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ORIGINAL: Vitamin D Deficiency as a Risk Factor for Gestational Diabetes Mellitus

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ABSTRACT

Introduction: Gestational diabetes mellitus (GDM) is a common complication affecting around 13.5% of pregnancies globally. This condition, characterized by insulin resistance and glucose metabolism disturbances, may be linked to vitamin D deficiency. A recent study aimed to investigate this potential connection to enhance prevention and treatment strategies.

Material and Methods: From 2019 to 2020, a cohort study was conducted to assess the prevalence of vitamin D deficiency in pregnant women with GDM across different clinical settings. Participants were categorized based on their vitamin D status, excluding those with unclear levels or a history of diabetes. Precise diagnostic criteria were established, and data analysis was carried out using SPSS software.

Results: From the study of 100 pregnant women revealed a significant association between vitamin D deficiency and GDM. Those deficient in vitamin D, with an average age of 28.82 years and weight of 73.20 kg, showed higher rates of GDM compared to those with sufficient vitamin D levels (average age: 30.52 years, weight: 78.59 kg). This correlation was particularly notable among women aged 26 to 35 and those with normal or high body mass index (BMI). No significant associations were found with comorbidities, parity, or gravidity.

Conclusion: Study shows 32% higher risk of GDM with low vitamin D levels vs normal levels (4%), especially in 26-35 age group. Larger, multi-center studies needed to confirm and build upon these findings due to limitations like sample size and regional scope.

Introduction

Gestational diabetes mellitus (GDM) represents a prevalent complication associated with pregnancy, characterized by glucose intolerance that is first identified during the gestational period. This condition poses considerable health risks for both the mother and the fetus, thereby necessitating prompt diagnosis and effective management strategies to mitigate adverse outcomes. The etiology of GDM is multifactorial, arising from an interplay of genetic predispositions and environmental influences that culminate in insulin resistance and disrupted glucose metabolism among pregnant women. The escalating global incidence of GDM, which exhibits variability across different populations, accentuates the imperative for a thorough comprehension of its underlying causes and associated risk factors. On a global scale, GDM impacts approximately 13.5% of pregnancies; conversely, in Iran, the prevalence is estimated at around 3.41%, thereby underscoring a significant public health challenge (1). In addition to complications during pregnancy, gestational diabetes mellitus (GDM) raises the chances of both the mother and child developing type 2 diabetes and other metabolic issues later in life. Furthermore, women with GDM are at a higher risk of developing pregnancy-related hypertension, while their newborns face an increased likelihood of complications such as macrosomia, which can result in birth injuries and a higher rate of cesarean deliveries. (2). The identification of risk factors and the elucidation of underlying mechanisms contributing to gestational diabetes mellitus (GDM) are imperative for the formulation and implementation of effective prevention and treatment strategies. A significant area of inquiry within GDM research pertains to the potential influence of vitamin D on metabolic processes. Vitamin D, a fat-soluble vitamin that is critical for calcium absorption and skeletal health, also exerts effects on immune function, insulin sensitivity, and inflammatory responses. The condition known as hypovitaminosis D, or vitamin D deficiency, is widespread on a global scale and exhibits variability across different populations. In the context of Iran, studies indicate that the prevalence of vitamin D deficiency stands at approximately 15.6%, with even more pronounced rates observed among pregnant women. (3). Vitamin D deficiency during pregnancy has been linked to several adverse outcomes, including preeclampsia, preterm birth, and gestational diabetes (4). Although the precise mechanisms through which vitamin D deficiency contributes to gestational diabetes mellitus (GDM) remain inadequately elucidated, existing research indicates that vitamin D plays a significant role in modulating glucose metabolism and insulin resistance, both of which are critical determinants in the pathogenesis of GDM. Insulin resistance is a physiological adaptation that typically occurs during pregnancy; however, it can lead to diminished insulin sensitivity, thereby escalating the demand for insulin production. If the pancreas is unable to fulfill this heightened demand, gestational diabetes may develop. (5). Vitamin D is believed to impact insulin secretion and sensitivity by acting on pancreatic β-cells and modulating the immune system, potentially explaining its role in GDM (6). Although there is increasing research connecting vitamin D deficiency to gestational diabetes mellitus (GDM), the results are still inconsistent. Some studies have found a significant link between low vitamin D levels and a higher risk of GDM, while others have not observed such a connection. For example, a study conducted in the United States indicated that women with low vitamin D levels had a 2.2 times greater risk of developing GDM compared to those with sufficient levels. (7). Conversely, a Korean study observed no significant difference in vitamin D levels between women with and without GDM (8). These conflicting results underscore the need for further research to elucidate the relationship between vitamin D deficiency and GDM, especially in diverse populations. Understanding this relationship is crucial for developing novel prevention strategies, such as vitamin D supplementation during pregnancy. This study aims to investigate the association between serum vitamin D levels and the risk of gestational diabetes in pregnant women, contributing to the existing knowledge base and informing clinical practice.

Methods

Study design and population

This study employed a descriptive-analytical observational cohort design. Participants were pregnant women attending Valiasr Hospital, Razi Hospital, and private clinics in Qaemshahr between 2019 and 2020.

Sample size

Sample size was determined based on the

study by Zhang et al., with a type I error (alpha) of 0.05 and a type II error (beta) of 0.2. The estimated prevalence of hypovitaminosis D was 33% in GDM cases and 14% in controls. An initial sample size of 48 was calculated, but this was increased to 50 participants per group (total of 100) to ensure adequate power.

$$N = \frac{\left((Z_{1-\alpha/2}\sqrt{P(1-P)} + Z_{1-\beta}\sqrt{[P_1(1-P_1)]+[P_2(1-P_2)]}\right)^2}{(P_1-P_2)^2}$$

$$N = \frac{\left(1.96\times\sqrt{0.235\times0.765} + 0.84\sqrt{(0.33+0.76)+(0.14\times0.86)}\right)^2}{(0.33-0.14)^2}$$

$$\Rightarrow N = 48$$

Exclusion criteria

Participants exhibiting indeterminate serum vitamin D concentrations, those with a documented history of diabetes mellitus, or individuals who were utilizing vitamin D supplements were systematically excluded from the study.

Study procedure

The research encompassed a cohort of 100 pregnant women who were recruited from Valiasr Hospital, Razi Hospital, and various private clinics located in Qaemshahr during the period spanning from 2019 to 2020. To gather demographic information, a structured questionnaire was employed. Blood samples were collected from participants between the 10th and 12th weeks of gestation for the purpose of measuring serum vitamin D levels utilizing the Enzyme-Linked Immunosorbent Assay (ELISA) methodology. The participants were subsequently classified into two groups: those with hypovitaminosis D and those with normal vitamin D levels. The prevalence of gestational diabetes was then compared between these two groups. Data analysis was conducted using SPSS software, version 21.

Diagnosis of gestational diabetes

Gestational diabetes mellitus (GDM) screening involved women meeting at least one of the following criteria: obesity (BMI ≥ 25), age over 25 years, personal or family history of diabetes, or history of delivering a baby weighing over 4000 grams. At the initial antenatal visit, if fasting blood glucose (FBS) was ≥95 mg/dl and a criterion was met, a glucose challenge test (GCT) was performed. A plasma glucose level ≥140 mg/dl or ≥130 mg/dl after one hour indicated an abnormal GCT. Abnormal GCT results led to a 100-gram oral glucose tolerance test (OGTT) with glucose levels measured fasting and at 1, 2, and 3 hours. GDM was diagnosed based on the American Diabetes Association's Coustan & Carpenter criteria, requiring two or more abnormal glucose values. A one-step 75-gram OGTT was used for high-risk patients or those with a history of postpartum GDM, with diagnostic criteria of fasting glucose ≥ 92 mg/dl, 1-hour glucose ≥ 180 mg/dl, or 2-hour glucose ≥ 153 mg/dl.

Diagnosis of vitamin D deficiency

Serum vitamin D levels were measured using ELISA, with deficiency defined as <20 ng/ml, insufficiency as 20-30 ng/ml, and sufficiency as >30 ng/ml.

Data collection and analysis

Data collected included age, BMI, medical history, gravidity, parity, vitamin D levels, and GDM status. Descriptive and inferential statistical analyses were conducted using SPSS version 26, including frequency, percentage, mean, standard deviation, Fisher's exact test, and chi-squared test. Statistical significance was set at $p < 0.05$.

Results

Descriptive Analysis

The investigation encompassed two randomly selected cohorts, each comprising 50 pregnant women: one cohort exhibited vitamin D deficiency, while the other maintained normal levels of vitamin D. The descriptive statistics corresponding to each group are delineated below.

Maternal Age

Table 1 summarizes age statistics for the participants. The mean age in the vitamin D deficiency group was 28.82 years (standard deviation, SD = 5.34 years), with a range of 14 to 40 years. The normal vitamin D group had a mean age of 30.52 years (SD = 5.22 years), with a range of 19 to 41 years.

Maternal Weight, Height, and BMI

Table 2 displays the statistics for height, weight, and body mass index (BMI) among the participants. In the group with vitamin D deficiency, the average height was 163.84 cm (SD = 5.12 cm), ranging from 150 to 176 cm. The group with normal vitamin D levels had an average height of 167.26 cm (SD = 3.43 cm), with a range of 158 to 176 cm. The average weight in the vitamin D deficiency group was 73.20 kg (SD = 14 kg), ranging from 49 to 108 kg. Conversely, the normal vitamin D group had an average weight of 78.59 kg (SD = 11.52 kg), with a range of 54 to 107 kg. The mean BMI for those with vitamin D deficiency was 27.19 (SD = 4.69), ranging from 19.63 to 39.67, while the normal vitamin D group had a mean BMI of 28.00 (SD = 3.28) with a range of 20.83 to 35.29.

Qualitative Variables

Connection Between Serum Vitamin D Levels and Gestational Diabetes

The primary hypothesis under investigation is whether there exists a significant correlation between serum vitamin D levels and the incidence of gestational diabetes. The data presented in **Table 3** substantiates a robust association between vitamin D deficiency and the occurrence of gestational diabetes. Specifically, it was observed that mothers exhibiting deficient levels of vitamin D were significantly more predisposed to developing gestational diabetes when compared to their counterparts with adequate vitamin D levels ($p < 0.05$).

Table 1. The descriptive statistics related to the age of mothers by group.

Group	Number	Mean	Standard Deviation	Minimum	Maximum
Vitamin D deficiency	50	28.82	5.34	14	40
Normal vitamin D	50	30.52	5.22	19	41
Total	100	29.67	5.32	14	41

Table 2. Descriptive statistics related to the height, weight, and body mass index (BMI) of mothers by group.

Variable	Group	Number	Mean	Standard Deviation	Minimum	Maximum
Height (cm)	Vitamin D Deficiency	50	163.84	5.12	150	176
	Normal vitamin D	50	167.26	3.43	158	176
Weight (kg)	Vitamin D Deficiency	50	73.20	14.00	49	108
	Normal vitamin D	50	78.59	11.52	54	107
Body Mass Index (BMI)	Vitamin D Deficiency	50	27.19	4.69	19.63	39.67
	Normal vitamin D	50	28.00	3.28	20.83	35.29

Table 3. Investigation of the relationship between serum vitamin D levels and gestational diabetes.

	Negative Gestational Diabetes	Positive Gestational Diabetes	Chi-Square Statistic	Sig.
Vitamin D Deficiency	34(68%)	16(32%)	13.279	0.0009
Normal vitamin D	48(96%)	2(4%)		
Total	82(82%)	18(18%)		

Connection Between Serum Vitamin D Levels and Gestational Diabetes by Age

First Hypothesis: Does the relationship between vitamin D deficiency and gestational diabetes vary by age? The analysis presented in **Table 4** indicates that there is no statistically significant difference in age between mothers diagnosed with gestational diabetes and those without such a diagnosis ($p > 0.05$). Furthermore, a Chi-square analysis stratified by age group (**Table 5**) identified a significant association between vitamin D deficiency and gestational diabetes exclusively within the age cohort of 26 to 35 years ($p = 0.006$). Conversely, no significant associations were observed for mothers aged below 25 years ($p = 0.175$) or for those aged above 35 years ($p = 0.077$).

Connection Between Serum Vitamin D Levels and Gestational Diabetes by BMI

Second Hypothesis: Does the relationship between vitamin D deficiency and gestational diabetes vary based on maternal BMI at term? No significant difference in maternal BMI was observed between women with and without gestational diabetes (mean BMI: 27.66 ± 3.56 vs. 27.28 ± 5.91, respectively, $p > 0.05$) (**Table6**). Chi-square analysis revealed a significant association between vitamin D deficiency and gestational diabetes among women with normal BMI ($p = 0.034$). However, no such association was found in the overweight group ($p = 0.430$). Interestingly, a significant association was observed between vitamin D deficiency and gestational diabetes among obese women ($p = 0.009$)(**Table 7**).

Table 4. Comparison of maternal age between groups with and without gestational diabetes

Group	Number	Mean	Standard Deviation	T statistic	Sig.
Negative Gestational Diabetes	82	29.44	5.41	- 0.925	0.357
Positive Gestational Diabetes	18	30.72	4.91		

Table 5. Association between serum vitamin D levels and gestational diabetes by age

	Vitamin D	Negative Gestational Diabetes	Positive Gestational Diabetes	Negative Gestational Diabetes		Positive Gestational Diabetes		Exact.Sig.
				Mean	Standard Deviation	Mean	Standard Deviation	
Normal	Vitamin D Deficiency	12 (80%)	3 (20%)	22.42	3.06	23.00	1.00	175.0
	Normal vitamin D	11 (100%)	0	22.18	2.23	-	-	
Overweight	Vitamin D Deficiency	20 (64.5%)	11 (35.5%)	30.45	2.78	30.91	2.66	0.006
	Normal vitamin D	28 (93.3%)	2 (6.7%)	30.71	2.58	33.00	2.83	
Older than 35 years	Vitamin D Deficiency	2 (50%)	2 (50%)	38.00	1.44	39.00	1.41	0.077
	Normal vitamin D	9 (100%)	0	37.78	83.1	-	-	

Table 6. Comparison of maternal body mass index between groups with and without gestational diabetes

Group	Number	Mean	Standard Deviation	T statistic	Sig.
Negative Gestational Diabetes	82	27.66	3.56	0.352	0.725
Positive Gestational Diabetes	18	27.28	5.91		

Table 7. Association between serum vitamin D levels and gestational diabetes based on body mass index (BMI).

BMI	Vitamin D	Negative Gestational Diabetes	Positive Gestational Diabetes	Negative Gestational Diabetes		Positive Gestational Diabetes		Exact.Sig.
				Mean	Standard Deviation	Mean	Standard Deviation	
Normal	Vitamin D Deficiency	11 (57.9%)	8 (42.1%)	23.17	1.28	22.28	1.95	034.0
	Normal vitamin D	8 (100%)	0	22.62	1.16	-	-	
overweight	Vitamin D Deficiency	17 (85%)	3 (15%)	22.65	1.23	27.82	1.38	0.430
	Normal vitamin D	26 (92.9%)	2 (7.1%)	27.65	1.25	27.26	1.53	
obese	Vitamin D Deficiency	6 (54.5%)	5 (45.5%)	32.97	3.43	34.98	4.00	0.009
	Normal vitamin D	14 (100%)	0	31.81	71.1	-	-	

Connection Between Serum Vitamin D Levels and Gestational Diabetes by Comorbidities

Third Hypothesis: Is there a difference in the relationship between vitamin D deficiency and gestational diabetes based on comorbidities? Among women without comorbidities, the prevalence of gestational diabetes was 15.9% (n = 13), compared to 27.8% (n = 5) among women with comorbidities. However, chi-square analysis revealed no significant association between comorbidities and gestational diabetes ($\chi^2 = 1.422$, p = 0.193). Further analysis (**Tables 9** and **10**) indicated no significant interaction between vitamin D status and comorbidities in relation to gestational diabetes risk.

Table 8. Examination of the association between underlying conditions and gestational diabetes.

Underlying condition	Negative Gestational Diabetes	Positive Gestational Diabetes	Chi-Square Statistic	Sig.
With underlying condition	69(84.1%)	13(15.9%)	1.422	0.193
Without underlying condition	13(72.2%)	5(27.8%)		
Total	82(82%)	18(18%)		

Table 9. Examination of the association between the type of underlying condition and gestational diabetes in mothers.

Group	Underlying condition	Gestational Diabetes		Chi-Square Statistic	Exact.Sig.
		Negative Gestational Diabetes	Positive Gestational Diabetes		
Vitamin D Deficiency	Has underlying condition	31(70.5%)	13(29.5%)	015.1	285.0
	Does not have underlying condition	3(50%)	3(50%)		
Normal vitamin D	Has underlying condition	38(100%)	0	6.597	0.054
	Does not have underlying condition	10(96%)	2(4%)		

Connection Between Serum Vitamin D Levels and Gestational Diabetes by Parity

Fourth Hypothesis: Is there a difference in the relationship between vitamin D deficiency and gestational diabetes based on parity? The prevalence of gestational diabetes was higher among multiparous women (21.4%, n = 9) compared to nulliparous women (15.5%, n = 9)(**Table 11**). However, chi-square analysis revealed no significant association between parity and gestational diabetes (χ^2 = 0.577, p = 0.308)(**Table12**). Furthermore, there was no significant interaction between vitamin D status and parity in relation to gestational diabetes risk.

Connection Between Serum Vitamin D Levels and Gestational Diabetes by Gravidity

Fourth Hypothesis: Is there a difference in the relationship between vitamin D deficiency and gestational diabetes based on gravidity? The prevalence of gestational diabetes was slightly higher among multigravida women (19.6%) compared to primigravida women (16.3%). However, this difference was not statistically significant (χ^2 = 0.182, p = 0.434). Furthermore, there was no evidence of an interaction between vitamin D status and gravidity in relation to gestational diabetes risk.

Table 10. Association between serum vitamin D levels and gestational diabetes based on underlying conditions.

Underlying condition	Gestational Diabetes	
	Negative Gestational Diabetes	Positive Gestational Diabetes
None	69(84.1%)	13(15.9%)
Hyperthyroidism	13(72.2%)	2(13.3%)
Diabetes	0	3(%100)
Total	82(82%)	8(%18)

Table 11. Examination of the association between parity and gestational diabetes in mothers.

Parity	Negative Gestational Diabetes	Positive Gestational Diabetes	Chi-Square Statistic	Exact.Sig.
Nulliparous	49(84.5%)	9(15.5%)		
Multiparous	33(78.6%)	9(21.4%)	0.577	0.308
Total	82	18		

Table 12. Correlation of vitamin D serum level with gestational diabetes based on parity.

Group	Parity	Gestational Diabetes		Chi-Square Statistic	Exact.Sig.
		Negative Gestational Diabetes	Positive Gestational Diabetes		
Vitamin D Deficiency	Nulliparous	17(65.4%)	9(34.6%)	0.170	457.0
	Multiparous	17(70.8%)	7(29.2%)		
Normal vitamin D	Nulliparous	32(100%)	0	3.704	0.125
	Multiparous	16(88.9%)	2(11.1%)		

Table 13. Investigating the relationship between gravidity and maternal gestational diabetes.

Gravid	Negative Gestational Diabetes	Positive Gestational Diabetes	Chi-Square Statistic	Exact.Sig.
prime gravid	41(83.7%)	8(16.3%)		
Multi gravid	41(80.4%)	10(19.6%)	0.182	0.434
Total	82	18		

Table 14. Correlation of vitamin D serum level with gestational diabetes based on gravid.

Group	Gravid	Gestational Diabetes		Chi-Square Statistic	Exact.Sig.
		Negative Gestational Diabetes	Positive Gestational Diabetes		
Vitamin D Deficiency	Prime gravid	15(65.2%)	8(34.8%)	0.152	465.0
	Multi gravid	19(70.4%)	8(29.2%)		
Normal vitamin D	prime gravid	26(100%)	0	2.257	0.225
	Multi gravid	22(96%)	2(4%)		

Discussion

Gestational diabetes mellitus (GDM) markedly enhances the probability of mothers developing type 2 diabetes in subsequent years and increases the overall susceptibility to metabolic disorders. Consequently, it is imperative to identify, manage, and comprehend the underlying causes of GDM. (3). Furthermore, infants born to mothers with diabetes often encounter physical issues, such as being large for their gestational age (LGA), and typically require more intensive care than other newborns (4). A comprehensive understanding of the factors contributing to gestational diabetes mellitus (GDM) is essential for effective management and prevention strategies. The present study investigated the relationship between vitamin D deficiency and the incidence of GDM, revealing a statistically significant association between diminished vitamin D levels and the occurrence of GDM (P = 0.0009). Notably, among the participants, 32% of those exhibiting vitamin D deficiency developed GDM, in contrast to only 4% of individuals with adequate vitamin D levels. Supporting these findings, a study conducted by Burris et al. in 2012, which involved a cohort of 1,314 pregnant women in the United States, indicated that 13.2% of patients diagnosed with GDM had vitamin D levels below 25 nmol/L, compared to just 4% of healthy pregnant women within the same population. The authors concluded that pregnant women with vitamin D deficiency were 2.2 times more likely to develop GDM than their counterparts with sufficient vitamin D levels. (9), which aligns with our findings. Similarly, A case-control study conducted in 2012 by Wang et al. in China, which comprised a sample of 200 women diagnosed with gestational diabetes mellitus (GDM) and an equal number of women with normal glucose levels, revealed that 61% of the GDM cohort exhibited vitamin D deficiency, in contrast to 46.5% of the control group. This elevated prevalence of insufficient vitamin D levels among the GDM participants corroborates our findings (10). Conversely, a subsequent study performed by Park et al. in South Korea in 2014, which included a larger sample size of 523 pregnant women, found no statistically significant difference in vitamin D concentrations between the GDM and non-GDM groups (11). This discrepancy may stem from genetic and dietary differences between Korean and Iranian populations. In a 2008 case-control study by Zhang et al. in the United States, which included 171 pregnant women (57 with GDM and 114 without), 33% of GDM patients and 14% of healthy pregnant women were vitamin D deficient, a statistically significant difference similar to our findings (12) In contrast, a separate investigation carried out by Chao-Yan Yue and Chun Mei Ying in China, which included a considerably larger cohort of 8,468 women, reported no significant correlation between vitamin D deficiency and GDM when controlling for variables such as age and body mass index (BMI) (13).

Our study also found no significant association between vitamin D levels and GDM in women under 25 years of age (P = 0.17), but a significant association in the 26-35 age group (P = 0.006) and no significant association in women over 35 years of age (P = 0.077). These variations may be attributed to differences in diet, physical activity, and cultural practices. A 2013 case-control study by Sayid Shafi Zahar et al. in Turkey, including 234 pregnant women with GDM and 168 without, found a significant association between higher parity and vitamin D deficiency in GDM (14), which contrasts with our findings. We found no significant association between parity and GDM in women with either vitamin D deficiency (P = 0.45) or normal vitamin D levels (P = 0.125). Additionally, A study conducted in 2016 by Valizadeh et al. in Zanjan, Iran, involved a cohort of 96 pregnant women. Among these participants, 48 exhibited vitamin D deficiency and were administered a total of 700,000 IU of vitamin D during their pregnancy. The remaining 48 participants had their stored serum samples analyzed postpartum. The findings of this investigation indicated that there were no statistically significant differences in gravidity or pre-existing medical conditions between the intervention group and the control group. (15). Our research also indicated no significant link between the number of pregnancies (gravidity) and gestational diabetes mellitus (GDM) in women with either vitamin D deficiency (P = 0.456) or normal vitamin D levels (P = 0.225). Additionally, we found no significant relationship between pre-existing medical conditions and GDM in women with either vitamin D deficiency (P = 0.285) or normal vitamin D levels (P = 0.054).

Conclusion

The present investigation, in conjunction with comparative analyses from existing literature, elucidates a substantial correlation between vitamin D deficiency and the onset of gestational diabetes mellitus (GDM). To substantiate these findings, it is imperative that future research endeavors incorporate larger sample sizes and adopt a multicenter approach. It is crucial to recognize the limitations inherent in this study, notably the restricted sample size and its concentration on a specific geographical locale within a singular county. Such constraints, along with regional variations in lifestyle practices and attire, may potentially influence the applicability of the results to broader populations. Furthermore, the exclusion of certain participants due to their unwillingness to engage in the study also had an effect on the overall findings. Future investigations should prioritize the inclusion of larger, multicenter studies to facilitate a more thorough exploration of pertinent variables. Additionally, subsequent research endeavors could examine supplementary factors such as a history of gestational diabetes, maternal smoking habits, prior occurrences of macrosomic births, and the administration of vitamin D supplements.

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Conflicts of interest

The authors declare no conflict of interest.

Authors' contributions

All authors were involved in the conception and design, analysis and interpretation of the data, drafting of the manuscript and revising it critically for intellectual content, approved the final version for submission, and agreed to be accountable for all aspects of the work.

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