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Research Article

Complication Spectrum

# Influence of Family History on the Age of Onset and Complication Spectrum in Patients with Type 2 Diabetes Mellitus

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Type 2 Diabetes Mellitus (T2DM) is a prevalent chronic health condition globally, with its onset and complications significantly influenced by genetic and environmental factors. This study aimed to assess the influence of family history on the age of onset and complication spectrum among T2DM patients.

**Methods**: This descriptive cross-sectional study recruited 500 participants diagnosed with T2DM. Data were collected through structured interviews and clinical assessments, focusing on demographics, medical and family history, age of onset, and diabetes-related complications. Chi-square and logistic regression analyses were employed to examine the association between family history and diabetes complications, adjusting for confounders.

**Results**: Among the participants, 73.8% reported a positive family history. The mean age of onset for those with a family history was significantly lower (43.8 ± 9.86 years) compared to those without (48.24 ± 9.87 years; $p < 0.001$). Patients with higher HbA1c levels were younger, had an earlier onset of diabetes, and a higher prevalence of hypertension. The age of onset was earlier, if more family members had a history of diabetes. Complications were present in 80.8% of the cohort, with the most common being diabetic peripheral neuropathy (70.6%). Logistic regression analysis indicated that having siblings with diabetes was a significant predictor for general diabetic complications (OR=2.589, CI: 1.481 to 4.53, p<.001), diabetic retinopathy (OR=1.981, CI: 1.20 to 3.26, p=0.007), and diabetic peripheral neuropathy (DPN) (OR=1.709, CI: 1.042 to 2.8, p=0.034).

**Conclusion**: The study highlights the significant influence of family history on the age of onset and the spectrum of complications in T2DM. These findings suggest the necessity for comprehensive family history assessments in clinical settings to identify at-risk individuals for early intervention and personalized management strategies.

**Keywords:** Type 2 Diabetes Mellitus, family history, age of onset, diabetes-related complications, cross-sectional study

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# Introduction

Diabetes Mellitus (DM) represents a significant global health challenge, with type 2 diabetes (T2DM) accounting for over 90% of cases worldwide [1]. The International Diabetes Federation has identified diabetes as a chronic and complex endocrine metabolic disorder and a leading cause of death, highlighting its status as a critical public health issue and a priority for international health intervention campaigns [2]. The global prevalence of diabetes is on an alarming rise, with current estimates indicating that approximately 537 million adults are living with the condition. This figure is projected to reach 643 million by 2030 and 783 million by 2045, with three-quarters of these individuals residing in Low- and Middle-income countries [3].

In India, the aggregated prevalence of diabetes was found to be 11.4%, and that of prediabetes was 15.3%, with urban areas reporting higher prevalence rates than rural areas [4]. This demographic variation signals the intricate interplay of genetic, environmental, and lifestyle factors contributing to disease proliferation. The etiology of T2DM is multifaceted, involving modifiable risk factors such as overweight, obesity, sedentary lifestyle, and hypertension, alongside non-modifiable risks including age, ethnicity, family history, and gestational diabetes history [5]. Furthermore, the complications arising from T2DM significantly contribute to the morbidity and mortality associated with the disease, including cardiovascular diseases, kidney failure, vision loss, and neuropathy [6]. These complications highlight the critical need for effective management and prevention strategies to mitigate the impact of T2DM on individuals and healthcare systems.

The role of family history in the onset and progression of T2DM is particularly significant, serving as a pivotal genetic marker and predisposition factor. Individuals with a familial background of diabetes exhibit a 2-4 fold increased risk of developing the condition, with studies indicating a higher transmission rate from diabetic mothers [7]. However, this pattern is not universally observed, with some populations exhibiting an equal or even paternal dominance in transmission rates, thus highlighting the complex interplay between genetics and environmental factors in the disease's pathogenesis [7].

Despite this known genetic predisposition, T2DM's etiology remains complex, influenced by a pattern of genetic and environmental factors. This complexity highlights the importance of understanding individual genetic predispositions to tailor management and preventive measures, aiming to enhance clinical outcomes and reduce complications. Furthermore, family history not only impacts the onset of diabetes but also plays a crucial role in disease management and progression, implicating it in the control and exacerbation of complications[1], [8].

The current study aims to address this gap by identifying the proportion of T2DM patients with a familial history of diabetes and investigating the impact of such history on the age of onset and the spectrum of complications associated with T2DM.

Through this, we seek to elucidate the association between family history and the clinical manifestations of T2DM, aiming to enhance the existing body of knowledge and inform clinical decision-making. Understanding these dynamics is vital for the development of personalized management strategies, contributing to improved patient outcomes and the formulation of targeted public health interventions.

# Methods

### Study Design and Setting

This descriptive cross-sectional study was conducted at the Karnataka Institute of Endocrinology and Research (KIER), focusing on individuals attending the outpatient department. The study aimed to evaluate the impact of family history on the age of onset and complications in a representative sample of the type 2 diabetic population. The data collection period spanned from June 2022 to November 2022.

### Participants

A total of 500 subjects with T2DM, both genders, were enrolled. The inclusion criteria mandated that participants must be diagnosed with T2DM (as per American Diabetes Association guidelines)[9], capable of providing informed consent, and were under follow-up care at KIER. No age restrictions were specified. Excluded were those with type 1 diabetes, gestational diabetes, or other forms of diabetes, and those who could not provide informed consent.

### Sample Size Estimation

The sample size was computed based on a dichotomous outcome, using prior research to predict incidences of 68.8% in the general T2DM population[10] and 75% in our cohort. To detect this with 85% power, alpha of 0.05, and beta of 0.15, we needed 479 participants. This calculation ensures that our study is sufficiently powered to detect a statistically significant difference in incidences, should one exist.

### Data Collection Process

Data was collected directly from patients during their routine visits to the OPD through a structured questionnaire. This questionnaire was used to gather comprehensive information on each patient's demographic profile, medical history, family history of diabetes (including mother, father, siblings, and second-degree relatives), age of onset, duration of diabetes, and the presence of diabetes-related complications such as diabetic retinopathy (DR), diabetic kidney disease (DKD), diabetic peripheral neuropathy (DPN), and Macrovascular-complications such as Coronary Artery Disease (CAD), Cerebrovascular disease (CVA), Peripheral artery Disease (PAD) were collected. Clinical measurements including body mass index (BMI), glycosylated hemoglobin (HbA1c), and blood pressure were taken by trained medical personnel.

### Statistical Analysis

Data were entered into a secure database and analyzed using JAMOVI, an open-source software using R program. Descriptive statistics summarized the demographic and clinical characteristics of the study population. The association between family history of diabetes and the age of onset of T2DM was assessed using the Chi-Square test of proportions. Logistic regression models were employed to explore the relationship between family history and diabetic complications, adjusting for confounders such as age, sex, BMI, and duration of diabetes. Statistical significance was set at a p-value of less than 0.05.

### Ethical Considerations

The study protocol was approved by the Institutional Review Board at KIER. All participants provided written informed consent after being informed about the study objectives, procedures, benefits, and risks. Confidentiality of patient data was strictly maintained throughout the study.

# Results

### Demographic and Clinical Characteristics of the Study Population

The study enrolled 500 patients diagnosed with type 2 diabetes mellitus, of which 58.6% were male (n=293) and 41.4% were female (n=207). The age of participants ranged from 25 to 87 years, with a mean age of 56.1 years (SD = ± 11.03). The mean body mass index (BMI) was 26.68 kg/m² (SD = ± 4.11).

**Table 1: Demographic and Clinical Characteristics of Study Participants**

| Variable | Total (n=500) | Family History: Yes (n=369) | Family History: No(n=131) | P-value |
|---|---|---|---|---|
| Age (years), mean ± SD | 56.13 ± 11.03 | 54.85 ± 11.13 | 59.72 ± 9.92 | <0.001a |
| Sex, n (%) | | | | |
| - Male | 293 (58.6%) | 209 (56.64%) | 84 (64.12%) | 0.135c |
| - Female | 207 (41.4%) | 160 (43.36%) | 47 (35.88%) | |
| BMI (kg/m²), mean ± SD | 26.68 ± 4.11 | 26.72 ± 4.22 | 26.59 ± 3.79 | .815a |
| Urban/Rural/Town, n (%) | | | | |
| - Urban | 311 (62.2%) | 240 (65.04%) | 71 (54.2 %) | 0.081c |
| - Town | 108 (21.6%) | 75 (20.33%) | 33 (25.19%) | |
| - Rural | 81 (16.2%) | 54 (14.63%) | 27 (20.61%) | |
| Age of Onset (years), mean ± SD | 44.96 ± 10.05 | 43.8 ± 9.86 | 48.24 ± 9.87 | <0.001b |
| Duration of Diabetes (years), mean ± SD | 11.22 ± 7.47 | 11.11 ± 7.08 | 11.54 ± 8.52 | 0.818a |
| Medication Usage | | | | |
| - OAD, n (%) | 494 (98.8%) | 365 (73.89%) | 129 (26.11%) | 0.689c |
| - Insulin Therapy, n (%) | 95 (19%) | 69 (18.7%) | 26 (19.85%) | 0.774c |
| - Both OADs and Insulin, n (%) | 95 (19%) | 69 (18.7%) | 26 (19.85%) | - |
| - No Medication, n (%) | 6 (1.2%) | 4 (66.67%) | 2 (33.33%) | - |
| HbA1c (%), mean ± SD | 7.87 ± 1.77 | 7.9 ± 1.72 | 7.69 ± 1.69 | 0.105a |
| Hypertension, n (%) | 264 (52.8%) | 185 (70.08%) | 79 (29.92%) | 0.045c |
| Dyslipidemia, n (%) | 484 (96.8%) | 359 (74.17%) | 125 (25.83%) | 0.296c |
| Diabetes Related Complications Present, n (%) | 404 (80.8%) | 298 (73.76%) | 106 (26.24%) | 0.969c |

The Age of Onset of diabetes was 44.96± 10.05 years and the average duration of diabetes was 11.22 ± 7.47 years. The majority of participants were from urban areas (62.2%), followed by town (21.6%) and rural (16.2%) regions (Table 1).

*Note: SD = Standard Deviation*

a denotes p value evaluated using Mann-Whitney U-Test

b denotes p value evaluated using t-Test for independent samples

c denotes p value evaluated using chi2 test

When splitting the total number of patients recruited (n=500) based on family history, the data showed that n=369 (73.8%) had a positive family history, with the highest being siblings (n=87, 17.4%) (Table 1). This was followed by a combination of mother and siblings (n=40, 8%), and father and siblings (n=31, 6.2%). The least common was the combination of mother and father (n=7, 1.4%). The presence of diabetes in second-degree relatives alone was noted in 25 participants (5%). These findings indicate that family history is a prevalent factor in the study group, with a range of familial connections associated with the disease.

Furthermore, the age of participants and the age of onset of type 2 diabetes varied significantly with family history. Participants with a family history of diabetes had a younger age (mean = 54.85 years, SD = ±11.13) compared to those without a family history (mean = 59.72 years, SD = ±9.92) ($p < 0.001$). Similarly, the participants with a family history of diabetes had a younger age of onset (mean = 43.8 years, SD = ±9.86) compared to those without a family history (mean = 48.24 years, SD = ±9.87) ($p < 0.001$) (See figure 1). Figure 2 shows the detailed relationship between different family medical histories and the age of onset.

**Figure 1: Age of Onset of diabetes in relation to family history**

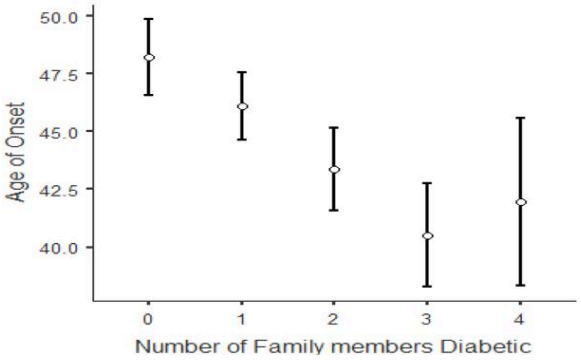


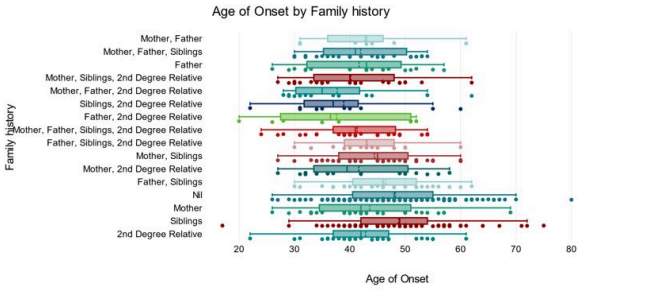

**Table 2: Distribution of family history types among participants**

| Variables | Number of Family members positive | | | | | F (4, 495) | P value |
|---|---|---|---|---|---|---|---|
| | None n=131 | One n=163 | Two n=109 | Three n=70 | Four n=27 | | |
| Age in years | 59.72 ± 9.92 | 56.29 ± 11.1 | 53.95 ± 11.5 | 53.54 ± 10.9 | 53.29 ± 9.9 | 6.20 | <0.001 |
| Age of Onset in years | 48.23 ± 9.8 | 46.10 ± 9.9 | 43.37 ± 9.5 | 40.51 ± 9.0 | 41.96 ± 7.6 | 9.60 | < 0.001 |
| Duration of diabetes in years | 11.54 ± 8.5 | 10.52 ± 6.6 | 10.65 ± 7.0 | 13.07 ± 8.2 | 11.44 ± 6.4 | 1.66 | 0.15 |
| BMI (Kg/m2) | 26.59 ± 3.78 | 26.54 ± 4.15 | 26.59 ± 4.29 | 27.25 ± 4.49 | 26.88 ± 3.59 | 0.42 | 0.74 |
| HbA1C levels (in %) | 7.69 ± 1.7 | 7.84 ± 1.6 | 7.93 ± 1.8 | 8.11 ± 1.9 | 7.58 ± 1.3 | 0.91 | 0.45 |

F= The F-statistic from the ANOVA test

Among those with a family history of diabetes, having a family history involving both parents was associated with an earlier onset of diabetes, with a mean difference of 4.50 (95% CI 2.03 to 6.98), followed by a history involving the mother, with a mean difference of 4.48 (95% CI 2.68 to 6.28), and the father, with a mean difference 3.86 (95% CI 1.95 to 5.77).

**Figure 2: Age of Onset of Diabetes Mellitus with Family History**




The mean age of onset for participants with a mother with T2DM was 44.45 years, compared to 41.67 years for those with a father with T2DM, and 48.24 years for those with no family history of diabetes. Individuals with a second-degree relative with a family history of diabetes constituted 27.4% (n=137) of the study population, while 46.4% (n=232) had a first-degree relative with the disease. While individuals with no family history but diagnosed with T2DM were 26.2% (n=131).

### Hypertension and Dyslipidaemia

Hypertension was present in 52.8% (n=264) of the participants, and dyslipidaemia in 96.8% (n=484).

The presence of hypertension (70.08% in patients with family history vs. 29.92% in patients without family history, p<0.04) and dyslipidaemia (74.17% vs. 25.83%, p<0.05) was more common among participants with a family history of diabetes (Table 1).

**Bivariate relationships between variables using Pearson's correlation**

The bivariate analysis of our study, as shown in Table 3, showed a significant positive correlation between patient age and the age of diabetes onset ($r = 0.731$, $p < 0.001$), suggesting that diabetes tends to manifest at an older age in our cohort. Body Mass Index (BMI), however, showed only a weak and negative correlation with age ($r = -0.125$, $p < 0.01$), indicating that younger patients had marginally higher BMI scores, but this correlation did not extend significantly to the age of diabetes onset. Moreover, the study found a significant negative correlation between both age and age of onset with HbA1c levels ($r = -0.163$, $p < 0.001$ and $r = -0.243$, $p < 0.001$, respectively), highlighting that higher HbA1c levels are associated with younger age and earlier onset of diabetes.

**Table 3: Bivariate relationships between variables using Pearson's correlation**

| | Age | Age of Onset | BMI |
|---|---|---|---|
| Age of Onset | 0.731*** | | |
| BMI | -0.125** | -0.034 | |
| HbA1c | -0.163*** | -0.243*** | 0.001 |
| Note. * p < .05, ** p < .01, *** p < .001 | | | |

**Prevalence of Diabetes-Related Complications**

Our study examined the prevalence of diabetes-related complications among 500 participants with T2DM (Table 1). We specifically investigated the impact of family history on the occurrence of these complications. The results, as summarized in Table 4, indicate a significant prevalence of various complications among the cohort.

Overall, 80.8% of participants (404 individuals) had at least one diabetes-related complication, indicating that the majority of individuals with T2DM are likely to suffer from additional health issues. This high percentage emphasizes the extensive impact diabetes can have on overall health.

In terms of specific complications, Diabetic Peripheral Neuropathy (DPN) was the most prevalent, affecting 70.6% of the participants.

Notably, among those with DPN, 73.65% had a family history of diabetes, suggesting a potential genetic predisposition or shared environmental factors leading to this condition. This was a common theme across all complications studied; individuals with a family history of diabetes were more likely to experience complications though not significant.

Diabetic Retinopathy (proliferative and non-proliferative) was observed in 35.4% of the cohort. Within this group, an even larger proportion of 76.3% had a family history of diabetes,

Coronary Artery Disease (CAD) and Diabetic Kidney Disease (DKD) were less common, affecting 10% and 3.8% of participants, respectively. However, the majority of individuals with these conditions reported a family history of diabetes (70% for CAD and 78.95% for DKD),. However, the overall family history did not significantly influence the presence of complications (See Table 4.)

**Table 4: Prevalence of Diabetes-Related Complications**

| Complications | Total | Family history Present | Family history Absent | $\chi^2$, p value |
|---|---|---|---|---|
| | n (% of cases) | n (%) within complication subtype | | |
| Complications present in entire cohort | 404 (80.8%) | 298 (73.76%) | 106 (26.24%) | 0.001, 0.97 |
| Specific Complication Types | | | | |
| - DPN | 353 (70.6%) | 260 (73.65%) | 93 (26.35%) | 0.01, 0.90 |
| - DR (PDR and NPDR) | 177 (35.4%) | 135 (76.3%) | 42 (23.7%) | 0.68, 0.40 |
| - CAD | 50 (10%) | 35 (70%) | 15 (30%) | 0.42, 0.52 |
| - DKD | 19 (3.8%) | 15 (78.95%) | 4 (21.05%) | 0.27, 0.63 |

*DPN- Diabetic Peripheral Neuropathy, DR- Diabetic Retinopathy, PDR- Proliferative Diabetic Retinopathy, NPDR- Non Proliferative Diabetic Retinopathy, DKD- Diabetic Kidney Disease, CAD- Coronary Artery Disease.*

**Analysis of the multifaceted risk factors for Diabetes-Related Complications**

In our regression analysis, see Table 5, we explored the factors that might increase the likelihood of developing various complications related to diabetes.

By examining the roles of gender, family history, and obesity, we sought to understand how each might contribute to the risk of general diabetic complications, as well as specific conditions like Diabetic Retinopathy (DR) (including NPDR and PDR), Diabetic Peripheral Neuropathy (DPN), Coronary Artery Disease (CAD), and Diabetic Kidney Disease (DKD).

**Table 5: Predictive Factors and their Impact on Diabetes-Related Complications**

| | Outcome Variables | | | | |
|---|---|---|---|---|---|
| Predictor variables | Complications | Diabetic Retinopathy | DPN | CAD | DKD |
| | Odds Ratio, p-value | | | | |
| Intercept | 3.742, <.001 | 0.315, <.001 | 2.096, 0.01 | 0.0674, <.001 | 0.0245, <.001 |
| Gender | 0.882, 0.604 | 1.786, 0.004 | 0.823, 0.352 | 2.9441, 0.004 | 1.4487, 0.46 |
| Family History | 0.527, 0.094 | 0.636, 0.178 | 0.663, 0.224 | 0.3341, 0.053 | 0.7994, 0.813 |
| Mother | 0.828, 0.491 | 1.104, 0.664 | 0.723, 0.17 | 1.5748, 0.23 | 1.1808, 0.989 |
| Father | 0.969, 0.909 | 1.097, 0687 | 1.294, 0.291 | 1.3078, 0.473 | 0.9528, 0.934 |
| Siblings | 2.589, <.001 | 1.981, 0.007 | 1.709, 0.034 | 2.1831, 0.082 | 2.8284, 0.16 |
| 2nd Degree | 1.435, 0.22 | 1.450, 0.124 | 1.24, 0.398 | 1.0708, 0.862 | 3.216, 0.054 |
| Obesity Category (BMI cut-off 25 kg/m2) | 1.37, 0.198 | 1.027, 0.898 | 1.532, 0.044 | 0.8106, 0.509 | 1.4487, 0.46 |

Gender was found to have a variable impact across different conditions. For general diabetic complications, gender did not significantly alter the risk (OR=0.882, CI: 0.548 to 1.42, p=0.604). However, it played a more pronounced role in diabetic retinopathy and CAD, with ORs of 1.786 (CI: 1.202 to 1.653, p=0.004) and 2.9441 (CI: 1.4174 to 6.115, p=0.004) respectively, indicating a substantial increase in risk for male gender category. For DPN and DKD, gender differences were not statistically significant.

While the overall presence of family history did not have a significant bearing on complications, the subgroup of family history, particularly the presence of siblings with diabetes, was a consistent and significant factor across multiple conditions. In general, diabetic complications, having siblings with the condition significantly increased the risk (OR=2.589, CI: 1.481 to 4.53, p<.001).

This pattern was reaffirmed in Diabetic retinopathy (OR=1.981, CI: 1.20 to 3.26, p=0.007) and DPN (OR=1.709, CI: 1.042 to 2.8, p=0.034), although the effect was not as pronounced in CAD and DKD, where the results were not statistically significant.

Obesity's impact on the risk of diabetic complications was mixed. While it showed a non-significant trend towards increased risk in general complications (OR=1.37, CI: 0.848 to 2.21, p=0.198) and CAD (OR=0.8106, CI: 0.4345 to 1.512, p=0.509), it was significantly associated with an increased risk of DPN (OR=1.532, CI: 1.011 to 2.32, p=0.044). Interestingly, for DKD, obesity did not significantly impact the risk (OR=1.4487, CI: 0.54153 to 3.8756, p=0.46), suggesting that the relationship between obesity and diabetic complications may be more complex and condition-specific.

# Discussion

Our investigation into the influence of family history on the age of onset and the spectrum of complications in patients with T2DM provides vital insights into the intricate web of genetic and environmental factors contributing to the disease. This study observed that 73.8% of patients had a strong family history. Patients with higher HbA1c levels were younger, had an earlier onset of diabetes, and a higher prevalence of hypertension.

The age of onset was earlier, if more family members had a history of diabetes. Furthermore, 80.8% of the participants had at least one complication. Complications were more prevalent in patients with a family history of diabetes than in those without, though the difference was not statistically significant. Logistic Regression analysis showed siblings as the primary predictor for overall complications, diabetic retinopathy and DPN. A history of second-degree relatives was the primary predictor for DKD. Additionally, gender was identified as the primary predictor of CAD.

Our findings align with previous studies highlighting the significance of family history in the development and progression of T2DM. For instance, Sirdah et al. (2020) and Papazafiropoulou et al. (2016) have discussed the genetic predisposition in individuals with a family history of diabetes, suggesting a significant risk increase for developing T2DM[1],[7].

Moreover, the relationship between family history and an earlier onset of diabetes aligns with the observations made by Ikwuka et al. (2023), further emphasizing the critical need for targeted interventions in populations with a familial predisposition [3].

The prevalence of diabetes-related complications among our cohort reinforces the extensive impact diabetes can have on overall health. The substantial presence of complications such as Diabetic Peripheral Neuropathy and Non-Proliferative Diabetic Retinopathy among those with a family history accentuates the need for vigilant screening and tailored management strategies.

The differential impact of gender on the risk of diabetic complications observed in our study, particularly the pronounced role in Diabetic retinopathy and CAD, reaffirms the findings of Fajtova (2019) [8], suggesting that gender-specific factors, possibly hormonal or behavioural, might influence the manifestation and severity of diabetic complications. Furthermore, the complex relationship between obesity and diabetic complications observed, aligns with the multifaceted nature of the disease described by Galicia-Garcia et al. (2020) [5], where the interplay of metabolic, genetic, and environmental factors is evident. In light of our findings, clinical practices must incorporate comprehensive family history assessments into the management and preventative strategies for diabetes. Such approaches should not only consider the presence of diabetes in parents but also extend to siblings and second-degree relatives. The evident younger age of onset in individuals with a family history of diabetes emphasizes the necessity for earlier screening and intervention in these populations.

In the context of the Indian population, our results are similar to other studies from India which have shown diabetes occurring at an earlier age in those with a family history of diabetes [11],[12],[13]. The study by Pradeepa et al. (2021)[14] has shown that the susceptibility to diabetes is significantly determined by a combination of factors including ethnic background, age, obesity, sedentary lifestyle, dietary patterns, and behavioural practices, alongside genetic predispositions and familial antecedents. Further accentuating the impact of familial history, individuals whose parents both suffer from diabetes presented with higher BMI, Waist circumference, waist-hip ratio (WHR), systolic and diastolic blood pressure, and fasting blood glucose compared to those without any family history of T2DM [13]. This delineation not only emphasizes the critical role of genetics and family history in the manifestation of diabetes but also highlights the importance of monitoring individuals with a familial predisposition for early indicators of metabolic syndrome [14].

In another study conducted by Chaudhuri et al., (2021)[15] an examination of metabolic variables in subjects with and without a Family History of Diabetes revealed significant differences, illustrating the profound influence of a familial history of diabetes (FHD) on metabolic health. This research, focusing on the relationship between mothers and their newborns, identified a significant correlation with the presence of PPARγ (rs1801282) C/G and TCF7L2 (rs7903146) C/T polymorphisms. The genotyping of mothers with FHD and their newborns indicated a remarkable genetic concordance, specifically demonstrating that a high percentage of mothers carrying the PPARγ risk allele G (74%) transmitted this allele to 64.5% of their newborns. Likewise, for the TCF7L2 risk allele T, 73% of mothers passed it on to 68.5% of their newborns. These findings highlight the critical role of hereditary factors in the predisposition to diabetes, emphasizing the necessity of considering familial genetic patterns in the early screening and intervention strategies for diabetes prevention [15].

In a comprehensive analysis by Chaudhuri et al., which encompassed an extensive cohort of 86,931 patients with type 2 diabetes across 11 countries showed a significant influence of familial history on the age of onset. The study found a wide regional variation in familial history prevalence, from 39.1% to 85.3%, with the most common being maternal diabetes (32.5%).

Importantly, those with a familial history were diagnosed earlier, about 4.6 years on average, than those without. Specifically, the earliest diagnosis occurred in patients with both parents affected (average age 44.6 years), followed by those with a single affected parent (average age 47.7 years), and those with only affected siblings (average age 51.5 years)[16]. Our findings align with these observations, indicating that individuals with multiple affected family members experience an earlier onset of DM.

Diabetes Mellitus stands as a formidable global health challenge, and with T2DM comprising the majority of cases, the escalating prevalence of diabetes worldwide mandates a deeper understanding of the factors driving its onset and progression. The core of our study illuminated the significant role of family history, particularly the presence of siblings with diabetes, as a consistent and substantial risk factor for various diabetic complications. This observation highlights the potential role of shared genetic predispositions and common environmental factors. Notably, while the presence of diabetic parents did not emerge as a statistically significant factor for increased complications, the pronounced impact of diabetic siblings suggests a complex interplay of shared household lifestyles and behaviours, in addition to genetic factors.

The probable mechanisms linking family history to the age of onset and the spectrum of complications in T2DM are multifaceted, involving a complex interplay of genetic, epigenetic, and environmental factors. Genetic predisposition plays a crucial role, with studies identifying various genetic markers associated with increased diabetes risk, such as TCF7L2, KCNJ11, and PPARG[15],[17]. Additionally, epigenetic modifications, which influence gene expression without altering the DNA sequence, can also contribute to T2DM development, as evidenced by changes in DNA methylation and histone modification patterns [18],[19].

Shared family environments and lifestyles significantly impact diet, physical activity, and obesity, all of which are key contributors to insulin resistance and T2DM [20]. The primary pathophysiological mechanisms of T2DM involve insulin resistance and beta-cell dysfunction, with genetic and environmental factors leading to impaired glucose tolerance and hyperglycemia[4]. Moreover, the genetic predisposition to microvascular and macrovascular complications, such as nephropathy, retinopathy, and cardiovascular disease, is mediated through pathways involving endothelial dysfunction, oxidative stress, and atherogenic lipid profiles, highlighting the role of vascular health in diabetes complications [21]. Collectively, these mechanisms elucidate the complex and interrelated pathways through which family history impacts the onset and progression of T2DM and its associated complications.

This evidence emphasizes the critical role of family history in the development of type 2 diabetes, suggesting the need for targeted screening and early intervention in individuals with a familial predisposition. Further, these strategies should be tailored to individual risk profiles, considering the multifaceted nature of T2DM, where genetic predisposition intermingles with lifestyle and environmental factors. In addition, primary prevention measures such as weight reduction in obese, and ensuring physical activity and fitness must be taken seriously in individuals with a strong family history of diabetes.

**Limitations**

The research has several limitations that need to be considered. Firstly, the cross-sectional design, while robust, is limited in establishing causality, thereby restricting the interpretation of temporal relationships between family history and the onset and complications of T2DM. The sample, while substantial, may not be generalizable across all demographics, and any self-reported data could introduce recall bias.

The absence of longitudinal data hampers the understanding of the progression and response to interventions over time. Potential confounders such as diet, physical activity, and socio-economic factors might not be fully accounted for, possibly influencing the results. The study does not explore specific genetic markers, which could provide a more nuanced understanding of hereditary risks.

Finally, the clinical variability and individual differences in T2DM manifestation are vast, and the study might not capture the entire spectrum of complications, underscoring the complex nature of the disease and the influence of multiple interrelated factors beyond family history. Acknowledging these limitations is crucial for contextualizing the findings and guiding future research to address these gaps.

**What does this study add to the already existing data**?

This study reiterates the importance of family history on the age of onset and the complication spectrum of diabetes. Family history of diabetes, particularly having siblings with diabetes, was associated with significant risk of diabetes onset. Having one parent or both parents with diabetes reduced the age of onset of diabetes significantly.

Positive family history was associated with significantly higher risk of developing diabetes complications compared to those with no family history of diabetes.

# Conclusion

Our investigation substantiates the significant impact of familial history, particularly the presence of siblings with diabetes, on the phenotypic manifestation and complication spectrum of T2DM and that of family history on the age of onset of the disease. It highlights the complex interplay of genetics and environment in T2DM's progression and stresses the need for detailed family history in clinical assessments to tailor individualized care. The strong link between family history and diabetic complications calls for targeted surveillance and early interventions for those at risk. Our findings advocate for a shift towards personalized, family-focused diabetes management and emphasize ongoing research to enhance precision medicine strategies in T2DM prevention and care.

**Disclosures**

**Author Contributions:** This study was carried out in collaboration among all authors. RV conceptualized and designed the study, recruited patients, and collected data. IG contributed to the data analysis and manuscript preparation. RM played a key role in advanced data analysis, and data interpretation, critically reviewed the manuscript for important intellectual content and provided final approval of the version to be published. All authors read and approved the final manuscript.

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