Is there association between Vitamin D receptor polymorphisms and gestational diabetes mellitus? A systematic review and meta-analysis.

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Abstract: Gestational diabetes mellitus (GDM) is glucose intolerance that occurs during pregnancy and can lead to various pregnancy complications. A common genetic factor proposed to be involved in GDM are polymorphisms in the vitamin D receptor (VDR) gene. Vitamin D binds to the VDR gene and leads to the transcription of other genes. Mutations in the VDR gene will impact the effect of vitamin D on the receptor. Vitamin D is involved in the implantation, differentiation, and growth of foetal cells and VDR polymorphisms have been associated with the occurrence of GDM, but findings are contradictory. We assessed the relationship between GDM and VDR polymorphisms. This systematic review and meta-analysis based on the association between VDR polymorphisms and GDM, retrieved from PubMed central, Medline, Google Scholar, EBSCOhost, LILACS, Cochrane Library, ScienceDirect, and Web of Science Core Collection databases. The eligibility of studies was assessed by the two independent reviewers with third reviewer serving as arbitrator following specific criteria. data was analysed with the Review Manager (RevMan) 5.3 software. This systematic review and meta-analysis revealed no statistical difference between GDM and control group for rs7975232, rs10735810, and rs731236 [OR = 1.08 (0.91, 1.28); p = 0.36], [OR= 0.81 (0.57,1.14); p = 0.22],

and [OR=1.80 (1.31, 2.46) p= 0.0002] respectively. VDR gene polymorphisms rs7975232, rs10735810 and rs731236 are not associated with gestational diabetes mellitus. The rs731236 has protective effects against GDM, whereas rs10735810 increases susceptibility to GDM. Further studies with lager sample size especially in low middle income countries are needed to confirm these findings.

Keywords: Gestational diabetes mellitus, Vitamin D polymorphism, rs7975232, rs10735810, rs731236

1. Introduction

Gestational diabetes mellitus (GDM), characterized by an intolerance to glucose during pregnancy, and premature labour are just two of the most common complications that can occur during pregnancy [1, 2]. Others include macrosomia, clinical neonatal hypoglycemia, fetal hyperinsulinemia, birth injury etc. The aetiology of GDM include several factors environmental, immunological and genetic factors [2]. Over the past few decades many studies have been performed in different populations to assess the association between genetic variants and adverse pregnant outcomes. Many gene polymorphisms have been identified and vitamin D receptor (VDR) gene polymorphisms are one of them.

The VDR gene is found on chromosome 12q and it can lead to the transcription of 900 other genes [3]. VDR's are found in the nucleus of cells and forms a heterodimer by

binding with retinoid X receptor alpha. Accordingly, 1 alpha, 25 $(OH)_2D$ (calcitriol), an active form of vitamin D [4], binds to the VDR, which in turn combines with other co-factors and causes the transcription of target genes [5, 6]. This leads to the effects involving differentiation and growth of fetal cells [5]. The polymorphisms affect the stability of the VDR mRNA or how effectively it is translated. This will affect how vitamin D interacts with the VDR and the effect VDR has on the transcription of other genes [3].

Specifically, the vitamin D pathway is associated with pregnancy and attracts attention for several reasons. It has been shown that calcium delivery, placental hormone secretion and the reduction of proinflammatory cytokine secretion of which syntheses is mediated via the action of vitamin D, and helps with normal pregnancy maintenance, fetal development support and the implantation process [3]. This is supported by two pieces of evidence. First, infections, gestational diabetes and pre-eclampsia risk is increased when 25(OH)D (vitamin D) levels in the mother is low [3]. Second, vitamin D receptors (VDR), which control the multiple effects of vitamin D, are expressed in the placental cells called extra villus trophoblasts and here the vitamin D system and VDR regulate immune responses by decreasing various cytokines, thus contributing to innate immune system maintenance, and encouraging implantation of the foetus and growth [3, 5, 7, 8].

Although the role of VD in normal pregnancy development has been reported by many researchers; however, there are several studies that have also associated VD polymorphisms with pregnancy complications such as gestational diabetes mellitus (GDM). A relationship between VD polymorphism (rs739837) and GDM was found by Wang *et al*., (2015). Similarly, In the Turkish and the Iranian population, a relationship between VD polymorphism (rs2228570) and GDM was found, but studies in other countries did not find this relationship [2]. In Iranian, Chinese and Saudi Arabian women an association was observed between VDR ApaI, TaqI and FokI SNP's and GDM, but El-Beshbishy *et al*., (2015) did not observe such an association in Saudi women regarding GDM and VDR

BsmI and FokI polymorphisms [5, 9]. A possible factor that can lead to contradictions include population differences, which make it difficult to do sub-group analyses of results, but it is evident that no clear answer exists for the association between VDR polymorphisms and gestational diabetes mellitus at the moment. Beta cell dysfunction has been linked to GDM development and vitamin D with its receptor helps to regulate the secretion of insulin from the beta cells, which may help to explain the relationship between VDR gene polymorphisms and GDM [10]. Decreased vitamin D concentrations have been shown to affect the secretion and synthesis of insulin [10]. This may help explain how VDR polymorphisms cause insulin resistance if vitamin D cannot bind to VDR receptors.

To the best of our knowledge, very few meta-analyses have been performed on the association between Vitamin D receptor polymorphisms and gestational diabetes mellitus. The only study performed was by Zhou *et al*., (2021). We argue that more meta-analysis should be conducted to establish more certain associations between VDR gene polymorphisms and GDM.

2. Research Question

Is there a relationship between Vitamin D receptor gene polymorphisms and gestational diabetes mellitus?

3. Objectives

This meta- analysis and systematic review aimed to establish the association between VDR gene polymorphisms and gestational diabetes mellitus.

4. Methods

Authors should discuss the results and how they can be interpreted from the perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible. Future research directions may also be highlighted.

4.1. Study research question design and eligibility criteria

This is a systematic review and meta-analysis of published studies. This systematic review is written in line with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analysis for (PRISMA) 2020 statement guidelines [11]. The article screening and selection process was demonstrated through a PRISMA flow diagram.

The eligibility of the research question was determined by the Population Intervention Comparison Outcomes Study design (PICOS) framework.

4.2. Search strategy and identification of studies

The following databases were searched for eligible studies: Medline, PubMed, Google scholar, EBSCOhost, Web of Science Core Collection, and the Cochrane Library, and LILACS. Medical subject headings (MeSH) and free text searches was used on Medline, Embase and PubMed databases and article titles were screened for eligibility. Articles returned by the search were saved on the citation manager, EndNote X7 (Thomson Reuters) which was also used to remove duplicates. The titles and abstracts of the articles remaining after exclusion of duplicates were assessed for eligibility according to the inclusion and exclusion criteria. The full text of all potentially eligible studies was then reviewed by two independent reviewers (HHP and WNP), and any disagreement between reviewers with respect to eligible studies for inclusion in the analysis was settled by a third reviewer (KM). The reference lists of eligible studies and reviews were also assessed

for more relevant studies. A list of the potentially eligible studies excluded from the final analysis were produced with the reasons for exclusion mentioned. A PRISMA flow chart detailing the number of articles identified, screened, included, and excluded was produced.

5. Study selection

The studies that were included in the review had the following characteristics: Pregnant women of any age, with no other pregnancy complications and they had a gestational diabetes mellitus diagnosis. The studies also had to have a pregnant– non-GDM diagnosis control group. Observational studies, cohort, cross sectional studies and randomized control trials were included. The specific SNPs also had to be identified. Studies that were excluded lacked specific VDR polymorphism identification in controls and experimental group, reviews, comments, dissertations, books, abstracts, conferences, and articles that were not yet published. Studies that included non-pregnant women as controls were excluded. And articles where the odds ratio (OR) and confidence intervals (95%) cannot be determined were not included.

6. Data abstraction, data analysis and quality assessment

A data table were used to extract background information and process the data items from each selected study. To ensure that all pertinent information regarding the relevant aspects for the study were collected, a data charting form were developed and piloted, and continually updated.

7. Risk of bias and quality assessment

The quality and scientific evidence of the studies was determined using the Newcastle-Ottawa scale [12]. The quality and risk of bias of selected studies were performed by

both reviewers (WNP and HHP) with consensus on disagreement being achieved with the assistance of another author (KM). This guideline takes in account the following domains: 1-Case definition Adequate? 2-Representativeness of the cases; 3- Selection of controls; 4-Definition of controls; 5-Based on design and analysis; 6- Ascertainment of exposure; 7-Same method for cases and controls; 8-non-response rate. The following authors (HHP and WNP) independently assessed the quality of the studies using the data extraction tool, with consensus on disagreement being achieved with the assistance of another reviewer (KM).

8. Data analysis

The data were analysed using Review Manager (RevMan) software (version 5.3). The generic inverse variance method was used for meta-analysis of both, individually and cluster randomised trials to estimate the effect size from odds ratio (OR) and relative confidence intervals (CI)s. In a case where we did not find at least two studies to produce a single estimate of the effect of intervention. We calculated the OR, and 95% CIs by computing the number of events and the number of patients from both control and GDM groups.

Statistical heterogeneity between studies was evaluated by I^2 statistic and classified as low if $I^2 < 20\%$ or moderate if $I^2 > 50\%$, the fixed effect model to estimate OR and relative confidence intervals. Statistical significance for effect estimates was set at $p < 0.05$.

9. Results

9.1 Literature search

We identified 30 studies through PubMed central, Medline, Google Scholar, EBSCO-host, LILACS, Cochrane Library, ScienceDirect, and Web of Science Core Collection databases and additional sources (Supplementary Table 1). A total of 12 studies were eligible for this study. After duplicates were removed, we screened 15 studies for eligibility and removed three studies because one lacked confidence intervals and odds ratios, one had a control group consisting of non-pregnant women and the third study had a GDM group with other complications. About 12 studies were eligible and included in our data synthesis, only meta- seven studies were relevant for meta-analysis (Figure 1).

9.2 Characteristics of eligible studies

Table 2 indicates the general characteristics of the eligible studies. We included five case-controls [2, 10, 14-17], and one cohort [18]. The studies were conducted in 5 countries, for instance two studies were conducted in Iran, two in Iraq, one in Brazil, one in Turkey, and one in China. There were no studies conducted in Africa exploring the association between VDR gene polymorphisms and gestational diabetes mellitus. All included studies were published in peer-reviewed journals between 2011 and 2021. The sample size for included population in the studies was 2853, with 1387 cases and 1466 controls.

10. Meta-analysis

10.1 Association between VDR gene polymorphisms and GDM

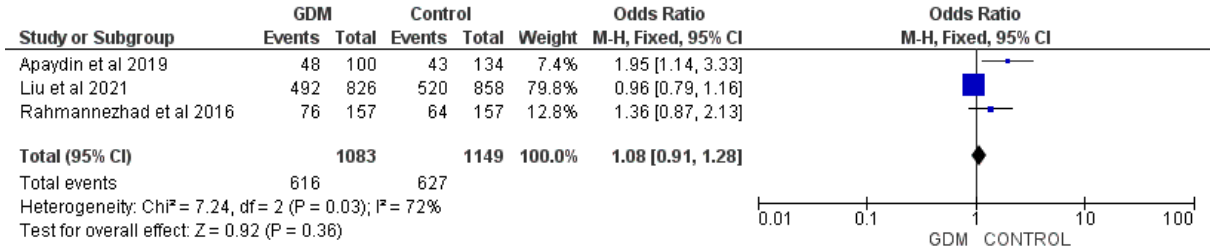
The association between VDR gene polymorphisms and GDM are displayed in figure 2. Only seven studies were included in our meta-analysis, the other studies' data were extracted but they reported on other SNP's and so could not be compared to the included studies.

For the VDR gene, rs7975232, our effect estimates showed no statistical difference was observed between GDM and control group [OR = 1.08 (0.91, 1.28); p = 0.36]. Hence, no statistical association between VDR gene, rs7975232 (AA or CC) polymorphism in GDM and control group. Interestingly, these showed a very was a substantial statistical heterogeneity (I^2 =72%, p = 0.03) Figure 2A. Due to minimal number of studies included, no subgroup analysis was performed.

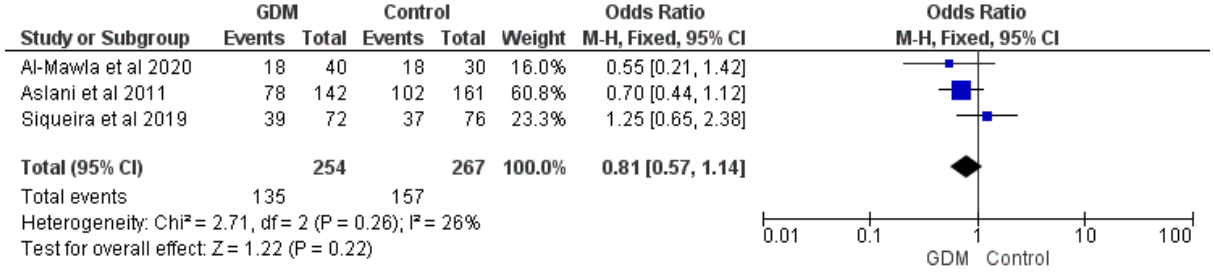
Similarly, for VDR gene, rs10735810 (FF) polymorphism, our generated effect estimates from quantitative analysis showed no statistical difference between GDM and control group as demonstrated by an [OR= 0.81 (0.57,1.14); p = 0.22]. Moreover, there was a minimal statistical heterogeneity as demonstrated by (I^2= 26, p = 0.26) Figure 2B.

In contrast for VDR gene, rs731236 (TT or CC) polymorphism our meta-analysis revealed a significant difference between the GDM and control group. This is noted by a significantly increased rs731236 polymorphism into control as compared to GDM group [OR=1.80 (1.31, 2.46) p= 0.0002]. Thus, showing a significant association between VDR gene, rs731236 (FF) polymorphism and Normotensive. Interestingly, there was no evidence of heterogeneity amongst the included studies (I^2= 19%, p =0.29) Figure 2C.

a)


GDM
Control
Odds Ratio
Odds Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Apaydin et al 2019 48 100 43 134 7.4% 1.95 [1.14, 3.33]
Liu et al 2021 492 826 520 858 79.8% 0.96 [0.79, 1.16]
Rahmannezhad et al 2016 76 157 64 157 12.8% 1.36 [0.87, 2.13]
Total (95% CI) 1083 1149 100.0% 1.08 [0.91, 1.28]
Total events 616 627
Heterogeneity: Chi² = 7.24, df = 2 (P = 0.03); I² = 72%
Test for overall effect: Z = 0.92 (P = 0.36)
0.01
0.1
1
10
100
GDM CONTROL

b)


GDM
Control
Odds Ratio
Odds Ratio
Study or Subgroup
Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Al-Mawla et al 2020 18 40 18 30 16.0% 0.55 [0.21, 1.42]
Aslani et al 2011 78 142 102 161 60.8% 0.70 [0.44, 1.12]
Siqueira et al 2019 39 72 37 76 23.3% 1.25 [0.65, 2.38]
Total (95% CI) 254 267 100.0% 0.81 [0.57, 1.14]
Total events 135 157
Heterogeneity: Chi² = 2.71, df = 2 (P = 0.26); I² = 26%
Test for overall effect: Z = 1.22 (P = 0.22)
0.01
0.1
1
10
100
GDM Control

c)

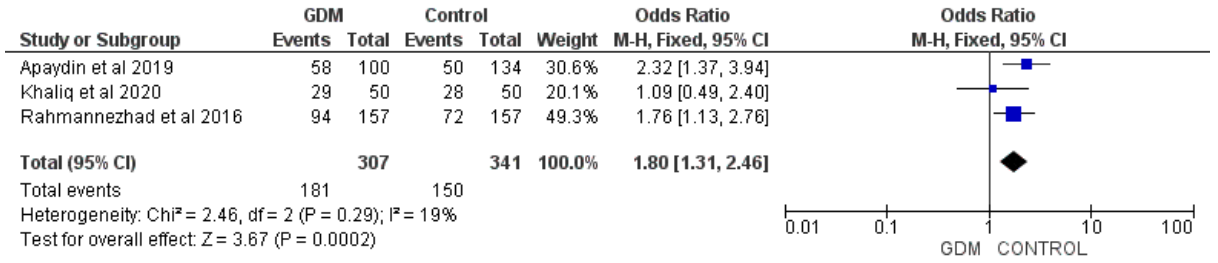


Figure 2: Forest Plots showing the association between the VDR gene polymorphism and GDM, classified as a dichotomous variable. a) Apal polymorphism (rs7975232) model (AA or CC); b) FokI polymorphism (rs10735810) model (FF); c) Taq1 polymorphism (rs731236) model (TT or CC).

11.1 Quality of studies and the risk of bias assessment

Details of the quality of bias assessment are presented in supplementary Table 2 and 3). The included studies were one cohort study and six case control studies. The cohort study was of good quality, scoring 8 stars (Supplementary Table 2). Interestingly, all the case control studies were also of good quality, scoring 9 starts (Supplementary Table 3).

11. Discussion

Gestational diabetes (GDM) can lead to various pregnancy complications [13]. It is therefore important to find the aetiology of this conditions to create effective prevention and intervention strategies. Research has shown an association between VDR gene polymorphisms and the occurrence of GDM [13]. In the present study we evaluated the association between VDR gene polymorphisms rs7975232 (Apal), rs10735810 (Fokl), and rs731236 (TaqI) and GDM.

The main findings from our study showed that there was no association between VDR gene rs7975232, rs10735810, and rs731236 polymorphisms with GDM (Figure 2A, Figure 2B, and Figure 2C). Our findings are in agreement with findings from previous studies [2, 10, 13-16]. Liu *et al*., (2021) reported no significant associations nor gene-gene interactions of rs7975232 with GDM in Wuhan, China [2]. Similarly, Apaydin *et al*., (2019) also reported that no association was observed between VDR gene ApaI rs7975232 and TaqI rs731236 GDM, although other studies have reported conflicting results [13, 17, 18]. Rahmannezhad *et al*., (2016) found a significant association between VDR rs7975232 and rs731236 gene polymorphisms and the GDM [17]. Their findings revealed that patients with the CC genotype were more at risk of GDM compared to those with AA genotype (AA vs.CC, OR = 2.996, 95% CI = 1.278–7.022, P = 0.012) [17]. Similar findings were also reported from two systematic reviews and meta-analysis by Liu *et al*., (2021) and Zhou *et*

al., (2021) which indicated that rs7975232 increases susceptibility to GDM [13, 18]. Interestingly, rs7975232 has also been shown to be associated with type 1 diabetes mellitus (T1DM). In an Egyptian study by Ahmed *et al*., (2019), it was observed that rs7975232 is associated with T1DM development among children [19].

Another gene polymorphism that we found to be not associated with GDM is rs10735810 (Fokl). In support of our findings, Shaat *et al*., (2020) and Wang *et al*., (2015) also reported no association of this polymorphisms with GDM [15, 16]. Moreover, Siqueira *et al*., (2019) and Al-Malwa *et al*., (2020) found no association of this gene with GDM among Brazilian and Iraqi pregnant women [20, 21]. Gestational diabetes mellitus is a pregnancy complication which can lead to pregnancy loss [22, 23]. In a study by Radzinsky *et al*., (2021) it was reported that there is no direct relation found between the pregnancy loss frequency in the first trimester and the variant of the vitamin D receptor gene polymorphism (VDR A > G [rs10735810]) [24].

Although our findings indicated no significant association of *Fokl* polymorphism rs10735810 with GDM (p=0.22), however the gene was found to be more prevalent in the GDM group. which is an indication that this gene increases susceptibility to GDM. This was also reported in previous studies whereby an association of *Fokl* polymorphisms with GDM was observed [10, 25]. *Fokl* polymorphism is found at the 5' end of the gene, close to the promoter region [26]. This gene has been associated with various inflammatory conditions [27] and autoimmune diseases [28]. To date, only two studies found a significant association of this gene polymorphism with GDM [10, 25]. According to Aslani *et al*., (2011), a meaningful association between FokI VDR genotypes and an increased risk of GDM in Iranian pregnant women was noted [25]. On the other hand, Apaydin *et al*., (2019) reported that VDR gene FokI SNPs rs10735810 was associated with having GDM in Turkish women, they further concluded that rs10735810 might contribute to insulin resistance

of developing GDM [10]. Since the association of rs10735810 with GDM reports conflicting results, therefore more studies are needed in order to validate the current findings, more especially studies conducted in the African population.

Lastly, we also evaluated the association between TaqI (rs731236) gene polymorphisms, and our findings indicated no association of this gene with GDM, interestingly this gene has shown to have protective effects against GDM. Several studies have documented similar findings [10, 29]. AbdulKhaliq *et al*., (2020) found no association between this gene and GDM in Iraqi women [29]. However, they noticed that the frequency of the T allele was 0.86 in GDM patients and 0.96 in control, while the rate of recurrence of the C allele was 1.14 in GDM patients and 1.16 in control, indicating that this gene was more prevalent in the control group. In contrast, a previous Turkish study has reported that there is association of TaqI gene with GDM [30]. To date, research on TaqI genes has been done on two populations (Iraqi and Turkish women), It is of importance to note that race can be variable that affects the results and should be accounted for. Since there is so little research in just one population it is difficult to do a meta-analysis that controls for race. Therefore, more studies reporting on this gene are needed in order to confirm our findings.

12. Limitations and strength

The first limitation of our study is size, very few studies have been conducted in relation to VDR gene polymorphism and GDM. Although we did an extensive search, only a few studies met the complete criteria for eligibility and not all the studies study the exact same polymorphisms and so only a few studies can be compared. So, our research should be considered with caution since we have a very small sample. There are many factors that influence the GDM, including race and lifestyle factors. The research has shown

variability in the distribution of polymorphisms in different races, which makes it difficult to draw conclusions and generalize findings.

13. Conclusion

Our data suggest that the VDR gene polymorphisms rs7975232, rs10735810 and rs731236 are not associated with GDM. Future studies should focus on various genotype models of the VDR gene polymorphisms as well as interactions among different gene polymorphisms. The research should also be conducted in other population groups more especially in the Africa countries.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Table S1: Search strategy piloted in PubMed Central, Medline, Google Scholar, Web of Science, Cochrane Library and LILACS and EBSCOhost; Table S2: Quality assessment for cohort study using modified NewCastle-Ottawa scale; Table S3: Quality assessment for case-control studies using modified Newcastle-Ottawa scale; Appendix S1: Prisma checklist.

Author Contributions: Conceptualization and designed, HHP and WNP.; methodology, HHP, WNP. and KM.; validation, WNP and KM; formal analysis, HHP, WNP and K.M.; resources, WNP and KM; writing—original draft preparation, HHP and WNP; writing—review and editing, WNP and KM; funding acquisition, WNP. All authors (HHP, WNP and KM) have read and approved the final version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable as this study involved the use of already published studies.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable as this study involved the use of already published studies.

Conflicts of Interest: authors declare no conflict of interest.

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