors, including BMI, blood pressure, insulin resistance, diabetes mellitus, inflammation and lipid profile.[7-9] Our earlier study on the FTO gene showed that it is a strong predictor of cardiovascular disease (CVD) in patients with type 2 diabetes mellitus (T2DM). Specifically, the AA genotype and A allele of the FTO gene variant rs9939609 were strongly associated with increased body weight, BMI, fasting blood glucose, HbA1c, blood pressure, lipid profile abnormalities, inflammation, and insulin resistance.[10] Similarly, our second study demonstrated that the FTO gene is potentially associated with both microvascular and macrovascular complications in T2DM patients.[10]

However, we did not previously investigate the therapeutic response to antidiabetic drugs in individuals with T2DM stratified by their FTO rs9939609 genotypes. Several classes of antidiabetic medications have shown beneficial effects on cardiovascular risk factors in T2DM patients.[6] Moreover, research focusing on the differential response to anti-diabetic therapies based on FTO genetic variants is virtually nonexistent in Pakistan. This gap in the literature highlights a critical need for comprehensive, population-specific studies to elucidate the potential mechanistic links between FTO gene variations, T2DM progression, and CVD risk factors. Therefore, in this study, we investigated the therapeutic response to antidiabetic medications in individuals with T2DM having FTO rs9939609 genotypes.

## METHODOLOGY

After obtaining ethical approval from the Institutional Review Board of Sheikh Zayed Medical College/Hospital (Ref. No. 58/IRB/SZMC /SZH, dated 17/06/2020), this prospective observational cohort study was conducted from January 2021 to June 2023 at Sheikh Zayed Medical College and Hospital, Rahim Yar Khan, located in the southern region of Punjab. Participants were enrolled from the diabetic clinic, and the coronary care unit of this institution. A total of 140 T2DM patients with and without CVD were enrolled. All participants, of either gender and taking antidiabetic medications were followed for a period of three months. The therapeutic response was evaluated based on glycemic control, primarily through changes in HbA1c levels.

T2DM patients were selected on the basis of WHO diagnostic criteria for diabetes. (WHO, 2022). Patients having CVD were diagnosed on the basis of history, echocardiography**,** cardiac bio-markers such as Troponin-T**,** as well as coronary angiography and computed tomography angio-graphy (CTA)**.** Patients with kidney dysfunction, liver disorders, various malignancies, autoimmune disorders, hormonal imbalances, gestation, breast feeding, neurological disorders, inflammatory conditions, and insulin treatment were system-atically excluded from the study. The response

study. The response to antidiabetic medication was assessed on the basis of glycemic control. An HbA1c value < 7% was considered adequate, while >7% was considered inadequate glycemic control, in accordance with the standards provided by the American Diabetes Association.

The sample size was determined on the basis of our previous research work**,** using an online sample size calculator (Rao Soft), with a 95% confidence interval and a 24% Minor Allele Frequency (MAF) of the FTO gene variant rs9939609, which is specifically linked to BMI measurements, as outlined by Hussain et al. (2025).[11]

All participants were fully briefed on the study's objectives and gave informed consent. The research protocols were carried out in line with the Declaration of Helsinki.

A 10 ml fasting blood sample was drawn by sterile venipuncture. Five milliliters were placed in an EDTA tube for DNA isolation and HbA1c measurement. The remaining 5 ml was centrifuged to separate serum for fasting blood glucose (FBG) testing. All procedures followed established laboratory protocols. FBG was measured enzymatically using glucose oxidase via an automated analyzer at baseline and at 3 months. HbA1c was quantified by high-performance liquid chromatography (HPLC).

Genomic DNA was extracted from the buffy-coat using the Promega Wizard® kit as per the manufacturer's instructions. DNA purity and concentration were assessed by spectrophotometry. The FTO rs9939609 region was amplified via ARMS-PCR using allele-specific primers, and PCR products were run on agarose gel to distinguish heterozygous (AT) from homozygous (AA/TT) genotypes.

Data were analyzed using SPSS version 24. Categorical variables are reported as percentages, while numerical variables are presented as mean ± standard deviation. An unpaired Student's t-test was used for continuous variables, and the chi-squared test was used for categorical variables. The chi-square test evaluated variations in genotype and allele frequencies of the FTO rs9939609 variant between antidiabetic drug responders and non-responders. To compare genotypic groups across responder status, one-way ANOVA was performed followed by Tukey's post hoc test for multiple comparisons. Statistical significance was defined as $p < 0.05$.

## RESULTS

The baseline demographic and clinical characteristics of 140 T2DM patients are summarized in Table 1. According to their response to antidiabetic therapy, 76 (54.3%) were classified as responders and 64 (45.7%) as non-responders.

**Table:1 Baseline characteristics of responders and non-responders**

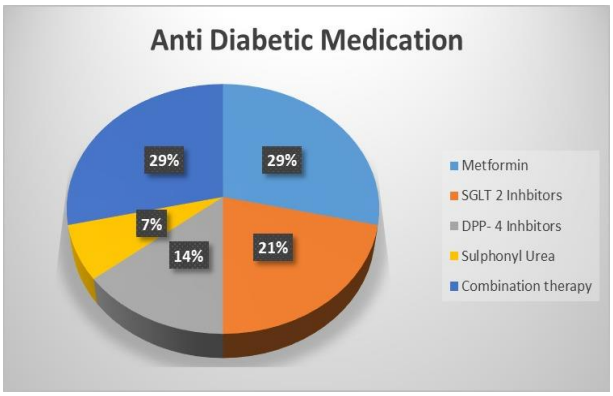
| Characteristics | Responder 76(54.3%) | Non-Responder 64(45.7%) | p-value[a] |
|---|---|---|---|
| Male: 92 (66%) | 48 (34.2%) | 44 (31.4%) | 0.231[b] |
| Female: 48 (34%) | 28 (20%) | 20 (14.2%) | |
| Age (years) | 46.5 (±7.7) | 48.4 (±8.2) | 0.381 |
| Duration of Diabetes (yrs) | 6.2 (±2.5) | 7.6 (±3.1) | 0.002 |
| Treatment duration (yrs) | 2.0 (±1.2) | 2.3 (±1.4) | 0.217 |
| BMI (kg/m$^2$) | 27 (±3.2) | 26.5 (±2.8) | 0.421 |
| HbA1c (%) | 7.0 (±1.2) | 7.3 (± 1.4) | 0.009 |
| **Antidiabetic Medications** | | | |
| Metformin (40) | 17 (42.5%) | 23 (57.5%) | |
| SGLT-2 inhibitors (30) | 14 (46.6%) | 16 (53.3%) | |
| DPP4-inhibitors (20) | 14 (70%) | 6 (30%) | |
| Sulphonyurea (10) | 6 (60%) | 4 (40%) | |
| Combination (40) | 25 (62.5%) | 15 (37.5%) | |
| **Concomitant Medication** | | | |
| Statins | 45 (32.14%) | 33 (23.57%) | |
| Aspirin | 40 (28.5%) | 45 (32.1%) | |
| Clopidegrol | 20 (14.2%) | 25 (18%) | |

Significant p value: < 0.05 ↕ Pearson Chi square test.

The cohort comprised 92 (66%) male and 48 (34%) female patients. Non-responders had a significantly longer average disease duration of 7.6 years versus 6.2 years in responders ($p = 0.002$). There was no meaningful difference in BMI between the two groups ($p = 0.421$). Baseline HbA1c was notably higher in non-responders than in responders

(p = 0.009), indicating poorer glycemic control in the former group. Antidiabetic medication usage among participants is illustrated in Figure 1.

**Fig: 1 Antidiabetic Medication use in study groups**




In our study cohort, 76 patients (54.3%) with T2DM possessing the FTO gene variant rs9939609 responded to antidiabetic medications, while 64 patients (45.7%) were classified as non-responders. Statistical analysis revealed no significant differences in genotype distribution (p = 0.404) or allele frequencies (p = 0.500) between responders and non-responders.

**Table: 2 Genotype and allele frequencies of FTO gene variant rs9939609 among responders and non-responders**

| FTO rs9939609 | | Responders 76(54.3%) | Non-responders 64(45.7%) | Total | p-value |
|---|---|---|---|---|---|
| SNP | AA | 13 (9.28%) | 16(11.4%) | 29(20.7%) | 0.404 |
| | TA | 29 (20.7%) | 23(16.4%) | 52(37.1%) | |
| | TT | 34 (24.3%) | 25(17.8%) | 59(42.1%) | |
| Allele | A-allele | 27.5 (19.6%) | 27.5(19.6%) | 55(39.2%) | 0.500 |
| | T-allele | 48.5 (34.6%) | 36.5(26.7%) | 85(60.7%) | |

Significant p value: < 0.05 ↕ Pearson Chi square test.

Abbreviations. BMI, body mass index; HbA1c, glycated hemoglobin. Mean ± standard deviation was used to express continuous variables [a] unpaired student t-test was used to express continuous variables.[b] chi-squared test

Detailed genotype and allele frequencies of the FTO rs9939609 variant in these groups are presented in Table 2. We also assessed the association between the FTO gene variant rs9939609 and treatment response to various classes of antidiabetic medications. Among patients treated with metformin (n = 40), no significant differences in genotype or allele frequencies were observed between responders and non-responders (p = 0.401 and p = 0.115, respectively).

**Table:3 Genotype and allele frequencies of FTO gene variant rs9939609 among different antidiabetic drugs responders and non-responders**

| Drugs | Genotypes/ Allele frequencies | Responders | Non-Responders | Total | p-value |
|---|---|---|---|---|---|
| Metformin (40) | AA | 3 (7.5%) | 7 (17.5%) | 10 (25%) | 0.401 |
| | TA | 9 (22.5%) | 10 (25%) | 19 (47.5%) | |
| | TT | 5 (12.5%) | 6 (15%) | 11 (27.5%) | |
| | A-Allele | 7.5 (18.7%) | 12 (30%) | 19.5 (48.7%) | 0.115 |
| | T-Allele | 9.5 (24%) | 11(27.5%) | 20.5 (51.2%) | |
| SGLT-2 inhibitors (30) | AA | 4 (13.3%) | 3 (10%) | 7 (23.3%) | 0.653 |
| | TA | 4 (13.3%) | 6 (20%) | 10 (33.3%) | |
| | TT | 6 (20%) | 7 (23.3%) | 13 (43.3%) | |
| | A-Allele | 6 (20%) | 6 (20%) | 12 (40%) | 0.698 |
| | T-Allele | 8 (26.6%) | 10 (33.33%) | 18 (60%) | |
| DPP-4 inhibitors (20) | AA | 1 (5%) | 1 (5%) | 2 (10%) | 0.274 |
| | TA | 5 (25%) | 2 (10% | 7 (35%) | |
| | TT | 8 (40%) | 3 (15%) | 11 (55%) | |
| | A-Allele | 3.5 (17.5%) | 2 (10%) | 5.5 (27.5%) | 0.386 |
| | T-Allele | 10.5(52.5%) | 4(20%) | 14.5 (72.5%) | |
| Sulphonylureas (10) | AA | 1(10%) | 1 (10%) | 2 (20%) | 0.321 |
| | TA | 2 (20%) | 1 (10%) | 3 (30%) | |
| | TT | 2 (20%) | 3 (30%) | 5 (50%) | |
| | A-Allele | 2 (20%) | 1.5 (15%) | 3.5 (35%) | 0.142 |
| | T-Allele | 3 (30%) | 3.5 (35%) | 6.5 (65%) | |
| Combination therapy (40) | AA | 4 (10%) | 4 (10%) | 8 (20%) | 0.259 |
| | TA | 9 (22.5%) | 4 (10%) | 13 (32.5%) | |
| | TT | 12 (30%) | 7 (17.5%) | 19 (47.5%) | |
| | A-Allele | 8.5 (21.2%) | 6 (15%) | 14.5(36.2%) | 0.362 |
| | T-Allele | 16.5 (41.2%) | 9 (22.5%) | 25.5(63.75%) | |

Significant p value: < 0.05 ↕ Pearson Chi square test.

Similarly, analysis of patients on SGLT-2 inhibitors (n = 30) revealed no significant association between FTO genotypes or allele distribution and treatment response (p = 0.653 and p = 0.698).

**Table 4. Comparison of response to antidiabetic medication on fasting blood glucose & HbA1c across various FTO rs9939609 genotypes**

| Drugs | Parameters | Genotypes | | | p value |
|---|---|---|---|---|---|
| | | AA | TA | TT | |
| Metformin | FBG baseline | 150.5±27.5 | 127.4±23.7 | 111.4±26.2 | <0.001* |
| | FBG After 3 Months | 148.2±25.4 | 125.6±21.5 | 109.5±24.5 | 0.432 [b] |
| | HbA1c baseline | 8.70±1.2 | 6.8±0.63 | 6.6± 0.9 | <0.001* |
| | HbA1c after 3 months | 8.34±0.9 | 7.1±0.74 | 6.5± 0.7 | 0.963 [b] |
| SGLT-2 inhibitors | FBG baseline | 154.5±24.5 | 132.4±20.5 | 115.4±22.5 | <0.001* |
| | FBG After 3 Months | 156.8±26.4 | 135.5±22.4 | 117.5±24.7 | 0.824 [b] |
| | HbA1c baseline | 8.21±0.8 | 6.9±0.83 | 6.2± 1.0 | <0.001* |
| | HbA1c after 3 months | 8.251±0.9 | 7.2±0.9 | 6.5± 0.8 | 0.231 [b] |
| DPP-4 inhibitors | FBG baseline | 152.5±24.2 | 123.4±22.6 | 119.4±24.5 | <0.001* |
| | FBG After 3 Months | 145.6±23.6 | 126.5±21.5 | 121.5±22.8 | 0.542 [b] |
| | HbA1c baseline | 8.05±0.8 | 6.7±0.73 | 6.2± 0.72 | <0.001* |
| | HbA1c after 3 months | 8.42±1.2 | 6.4±0.42 | 6.4± 0.82 | 0.834 [b] |
| Sulphonylureas | FBG baseline | 138.5±24.5 | 126.4±22.5 | 128.4±24.0 | <0.001* |
| | FBG After 3 Months | 135.5±22.8 | 124.4±20.4 | 126.5±22.8 | 0.321 [b] |
| | HbA1c baseline | 8.42±0.7 | 6.8±0.63 | 6.4± 0.7 | <0.001* |
| | HbA1c after 3 months | 8.92±0.9 | 6.92±0.42 | 6.6± 0.9 | 0.765 [b] |
| Combination therapy | FBG baseline | 140.5±17.4 | 117.4±15.5 | 125.4±11.5 | <0.001* |
| | FBG after 3 Months | 138.4±15.5 | 114.4±13.6 | 123.5±13.4 | 0.183 [b] |
| | HbA1c baseline | 8.90±0.9 | 6.9±0.72 | 6.8± 0.42 | <0.001* |
| | HbA1c after 3 months | 8.45±1.1 | 7.2±0.94 | 6.9± 0.85 | 0.432 [b] |

FBG: Fasting Blood Glucose; HbA1c: Glycated Hemoglobin * $p < 0.05$ indicates a significant difference between genotype at baseline. [b] $p > 0.05$ indicates a non-significant difference between genotypes after 3 months.

For those receiving DPP-4 inhibitors (n = 20), genotypic and allelic frequencies did not differ significantly between responders and non-responders (p = 0.274 and p = 0.386). Among the sulphonylurea-treated group (n = 10), no association was found between FTO genotype and drug response (p = 0.321 and p= 0.142 for both genotype and allele frequency). Lastly, in patients on combination therapy (n = 40), there were no significant differences in genotype or allele frequencies between treatment responders and non-responders (p = 0.259 and p = 0.362).

Overall, the findings suggest that the FTO rs9939609 variant does not significantly influence the therapeutic response to metformin, SGLT-2 inhibitors, DPP-4 inhibitors, sulphonylureas, or combination therapy in T2DM patients within this cohort. The detailed genotypic and allelic distribution data are provided in Table 3.

When evaluating the entire treatment cohort, baseline FBG and HbA1c levels differed significantly across the three genotype groups. However, following a standardized three-month follow up of antidiabetic treatment, no statistically significant changes in FBG or HbA1c were observed within any genotype group when compared to their respective baseline levels ($p > 0.05$). These findings indicate that, while FTO rs9939609 genotype may be associated with baseline glycemic status, it does not appear to influence short-term glycemic response to antidiabetic therapy. Full statistical analyses and genotype-specific comparisons are presented in Table 4.

## DISCUSSION

Insulin resistance plays a central role in the pathogenesis of T2DM and CVD, contributing to a cluster of metabolic abnormalities that heighten cardiovascular risk. Addressing insulin resistance is crucial for managing both glycemic control and cardiovascular health in patients with T2DM. Several antidiabetic medications such as biguanides, glitazones, DPP-4, and SGLT-2 inhibitors have been shown to improve insulin sensitivity and mitigate cardiovascular risk factors. These medications not only improve insulin sensitivity but also positively influence cardio-vascular risk factors, underscoring their role in comprehensive T2DM management.[12,13]

T2DM is a complex metabolic disorder resulting from the interplay of genetic and environmental factors. While lifestyle changes remain the primary approach for managing T2DM, many patients require medication to effectively control blood glucose levels. However, responses to antidiabetic

drugs vary widely among individuals, a variability that is partly due to genetic differences influencing how drugs are metabolized, transported, and interact with their targets.[14] The rs9939609 variant in the FTO gene, in particular, has been linked to higher risks of obesity and insulin resistance, as well as differences in how patients respond to diabetes treatments. Investigating these genetic influences is important for developing more tailored and effective therapies for T2DM.[15]

Our previous research demonstrated that the FTO gene variant rs9939609 is not only a robust predictor of cardiovascular disease, but is also strongly associated with diabetes-related microvascular complications (such as retinopathy, nephropathy, and neuropathy).[10,11] In our current study, individuals with the AA genotype or carrying the A allele of the FTO rs9939609 variant exhibited poorer baseline glycemic control compared to those with the TT genotype, regardless of the antidiabetic therapy used. After a 3-month follow-up**,** the therapeutic response to different oral hypoglycemic agents was evaluated. No significant differences in metformin-induced changes in glycemic control were observed among the different FTO rs9939609 genotypic groups. Metformin is widely used as the initial therapy for T2DM, acting primarily by decreasing glucose production in the liver and enhancing insulin sensitivity. Nevertheless, its effectiveness can vary due to genetic differences. Individuals carrying the A allele of the rs9939609 variant tend to have increased insulin resistance and higher levels of body fat, which may reduce metformin's ability to lower blood glucose.[16] Furthermore, these genetic variations might also affect how metformin is absorbed in the gastrointestinal tract and eliminated by the kidneys, influencing the overall response to treatment.

Similarly, no significant differences were observed in sulfonylurea-induced changes in glycemic control among the different FTO rs9939609 genotypic groups after 3 months period. Sulfonylureas function by stimulating insulin release through their interaction with sulfonylurea receptors on pancreatic β-cells.[17] The presence of the A allele at rs9939609 has been linked to greater β-cell mass and enhanced insulin secretion. However, due to the elevated insulin resistance observed in carriers of this allele, higher doses of sulfonylureas may be required to reach effective blood glucose control, which could increase the likelihood of hypoglycemic events.

DPP-4 Inhibitors such as sitagliptin, linagliptin and vildagliptin, stimulate insulin secretion and suppress glucagon release in a glucose-dependent manner. The rs9939609 A allele, which is linked to higher adiposity and insulin resistance, may impact the effectiveness of these agents. Although GLP-1 receptor agonists are known to promote weight loss, carriers of the A allele might experience variations in both the extent of weight reduction and improvements in blood glucose control.[18]

After 3-month treatment regimen with SGLT-2 inhibitors, no statistically significant differences were observed in the alterations of glycemic control among the different FTO rs9939609 genotypes. SGLT2 inhibitors reduce blood glucose levels by increasing glucose excretion through the urine. Although the effects of the rs9939609 A allele on the response to SGLT2 inhibitors have not been extensively investigated, its link to higher adiposity and insulin resistance suggests that individuals with this allele might respond differently to these drugs, which could influence both their effectiveness and safety.[19]

At the commencement of our study, individuals carrying the AA genotype and A allele of the FTO rs9939609 variant demonstrated elevated FBG levels and higher HbA1c percentages, indicative of suboptimal glycemic control. Nevertheless, after a 3-month treatment period involving antidiabetic combination therapy, no statistically significant differences were observed in the changes in glycemic control among the various FTO rs9939609 genotypes.

The rs9939609 polymorphism in the FTO gene has been implicated in influencing obesity and insulin resistance, which are key factors in T2DM. Beyond

these metabolic effects, this genetic variant also appears to affect how patients respond to antidiabetic medications, especially when multiple drugs are used in combination. Since combination therapy is a common approach for managing T2DM, understanding the role of this polymer-phism is essential for improving treatment outcomes.

Individuals who carry the A allele of rs9939609 often have higher levels of adiposity and greater insulin resistance, both of which can reduce the effectiveness of combined antidiabetic treatments. For example, while metformin primarily decreases hepatic glucose production and sulfonylureas stimulate insulin secretion, the presence of this variant may blunt their synergistic effect. Additionally, the polymorphism may influence drug pharmacokinetics and pharmacodynamics by altering insulin sensitivity and β-cell function, potentially requiring adjustments in drug dosing or the selection of alternative therapies.

Given these challenges, patients with the rs9939609 A allele might benefit from personalized treatment strategies that include early use of insulin sensitizers such as thiazolidinediones or GLP-1 receptor agonists, alongside lifestyle interventions like diet and exercise. Although initial studies suggest that this genetic variant affects the response to combination therapy, more extensive clinical research involving diverse populations is necessary. Such investigations will help clarify the mechanisms involved and support the integration of genetic testing into routine diabetes care to tailor therapies more effectively.[20]

Recognizing how the FTO rs9939609 variant affects drug response is essential for advancing personalized treatment approaches. Genetic testing for this variant can assist in pinpointing patients who might benefit from tailored medication doses or different therapeutic options to attain better blood sugar control. Additionally, lifestyle changes such as diet improvements and increased physical activity can help counteract the negative effects linked to the A allele, potentially improving the effectiveness of antidiabetic treatments.[21]

The rs9939609 variant in the FTO gene plays a notable role in modulating the effectiveness of several antidiabetic medications. Identifying this genetic variation enables the development of more individualized and efficient treatment plans for patients with T2DM. However, additional studies are necessary to fully understand the specific biological mechanisms through which this variant-impacts drug metabolism and response, ultimately supporting the advancement of personalized therapies.[22]

In our study, we found no significant response of antidiabetic drugs on glycemic control and risk factor of CVD in individuals with FTO gene rs9939609 variants. Although individuals with the AA genotype and risk allele (A) exhibited substantially higher HbA1c and FBG as compared to others. However, no notable correlation was detected between antidiabetic medications and risk allele and genotypes. The cause might be the small sample size and cross-sectional study. For a broader perspective, it would be far preferable to execute a randomized controlled trials to ascertain the response of antidiabetic drugs on glycemic management and the determinants of CVD risk in individuals with different FTO gene variants. This may aid in the identification of precision medicine to improve risk prediction by integrating clinical, demographic and genetic data.

***Limitation of Study*:** The primary constraint of this research was the relatively limited sample size. To acquire a more comprehensive picture, these findings should be reproduced in a large cohort of people of various ethnicities in the future. We also observed an absence of cardio-protective advantages conferred by SGLT-2 inhibitors in individuals with T2DM. Nonetheless, elucidation is anticipated in forthcoming longitudinal trials aimed at assessing the advantageous impacts of glucose lowering therapies across various FTO genotypic variants**.** We aligned the diverse study population parameters that could influence allele sizes.

A number of confounding variables were considered in our research to ensure the results are both reliable and precise.

***Future Directions:*** For a broader perspective, it would be preferable to conduct randomized controlled trials to determine the response of antidiabetic drugs on glycemic management and the determinants of cardiovascular disease (CVD) risk in individuals with different FTO gene variants. This approach may aid in identifying precision medicine strategies to improve risk prediction by integrating clinical, demographic, and genetic data.

## CONCLUSION

In our study, we found no significant response of antidiabetic drugs on glycemic control and risk factor of CVD in individuals with FTO gene rs9939609 variants. Although individuals with the AA genotype and risk allele (A) exhibited substantially higher HbA1c and FBG as compared to others.

***Conflict of Interest:*** None
***Funding Sources:*** None

## REFERENCES

1. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022; 183:109119. doi: 10.1016/j.diabres.2021.109119.
2. Hossain MJ, Al-Mamun M, Islam MR. Diabetes mellitus, the fastest growing global public health concern: Early detection should be focused. Health Sci Rep. 2024;(3): e2004. doi:10.1002hsr2.2004
3. Magliano DJ, Boyko EJ. *IDF Diabetes Atlas.* 10th ed. Brussels: International Diabetes Federation; 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK581934/
4. Shahid MB, Saeed M, Naeem H, Kumari U. Diabetes mellitus: Is Pakistan the epicenter of the next pandemic? Chronic Dis Transl Med. 2024;10(01):75-77. doi:10.1002/cdt3.96
5. Młynarska E, Czarnik W, Dzieża N, Jędraszak W, Majchrowicz G, Prusinowski F, et al. Type 2 diabetes mellitus: new pathogenetic mechanisms, treatment and the most important complications. Int J Mol Sci. 2025;26(3):1094. doi:10.3390 /ijms26031094
6. Sohn M, Frias JP, Lim S. Cardiovascular efficacy and safety of antidiabetic agents: A network meta-analysis of randomized controlled trials. Diabetes Obes Metab. 2023;25(12):3560-3577. doi:10.1111/dom.15251
7. Huang C, Chen W, Wang X. Studies on the fat mass and obesity-associated (FTO) gene and its impact on obesity-associated diseases. Genes Dis. 2023;10(6):2351-2365. doi: 10.1016/ j.gendis. 2022.04.014
8. Xu ZY, Jing X, Xiong XD. Emerging role and mechanism of the FTO gene in cardiovascular diseases. Biomolecules. 2023;13(5): 850. doi: 10.3390/biom13050850
9. Yin D, Li Y, Liao X, Tian D, Xu Y, Zhou C, Liu J, Li S, Zhou J, Nie Y, Liao H. FTO: a critical role in obesity and obesity-related diseases. Br J Nutr. 2023;130(10):1657-1664. doi: 10.1017/sooo 7114523000764.
10. Hussain M, Waheed A, Elahi A, Mustafa G. Fat mass and obesity-related (FTO) gene variant is a predictor of CVD in T2DM Patients. J Diabetes Res. 2024;2024(1):5914316. doi:10.1155/2024/5914316.
11. Hussain M, Waheed A, Elahi A, Iqbal J. FTO Gene rs 9939609 is potentially associated with diabetes related complications in T2DM patients. Curr Diabetes Rev. 2025;21(1):10–11. doi: 10.2174/0115733998343753250226081 545.
12. Grover A, Sharma K, Gautam S, Gautam S, Gulati M, Singh SK. Diabetes and its complications: therapies available, anticipated and aspired. Curr Diabetes Rev. 2021;17(4):397-420. doi: 10.2174/1573399816666201103144231.
13. Mastrototaro L, Roden M. Insulin resistance and insulin sensitizing agents. Metabolism. 2021; 125:154892. doi: 10.10 16/j.metabol. 2021.154892.
14. Saiti A, Giannopoulos-Dimitriou A, Kazakos I, Galatou E, Vizirianakis IS. Systems pharmacology and network analysis to advance pharmacogenomics and precision medicine decisions in type-2 diabetes therapy. Future Pharmacol. 2023;3(1): 329-363.doi: 10.3390/futurepharmacol3010021
15. Popović AM, Huđek Turković A, Žuna K, Bačun-Družina V, Rubelj I, Matovinović M. FTO gene polymorphisms at the crossroads of metabolic pathways of obesity and epigenetic influences. Food Technol Biotechnol. 2023;61(1): 14-26.doi: 10.17113/ftb.61.01.23.7594
16. Yanasegaran K, Ng JY, Chua EW, Nawi AM, Ng PY, Abdul Manaf MR. Single nucleotide polymorphisms (SNPs) that are associated with obesity and type 2 diabetes among Asians: a systematic review and meta-analysis. Sci Rep. 2024;14(1):20062. doi:10.1038/s41598-024-70674-2
17. Tomlinson B, Patil NG, Fok M, Chan P, Lam CW. The role of sulfonylureas in the treatment of type 2 diabetes. Expert Opin Pharmacother. 2022;23(3):387-403. doi:10.1080/1465 6566. 2021.1999413
18. de Soysa AK, Langaas M, Grill V, Martins C, Løvold Mostad I. Exploring associations between the FTO rs9939609 genotype and plasma concentrations of appetite-related hormones in adults with obesity. PloS one. 2025 ;20(1): e0312815. doi: 10.1371 /journal.pone.0312815
19. Gul H, Joya F, Zafar A, Sikander S, Akhlaq H. Understanding the Genetic Basis of Type 2 Diabetes: Implications for Precision Medicine and Novel Therapeutic Approaches. Int J Biomed Res. 2025; 3(3): 559-573. doi: 10.70749/ijbr. v3i3.864 10.70749/ijbr. v3i3.864.

20. Benak D, Sevcikova A, Holzerova K, Hlavackova M. FTO in health and disease. Front Cell Dev Biol. 2024; 12:1500394. doi:10.3389/fcell.2024.1500394
21. Galiero R, Caturano A, Vetrano E, Monda M, Marfella R, Sardu C, et al. Precision Medicine in Type 2 Diabetes Mellitus: Utility and Limitations. Diabetes Metab Syndr Obes. 2023;16:3669–3689. doi:10.2147/DMSO.S390752.
22. Poosri S, Boonyuen U, Chupeerach C, Soonthornworasiri N, Kwanbunjan K, Prangthip P, et al. Association of FTO variants rs9939609 and rs1421085 with elevated sugar and fat consumption in adult obesity. Sci Rep. 2024;14:25618. doi:10.1038-/s41598-024-77004-6.

***Author Contributions:***

**Mazhar Hussain:** conceived the study designed, carried out the data collection and statistical analysis and drafted the manuscripts.

**Asif Hussain:** Participated in its design and coordination. drafted, read and approved the final manuscript.

**Haroon Aziz:** Participated in its design and coordination. Statistical analysis, drafted, read and approved the final manuscript.

All authors are equally accountable for research work

**Asim Elahi:** Participated in its design and coordination. Statistical analysis, drafted, read and approved the final manuscript.

**Abid Hussain:** Participated in its design and coordination. Statistical analysis, drafted, read and approved the final manuscript.

**Syed Abdullah Faiz:** Participated in its design and coordination. Statistical analysis, drafted, read and approved the final manuscript.

Date of Submission: 23-08-2025
Revised Date: 15-10-2025
Accepted Date: 05-11-2025