RESEARCH ARTICLE

# Relationship between Genetic Variant of OXTR (rs53576) and MTNR1B (rs1387153) and Symptoms of Psychological Stress in Females with Gestational Diabetes Mellitus

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## Abstract

**Objective:** To assess the association of oxytocin receptor (rs53576) and melatonin hormone receptor 1B (rs1387153) gene single nucleotide polymorphisms with psychological symptoms in women with gestational diabetes mellitus.

**Method:** The case-control study was conducted from May 1 to June 1, 2022, at the Department of Physiology, University of Karachi, in collaboration with the Department of Biological and Biomedical Sciences, Aga Khan University, Karachi, and the Department of Obstetrics and Gynaecology, Jinnah Postgraduate Medical Centre, Karachi. Fifty gestational diabetic pregnant women and ninety healthy pregnant women were recruited. Sanger sequencing was performed to assess the genotypic frequency and polymorphic variation of all subjects. Perceived stress scale and diabetes-related distress scale were used to assess the stress levels. Data was analysed using SPSS 23.

**Results:** Of the 140 subjects, 90 (64.3%) were controls with mean age 24.96±4.35 years, and 50 (35.7%) were cases with mean age 28.78±5.25 ($p<0.05$). Mean body weight and mean gestational age were not significantly different between the groups ($p>0.05$). Melatonin hormone receptor 1B rs1387153 frequency was significantly different between the groups ($p<0.05$). Among the cases, a significant mean difference for regimen distress scores between AA and GG was observed for oxytocin receptor rs53576 ($p=0.04$). A significant mean difference in sum of PSS, diabetes-related stress, total diabetes-related stress and emotional distress was noted between CC and TT genotypes for melatonin hormone receptor 1B rs1387153 ($p=0.001$).

**Conclusion:** MTNR1B rs1387153 genotypes were associated with perceived stress, diabetes-related stress, diabetic distress, and emotional burden, while OXTR rs53576 genotypes were associated with regimen distress in GDM women.

**Keywords:** Diabetes, Distress, Gestational diabetes mellitus, Genotypes, Stress, Psychological stress, Pregnancy.

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## Introduction

One of the most common conditions that affect pregnant women is gestational diabetes mellitus (GDM), which has a prevalence rate ranging 1-45% across the globe.[1] In Asian countries, its prevalence rate is reported to be 11.5%.[2] Increase in obesity, sedentary lifestyles, and old-age pregnancies are associated with an increase in GDM prevalence.[2] If GDM remains untreated, it can result into adverse foeto-maternal outcomes, such as preterm labour, caesarean section (CS), pre-eclampsia, polyhydramnios, inherent disorders, birth trauma, intrauterine growth restriction (IUGR), respiratory distress syndrome (RDS), macrosomia, neonatal hyperbilirubinaemia and hypoglycaemia, polycythaemia, intellectual disability, and prenatal mortality.[3-6]

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During pregnancy, the diagnosis of GDM is a traumatic event and it negatively influences the females' perception regarding their mental health and quality of life.[7,8] Females with GDM have high prevalence of stress (63%), anxiety (58%) and depression (57%).[9,10] Diabetes-related distress is more common in GDM women who carry greater odds of having adverse foeto-maternal outcomes compared to healthy controls.[11]

Genetics play a part in the emergence of psychological disorders, like stress, anxiety and discomfort, with heritability rates ranging from 45% to 50%.[12,13] The psychological signs of anxiety, depression and/or stress are not only due to one gene, but rather result from the complex interplay of several genes, sociodemographic variables, clinical factors and physiological modifiers. Finding the genetic changes causing these psychological issues is difficult.[14] There are very few studies that show a strong connection between genetics and psychiatric disorders.[15-18]

There is a paucity of local data on how the genetic component affects stress in Pakistani women with GDM.

The current study was planned to fill the gap by assessing the association of oxytocin receptor (OXTR) (rs53576) and melatonin hormone receptor 1B (MNTR1B) (rs1387153) gene single nucleotide polymorphisms (SNPs) with psychological symptoms in women with GDM.

## Subjects and Methods

The case-control study was conducted from May 1 to June 1, 2022, at the Department of Physiology, University of Karachi (UOK), in collaboration with the Department of Biological and Biomedical Sciences, Aga Khan University (AKU), Karachi, and Unit 8 of the Department of Obstetrics and Gynaecology, Jinnah Postgraduate Medical Centre (JPMC), Karachi. Pregnant women diagnosed with GDM were in group B (n=50), while healthy pregnant women were in the control group A (n=90). After approval from the institutional ethics review boards of UOK (ASRB/No/06213/Sc) and JPMC (No.F.2-82/2021-GENL/61621/JPMC), the patients were enrolled at 24-28 weeks of pregnancy after taking written informed consent. The sample size was estimated based on OXTR (rs53576) and MTNR 1B (rs1387153) gene polymorphism frequency data available from SNPedia.[19] The global minor allele frequency (MAF) for OXTR reported as 0.4128[20] and for MTNR as 0.3466.[21] The minimal sample size of n=50 in each group was required to detect a relationship between the alleles and GDM calculated using OpenEpi with 80% power and two-tailed alpha of 0.05.[22]

GDM was defined as per the American Diabetic Association (ADA) guidelines, which stipulate fasting plasma glucose (FPG) 90mg/dl or a 75g two-hour oral glucose tolerance test (OGTT) 153mg/dl.[23] Females with hypertension, pregnancy-induced hypertension, multiple gestations, pre-eclampsia, immune illness, multiple cystic ovarian syndromes, chronic systemic diseases, like cardiovascular, urogenital, immunological conditions, and history of diabetes were excluded.

Clinical and socio-demographic data was collected using a structured questionnaire. The 10-item Perceived Stress Scale (PSS-10) in English and Urdu languages was used to evaluate the level of stress in pregnant females.[17] The scale, which ranges from 0=never to 4=very often, uses 5 points to indicate how frequently individuals reported experiencing stress symptoms during the preceding month. Total PSS-10 score was the sum of all the 10 elements, ranging 0-40, with higher results indicating more severe subjective stress symptoms. Scores 21-40 indicated the existence of felt stress symptoms.

Also used was the 17-item Diabetes-related Distress Scale (DDS) to explore how well the respondents had adjusted to and accepted their diabetes psychologically.[18,24] DDS specifically evaluated 4 possible issues that individuals with diabetes could encounter, which were Physician, Emotional, Regime and Interpersonal distress. The replies were recorded on a 5-point Likert scale, ranging from strongly disagree to strongly agree, with total score ranging from 0 to 100. Higher scores indicated more stress.

All the questionnaires used were translated into Urdu, the local language, by two bilingual translators. Using Cronbach's alpha, the reliability of the Urdu version of PPS was 0.71 and that of DDS was 0.73.

Fasting blood samples (10 ml) were collected in the second trimester (24-48 weeks) of the pregnancy. Blood was centrifuged and deoxyribonucleic acid (DNA) was extracted via white blood cells using commercially available genomic DNA extraction kit (QIAamp DNA Mini Kit, Catalogue No. 51304 QIAGEN, Germany). Nanodrop-ND1000 (Thermo Fisher Scientific, USA) was used to measure ultraviolet (UV) absorbance, and the extracted DNA was quantified. The accepted benchmark for determining DNA's purity was a ratio of 1.8. Extracted DNA was frozen and kept at -80°C until further analysis.

Genes were chosen based on literature demonstrating a relationship between investigations of SNPs and a clinical set of stress symptoms[25-28] classified in accordance with the Diagnostic and Statistical Manual of Mental Disorders, or the International Statistical Classification of Diseases[24] or both. Integrated DNA technology was used to design primers (IDT, USA). The primers were designed as follows for OXTR rs53576 (Forward 5′-GCCCACCATGCTCTCCACATC-3′; Reverse 5′-GCTGGACTCAGGAGGAATAGGGAC-3′) and MTNR1B rs1387153 (Forward 5′-ACCATTCTCAGTGGTCCTTACT-3′; Reverse 5′-GGGCCTAAGAGCCTCCATTT-3′). Polymerase chain reaction (PCR) was performed using a Hot-Start GoTaq DNA Polymerase (Promega, USA Catalogue No. M7422) as per the manufacturer's instructions. Gel electrophoresis was performed by running a 1ul sample against a 1kb ladder in 1% agarose gel. Horizontal electrophoresis was used for gel electrophoresis and gel documentation using ChemiDoc imaging systems (Biorad, USA). Samples were then sent for sequencing to identify polymorphic variations (Macrogen Korea). Genotypes were sorted and blasted using National Library of Medicine Basic Local Alignment Search Tool (NCBI-BLAST) by a researcher who was blinded to the case/control status of the subjects (https://blast.ncbi.nlm.nih.gov/Blast.cgi).

Data was analysed using SPSS 23. Mean and standard deviations were calculated for quantitative variables, and frequencies and percentages were reported for qualitative variables. Mean comparison was done for quantitative

variables using independent t-test. Chi-Square/fisher exact test were used to determine the association between qualitative variables. Pearson's correlation coefficient was applied to determine the relationship between quantitative variables. P<0.05 was considered significant.

## Results

Of the 140 subjects, 90 (64.3%) were controls with mean age 24.96±4.35 years, and 50 (35.7%) were cases with mean age 28.78 ± 5.25 ($p$<0.05). Mean body weight and mean gestational age were not significantly different between the groups ($p$>0.05). Gravida, parity, family history of DM, FBG, OGTT and glycated haemoglobin (HbA1c) were significantly different between the groups (Table 1)

**Table-1:** Baseline characteristics.

| Variables | **Controls** (n=90) | **Cases** (n=50) | ***p*-value** |
|---|---|---|---|
| **Mean Age** (years) | 24.96±4.35 | 28.78±5.25 | 0.001 |
| **Mean Weight** (kg) | 69.44±11.04 | 66.02±8.53 | 0.06 |
| **Gestational age** (weeks) | 28±0.001 | 28.12±7.70 | 0.81 |
| **Gravida** | | | |
| ≤2 | 90 (100) | 25 (50) | 0.001 |
| >2 | 0 | 25 (50) | |
| **Parity** | | | |
| ≤1 | 90 (100) | 26 (52) | 0.001 |
| >1 | 0 | 24 (48) | |
| **Family history of DM** | | | |
| Yes | 28 (31.1) | 31 (62) | 0.001 |
| No | 62 (68.9) | 19 (38) | |
| Fasting blood glucose (mg/dL) | 96.83±19.34 | 112.28±34.2 | 0.001 |
| OGTT 1HR | 144.04±19.2 | 156.70±39.45 | 0.03 |
| OGTT 2HR | 130.82±10.27 | 147.06±34.71 | 0.001 |
| HbA1c (%) | 4.51±0.39 | 6.45±0.69 | 0.001 |

Data presented as Mean ±SD or n (%); DM: Diabetes mellitus, OGTT: Oral glucose tolerance test, hbA1c: Glycated haemoglobin, SD: Standard deviation.

**Table-2:** Genotype frequency.

| Genotypes | | **Control** (n=90) | **Cases** (n=50) | ***p*-value** |
|---|---|---|---|---|
| OXTRrs53576 | AA | 87 (96.7) | 46 (92) | 0.22 |
| | GG | 3 (3.3) | 4 (8) | |
| | AG | 00 | 00 | -- |
| MTNR1Brs1387153 | CC | 90 (100) | 43 (86) | 0.001 |
| | TT | 00 | 7 (14) | |
| | CT | 00 | 00 | -- |

Data presented as n (%); OXTR: Oxytocin receptor, MTNR1B: Melatonin hormone receptor 1B.

**Table-3:** Mean comparison of stress and diabetes-related distress scores across genotypes.

| Parameters | OXTRrs53576 GENOTYPE | | *p*-value | MTNR1Brs1387153 | | *p*-value |
|---|---|---|---|---|---|---|
| | AA | GG | | CC | TT | |
| Sum of PSS Scale | 9.74±6.14 | 12±7.83 | 0.501 | 9.07±6.14 | 15.14±3.98 | 0.001 |
| Sum of Diabetes-related Stress Scale Score | 24.24±6.67 | 29.75±7.8 | 0.091 | 23.37±5.31 | 32.71±9.91 | 0.001 |
| Total DDS score | 24.22±6.69 | 30.51±8.81 | 0.091 | 23.35±5.33 | 33.14±10.19 | 0.001 |
| Emotional burden | 8.57±3.31 | 11±4.55 | 0.201 | 8.12±2.71 | 12.71±4.86 | 0.001 |
| Physician distress | 5.52±1.67 | 7.5±3.11 | 0.201 | 5.4±1.38 | 7.43±3.26 | 0.14 |
| Regimen distress | 6.63±2.20 | 9±2.45 | 0.04 | 6.49±1.87 | 8.86±3.58 | 0.09 |
| Interpersonal distress | 3.5±1.64 | 3±0.01 | 0.69 | 3.35±1.45 | 4.14±2.27 | 0.421 |

OXTR: Oxytocin receptor, MTNR1B: Melatonin hormone receptor 1B, PSS: Perceived stress scale, DDS: Diabetes-related distress scale.

**Table-4:** Association of diabetes-related distress with genotypes using DDS.

| Genotype | | Group | | *p*-value |
|---|---|---|---|---|
| | | Low Distress | Moderate Distress | |
| OXTRrs53576 | AA | 41 (89.1) | 5 (10.9) | 0.03* |
| | GG | 2 (50) | 2 (50) | |
| MTNR1Brs1387153 | CC | 39 (90.7) | 4 (9.3) | 0.01* |
| | TT | 4 (57.1) | 3 (42.9) | |

Data presented as n (%); OXTR: Oxytocin receptor, MTNR1B: Melatonin hormone receptor 1B, DDS: Diabetes-related distress scale.

**Table-5:** Correlation analysis of OXTRrs53576 with diabetes-related distress.

| Parameters | *r*-value | *p*-value |
|---|---|---|
| Sum of Diabetes-related Stress Scale Score | 0.244 | 0.08 |
| Total DDS Score | 0.246 | 0.08 |
| Emotional Burden | 0.189 | 0.18 |
| Physician Distress | 0.194 | 0.17 |
| Regimen Distress | 0.300 | 0.03* |
| Interpersonal Distress | -0.109 | 0.45 |

*$p$<0.05 was considered statistically significant for correlation; OXTR: Oxytocin receptor, DDS: Diabetes-related distress scale.

**Table-6:** Correlation analysis of MTNR1Brs1387153 with diabetes-related distress.

| Parameters | *r*-value | *p*-value |
|---|---|---|
| Sum of Diabetes-related Stress Scale Score | 0.38 | <0.01* |
| Total DDS Score | 0.38 | <0.01* |
| Emotional Burden | 0.35 | 0.01* |
| Physician Distress | 0.21 | 0.12 |
| Regimen Distress | 0.25 | 0.07 |
| Interpersonal Distress | 0.20 | 0.14 |

*p<0.05 was considered statistically significant for correlation; MTNR1B: Melatonin hormone receptor 1B, DDS: Diabetes-related distress scale.

MTNR1B rs1387153 frequency was significantly different between the groups ($p$<0.05), but that was not the case with OXTR rs53576 (Table 2).

The mean sum of PSS score was 9.92±6.23, mean sum of DDS was 24.68±6.85, mean total DDS was 24.72±6.99, mean emotional burden score was 8.76±3.43, mean physician distress score was 5.68±1.86, mean regimen distress scores was 6.82±2.29 and mean interpersonal distress score was 3.46±1.58. A significant mean difference for regimen distress scores between AA and GG samples for OXTR rs53576 genotype was observed ($p$=0.04). Additionally, a significant mean difference in sum of PSS ($p$=0.001), sum of DDS ($p$=0.001), total DDS ($p$=0.001), and emotional distress scores ($p$=0.001) between CC and TT samples for MTNR1B rs1387153 was noted (Table 3).

Among the cases, there was significant difference between those with low distress and those with moderate distress (Table 4).

A weak positive correlation was seen of OXTR SNP with regimen distress in GDM cases ($r$=0.30; $p$=0.03) (Table 5), and of MTNR1B SNP with sum of DDS ($r$=0.38; $p$<0.01), total DDS ($r$=0.38; $p$<0.01) and emotional stress (r=0.35; $p$=0.01) (Table 6).

## Discussion

The current study found regimen distress was significantly different in AA and GG genotypes of OXTR rs53576 ($p$=0.04). Additionally, in samples with GG genotype of OXTR rs53576, it was found that 50% had low distress and the rest had moderate distress, whereas in samples with AA genotype, 89.1% had low distress and 10.9% had moderate distress. The distress level showed a weak significant association with OXTR rs53576 genotype ($p$=0.03). Onodera et al. found that OXTR gene (AA+AG genotype) had a protective effect against panic disorders compared to GG genotypes in both rs2254298 and rs53576. There was no relationship between either gene's variants with social anxiety disorder.[17] According to a substantial interaction, those who have both the variant form of the OXTR gene (rs139832701) and early life stress had considerably worse symptoms of both depression and associated symptoms of stress (at tendency level), and anxiety compared to those who did not have the variant form of the gene or did not have early life stressors individually and together.[29] The G allele and TG/GG genotype of rs2241766 were shown to be more prevalent in GDM patients compared to healthy pregnant women ($p$=0.05). Participants with the TG/GG genotype had a higher risk of developing GDM than those with the TT genotype, according to multivariate logistic regression analysis ($p$=0.030).[30] An Iranian study concluded that the ADIPOQ (Adiponectin, C1Q And Collagen Domain Containing gene) variation at position +45 T>G (rs2241766; Gly15Gly) is a unique risk factor for developing GDM in the Iranian population.[30] Another study explored the connection between candidate genes and psychological symptoms in Malaysian females with GDM and discovered that SNPs in the OXTR gene were linked to an increased likelihood of stress symptoms. SNP rs53576 was linked to a 2.9-fold increase in the likelihood of experiencing stress symptoms.[24] Anxiety disorders and/or depression in older women are associated with methylation of the OXTR gene, and only individuals with AA type SNP at 1 of the 7 CpGs analysed had higher levels of DNA methylation.[31]

In the current study, mean sum of PSS, sum of DDS, total DDS, and emotional distress scores between CC and TT samples for MTNR1B rs1387153 were significantly different. These and other current findings were like those reported by Wang et al. who found that those with early life trauma and either the C allele of rs3800373, or the T allele of rs9470080, or the T allele of rs1360780, were more likely to develop depression or post-traumatic stress disorder.[32]

The current study is unique for the Pakistani population since there is a dearth of local studies demonstrating a relationship between stress and GDM in the context of genetic alterations. By addressing the mental health of pregnant women, it might be helpful to understand the molecular mechanisms of stress and GDM. Also, the study would assist medical professionals in treating the expectant mothers in the most appropriate manner and in determining if the baby may be predisposed to psychiatric issues in the future.

The current study has a few limitations as well. The sample size of study was small as it was estimated based on existing data of OXTR rs53576 and MTNR 1B rs1387153 gene polymorphism frequency. Limited genetic assays were included due to unavailability of funds and resources in resource-constrained underdeveloped country. The findings, as such, lack generalisability, and need future studies for validation.

## Conclusion

MTNR1B rs1387153 genotypes were associated with perceived stress, diabetes-related stress, diabetic distress, and emotional burden, while OXTR rs53576 genotypes were associated with regimen distress in GDM women.

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