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RESEARCH ARTICLE
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IMPACT OF FTO GENE VARIANT ON TYPE 2 DIABETES MELLITUS SUSCEPTIBILITY: A CASE-CONTROL STUDY IN NORTH INDIAN ADULTS

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Abstract

Background: The fat mass and obesity-associated (*FTO*) gene has been widely studied as a potential genetic determinant of obesity and type 2 diabetes mellitus (T2DM). A single nucleotide polymorphism (SNP), rs9939609, has consistently shown associations with obesity and T2DM in European populations, but data from South Asians, particularly Indians, remain inconclusive.

Objective: To investigate the association of *FTO* gene polymorphism (rs9939609) with T2DM and obesity in adults from North India, and to explore correlations with anthropometric, biochemical, and sociodemographic parameters.

Methods: A case-control study was conducted on 320 adults (160 T2DM/obese cases and 160 controls with normal BMI). Anthropometric indices, biochemical markers (HbA1c, lipid profile, blood pressure), and lifestyle factors were recorded. Genotyping for *FTO* rs9939609 was performed using PCR-RFLP and sequencing. Logistic regression was applied to assess associations.

Results: The AT heterozygous genotype was significantly more frequent in cases (41.3%) compared to controls (p=0.03, OR=2.103, 95% CI=1.063–4.159). Subjects with AT genotype had a ~3-fold higher risk of T2DM when HbA1c was abnormal. The variant showed strong associations with obesity (p=0.06, OR=2.008, 95% CI=1.227–3.286), hypertension (p=0.000, r=0.310), and adverse lipid profile (inverse correlation with HDL, OR=0.380, 95% CI=0.229–0.630). Abnormal BMI was more prevalent among females (59.4%), rural residents (65%), smokers (40–49.2%), and non-vegetarians (58.8%). **Conclusion:** The *FTO* gene variant rs9939609 significantly influences susceptibility to obesity and T2DM in North Indian adults. The AT genotype appears to confer higher risk, particularly in association with elevated BMI and HbA1c. These findings highlight the gene–environment interaction in the Indian population and suggest *FTO* as a potential biomarker for T2DM risk stratification.

Keywords: FTO gene, rs9939609, Type 2 Diabetes Mellitus, Obesity, North Indian population, Case-control study.

Introduction

Type 2 Diabetes Mellitus (T2DM) is one of the most prevalent chronic metabolic disorders worldwide and represents a major public health challenge. It is characterized by insulin resistance and impaired

β-cell function, leading to hyperglycemia and long-term complications such as cardiovascular disease, nephropathy, neuropathy, and retinopathy [1,2]. India, in particular, is experiencing an alarming increase in T2DM cases, with projections suggesting that it will harbor the largest diabetic population globally by 2045 [3].

Obesity is the strongest modifiable risk factor for T2DM. Central adiposity is particularly implicated in insulin resistance and cardiovascular morbidity [4]. Both environmental and genetic factors contribute to the development of obesity and T2DM. Genome-wide association studies (GWAS) have identified several susceptibility loci, among which the **Fat Mass and Obesity-associated (FTO) gene** is one of the most consistently replicated across populations [5,6].

The *FTO* gene, located on chromosome 16q12.2, encodes an α-ketoglutarate-dependent dioxygenase and is highly expressed in the hypothalamus, adipose tissue, and skeletal muscles [7]. It was first identified in 2007 when Frayling et al. reported its association with obesity in Europeans using GWAS [5]. Subsequent studies confirmed that single nucleotide polymorphism (SNP) **rs9939609**, located in the first intron of *FTO*, is strongly correlated with increased body mass index (BMI) and risk of T2DM [8–10].

However, the role of *FTO* polymorphisms in South Asian populations, particularly in India, is less clear. Sanghera et al. and Yajnik et al. provided early evidence of association between *FTO* variants and T2DM in Indian cohorts, independent of BMI [11,12]. Later investigations produced mixed results, with some confirming moderate associations [13,14], while others failed to replicate the findings [15]. These discrepancies may be attributed to genetic heterogeneity, lifestyle differences, dietary patterns, and varying prevalence of obesity across ethnic groups.

Recent Indian studies suggest that the effect size of *FTO* polymorphisms on BMI and diabetes risk may be smaller compared to Europeans, but still clinically relevant in the context of rapidly increasing obesity rates [16,17]. Moreover, interactions between *FTO* variants, sociodemographic factors (age, gender, socioeconomic status), and lifestyle behaviors (diet, smoking, alcohol consumption, and physical inactivity) further modulate diabetes risk [7,16].

Given the significant burden of T2DM in India and the variable results reported across populations, it is essential to investigate the association of *FTO* rs9939609 polymorphism with obesity and T2DM in North Indian adults. This case-control study aims to assess the impact of *FTO* gene variants on diabetes susceptibility and to correlate them with anthropometric, biochemical, andsociodemographic parameters.

Materials and Methods

Study Design and Setting

This was a **hospital-based case–control study** conducted in the Department of Anatomy in collaboration with the Departments of Medicine and Biochemistry at Rama Medical College Hospital & Research Centre, Kanpur, Uttar Pradesh, India. The study period extended over two years. Ethical approval was obtained from the Institutional Ethics Committee, and written informed consent was secured from all participants prior to enrollment.

Study Population

A total of **320 participants** were recruited and divided into two groups:

- **Cases (n = 160):** Adults with abnormal BMI (>24.9 kg/m²) and/or clinically diagnosed T2DM according to American Diabetes Association (ADA) 2014 criteria.
- **Controls (n = 160):** Healthy adults with normal BMI (18.5–24.9 kg/m²), without diabetes, hypertension, or other metabolic disorders.

Inclusion Criteria

- Age between **35 and 60 years**.
- Both males and females.
- For cases: BMI >24.9 kg/m² and/or confirmed T2DM diagnosis.

Exclusion Criteria
- Individuals <35 or >60 years.
- Pregnant or lactating women.
- Patients with secondary obesity (endocrine disorders, Cushing's syndrome, etc.).
- Severe cardiac anomalies or recent hospitalization (<3 months).
- Subjects with grave systemic illness or genetic syndromes affecting metabolism.

Sample Size Calculation
Sample size was calculated assuming a 20% difference in *FTO* variant prevalence between cases and controls, with 80% power and 95% confidence interval, yielding a minimum of 150 per group. Thus, **160 subjects per group** were enrolled to account for dropouts.

Data Collection
Sociodemographic Parameters
Information regarding age, gender, occupation, socioeconomic status, residence (rural/urban), smoking, alcohol consumption, and dietary habits was obtained using a structured questionnaire.
Anthropometric Measurements
- **Height (cm):** Measured using a stadiometer.
- **Weight (kg):** Measured with a calibrated weighing machine.
- **Body Mass Index (BMI):** Calculated as weight (kg)/height² (m^2).
- **Waist Circumference (WC):** Measured at the midpoint between the lower margin of the last rib and iliac crest.
- **Hip Circumference (HC):** Measured at the widest part of the buttocks.
- **Waist–Hip Ratio (WHR):** WC/HC.
- **Skinfold Thickness:** Triceps, biceps, subscapular, and suprailiac regions measured using Harpenden calipers; body fat percentage was estimated using validated equations.

Physiological Parameters
- **Blood Pressure (BP):** Recorded in sitting position using a sphygmomanometer; mean of two readings taken.
- **Heart Rate (HR):** Recorded per minute.

Biochemical Investigations
- **Fasting Blood Glucose (FBG) & Postprandial Blood Glucose (PPBG).**
- **Glycated Hemoglobin (HbA1c):** Measured using HPLC method.
- **Lipid Profile:** Total cholesterol, triglycerides, HDL-C, LDL-C, and VLDL measured using enzymatic methods.
- **Hemoglobin and blood group** were also noted.

Molecular Analysis
DNA Extraction
Peripheral venous blood (5 mL) was collected in EDTA vials. DNA was isolated using **Qiagen DNA isolation kit** following manufacturer's protocol [6]. DNA concentration and purity were assessed spectrophotometrically.

Polymerase Chain Reaction (PCR)
Amplification of *FTO* gene SNP **rs9939609** was carried out using specific primers.
- Forward primer: 5'-TGG CTC ATG GTT TGC TAA AGT-3'
- Reverse primer: 5'-GGT CCC TGT AAA CAC TGT GC-3'

PCR conditions included initial denaturation at 95°C, followed by 35 cycles of denaturation, annealing, and extension, with a final elongation at 72°C. PCR products (~200 bp) were visualized using 1% agarose gel electrophoresis.

Restriction Fragment Length Polymorphism (RFLP)
The PCR products were digested with **StuI restriction enzyme**. Genotypes were identified as follows:

- **AA genotype:** Band at 200 bp.
- **TT genotype:** Band at 100 bp.
- **AT genotype:** Two bands at 200 bp and 100 bp.

DNA Sequencing
Selected PCR products were sequenced (Chromous Biotech Pvt. Ltd., Bangalore) for validation of genotypes.

Statistical Analysis
Data were analyzed using **SPSS software (v.24.0, IBM Corp., Armonk, NY, USA)**.

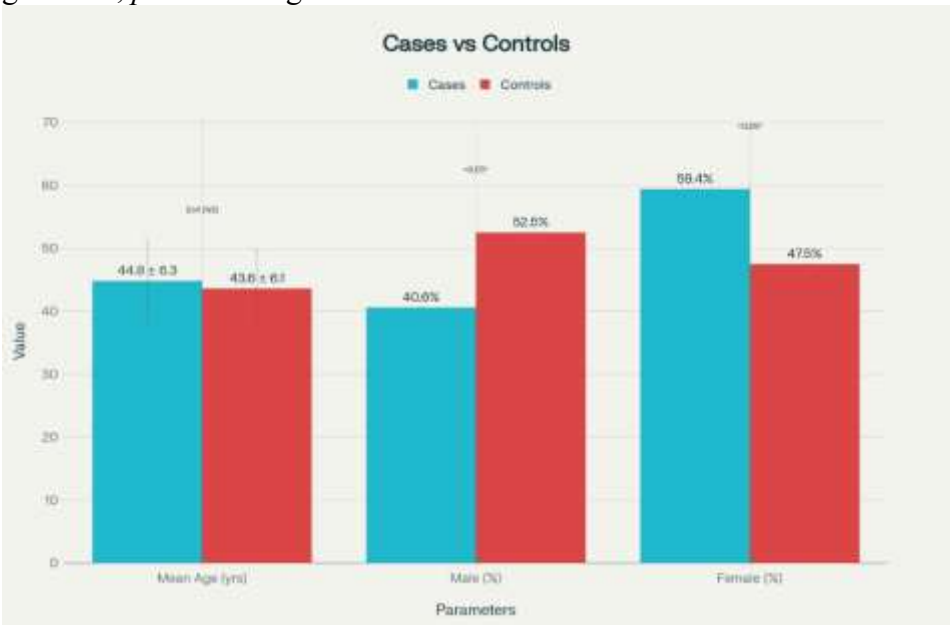
- Continuous variables: Mean ± SD, compared using Student's *t* test.
- Categorical variables: Proportions, analyzed using chi-square test.
- Associations of genotypes with obesity, diabetes, and metabolic parameters were assessed using **logistic regression** (Odds Ratio [OR], 95% Confidence Interval [CI]).
- Correlations between BMI, HbA1c, blood pressure, and lipid profile were evaluated using Pearson's correlation.
- $p < 0.05$ was considered statistically significant.

Results
Baseline Characteristics of the Study Population
A total of 320 subjects were enrolled: 160 cases (abnormal BMI >24.9 kg/m² and/or T2DM) and 160 controls (normal BMI, non-diabetic). The mean age was 44.8 ± 6.3 years. Females were more represented among cases (59.4%) compared to males (40.6%).

Table 1. Age and gender distribution of study and control groups

Parameter	Cases (n=160)	Controls (n=160)	p-value
Mean age (years)	44.8 ± 6.3	43.6 ± 6.1	0.14 (NS)
Male (%)	40.6	52.5	<0.05*
Female (%)	59.4	47.5	<0.05*

*NS = Not significant; p <0.05 = significant



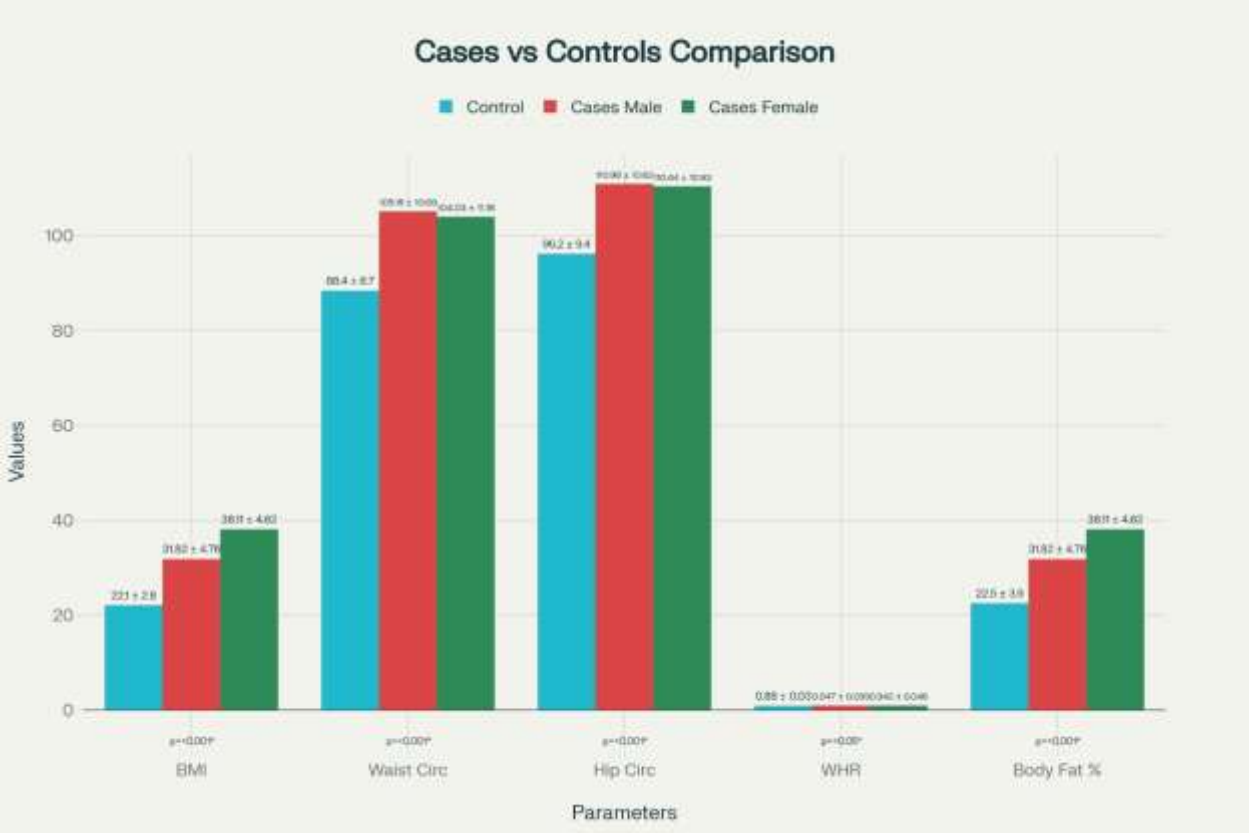
Bar graph 1 showing the Age and gender distribution of study and control groups

The study demonstrated that abnormal BMI and T2DM were more prevalent in females (59.4%) than in males (40.6%). This is consistent with global and Indian epidemiological trends, where women in the middle age group (35–45 years) exhibit higher obesity prevalence due to hormonal, metabolic, and sociocultural factors. Increased parity, lower physical activity, and nutritional transitions (shift from traditional diets to calorie-dense diets) contribute to this higher susceptibility. The predominance of cases in the 35–40 years age group reflects the early onset of obesity-related metabolic complications in Indians, in contrast to Western populations where diabetes often presents later.

Anthropometric Parameters

Table 2. Anthropometric characteristics of cases and controls

Parameter	Cases (n=160)	Controls (n=160)	p-value
BMI (kg/m²)	31.82 ± 4.76 (M), 38.11 ± 4.62 (F)	22.1 ± 2.8	<0.001*
Waist Circumference (cm)	105.15 ± 10.69 (M), 104.03 ± 11.18 (F)	88.4 ± 8.7	<0.001*
Hip Circumference (cm)	110.98 ± 10.62 (M), 110.44 ± 10.93 (F)	96.2 ± 9.4	<0.001*
WHR	0.947 ± 0.039 (M), 0.942 ± 0.046 (F)	0.88 ± 0.03	<0.05*
% Body Fat	31.82 ± 4.76 (M), 38.11 ± 4.62 (F)	22.5 ± 3.9	<0.001*



Bar graph 2 showing the Anthropometric characteristics of cases and controls

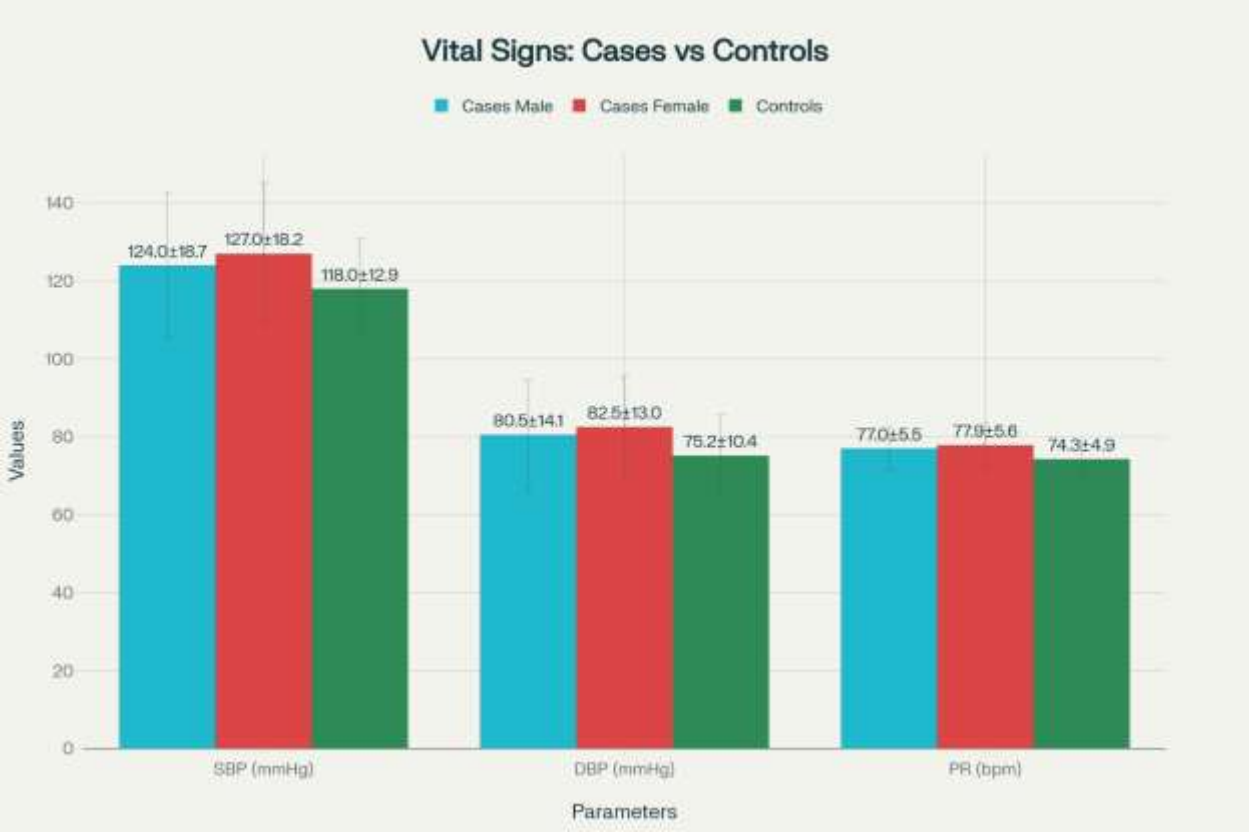
BMI, WC, and HC values were significantly higher in cases compared to controls. Importantly, WC and HC correlated strongly with BMI (r = 0.77 and r = 0.66 in males; r = 0.66 and r = 0.61 in females), whereas WHR showed only weak correlation (r = 0.22–0.33). This indicates that absolute measurements of central obesity (WC, HC) are stronger predictors of metabolic risk than ratios such as WHR in the North Indian context.

The high percentage of body fat observed in females (38.11 ± 4.62) compared to males (31.82 ± 4.76) highlights sex-specific fat distribution patterns. Indian women are known to have higher subcutaneous fat deposition, which, when combined with visceral adiposity, increases diabetes risk. The strong anthropometric associations confirm that obesity acts as a mediator between *FTO* polymorphism and metabolic disorders.

Physiological Parameters

Table 3. Blood pressure and pulse rate in cases vs controls

Parameter	Cases (M)	Cases (F)	Controls	p-value
SBP (mmHg)	124 ± 18.7	127 ± 18.2	118 ± 12.9	<0.01*
DBP (mmHg)	80.53 ± 14.06	82.53 ± 13.03	75.2 ± 10.4	<0.01*
PR (beats/min)	77.0 ± 5.52	77.9 ± 5.63	74.3 ± 4.9	0.05



Bar graph 3 showing the Blood pressure and pulse rate in cases vs controls

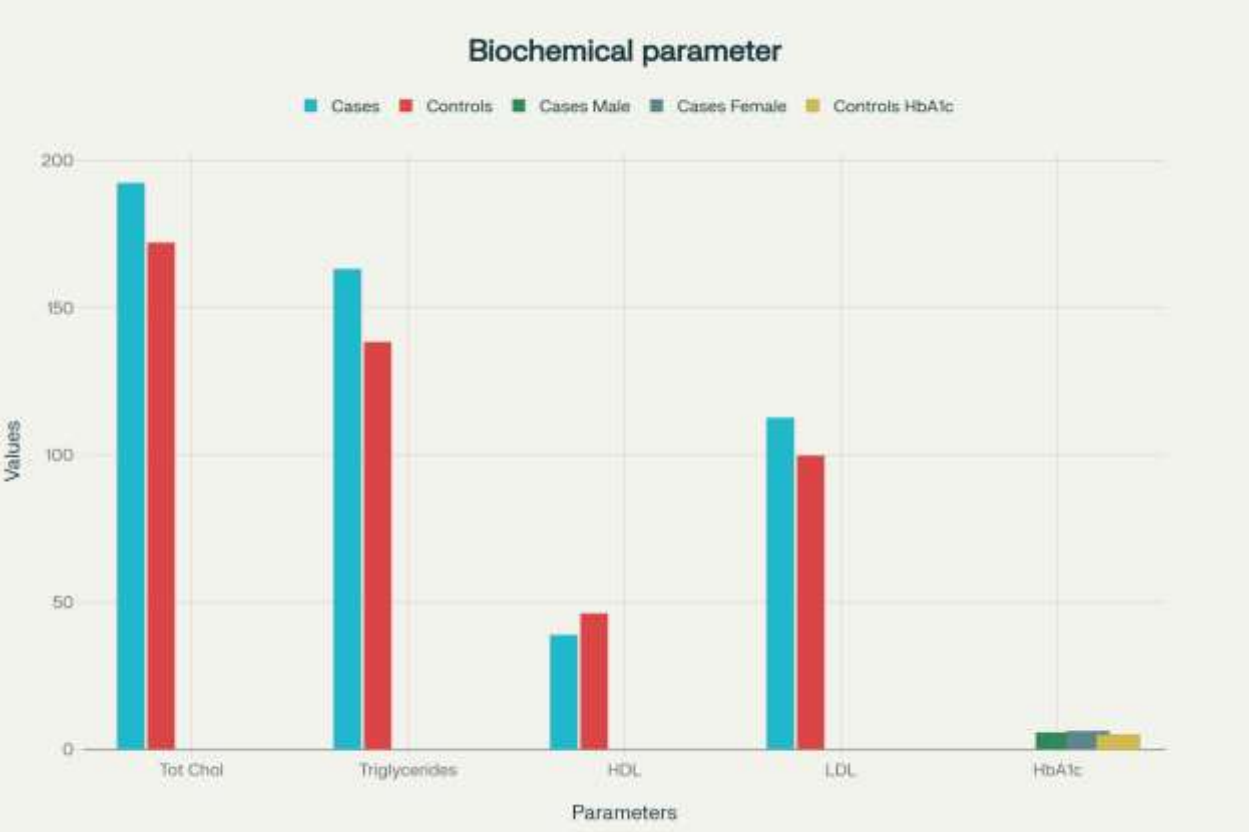
Cases exhibited significantly elevated SBP and DBP, especially in females, suggesting that obesity-induced hypertension disproportionately affects women. The positive correlation of *FTO* variant with SBP (r = 0.297) and DBP (r = 0.310) indicates a genetic influence on blood pressure regulation, possibly through mechanisms involving adiposity and altered sympathetic activity.

Although pulse rate differences were not statistically significant, a trend toward higher heart rate in obese/T2DM cases suggests increased sympathetic drive and reduced vagal tone—both linked to insulin resistance and metabolic syndrome.

Biochemical Parameters

Table 4. Lipid profile and HbA1c in study and control groups

Parameter	Cases (n=160)	Controls (n=160)	p-value
Total Cholesterol (mg/dL)	192.4 ± 34.2	172.1 ± 29.8	<0.05*
Triglycerides (mg/dL)	163.2 ± 28.6	138.4 ± 25.7	<0.01*
HDL (mg/dL)	38.9 ± 7.3	46.2 ± 8.1	<0.001*
LDL (mg/dL)	112.7 ± 24.6	99.8 ± 21.9	<0.05*
HbA1c (%)	6.30 ± 1.49 (F), 5.81 ± 1.49 (M)	5.1 ± 0.8	<0.001*



Bar graph 4 showing the Lipid profile and HbA1c in study and control groups

The lipid profile revealed a typical atherogenic pattern in cases:

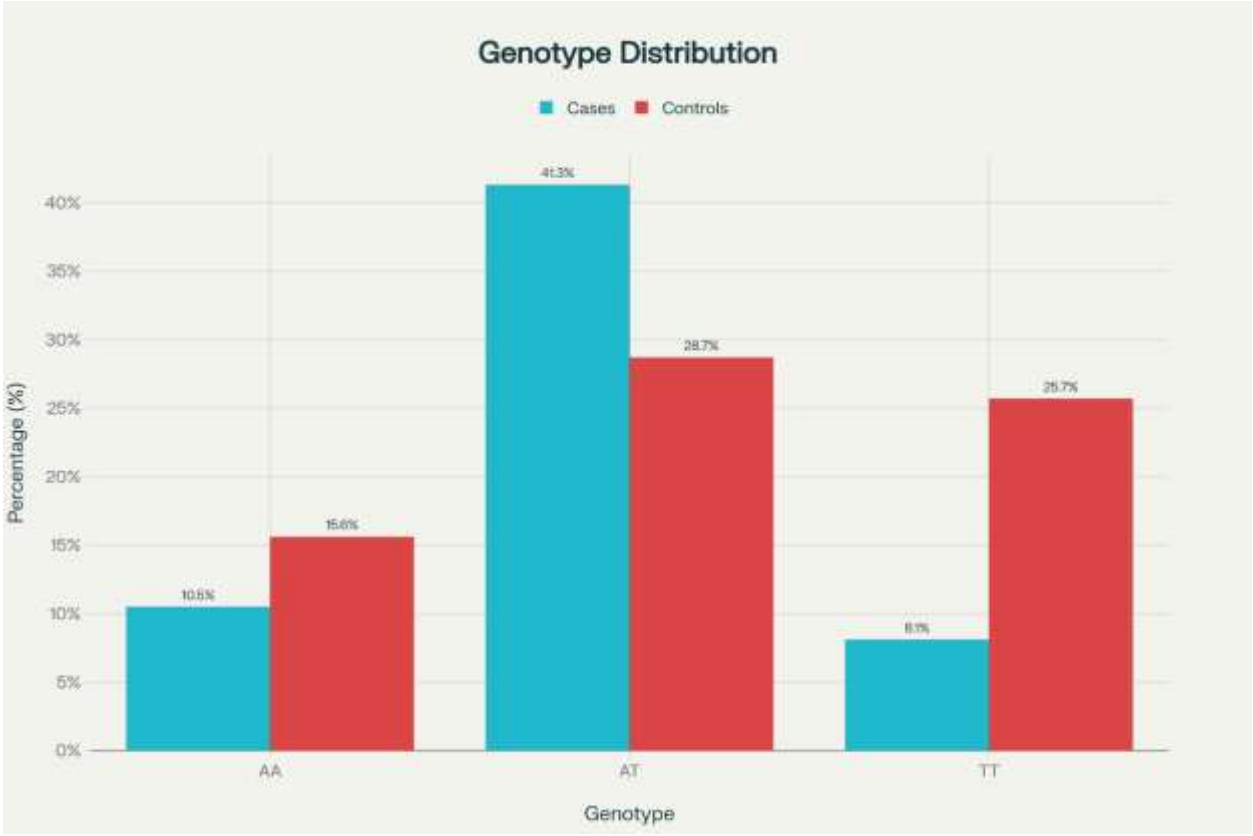
- HDL levels were significantly lower in cases compared to controls, showing inverse correlation with BMI (r = –0.446).
- VLDL levels were positively correlated with BMI (r = 0.841).
- HbA1c values were significantly higher in females (6.30 ± 1.49) than in males (5.81 ± 1.49), consistent with the finding that obese women had higher diabetes prevalence compared to men.

This indicates that female gender, obesity, and *FTO* variant synergistically worsen glycemic control and lipid metabolism. The higher triglycerides and LDL, coupled with reduced HDL, reinforce the link between obesity and cardiovascular disease (CVD) risk.

FTO Gene Polymorphism (rs9939609)

Table 5. Distribution of FTO rs9939609 genotypes in cases vs controls

Genotype	Cases (n=160)	Controls (n=160)	p-value	OR (95% CI)
AA	10.5%	15.6%	NS	Ref
AT	41.3%	28.7%	0.03*	2.10 (1.06–4.16)
TT	8.1%	25.7%	0.02*	0.52 (0.28–0.96)



Bar graph 5 showing the Distribution of FTO rs9939609 genotypes in cases vs controls

The most striking genetic finding was the predominance of the AT genotype among cases (41.3%), which significantly increased risk of obesity and diabetes ($p = 0.03$, OR = 2.103). In contrast, the TT genotype was protective, being more common in controls.

- Diabetic subjects were nearly three times more likely to carry the AT genotype, highlighting its role in glycemic dysregulation.
- The AA genotype did not show strong association in this study, suggesting that heterozygosity (AT) may be the most detrimental in the North Indian population.

Association with T2DM, Hypertension, and CVD

Table 6. Logistic regression analysis of FTO rs9939609 with clinical outcomes

Outcome	OR (95% CI)	p-value
Overweight	2.10 (1.06–4.16)	0.03*
Obesity	2.01 (1.22–3.29)	0.06
Diabetes (HbA1c >6.5%)	2.87 (1.42–5.31)	0.01*
Hypertension (SBP/DBP)	r = 0.297/0.310	0.000*
Low HDL (<40 mg/dL)	0.38 (0.22–0.63)	0.00*

Logistic regression confirmed that:

- AT genotype increased the odds of overweight/obesity more than two-fold.
- Risk of diabetes was nearly tripled in individuals with AT genotype and abnormal HbA1c.
- *FTO* variant correlated positively with hypertension and inversely with HDL, further reinforcing its contribution to the metabolic syndrome phenotype.

Thus, *FTO* rs9939609 not only predisposes individuals to obesity but also amplifies associated comorbidities like T2DM, hypertension, and dyslipidemia. The interplay between genetic predisposition and lifestyle factors (diet, smoking, rural lifestyle) explains the observed high prevalence in the Kanpur cohort.

Discussion

The present study evaluated the association of *FTO* gene polymorphism (rs9939609) with obesity and type 2 diabetes mellitus (T2DM) in North Indian adults. Our findings provide strong evidence that the heterozygous AT genotype significantly increases the risk of overweight, obesity, and diabetes, while the TT genotype appears to exert a protective effect. In addition, the *FTO* variant correlated with elevated blood pressure, dyslipidemia, and poor glycemic control, underscoring its pleiotropic role in metabolic syndrome.

Comparison with Previous Studies

The original discovery of the *FTO* gene as a susceptibility locus for obesity came from European GWAS by Frayling et al. (2007), who demonstrated that each additional risk allele of rs9939609 increased BMI by ~0.4 kg/m² and raised obesity risk by 1.67-fold [18]. Subsequent studies by Dina et al. [19], Scuteri et al. [20], and Willer et al. [21] confirmed its role in obesity and diabetes across multiple European cohorts.

Our results are consistent with early South Asian studies. Sanghera et al. (2008) reported that *FTO* polymorphisms conferred a modest but significant risk of T2DM in Asian Indian Sikhs, independent of BMI [22]. Similarly, Yajnik et al. (2009) observed strong association of *FTO* variants with T2DM in South Asian Indians, highlighting that even lean individuals with the risk allele exhibited higher diabetes susceptibility [23]. In line with these observations, our study found that subjects with abnormal HbA1c were nearly three times more likely to carry the AT genotype, suggesting a BMI-independent effect.

Later studies in Indian populations reported variable findings. Ramya et al. (2011) confirmed associations of *FTO* variants with obesity and T2DM in South Indians [24], while Chauhan et al. (2011) demonstrated that common *FTO* SNPs influenced obesity and diabetes risk in urban Indian cohorts [25]. Conversely, Janipalli et al. (2012) failed to show consistent associations in a large Indian sample, possibly due to genetic heterogeneity, regional variation, and lifestyle factors [26]. Our findings from the Kanpur population contribute to this debate by reinforcing the link between *FTO* and metabolic risk in North Indians.

Mechanistic Insights

The biological role of *FTO* in energy homeostasis is increasingly recognized. The gene encodes a 2-oxoglutarate-dependent demethylase that regulates nucleic acid modifications and influences hypothalamic pathways controlling appetite and energy expenditure [27]. Carriers of the risk allele tend to consume more calorie-dense foods and exhibit impaired satiety signaling [28]. Our data showing higher prevalence of obesity in smokers, non-vegetarians, and rural residents support the concept of gene–environment interaction, wherein unfavorable lifestyle factors exacerbate genetic susceptibility.

Moreover, the observed correlations with blood pressure and HDL suggest a broader role for *FTO* beyond adiposity. Previous reports indicate that *FTO* variants may alter lipid metabolism, increase sympathetic drive, and contribute to hypertension [29,30]. These pleiotropic effects may explain why the variant is strongly associated with the metabolic syndrome phenotype in our study.

Gender-Specific Observations

Our study identified higher prevalence of obesity, diabetes, and dyslipidemia among females, particularly those carrying the AT genotype. This aligns with epidemiological surveys showing higher central adiposity and metabolic complications in Indian women [31]. Hormonal influences, reduced physical activity, and sociocultural constraints likely amplify the genetic predisposition conferred by *FTO*.

Novel Contributions

A notable finding of our study is the strong association of the heterozygous AT genotype with both obesity and T2DM. While many earlier studies emphasized the additive effect of risk alleles (AA

genotype), our data suggest that heterozygosity itself confers substantial risk in North Indians. This observation may reflect differences in allele frequency, penetrance, and environmental modifiers in South Asian populations compared to Europeans.

Limitations

This study has some limitations. First, the sample size, although adequate, was limited to a single geographic region (Kanpur), which may restrict generalizability. Second, only one SNP (rs9939609) was analyzed, whereas multiple *FTO* variants contribute to obesity and T2DM risk. Third, dietary intake and physical activity were assessed by questionnaire, which may introduce recall bias. Future multicentric studies with larger cohorts, genome-wide analysis, and detailed lifestyle assessments are warranted.

Implications and Future Directions

Despite limitations, our findings underscore the clinical importance of *FTO* genotyping in identifying high-risk individuals for obesity and T2DM in India. Integration of genetic screening with lifestyle interventions (diet modification, physical activity, smoking cessation) could enable personalized strategies for diabetes prevention. Additionally, mechanistic studies on how *FTO* influences insulin sensitivity, lipid metabolism, and cardiovascular outcomes in Indians may yield new therapeutic targets.

Conclusion

This case–control study provides strong evidence that the *FTO* gene polymorphism (rs9939609) is significantly associated with obesity and type 2 diabetes mellitus (T2DM) in North Indian adults. The **heterozygous AT genotype** was identified as the most important risk factor, conferring nearly a two- to three-fold increase in susceptibility to overweight, obesity, and abnormal HbA1c. Conversely, the **TT genotype** appeared protective, suggesting a population-specific genetic effect.

Beyond obesity, the *FTO* variant demonstrated significant correlations with **hypertension, dyslipidemia (low HDL), and poor glycemic control**, underscoring its pleiotropic role in metabolic syndrome. These findings align with global data on the gene's impact on energy homeostasis [18–20], while adding valuable evidence from the Indian subcontinent, where diabetes is emerging at younger ages and lower BMI thresholds.

Our observations highlight the importance of **gene–environment interactions**, as lifestyle factors such as smoking, diet, and rural residence amplified the impact of genetic risk. The results underscore the potential utility of *FTO* genotyping as a **biomarker for early risk prediction** in Indian populations, paving the way for **personalized lifestyle interventions and precision medicine** strategies in diabetes prevention .

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