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Diabetes Update

Vol. 5 | Issue 49| 2024

Dear Doctor,

Greetings from Micro Labs Limited. We are happy to bring you "DIABETES UPDATE" which contains latest and interesting news in the field of Diabetes and Endocrinology.

- **Association of Glycosylated Hemoglobin Variability with Coronary Artery Disease Severity in Type 2 Diabetes Mellitus Patients**
- **Correlation between bone turnover indicators, bone mineral density, and serum osteoglycin levels in middle-aged men with Type 2 Diabetes Mellitus**
- **Expression of TGFβ1, SNAIL2, and PAPP-A in the Placenta of Patients with Gestational Diabetes Mellitus**
- **Management of Glycemia and Pregnancy Outcomes in a Woman with the Insulin Receptor Mutation p.Met1180Lys: A Rare Case Report**

Should you require any specific article or medical information, please feel free to contact us at medicalservices@microlabs.in

Looking forward to your valuable feedback

Best Regards,

Medical Team, Micro Labs Limited

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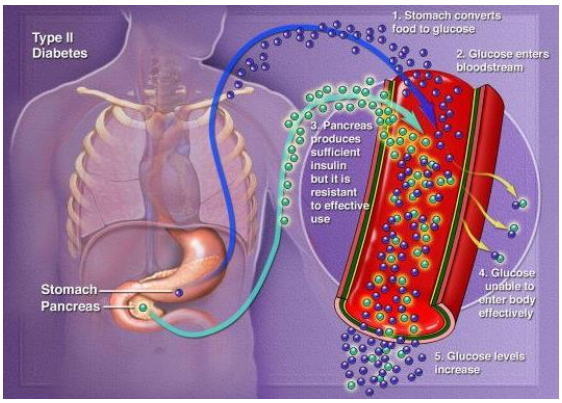
Association of Glycosylated Hemoglobin Variability with Coronary Artery Disease Severity in Type 2 Diabetes Mellitus Patients

INTRODUCTION

Diabetes has emerged as a major global health issue and poses a significant threat to human well-being. Individuals with Type 2 Diabetes Mellitus (T2DM) are at a greater risk of cardiovascular diseases compared to healthy individuals. Glycosylated hemoglobin (HbA1c) is considered the gold standard for managing blood glucose levels. The American Diabetes Association (ADA) recommends maintaining an HbA1c level of 7.0% or lower to potentially prevent or delay the onset and progression of diabetes-related complications.[1] The global consensus suggests that the time in range (TIR), which measures the percentage of time blood glucose levels are between 70–180 mg/dL (3.9–10 mmol/L), can indicate short-term glucose variability and overall blood glucose management. Monitoring TIR may help reduce the risk of complications associated with both hypoglycemia and hyperglycemia.[2] Research has indicated that three primary glycemic disturbances—hyperglycemia, hypoglycemia, and glucose variability (GV)—can all contribute to the acceleration of cardiovascular complications in individuals with Type 2 Diabetes Mellitus.[3] The severity of coronary artery disease (CAD) can influence patient outcomes, yet research examining the relationship between long-term glucose variability and CAD severity in individuals with Type 2 Diabetes Mellitus is sparse. So, this study aimed to investigate the association between variability in HbA1c and CAD severity, as measured by the Gensini score and the number of affected vessels, with the goal of enhancing survival rates in T2DM patients.



TYPE 2 DIABETES

In T2DM patients, the degree of CAD was influenced by HbA1c fluctuation, particularly HbA1cTIR. Even when the blood sugar is within the therapeutic range, HbA1c fluctuation may reveal more information and need to be managed.

METHODS

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A retrospective study was performed involving 147 T2DM patients who underwent coronary arteriography (CAG) due to angina. The study included participants meeting the following criteria (n = 8437): (1) individuals aged 18 or older, (2) those diagnosed with T2DM according to the 2020 guidelines for the prevention and treatment of Type 2 diabetes in China, and (3) those who had undergone coronary angiography. Basic demographic and clinical data were collected from these participants. HbA1c variability was assessed using the coefficient of variation (CV), standard deviation (SD), variability independent of mean (VIM), and time in range (TIR). CAD severity was evaluated based on the number of affected vessels and the Gensini score. Multivariate regression models were used to examine the relationships between HbA1c variability, the number of involved vessels, and the Gensini score, followed by linear regression analysis.

RESULTS

The percentages of patients with 3-vessel and multivessel disease, as well as the Gensini scores, decreased with higher tertiles of HbA1c time in range (HbA1c TIR). Conversely, Gensini scores increased with higher tertiles of HbA1c standard deviation (SD-HbA1c) and coefficient of variation (CV-HbA1c). Multivariate analysis identified variability independent of mean HbA1c (VIM-HbA1c) and HbA1cTIR as

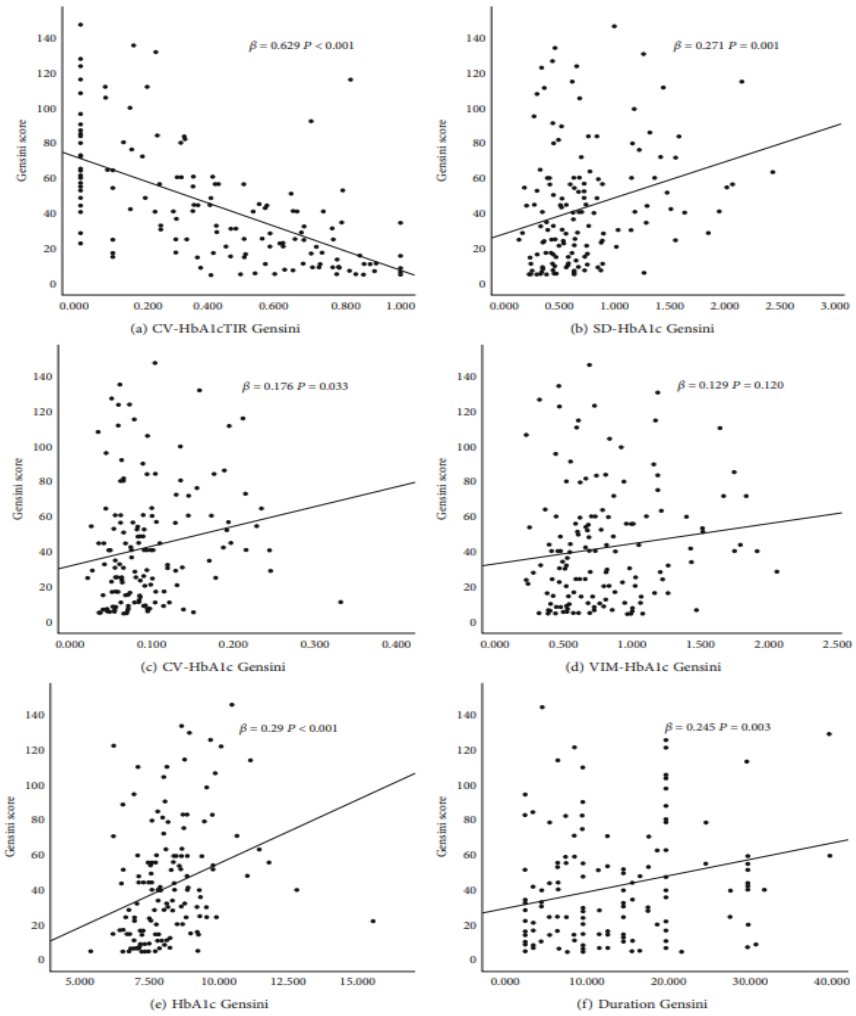

Figure 1. Relationship between HbA1c variability and Gensini score using univariate linear regression analysis

independent risk factors for the number of involved vessels, with odds ratios (OR) of 2.604 (interquartile range [IQR]: 1.15, 5.90; p = 0.026) and 0.13 (IQR: 0.04, 0.41; p <0.001), respectively. For the Gensini score, HbA1cTIR, SD-HbA1c, CV-HbA1c, and VIM-HbA1c were also identified as risk factors, with ORs of 0.007 (IQR: 0.002, 0.03; p < 0.001), 4.15 (IQR: 2.03, 8.48; p < 0.001), 1.42 (IQR: 1.08, 1.86; p = 0.004), and 2.10 (IQR: 1.01, 4.36; p = 0.036), respectively. After adjusting for confounding factors such as sex, age, diabetes duration, HbA1c, systolic and diastolic blood pressure, LDL levels, and insulin use, HbA1cTIR (OR = 0.01; IQR: 0.002, 0.04; p < 0.001), SD-HbA1c (OR = 4.12; IQR: 1.64, 10.35; p = 0.001), CV-HbA1c (OR = 1.41; IQR: 1.04, 1.92; p = 0.007), and VIM-HbA1c (OR = 3.26; IQR: 1.43, 7.47; p = 0.003) remained independent risk factors for the Gensini score. Linear regression analysis showed that the Gensini score was negatively associated with HbA1cTIR ($\beta = -0.629$; $p < 0.001$) and positively associated with SD-HbA1c ($\beta = 0.271$; $p = 0.001$), CV-HbA1c ($\beta = 0.176$; $p = 0.033$), HbA1c ($\beta = 0.29$; $p < 0.001$), and diabetes duration ($\beta = 0.245$; $p = 0.002$) (Figure 1). Subgroup analysis indicated that HbA1cTIR was a risk factor for the number of involved vessels, and the Gensini score was negatively correlated with HbA1cTIR and positively correlated with SD-HbA1c among subjects with a mean HbA1c ≤7%.

DISCUSSION

The findings of this study indicate that fluctuations in HbA1c levels, particularly HbA1cTIR, could be linked to the severity of CAD in individuals with T2DM. Additionally, meta-analyses have shown that long-term glucose variability in T2DM patients was associated with nearly all forms of cardiovascular complications. While maintaining an average glucose level is crucial for preventing cardiovascular events in these patients, study has also identified HbA1c variability as an independent risk factor for cardiovascular disease, even when glycemic targets are met.[4] To understand the underlying reasons, it is possible that patients with greater HbA1c variability may have suboptimal blood glucose management and poorer baseline vascular health. Additionally, hypoglycemia might play a role in linking HbA1c variability with the severity of CAD. Recent research has also highlighted that long-term glucose variability can be associated with cardiovascular disease in individuals who are within their HbA1c target range.[5]

CONCLUSION

HbA1c variability, particularly HbA1cTIR, could be linked to the severity of coronary artery stenosis in individuals with T2DM. This study indicates that, beyond average HbA1c levels, long-term blood glucose variability plays a crucial role in managing blood glucose and warrants further investigation. Additionally, the findings underscore the importance of adopting a personalized strategy for setting and maintaining HbA1c targets, especially for older patients with diabetes.

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Correlation between bone turnover indicators, bone mineral density, and serum osteoglycin levels in middle-aged men with Type 2 Diabetes Mellitus

INTRODUCTION

BMD was significantly improved by serum osteoglycin and body mass index. Increases in both bone production and resorption indicators suggest that people with type 2 diabetes have higher bone turnover.

Individuals with type 2 diabetes mellitus (T2DM) face a range of complications, including macrovascular and microvascular diseases. Recently, an elevated risk of fragility fractures has emerged as an additional significant complication associated with diabetes.[1] Research has found that people with T2DM face a 69% higher risk of fractures compared to healthy individuals. Interestingly, those with T2DM often have normal or even higher bone mineral density (BMD), suggesting that BMD alone does not fully reflect bone strength. This discrepancy may be due to changes in bone turnover rates and collagen production. Measuring serum levels of bone turnover markers (BTMs) has emerged as a valuable method for assessing bone metabolism and quality. Osteoglycin, a newly identified regulator, plays a role in both bone and glucose regulation.[2] Metabolically, it may enhance insulin secretion from the pancreas and reduce insulin resistance in the muscle and liver.[3] This study aimed to assess serum levels of BTMs, which indicate bone formation and resorption, along with BMD at three sites (lumbar spine, femoral neck, and total femur) in middle-aged men with type 2 diabetes. Additionally, the study sought to explore the

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relationship between these variables and to investigate serum osteoglycin as a novel marker, examining its association with BTMs, BMD, and diabetic status.

METHODS

This cross-sectional descriptive-analytic study included 78 male patients with T2DM and 13 non-diabetic male volunteers as a control group. The participants, aged 40–65 years, underwent comprehensive assessments including medical history (age, duration of diabetes, history of hypertension or current antihypertensive use, ischemic heart disease, and smoking history) and a complete physical examination. BMD was measured via DEXA scan. The study analyzed bone turnover markers (carboxy-terminal crosslinking telopeptide of type 1 collagen [CTX] and procollagen type 1 N propeptide [P1NP]), osteoglycin, parathyroid hormone (PTH), and vitamin D levels. Data were compared between groups and subjected to statistical analysis.

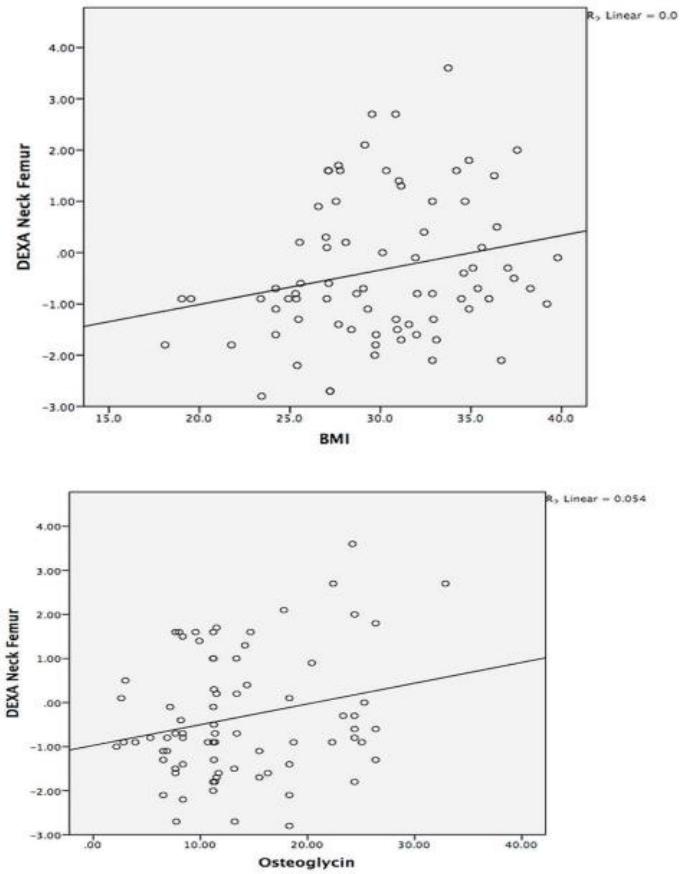

Figure 1. Relationship between DEXA scan neck femur, serum osteoglycin, and body mass index.

Body mass index = BMI.

RESULTS

Body Mass Index (BMI) showed a positive correlation with waist circumference (r=0.724; P<0.001). HOMA-IR had a negative correlation with vitamin D (r=-0.313; P=0.006). CTX was inversely related to both BMI (r=-0.233; P=0.042) and waist circumference (r=-0.247; P=0.030). P1NP exhibited a positive correlation with BMI (r=0.225; P=0.050) and a negative correlation with HOMA-IR (r=-0.225; P=0.049). DEXA lumbar spine measurements were positively associated with BMI (r=0.234; P=0.042) and waist circumference (r=0.300; P=0.008). DEXA neck femur measurements showed positive correlations with BMI (r=0.230; P=0.044) (Figure 1), waist circumference (r=0.241; P=0.035), and vitamin D (r=0.258;

P=0.023). DEXA total femur measurements were positively correlated with BMI (r=0.265; P=0.020). Osteoglycin was positively related to DEXA neck femur measurements (r=0.233; P=0.041). Multiple regression analysis revealed that only BMI and osteoglycin significantly influenced DEXA lumbar spine measurements.

DISCUSSION

In present study, BTMs were correlated with BMI, showing a significant positive relationship between P1NP and BMI, while CTX was significantly negatively correlated with BMI. Similarly, Bilić-Ćurčić's 2017 study found that overweight postmenopausal women with T2DM had lower levels of CTX and higher femoral BMD.[4] In this study, osteoglycin did not exhibit any correlation with BTMs, HbA1c, insulin resistance, or other variables. This contrasts with findings from another study, which also reported no association between osteoglycin levels and bone mineral density at the hip, femur, lumbar spine, or distal forearm.[5] In contrast, another study found that osteoglycin levels were linked to lower BMD and the occurrence of vertebral fractures. These results suggested that osteoglycin could be a marker for reduced BMD and vertebral fractures in type 2 diabetes mellitus, which contradicted these findings.[6]

CONCLUSION

BMI and serum osteoglycin significantly positively influence BMD. Elevated levels of both bone formation and bone resorption markers suggest an increased rate of bone turnover in T2DM.

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Expression of TGFβ1, SNAIL2, and PAPP-A in the Placenta of Patients with Gestational Diabetes Mellitus

INTRODUCTION

SNAIL2 and PAPP-A were significantly underexpressed whereas TGFβ1 was significantly overexpressed in the placenta of pregnant women diagnosed with GDM, necessitating further investigation.

Gestational diabetes mellitus (GDM) is characterized by carbohydrate intolerance that is first detected during pregnancy. The incidence of GDM is rising globally.[1] Inadequately managed blood glucose levels during pregnancy not only elevate the risk of maternal pre-eclampsia (PE) and premature delivery but can also result in spontaneous abortion, congenital malformations, hypoxia, and, in severe instances, intrauterine death. Hyperglycemia frequently causes fetal macrosomia and raises the likelihood of dystocia. Newborns may face complications including neonatal respiratory distress syndrome, postnatal hypoglycemia, and, in severe cases, death.[2] Chronic high glucose levels and oxidative stress linked with GDM may cause damage to the placenta. The rapid progress in high-throughput microarray hybridization and sequencing technologies has greatly expanded the availability of nucleic acid sequence data. The Gene Expression Omnibus (GEO) is now the largest open database for gene expression. Thus, identifying genes associated with GDM and predicting and validating their functions could help clarify the mechanisms involved in GDM.[1] This study identified differentially expressed genes (DEGs) associated with vascular endothelial cells from the GDM database and confirmed their expression in the placenta. The primary aim was to investigate the cellular processes involved in GDM and uncover potential new mechanisms.

METHODS

This study utilized GDM microarray datasets from the GEO database. DEGs were identified through functional annotation and protein–protein interaction (PPI) analyses. Singleton pregnant women who had cesarean sections and were closely monitored postpartum were included. GDM diagnosis was confirmed using an oral glucose tolerance test (OGTT). Placental samples were collected from 20 women with GDM and 20 healthy controls, and differential gene expression in these samples was validated using qRT-PCR, western blotting, and immunofluorescence techniques.

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RESULTS

The qRT-PCR results revealed that TGFβ1 expression levels were significantly higher in the GDM group compared to the control group, while PAPP-A and SNAIL2 levels were significantly lower in the GDM group ($p < 0.05$). Western blot analysis confirmed these findings, showing elevated TGFβ1 levels and reduced PAPP-A and SNAIL2 levels in the GDM group ($p < 0.05$) (Figure 1). Immunofluorescence studies also supported these results, with increased TGFβ1 expression and decreased PAPP-A and SNAIL2 expression in the GDM group relative to the controls ($p < 0.05$).

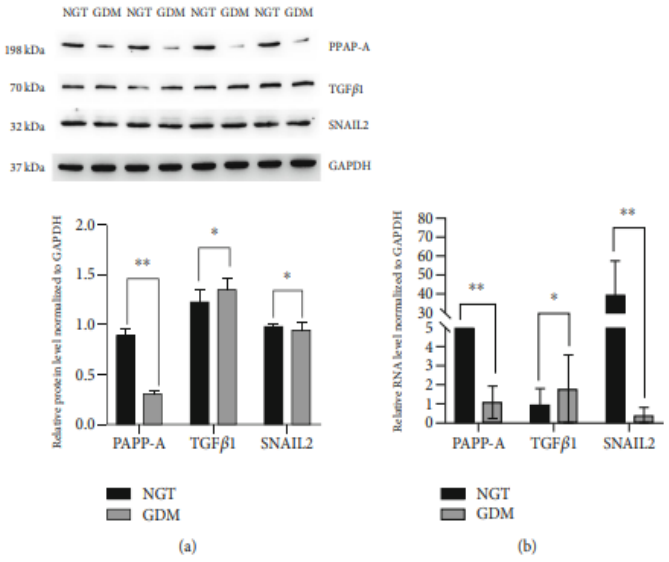

Figure 1. Detection of DEG expression in the placenta (n = 20). (a) Western blot analysis, (b) qPCR analysis

DISCUSSION

TGFβ1 helps the pancreas maintain homeostasis and has a physiological function similar to insulin. It is a crucial cytokine involved in insulin resistance and obesity[3] and exhibits differential expression in the human endometrium and placenta.[4] The results of this study indicated that TGFβ1 expression was increased in the placenta of patients with GDM. TGFβ1, a key factor in endothelial cell differentiation during angiogenesis, might contribute to the "hypervascularization" observed in the placentas of GDM patients. Research suggests that PAPP-A may facilitate the elongation of vascular endothelial cells. Additionally, the PI3K/Akt and mTORC1 pathways were linked to vascular endothelial growth factor A.[5] However, this study found no significant change in PAPP-A expression, which contrasts with the findings reported by Varberg et al.[6] This discrepancy necessitates further investigation to understand its cause.

CONCLUSION

In the placentas of pregnant women with GDM, SNAIL2 and PAPP-A were significantly underexpressed, however, TGFβ1 was notably overexpressed, indicating a need for further investigation.

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Management of Glycemia and Pregnancy Outcomes in a Woman with the Insulin Receptor Mutation p.Met1180Lys: A Rare Case Report

INTRODUCTION

The p.Met1180Lys mutation causes oligomenorrhea, hyperglycemia, and hirsutism as phenotypes.

The insulin receptor (INSR) is a transmembrane protein belonging to the tyrosine kinase family, with insulin binding at two distinct sites on each receptor subunit. Mutations in INSR are linked to severe insulin resistance (IR) conditions, including Rabson-Mendenhall syndrome, Donohue syndrome, and type A IR syndrome. Rabson-Mendenhall and Donohue syndromes are inherited recessively, resulting in reduced receptor expression, impaired receptor transport to the plasma membrane, or decreased insulin binding, leading to extreme IR. Type A IR is caused by monoallelic INSR missense mutations, which result in a milder phenotype and are typically found within the tyrosine kinase domain.[1] So far, only three cases involving pregnant women with type A insulin resistance syndrome have been reported. Additionally, there have been instances of small for gestational age (SGA) babies born to women with INSR mutations.[2] This report described a case of a woman with type A insulin resistance caused by a heterozygous missense mutation, p.Met1180Lys, in the β-subunit of the insulin receptor. It highlighted the variations in phenotype, glycemic management strategies, treatment options during pregnancy, neonatal outcomes, and the differing phenotypic expressions observed in the offspring.

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CASE PRESENTATION

A 20-year-old woman presented with secondary amenorrhea, subfertility, and hirsutism. Her father had diabetes. On examination, she had a blood pressure of 136/88 mmHg, a Body Mass Index (BMI) of 28.6 kg/m², central obesity, and hirsutism, but no signs of acanthosis nigricans, lipodystrophy, or Cushing's syndrome. An oral glucose tolerance test (OGTT) confirmed diabetes, and she was prescribed metformin 500 mg twice daily. Her luteinizing hormone (LH) to follicle-stimulating hormone (FSH) ratio was 2.4, and her free androgen index (FAI) was elevated at 15 units (reference range 0.5–8.5). Overnight dexamethasone suppression testing excluded Cushing's syndrome, and a pelvic ultrasound showed no polycystic ovaries. During her first pregnancy, she had a late pregnancy loss in 2003 and a preterm birth in 2005. Her surviving child, born extremely preterm and SGA, had a ventricular septal defect and pulmonary hypoplasia. At one year, this child was diagnosed with hyperinsulinemic hypoglycemia and managed with increased enteral feeds. At age 9, the child was found to have a heterozygous missense INSR mutation (p.Met1180Lys, c.3539T>A), which was also confirmed in the mother. By age 37, the woman's BMI was 26.8 kg/m². A repeat OGTT showed severe insulin resistance (fasting insulin >150 pm ol/L), with an HbA1c of 97 mmol/mol (11.0%) due to non-compliance with metformin and lifestyle changes. She had background diabetic retinopathy, dyslipidemia (total cholesterol 5.6 mmol/L, triglycerides 3.91 mmol/L, LDL 3.5 mmol/L, HDL 1.18 mmol/L), and positive glutamic acid decarboxylase (GAD) antibodies. She was diagnosed with Graves' disease and treated with carbimazole 10 mg daily. Anti-tissue transglutaminase antibodies were positive, and a duodenal biopsy confirmed coeliac disease. She had eleven pregnancies from a consanguineous relationship and smoked throughout. Eight of these

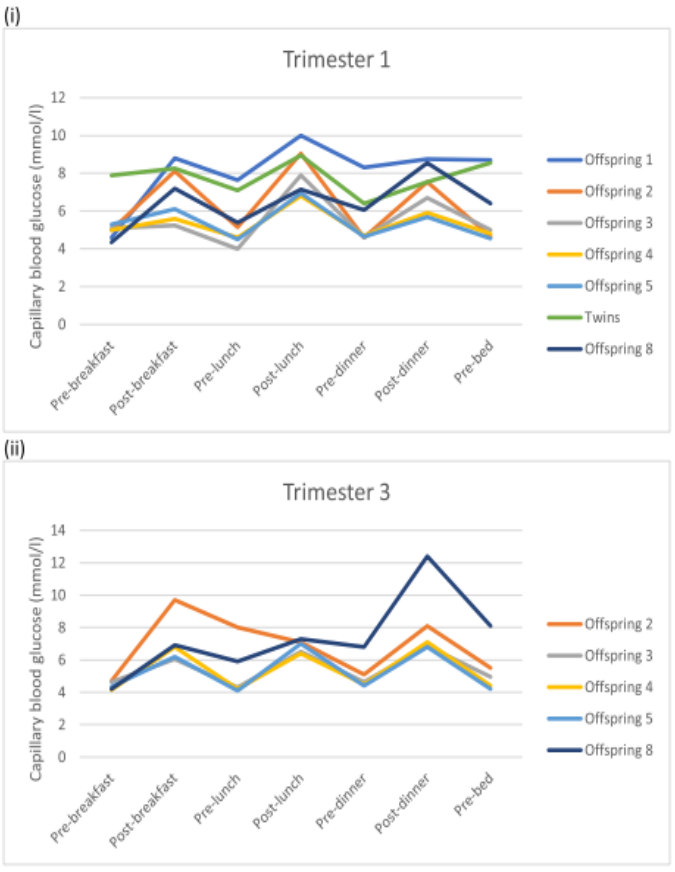

Figure 1. Average blood glucose levels that are self-monitored for each pregnancy for (i) one week during the first trimester (8 ±4 weeks) and (ii) one week during the third trimester (29 ±4.9 weeks)

pregnancies occurred after her genetic diagnosis. Fetal loss in the first pregnancy was attributed to placental insufficiency, while other cases of intrauterine death were associated with poor glycemic control and large for gestational age offspring. Figure 1 showed glucose profiles from pregnancies. Among the five children who survived into childhood, those with the INSR mutation had a mean birthweight at the 37th percentile, compared to the 94th percentile for those without the mutation. One child with the INSR mutation developed autoimmune type 1 diabetes at age two, with diabetic ketoacidosis and positivity for IA-2A and ZnT8 antibodies. The remaining siblings are unaffected and range from five to eight years old. The woman, now 41, has variable medication compliance, an HbA1c of 99 mmol/mol, and elevated fasting insulin and C-peptide levels. Metformin has been increased to the maximum dose, pioglitazone added, and she is on a gluten-free diet with a Mirena coil in place, with no plans for additional pregnancies.

DISCUSSION

This case exhibited some characteristics of an INSR mutation, such as diabetes, hirsutism, and oligomenorrhea, but lacked a history of hyperinsulinemic hypoglycemia. The fasting insulin level of 261.5 pmol/L suggests insulin resistance. Although oligomenorrhea and reduced fertility were notable in early adulthood, these issues seemed to improve over time as she managed to conceive naturally. The only other documented case of the p.Met1180Lys mutation involves a woman with a normal BMI who experienced diabetes only during pregnancy, without symptoms of insulin resistance, hypoglycemia, or menstrual irregularities.[1] This case outlines the medical and obstetric history derived from a retrospective review of case notes. Recurrent pregnancy loss has been linked to insulin resistance.[3] The frequency of pregnancy loss in women with INSR mutations has not been determined. This report was the first to document the use of metformin during pregnancy in a case with the p.Met1180Lys INSR mutation. Metformin has been demonstrated to be both effective and safe for managing gestational diabetes.[4] Offspring with INSR mutations were associated with growth restriction.[1]

CONCLUSION

INSR mutations are uncommon, with the p.Met1180Lys mutation leading to diabetes, hirsutism, and oligomenorrhea. This case also involved the presence of autoimmune disease. During pregnancy, the woman's insulin needs were comparable to those typically seen in women with type 2 diabetes. Metformin could potentially enhance insulin sensitivity in pregnant women with INSR mutations. Offspring inheriting the mutation often appeared smaller for their gestational age. In the future, diagnosing INSR mutations before pregnancy could provide clearer guidance for managing both the mother and her child.

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