Screening of mitochondrial mutations in Saudi women diagnosed with gestational diabetes mellitus: A non-replicative case-control study

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A B S T R A C T

Introduction: Among metabolic disorders, gestational diabetes mellitus (GDM) is specified as hyperglycemia caused by glucose or carbohydrate intolerance defects. GDM is distinguished by oxidative stress, and has been connected to mitochondrial dysfunction. Previous studies have documented the relation between A12026G, A8344G and A3243G mutations in ND4, tRNALeu(UUR) and tRNALys genes in different modes of diabetes.

Aim: The purpose of this study was to investigate into the relationship between GDM women and common mitochondrial mutations including A12026, A8344G, and A3243G in Saudi women.

Methods: In this case-control study, we have opted 96 GDM and 102 non-GDM pregnant women and DNA was extracted using EDTA blood and based on specific primers, Polymerase Chain Reaction was followed and then Restriction Fragment Length Polymorphism (RFLP) analysis was performed. Restriction enzymes was cross-checked with Lambda DNA and 10% of the purified PCR products were performed the Sanger sequencing analysis to reconfirm the RFLP analysis of the studied results.

Results: None of the heterozygous and homozygous mutations were not observed in our study. All the subjects were turned to be homozygous normal genotypes.

Conclusion: This study confirms that A12026, A8344G, and A3243G mutations have no role in the Saudi women with GDM.

1. Introduction

O’Sullivan has been described Gestational diabetes mellitus (GDM) as carbohydrate intolerance of various severities when first identified during pregnancy. As in other words, GDM can be described as any degree of glucose intolerance with onset or first recognized during second-third trimesters of pregnancy (Saeedi et al., 2021; Khan et al., 2019). GDM affects ~14% of pregnancies throughout the global women (Plows et al., 2018) and surprisingly in Saudi Arabia, the prevalence rate of GDM was documented to be around 39% (Alfadhli et al., 2015). The current risk factors are advanced maternal age, BMI, race, a family history of GDM, T2DM, and a prior child with macrosomic infants (Alharbi et al., 2019). Though its precise cause of GDM remains unclear, genetic mutations due to β-cell dysfunction and insulin resistance have been connected to progression of the disease (Liu et al., 2021). Adapting women’s metabolism during pregnancy implies that plasma glucose and amino acids are reduced more than accelerated starving in association with hepatic resistance to insulin and free fatty acids are increasing at overnight fasting (McCance, 2011). The increase in GDM is exacerbated by weight gain, which is attributed to obesity (Khan et al., 2014). The prevalence of GDM may be increasing because being clinically obese during pregnancy increases the risk of maternal GDM significantly (Seshiah et al., 2009). Systemic reviews and meta-analysis have shown that obese mothers have more than a triple higher risk of GDM construction between obesity and diabetes in the pregnancy (Herring, 2011). It is well established that pregnant women include a subpopula-
tion that has an increased risk of obesity due to weight gain. Maternal obesity and excessive gestational weight gain are also linked to spontaneous abortions, caesarean delivery, preeclampsia, and neonatal macrosomia (Miao et al., 2017). Maternal obesity is a significant risk factor for both type 2 diabetes mellitus (T2DM) and gestational diabetes (Catalano, 2010). Others believe that GDM is a form fruste of T2DM that has emerged as a result of universal screening and the drastic improvements in glycemic physiology that arise during pregnancy (Powe, 2020). T2DM and GDM are chronic metabolic disorders characterized by insulin resistance and pancreatic β-cell dysfunction, which includes defects in multiple molecular pathways (Khan et al., 2014). For the management of GDM, a specific diet, if not insulin, should be used (Seshadri, 2002).

Human mitochondrial DNA (mtDNA) is a double-stranded, spherical molecule that encodes a couple of rRNAs, 22 tRNAs, and 13 protein subunits of respiratory chain complexes, as well as maternally inherited genes (Reardon et al., 1992). Mitochondrial involvement is critical in preserving proper glucose homeostasis, and changes in mitochondrial content or function can contribute to insulin resistance over time (Crovetto et al., 2013). The mtDNA mutations are associated with diabetes and other human diseases. Mutations in mtDNA were found to be important in diabetes of insulin resistance and pancreatic β-cell dysfunction. Half of the mtDNA mutations are existed in 22 mitochondrial tRNA genes. Observational studies confirm the connection between specific mutations or single nucleotide polymorphisms (SNPs) and human diseases, as well as their role in disease progression. Previous studies have reported that mtDNA mutations that modify mitochondrial function may play a role in the production of GDM (Chen et al., 2000; Khan et al., 2015; Liu et al., 2007). Diabetes is caused by a variety of mutations in the mitochondrial DNA, and these mtDNA mutations have been related to insulin secretion defects. A nucleotide 3243 mutation in the tRNALeu(UUR) gene sequence causes β-cell instability and impaired insulin secretion defects (Wang et al., 2016). The A3243G mutation in tRNALeu(UUR) gene is the most frequently identified mtDNA mutation correlated with different modes of diabetes (Crispim et al., 2008). The A12026G mutation in ND4 gene was associated with T2DM in the Chinese Han population (Liu et al., 2007). Based on previous studies, we chose three related mutations (A12026G, A3243G, and A8344G) from the ND4, tRNA^Met^mt(UCU), and tRNA^{lys} genes (Khan et al., 2015; Yu and Li, 2005). However, no previous or documented studies on GDM or any other human disease have been conducted in Saudi Arabia. As a result, the current study was primarily aimed at the screening of mitochondrial mutations in ND4, tRNA^Leu^mt(UCU) and tRNA^{lys} genes in Saudi women with GDM.

2. Materials and methods

2.1. Ethical approval

The ethical approval was sanctioned from College of Applied Medical Sciences (CAMS) at King Saud University with the endorsed number (CAMSO52-3839). Informed consent was received from all the pregnant women who have participated in this study.

2.2. Study subjects

This is a case-control study carried in CAMS premises. In this study, we have selected 198 pregnant women who were eligible to participate. GDM (cases) and non-GDM (controls) samples were obtained from Department of Obstetrics and Gynecology within the university premises as per the American Diabetes Association and World Health Organization criteria. The inclusion criteria of the GDM subjects was diagnosed with GDM during 2nd or 3rd trimesters of pregnancy within the Saudi nationality. The exclusion criteria of the GDM women was diagnosed with diabetes during the pregnancy. The exclusion criteria of the non-GDM subjects were non-Saudi with or without diagnosed with GDM during pregnancy. Inclusion criteria of non-GDM women should not be diagnosed with GDM during pregnancy within the Saudi nationality (Alharbi et al., 2019). Based on mentioned criteria, we have selected 96 GDM women and 102 women as non-GDM/control subjects.

2.3. Biochemical and laboratory assays

From this study, we will be recruiting anthropometric, biochemical and clinical details of the pregnant women’s involved in this study. Age (Years), height (cms), weight (kg) and gestational week will be recorded from both GDM and non-GDM women. Fast ing blood glucose (FBG), post prandial blood glucose (PPBG) and lipid profile will be performed. Pregnant women participated in this study will undergo Glucose challenge test (GCT) and oral glucose challenging test (OGTT) and the protocol was followed as per the Khan et al., (2019) studies.

2.4. Blood

A total of 5 ml of the peripheral blood was collected and bifurcated into coagulant (3 ml) and anticoagulant (2 ml) tubes. The 3 ml of the serum sample will be used for FBG, PPBG and for lipid profile such as total cholesterol (TC), triglycerides (TG), high density lipoprotein-cholesterol (HDL-c) and low-density lipoprotein-cholesterol (LDL-c). EDTA blood of 2 ml will be used for molecular analysis.

2.5. Molecular analysis

Genomic DNA was extracted using Norgen Biotec kit. NanoDrop was performed to check the DNA quality and quantity. The oligonucleotide sequences for the A12026G, A3243G and A8344G mutations were adapted from Khan et al (2015) studies. Primers were synthesized from Bioserve Biotechnologies limited in the capital city of Telangana, India. Genotyping was performed with the total volume of 50 µl which includes 60 ng of genomic DNA along with sense and antisense primers. Denaturation (95 °C-5 min), initial denaturation (95 °C-30 s), extension (72 °C-45 s) and final extension (72 °C-5 min) was found to be similar in all the mutations except the denaturation temperatures i.e., 60 °C for A12026G and A3243G mutations and 62 °C for A8344G mutation. All the restriction enzymes HpaI (A12026G), Apal (A3243G), BstNI (A8344G) used in this study were digested at 37 °C. The details used in this study are tabulated in Table 1. Digested and undigested PCR products along with 100 bp DNA marker were separated by agarose gel electrophoresis for A12026G, A3243G and A8344G mutations. To reconfirm the genotyping analysis performed by restriction fragment length polymorphism (RFLP), we run 10% of our samples through the Sanger sequencing analysis. Figs. 1–3 consists of 2% agarose gel pictures and chromatograms for A12026G, A3243G and A8344G mutations. Simultaneously, we run the restriction enzymes through λ (Lambda) DNA (Fig. 4) and reconfirm the enzyme activity for all the restriction enzymes used in this study.

2.6. Statistical analysis

Hardy Weinberg equilibrium (HWE) was performed in this study. Data was analyzed by mean and standard deviation with SPSS software. Categorical variables were represented with fre-
frequencies and percentages. Using openepi software, genotype and allele frequencies were calculated. Yates correction was performed between GDM cases and non-GDM controls (Khan et al., 2019).

3. Results

3.1. Clinical characteristics

In this study, 198 samples were enrolled and divided into 96 GDM cases and 102 non-GDM subjects. The baseline characteristics of GDM and non-GDM subjects were shown in Table 2. The mean age of GDM and non-GDM were obtained in this study was 33.3 ± 5.9 and 28.0 ± 6.7 years of age and found to be statistically significant (p = 0.001). Other anthropometric measurements such as weight and BMI were significantly associated (p < 0.05) and height was almost all constant in GDM and non-GDM subjects (p = 0.92). Biochemical parameters such as FBG, PPBG, GCT and OGTT values were significantly associated in the pregnant women (p < 0.05). However, LDL-c were non-significantly associated (p = 0.54). Family histories was found strongly associated in GDM rather than non-GDM (p < 0.05). All GDM women were under dietary control and insulin therapy until further delivery.

3.2. HWE tests and mitochondrial mutational analysis

The genotype frequencies for A12026G, A3243G and A8344G mutations doesn’t deviate the HWE (p = 1.00). None of the genotypes were exists either in GDM and non-GDM cases in either A12026G, A3243G and A8344G mutations. Table 3 describes the genotype and allele frequencies between GDM and non-GDM subjects in the Saudi population. AA, AG and GG genotypes did not present in any of the mutations in the list of mitochondrial genes. Yates correction was performed between GDM cases and non-GDM subjects (OR-1.00 (95 %CI: 0.003–255.5); p = 0.99). The similar statistical analysis was applied in the allele frequencies also in all the mutations.

4. Discussion

GDM is defined as glucose intolerance initially detected in women during the pregnancy and resolves after the delivery. Glucose homoeostasis is returned to pre-pregnancy values shortly after delivery, but impacted women are also at elevated risk of developing T2DM in the future (Bellamy et al., 2009). This occurs in pregnant women as abnormal glucose levels migrate through the placenta into the fetal circulation. In response to hyper-
Glycemia, the fetal pancreas secretes insulin, resulting in hyperinsulinemia in the second trimester. This combination of hyperinsulinemia and hyperglycemia enhances the fetus’s fat and protein supplies, resulting in macrosomia (Kamana and Shakya, 2015).

GDM has an effect on both mother and the human foeto-placental complex, culminating in mitochondrial dysfunction (Sobrevia et al., 2020). However, the mitochondria are located in the tail of the sperm during spermatogenesis, because upon fertilization, the whole genome is transferred into the nucleus. This describes why the zygote consumes a large portion of the egg’s cytoplasm i.e., primarily the mitochondria and their mitochondrial DNA. In general, mitochondrial DNA transition from mothers to children is the routine. In certain cases, mitochondrial diabetes can be a major contributor to T2DM, although it is relatively poorly established. This discovery has caused the scope for a genetic cure in diabetes to gain momentum. However, lyonization, imprinting, and prenatal climate may also be possible explanations for the maternal diabetes (Alcolado, 1995). The current study was carried out with mtDNA mutations in the GDM women in the Saudi Arabia. The current study results confirmed the negative association between GDM and non-GDM women. In our population examined, all case-controls genotypes were found to be zero. The possible explanation for achieving zero numbers in genotypes may be due to the fact that these specific (A12026G, A3243G and A8344G) mutations would not play any role in the human diseases with mitochondria in the Saudi women diagnosed with GDM. Another reason could be that mitochondrial mutations do not play any role in our enrolled women. However, mitochondrial dysfunction is a crucial pathogenesis mechanism for metabolic disorders including diabetes (Alexandar et al., 2017).

SNPs are progressively forming the backbone of the genetic studies. SNPs having a certain minimum allele frequency (ex: 0–10) are then genotyped in the sample of interest and an association test is performed. In a case-control genetic association studies, the ultimate analysis is to test an association between n (n = 1, 2, 3, ...) number of genetic mutations, phenotype of interest and estimate the magnitude of the significant association. Additionally, power analysis approaches have been well established for continuous and binary phenotypes where the sample sizes in two or more classes are set (Ambrosius and Lange, 2004). Numerous results could explain for obtaining zero genotypes and in both the case-control population for negative result. As GDM is a polygenic, complex and multifactorial inheritance without the inheritance pattern (Khan et al., 2015). Throughout the global population, mitochondrial mutations are obtained with in the limited studies. The relationship between mitochondrial mutation and gestational diabetes is documented as mitochondria is maternally

**Table 2**
Baseline characteristics of GDM and non-GDM Saudi subjects.

| 95% CI | P       | Non-GDM (n = 102) | GDM (n = 96) | Units | Profiles |
|--------|---------|-------------------|--------------|-------|----------|
| 3.5–7.1 | 0.001   | 28.0 ± 6.7        | 33.3 ± 5.9   | Years | Age      |
| 2.3–9.2 | 0.001   | 73.4 ± 11.8       | 78.2 ± 12.9  | Kgs   | Weight   |
| (-1.4) - (1.5) | 0.025 | 157.7 ± 4.96      | 157.9 ± 5.5  | cm    | Height   |
| 1.1–3.5 | 0.001   | 294 ± 41          | 317 ± 46     | Kg/m² | BMI      |
| 0.4–1.5 | 0.001   | 4.3 ± 0.43        | 5.2 ± 1.2    | mmol/L| FBG      |
| 1.98 – 3.04 | 0.001 | 4.5 ± 1.1         | 7.02 ± 1.7   | mmol/L| PPBG     |
| 2.4–4.4 | 0.001   | 6.3 ± 1.03        | 9.7 ± 2.02   | mmol/L| GCT      |
| NA     | 0.001   | 157.7 ± 4.96      | 5.2 ± 0.84   | mmol/L| OGTT (f) |
| 2.5–4.8 | 0.001   | 7.2 ± 1.8         | 10.9 ± 2.1   | mmol/L| OGTT.1hr |
| 1.4–3.7 | 0.001   | 6.4 ± 1.6         | 8.9 ± 2.1    | mmol/L| OGTT.2hr |
| 0.4–2.8 | 0.009   | 4.3 ± 1.1         | 5.9 ± 1.9    | mmol/L| OGTT.3hr |
| NA     | NA      | NA                | 55 ± 30.3    | Years | AGE of ONSET |
| NA     | NA      | 27 (26.5)         | 96 (100)     | NA    | Family history of T2DM (%) |
| NA     | NA      | 9 (8.8)           | 30 (31.3)    | NA    | Family history of GDM (%) |
| NA     | 0 (0)   | 96 (100)          | 56 ± 1.3     | mmol/L| Total Cholesterol |
| NA     | NA      | NA                | 2.3 ± 1.5    | mmol/L| Triglycerides |
| 0.3–0.9 | 0.001   | 5.2 ± 1.1         | 5.8 ± 1.3    | mmol/L| HDL-C     |
| 0.34–1.01 | 0.001 | 1.7 ± 0.9         | 2.3 ± 1.5    | mmol/L| LDL-C     |
| 0.2–0.4 | 0.001   | 0.67 ± 0.25       | 0.93 ± 0.42  | mmol/L|        |
| (-0.2) - (0.4) | 0.549 | 3.7 ± 1.1         | 3.7 ± 0.9    | mmol/L|        |

NA = Not applicable/Not analyzed.
inherited and mitochondria plays an essential role in numerous cellular processes such as apoptosis, cell proliferation and differentiation (Sato, 2013). In addition, race and country-wide disparities are likely to influence outcomes. A case-control analysis of any genetic population compares the genotype and allele frequencies in various genes involved with environmental factors to cause the disease (Robitaille and Grant, 2008). Deletions and point mutations affect the transcription and translation process of mt DNA which have been suggested to be potential genetic aetiology for both GDM and T2DM (Khan et al., 2014). Large sample-size and unbiased predisposition gene polymorphism epidemiological studies may provide insight into the in vivo relationship between candidate genes and complex diseases (Mao et al., 2012). Obesity is known to be one of the environmental factors (Ren et al., 2016) for occurrence of any human disease especially in women (Hruby and Hu, 2015). The relation between GDM and obesity has been well documented in relation to age (Clausen et al., 2009). The relationship between GDM and environmental factors such as unregulated diet, irregular physical activity and obesity can contribute to the development of T2DM, Metabolic syndrome and other diseases (Khan et al., 2015; Carroll et al., 2018).

Restriction enzymes (RE) or restriction endonucleases are the proteins which recognize and cleave accurate nucleotide sequences which are 4–6 base pairs (bp) in length of double stranded DNA. RE are categorized into specific temperature (type-I), ionic strength (type-II) and pH (type-III). Type-I and III will be varying from type-II because type-II will cut at close proximity towards recognition site, whereas type-I and III at certain DNA sequences which will be varying with the bp sequences in the palindromic sequences. Lambda DNA is a linear and has double stranded phage DNA with 48,502 bp in length. It is also used as molecular weight size marker during the nucleic acid analysis. Lambda DNA can be applied as a substrate in the restriction enzyme activity assays (Haber, 2000; Farge et al., 2012). RE are used to document accurate mutations in the DNA which is instigated due to an alteration in the nucleotide sequence which is responsible for the specific documented mutation is known as SNP (Khan et al., 2016). One of the applications of RFLP analysis was to crisps certain human genomic DNA sites and bifurcated fragments are subjected towards electrophoresis. In our study, we have screened 3 mutations with RFLP analysis and both the alleles and genotypes were turned to zero. Then our next step was, we have used lambda DNA to check and assess the quality of certain REs. However, as per the companies' recommendations and protocols, we have digested the RE.

Alexander et al (2017) performed a meta-analysis study of mitochondrial mutations in both T2DM and GDM diseases and confirmed strong association between T2DM and mitochondrial mutations. The association with GDM has been verified but in a limited number of global studies. One of the limitation of Alexander et al (2017) was the poor representation of the work. Global studies confirmed the negative association with A3243G mutation in the GDM women (Chen et al., 2000; Allan et al., 1997) and our study was in agreement with the documented studies. Although, Khan et al (2015) studies showed the positive association in GDM women in the Indian population. The same criteria were followed with A8344G mutation when compared between Saudi and Indian women.

The current study has certain limitations as one of the major limitations is not obtaining three-digit sample size. Unfortunately, none of the genotype frequencies were not appeared in any of the studies mitochondrial mutations. The strength of this study was we cross-checked the restriction enzyme with lambda DNA and 10% of the samples were performed the Sanger sequencing to cross check the RFLP analysis. All the subjects recruited were Saudi nationality.

5. Conclusion

This study concludes as there is no role between GDM and mitochondrial mutation in the Saudi population. Meta-analysis can be reducted to represent properly in GDM and mitochondria mutations from the global wide studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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