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Mediating effect of osteocalcin underlying the link between insulin-like growth factor-I and gestational diabetes mellitus

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Abstract

Purpose To investigate the associations of serum insulin like growth factor I (IGF-I) and Osteocalcin (OC) concentrations with gestational diabetes mellitus (GDM) risk among Chinese women.

Methods A case-control study was conducted in China, involving 125 GDM and 153 healthy pregnant women at 24–28 gestational weeks from 2019 to 2022. The study was approved by the Clinical Trial Ethics Committee of the Third Afliated Hospital of Zhengzhou University in January 04, 2020, and the study had been registered with the Chinese Clinical Trial Registry (ChiCTR2000028811). Maternal serum IGF-I and OC levels were measured in the second trimester. Logistic regression models and restricted cubic spline (RCS) were employed to calculate the association of IGF-I and OC levels with the risk of GDM, and and receiver operating characteristic (ROC) curves were generated to evaluate the predictive capacity of IGF-I and OC for GDM. Mediation analyses were used to investigate the mediation effect of OC on the association between IGF-I and the risk of GDM.

Results Both serum IGF-I and undercarboxylated Osteocalcin (ucOC) concentration were positively associated with the risk of GDM. The relationship between serum IGF-I and the risk of GDM is not linear (P-value < 0.001, P-Nonlinear < 0.001). Mediation analyses suggested that 48.61% of the associations between IGF-I and GDM might be mediated by ucOC. The areas under the ROC curves for IGF-I and integrated model were 74.5% and 76.2%.

Conclusions Serum IGF-I might provide a new dimension in the diagnosis of GDM for clinical application, and ucOC might serve as a mediator between IGF-I and GDM.

Keywords Mediating effect, Insulin-like growth factor-I, Osteocalcin, Gestational diabetes mellitus

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Introduction

Gestational Diabetes Mellitus (GDM) is a common endocrine disease that occurs during pregnancy and results in glucose intolerance [1]. The prevalence of GDM in Asia and China reached 14.0% and 14.8%, respectively [2, 3]. In addition, GDM may contribute to the development of adverse effects in both mothers and their offspring, resulting in a range of obstetric difficulties. GDM is associated with adverse pregnancy outcomes including neonatal adiposity, hyperinsulinemia, microsomia [4, 5], intrauterine growth distraction, low birth weight, congenital birth defects [6]. Moreover, GDM also has adverse effects on the health of offspring, such as long-term risk of diabetes, obesity, and cardiovascular disease [7–9]. Hence, it is crucial to identify possibly alterable risk factors to prevent the occurrence of GDM.

IGF-I plays an important role in glucose metabolism [10, 11]. Recently investigators have examined that IGF-I plays a crucial role in glucose homeostasis in pregnancy. During pregnancy, IGF-I signalling decreased, lead to disorders of lipid metabolism, which impaired glucose tolerance and enhanced insulin resistance [12]. Recent research found a positive correlation between greater serum IGF-I levels and the risk of GDM in the second trimester, as well as an increased risk [13, 14]. Nevertheless, the precise mechanism behind the connection between IGF-I and GDM remains incompletely understood.

Osteocalcin (OC), a bone-derived hormones, contains 49 amino acids, indicating bone transformation. Recent evidence has demonstrated that OC could regulate carbohydrate [15, 16]. OC without carboxylation is called undercarboxylated osteocalcin (ucOC). Recently, ucOC was demonstrated to affect the proliferation of islet β-cells [17–19], and is secreted by osteoblasts in an insulin-dependent manner [20]. Excess ucOC in pregnant women results in a massive release of insulin, which promotes β-cell exhaustion. Likely, OC was significantly elevated in the second trimester of pregnancy in GDM women, and positively associated with blood glucose level [21].

Numerous studies have demonstrated that serum OC concentrations correlate with IGF-I, which in turn affects the generation and metabolism of OC. Serum IGF-I stimulate skeletal growth and promote production of OC [22, 23]. Bianda et al. discovered that IGF-I promotes the secretion of OC produced by 1,25-dihydroxyvitamin D3 in a manner that depends on its concentration [24, 25]. Recent research has shown that the significant increase in serum OC concentration in mid-pregnancy and the positive correlation between serum OC and blood glucose levels found in patients with GDM. In the second trimester, pancreatic β-cells overproduce insulin and promote OC secretion via the GH/IGF-I axis [26], resulting in hyperglycemia. The limited research in recent years found, the link between OC and the risk of GDM has shown inconsistent findings, and the precise processes behind these relationships still remain unknown. We speculated that changes in OC metabolism induced by IGF-I might contribute to GDM. To our knowledge, the mediation effects of OC on the associations between IGF-I and GDM have never been investigated in epidemiological studies previously. To investigate the association between serum IGF-I, ucOC, and the risk of GDM and evaluate the mediation effects of OC on the relationship between IGF-I and GDM, a Chinese case-control study was conducted.

Methods

Study design and population

In this study, from June 2019 to May 2022, 278 enrolled patients with singleton pregnant women who came for prenatal follow-up in the obstetrics department of a Third Affiliated Hospital in China. The participants included were all women with singleton pregnancies between 18 and 45 years of age, having 24–28 weeks of gestation. According to the guidelines from the International Association of Diabetes and Pregnancy Study Groups (IADPSG), GDM is diagnosed by specialist doctors. During the same period, control group, which maintained normoglycemic status, selected one participant from the study population, matched by age (± 3 years).

Exclusion criteria: (1) a history of thyroid disease or a member of their immediate family; (2) with hypertension, diabetes, cardiovascular, liver, and other diseases before pregnancy; (3) a history of pregnancy comorbidities; (4) took medications that affect hormone production before pregnancy; (5) took drugs that interfere with glucose and lipid metabolism; (6) a history of alcohol consumption and smoking; (7) with multiple pregnancies or received assisted reproduction technology. All of the participants have signed the informed consent forms before enrollment. The study protocol has been approved by the Ethics Committee of Zhengzhou University.

Biochemical measurement

Fasting blood was drawn from pregnant women and centrifuged at 3000 × rpm for 10 min at 4 °C to obtain serum. Serum samples were put into the liquid nitrogen container and then stored at − 80 °C in a refrigerator until analysis. Concentrations of serum fasting insulin (Wuhan Elabcience Company, China), 25(OH)D3 (Wuhan Elabcience Company, China), and IGF-I (Wuhan CUSABIO Company, China) were determined by enzyme-linked immunosorbent assay (ELISA) following the manufacturer's protocol, which has been extensively used in the previous publication.

Outcome assessment

The plasma glucose of pregnant women was measured during a 75-g oral glucose tolerance test (OGTT) between 24 and 28 weeks gestation. The diagnosis of GDM was based on the recommended criterion by IADPSG of exceeded glucose values of 5.1, 10.0, and 8.5 mmol/L at fasting, 1 h, and 2 h. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: HOMA-IR = fasting plasma insulin (μIU/L) × fasting plasma glucose (FPG) (mmol/L)/22.5. The area under the curve of glucose (AUCGlucose) was using the following formula: AUCGlucose = fasting plasma glucose (FPG) (mmol/L) + (OGTT 1 h + OGTT 2 h)/2.

Statistical analysis

Data are presented as the mean ± standard deviation (SD) for continuous variables. Normally distributed continuous variables were compared by Student's t-test, while non-normally distributed continuous variables were analyzed by the Mann-Whitney U test. Categorical variables were analyzed by χ2 test. Logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) for the relationships of IGF-I and ucOC concentrations with the risk of GDM. Due to the serum levels of IGF-I and ucOC were non-normally distributed, the data were analyzed as categorical variables based on the quartile distributions (the lowest quartile was defined as the referent group). Three models were fitted as follows: Model 1 was an unadjusted analysis; Model 2 was adjusted for age, prepregnant body mass index (Pre-BMI), parity, abnormal gestation and birth, and history of chronic disease. Model 3 was further adjusted for place of residence, educational level, family history of chronic disease, systolic blood pressure (SBP), and diastolic blood pressure (DBP) based on Model 2. Restricted cubic spline (RCS) was used in multivariable analysis to examine the nonlinear association between IGF-I, OC, ucOC levels, and ucOC/OC ratio and the risk of GDM. To mediate the role of IGF-I on the relationship between OC, ucOC, and ucOC/OC ratio, and GDM, we conducted a mediation analysis, which Bootstrap repetition times was 5000. The principle of mediation analysis was as follows:

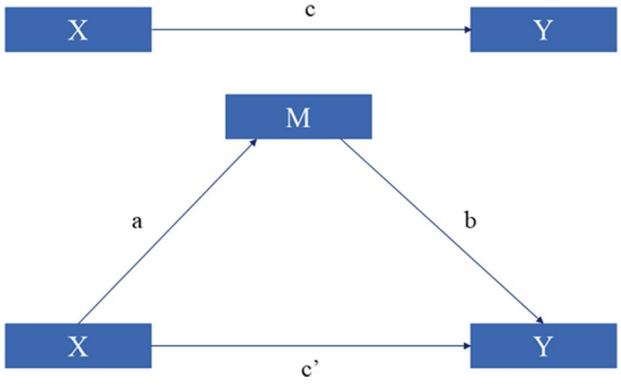

Fig. 1 Schematic diagram of a simple intermediary model

As shown in the Fig. 1, illustrates that if the independent variable X influences the dependent variable Y through the variable M, and the variable M is referred to as a mediator. The 'mediation analysis' is to evaluate the magnitude of the mediating role of the mediating variable M in the 'X-M-Y' association. The correlation among the three variables can be articulated by the subsequent equation.

The coefficient c in Eq. (1). represents the total effect of X on Y; the coefficient a of Eq. (2). is the effect of X on M; the coefficient b of Eq. (3). is the effect of M on Y after controlling for the effect of X; the product of coefficients a and b constitutes the indirect effect of X on Y; the coefficient c' indicates the direct effect of X on Y after controlling for M; and e_1, e_2, and e_3 are the regression residuals. Therefore, if coefficient c, coefficient a and coefficient b are significant, the mediation effect is significant. If the mediation effect is significant and the coefficient c' is not significant, it indicates full mediation; conversely, if the coefficient c' is significant, it denotes partial mediation. Models that incorporate a single mediating variable are referred to as simple mediation models.

$$Y = cX + e_1 \tag{1}$$

$$M = aX + e_2 \tag{2}$$

$$Y = c'X + bM + e_3 \tag{3}$$

All statistical analyses were conducted in SPSS version 25.0 and R version 4.3.3. Statistical significance was set at two-sided $P < 0.05$ unless otherwise stated.

Results

Sample characteristics

According to the OGTT, 125 individuals were diagnosed with GDM, and the remaining 153 women were normal controls. The baseline characteristics of the subjects are shown in Table 1. The mean age of the case and control groups was 31.74 ± 3.70 and 29.36 ± 3.76, respectively. The pre-pregnancy BMI differences between the two groups did not show statistical significance ($P = 0.152$). Women with GDM had a higher educational level and were more prone to having a family history of chronic illness, as well as a history of abnormal gestation and birth (all $P < 0.05$).

The values of FPG, OGTT 1hPG, AUCGlucose, HOMA-IR and OGTT 2hPG were substantially higher in the patients with GDM compared to the control group. The serum IGF-I, OC, and ucOC levels were found to be significantly different between the non-GDM and GDM

Table 1 Baseline characteristics of participants

Variables	GDM($n=125$)	non-GDM($n=153$)	*P*
Age(years)	31.74 ± 3.70	29.36 ± 3.76	< 0.001
Pre-BMI(kg/m^2)	22.37 ± 3.13	21.87 ± 2.58	0.152
Education level(%)			0.028
Below junior school	4(3.2)	7(4.6)	
Senior school and Associate College	39(31.2)	70(45.8)	
Bachelor and above	82(65.6)	76(49.7)	
Place of residence(%)			0.236
Town	71(56.8)	76(49.7)	
Rural areas	54(43.2)	77(50.3)	
Parity(%)			0.015
0	68(54.4)	105(68.6)	
≥ 1	57(45.6)	48(31.4)	
Abnormal Gestation And Birth(%)			0.004
Yes	14(11.2)	4(2.6)	
No	111(88.8)	149(97.4)	
Family history of chronic disease(%)			0.121
Yes	19(15.2)	14(9.2)	
No	106(84.8)	139(90.8)	
History of chronic disease(%)			0.041
Yes	10(8.0)	4(2.6)	
No	115(92.0)	149(97.4)	
SBP(mmHg)	111.02 ± 10.59	111.40 ± 10.39	0.767
DBP(mmHg)	65.62 ± 7.68	65.71 ± 8.73	0.930
Waist-hip ratio	0.89 ± 0.06	0.88 ± 0.05	0.159

Continuous variables are presented as the mean ± SD; categorical variables are presented as the n (%). GDM, gestational diabetes mellitus. BMI, body mass index. SBP, systolic blood pressure. DBP, diastolic blood pressure

Table 2 Comparisons of clinical characters of participants in the second trimester

Variables	GDM($n=125$)	non-GDM($n=153$)	*P*
FPG(mmol/L)	4.98 ± 0.48	4.49 ± 0.31	**< 0.001**
OGTT 1hPG(mmol/L)	9.18 ± 1.77	7.02 ± 1.13	**< 0.001**
OGTT 2hPG(mmol/L)	8.47 ± 1.34	6.56 ± 0.94	**< 0.001**
$AUC_{Glucose}$[mmol/(L • h)]	15.91 ± 2.20	12.55 ± 1.40	**< 0.001**
FINS(μIU/mL)	22.09 ± 14.32	21.58 ± 11.40	0.738
HOMA-IR	4.92 ± 3.17	4.29 ± 2.13	**0.049**
GH(ng/mL)	0.60 + 0.73	0.92 + 1.33	**0.015**
OC(ng/mL)	0.89 ± 0.83	0.71 ± 0.67	**0.045**
ucOC(ng/mL)	0.53 ± 0.50	0.39 ± 0.38	**0.011**
ucOC/OC	0.64 ± 0.24	0.62 ± 0.27	0.463

Continuous variables are presented as the mean ± SD.FPG, fasting plasma glucose. OGTT, oral glucose tolerance test. $AUC_{Glucose}$, the he area under curve of glucose. FINS, fasting insulin. HOMA-IR, Homeostatic model assessment - insulin resistance. IGF-I, insulin-like growth factor 1.OC, Osteocalcin. ucOC, undercarboxylated osteocalcin

groups. (all $P < 0.05$, Table 2, Figure S1). In contrast, when comparing the two groups based on the ucOC/OC ratio, there was no statistically significant difference observed ($P = 0.463$, Table 2).

Associations between OC, UcOC, and the risk of GDM

In the binomial logistic regression analysis, both serum IGF-I and ucOC levels were found to significantly elevate the risk of GDM in Model 3 (Fig. 2). There was no observed association between other blood biomarkers, such as OC and the ratio of ucOC/OC, and the risk of GDM. Compared to the first quartile of IGF-I, the ORs (95% CI) of GDM risk were 5.174 (2.287, 11.705) for the third quartile and 12.784 (5.292, 30.879) for the fourth quartile (all $P < 0.05$). Compared to the first quartile of ucOC, the ORs (95% CI) of GDM risk were 3.114 (1.428, 6.791) for the third quartile and 3.346 (1.519, 7.370) for the fourth quartile (all $P < 0.05$).

In Fig. 3, we used restricted cubic splines to flexibly model and visualize the relation of serum IGF-I, OC, ucOC and the ratio of ucOC/OC with the risk of GDM in participants. The results of RCS analysis showed a nonlinear relationship between IGF-I level and the risk of GDM even after adjusting for all confounders, which was statistically significant (P-Nonlinear < 0.001, *P*-value < 0.001, Fig. 3). The risk of GDM was relatively flat until around 3.83 ng/mL of serum IGF-I concentration and then started to increase rapidly afterwards until reached its peak. Consistently, from Table S1 we can see that the odds ratio higher than 1.0 when IGF-I is more than 3.83 ng/mL. Although RCS analysis revealed serum ucOC level and odds ratio of GDM were related (*P*-value = 0.015), the relationship was not nonlinear (P-Nonlinear = 0.10). No significant associations were

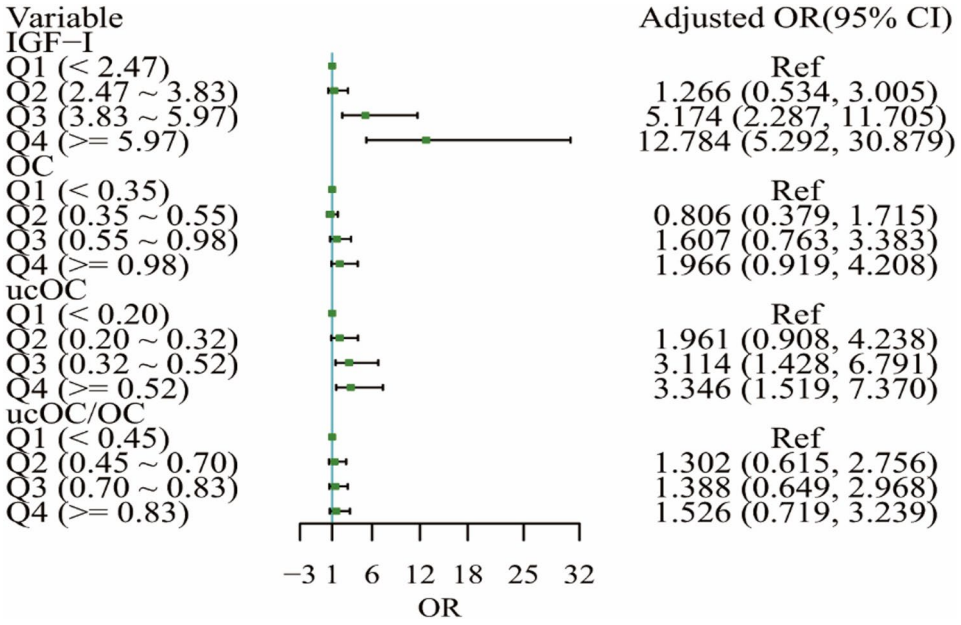

Fig. 2 Adjusted logistic regression model of serum markers and risk factors of GDM in the second trimester

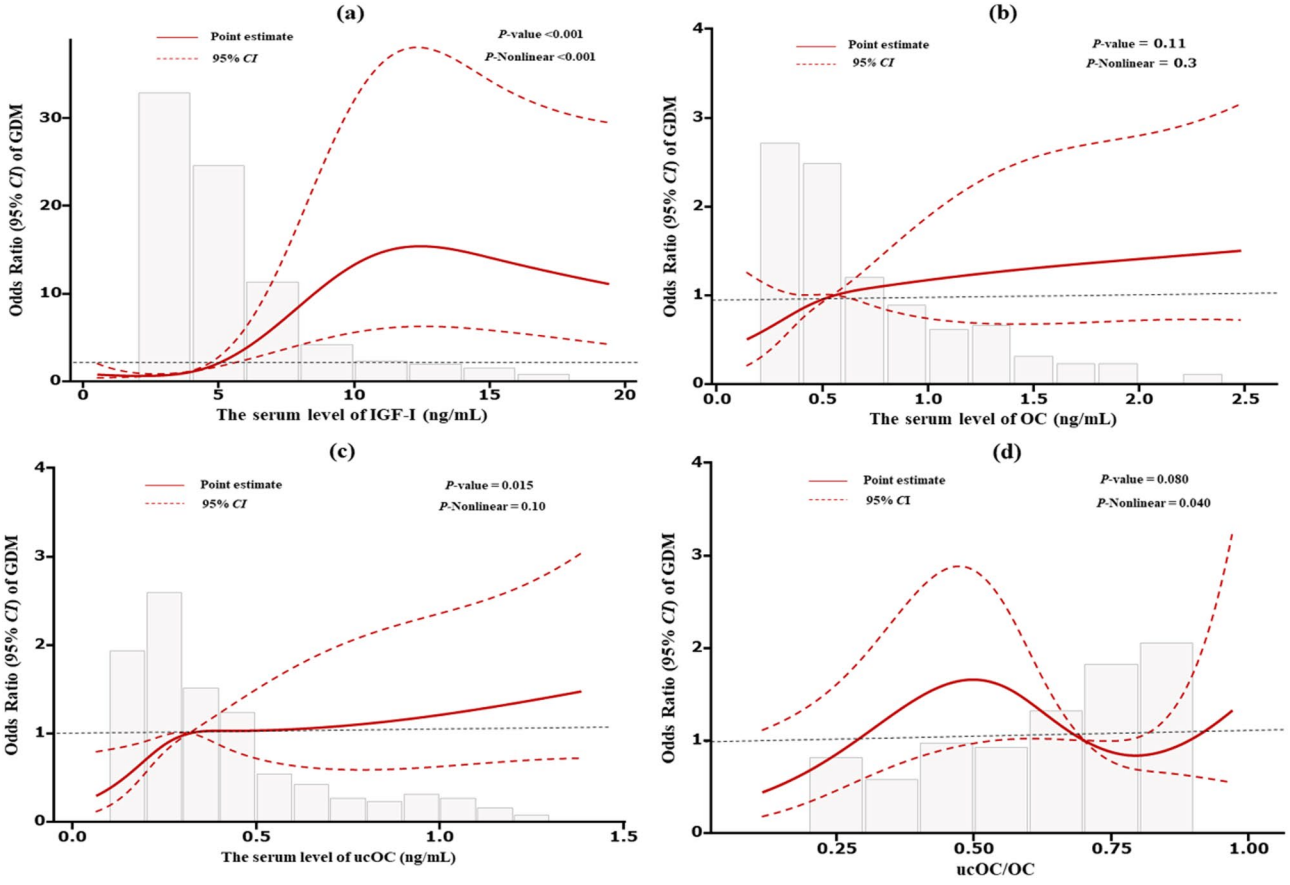

Fig. 3 RCS analysis on the association between the serum level of IGF-I, OC, ucOC, ucOC/OC and the risk of GDM Relationship between serum level of IGF-I (**a**), OC (**b**), ucOC (**c**), the ratio of ucOC/OC (**d**) and odds ratio of GDM. Odds ratios are indicated by solid lines and 95% CIs by shaded areas

found between OC, ucOC/OC ratio, and the risk of GDM ($P > 0.05$).

Subgroup analysis

As shown in Table S2 and Fig. 4, to further explore the relationship between serum IGF-I and ucOC levels and the risk of GDM, we conducted subgroup analysis by BMI. In the subgroup of BMI < 24 kg/m2, the higher IGF-1 and ucOC level led to a statistically significant higher risk of GDM than the lower level in model 3 (all $P < 0.05$). The results indicated that there was no statistically significant correlation between the risk of GDM and the serum levels of OC and the ratio of ucOC/OC ($P > 0.05$). In the subgroup of BMI ≥ 24 kg/m2, the higher IGF-1 and OC level led to a statistically significant higher risk of GDM than the lower level in crude model (all $P < 0.05$).

Predictive models for GDM

The receiver operating characteristic (ROC) curves were plotted, and the area under the ROC curves (AUCs) was calculated to evaluate the clinical usefulness and predictive ability of potential GDM biomarkers. The findings indicated that the most effective ability to differentiate GDM patients, with a reasonably accurate test, was observed for IGF-I (AUC = 0.745, $P < 0.001$, Fig. 5). However, ucOC/OC was not statistically significant in predicting the risk of developing GDM ($P > 0.05$, Table S3). The ROC curve and the corresponding AUC were significantly improved when combining the selected biomarkers into different models. The combination of IGF-I, ucOC, and OC was found to have a good predictive ability (AUC = 0.762, $P < 0.001$). The cutoff value of IGF-I, ucOC, OC and Integrated Model in the second trimester was 4.500, 0.340, 0.483, and 0.403, respectively (Table S3).

Mediation of serum IGF-I between UcOC and the risk of GDM

The mediator of ucOC contributed about 48.61% to the association between IGF-I and GDM risk (Figure S2). The direct effect of ucOC between IGF-I and GDM was 0.0286 (95% CI 0.0191–0.0406), and the indirect effect was 0.0029 (95% CI 0.0004–0.0061), accounting for 9.21%. The mediating effect of OC and ucOC/OC between IGIF-I and GDM was not statistically significant ($P > 0.05$, Table 3).

Discussion

To investigate the association between IGF-I, OC, and the risk of GDM, we conducted an exploratory metabolomic analysis on 278 Chinese pregnant women in the second trimester. In our study, we observed a significant association between serum IGF-I level and an increased risk of GDM. The results showed that higher IGF-I (< 3.83ng/mL) and ucOC (> 0.32ng/mL) were positively correlated with risk of GDM. The RCS curve indicated a non-linear relation between serum IGF-I and the risk of GDM. Moreover, serum IGF-I levels in mid-pregnancy can be used to predict and diagnose GDM. Additionally, the combined detection of IGF-I, OC, ucOC, and ucOC/OC in midgestation is more beneficial for predicting and diagnosing GDM. More importantly, this study represented the mediating role played by ucOC in the relationship between IGF-I and the risk of psychiatric disorders. Utilizing mediation analysis, we identified ucOC have strong mediating effect.

IGF-I is a polypeptide co-secreted by osteoblasts and the liver that plays an important role in blood glucose metabolism. Studies have shown that IGF-I concentrations increased in GDM women, which might partly reflect metabolic disturbances, especially insulin resistance and hyperinsulinemia [27, 28]. Our research indicated that IGF-I level was positively associated with blood glucose in the second trimester, which may potentially

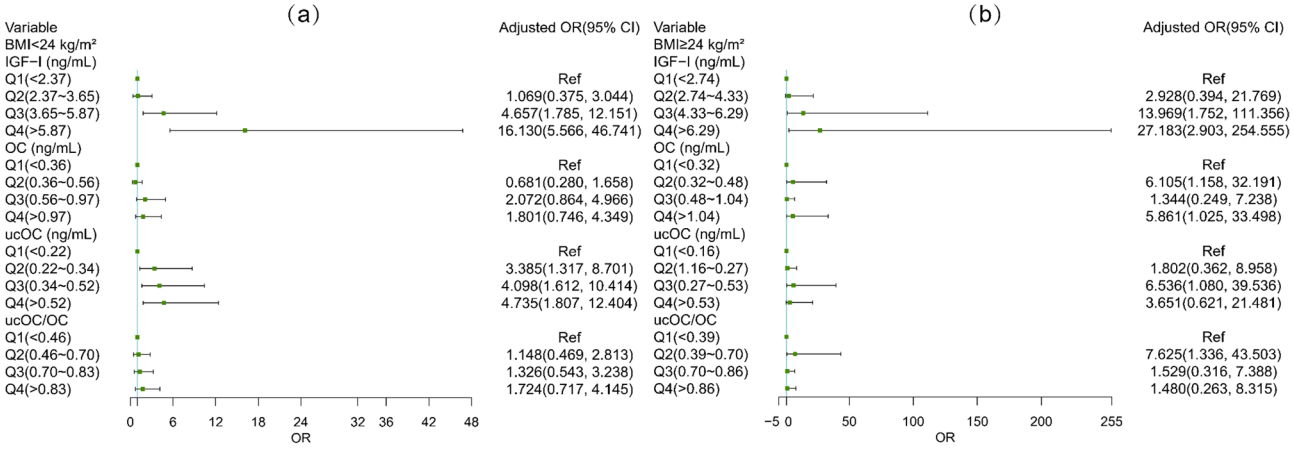

Fig. 4 Subgroup analysis on the association between the serum level of IGF-I, OC, ucOC, ucOC/OC and the risk of GDM, according to serum BMI

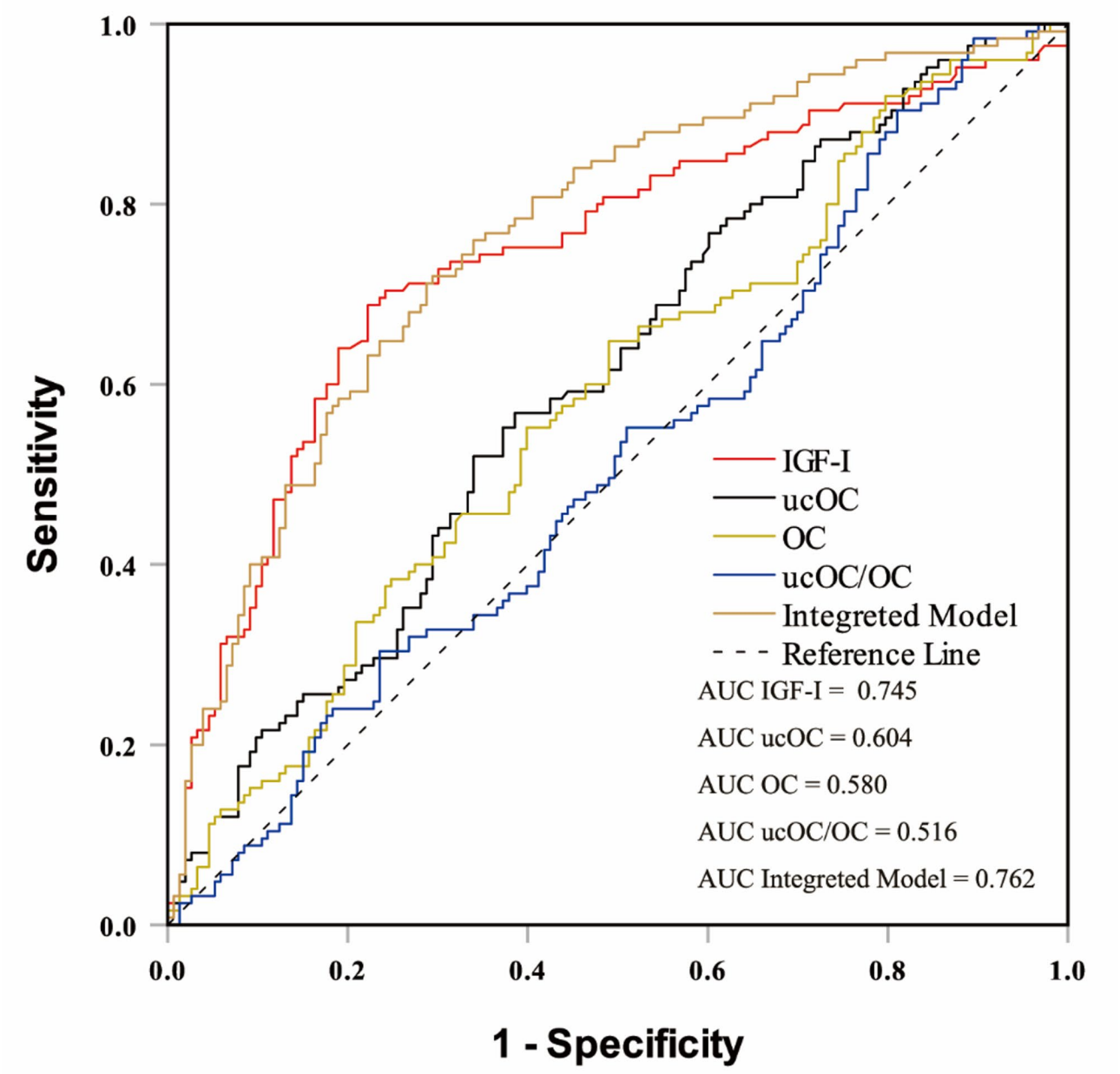

Fig. 5 ROC curves for different predictive factors and integrated model. Note: AUC: area under curve; PPV: positive predictive value; NPV: negative predictive value

Table 3 Mediation effects of UcOC, OC and UcOC on the association between GMD and glucose

Factor	IGF-I→ucOC→GDM		IGF-I→OC→GDM		IGF-I→ucOC/OC→GDM	
	β(95%CI)	*P*	β(95%CI)	*P*	β(95%CI)	*P*
a	0.0168(0.0071, 0.0265)	0.001	0.0211(0.0044, 0.0377)	0.013	0.0016(-0.0041, 0.0073)	0.584
b	0.1712(0.0574, 0.2297)	0.023	0.0479(-0.0271, 0.1229)	0.210	0.0649(-0.1538, 0.2835)	0.560
c	0.0315(0.0210, 0.0421)	< 0.001	0.0315(0.0210, 0.0421)	< 0.001	0.0315(0.0210, 0.0421)	< 0.001
c′	0.0286(0.0191, 0.0406)	< 0.001	0.0305(0.0199, 0.0412)	< 0.001	0.0314(0.0209, 0.0420)	< 0.001

raise the risk of GDM. A previous case-control study in Poland found that patients with GDM had higher serum IGF-I levels compared to normal pregnant women [28]. During pregnancy, the placenta secretes more growth hormone, which stimulates insulin secretion [29, 30], leading to an IGF-I level increase. It has been suggested that elevated IGF-I levels in GDM patients may be a response to insulin resistance and hyperinsulinemia, serving as a compensatory mechanism. To ensure normal glycemia in patients with GDM, higher than physiological IGF-I concentrations are required to trigger many cross-reactions between IGF-I, insulin, and its receptors [31], making IGF-I a potential biomarker for better screening GDM. Furthermore, the study revealed a nonlinear association characterized by an inverted U-shaped curve (where maximum response is observed at intermediate doses) between concentrations of IGF-I and the risk of GDM. Similar to endocrine disruptors, there may be a non-monotonic dose–response curves relationship in IGF-I levels in GDM women, typically exhibiting an inverted U-shape [32]. In second trimester, compensatory secretion of IGF-I indirectly leads to pancreatic β-cells. However, higher IGF-I concentrations could ameliorate pancreatic β cell dysfunction by activating IRS1/PI3K/Akt/FOXO1 pathway [33]. Consequently, different IGF-I concentration influence pancreatic β-cells and insulin in distinct manners.

ROC curve showed that serum IGF-I level was a discriminator between patients with and without GDM. Notably, patients with a serum IGF-I level of >4.50 ng/mL were found to be more likely to have GDM. At a cut-off value of 4.50 ng/mL, the sensitivity of the test was 68.8% and the specificity was 77.8%. This indicates that IGF-I level has a high ability to accurately detect those without GDM. IGF-I level seems to be used as a screening test in the diagnosis of GDM.

Previous studies have demonstrated that OC is not only involved in regulating bone metabolism but also plays an important role in glucose metabolism. OC is distinguished into three forms: carboxylated osteocalcin (cOC), uncarboxylated carboxylated osteocalcin (ucOC), and total osteocalcin (tOC) [34, 35]. In A meta-analysis including 31 studies, we found that higher serum levels of OC, especially ucOC, were associated with an increased risk of GDM [36]. We speculated OC might have the potential to help identify at-risk women in the second trimester. Another meta-analysis showed that no significant differences were found in tOC level between the GDM patients and controls, ucOC in GDM gravida was higher than the other participants [37], which indicates ucOC is a potential biomarker to predict the onset of GDM. However, the relationship between OC levels and glucose metabolism is not fully established, and a case-control study found that elevated OC levels in third pregnancy were associated with a reduced risk of progression to postnatal glucose metabolism abnormalities [38]. Another study showed that there was no statistically significant difference between the GDM and non-GDM groups in terms of OC levels. Nonetheless, this study also showed that serum OC levels were higher in the GDM group than in the GDM group, and it was also possible to find that the OC levels of GDM pregnant women with two impaired glucose tolerance levels were higher than those with one impaired level [39]. The reason may be the change in the metabolic state of OC from mid to late pregnancy. At present, the underlying mechanism between OC and GDM is not clear. One possible explanation is that placenta-induced insulin resistance reaches its peak at 24–28 weeks of gestation, which might lead to increased insulin secretion from pancreatic β cells, through IGF-I, as a compensatory mechanism to increase bone metabolism and anabolism, thereby increasing OC levels.

Although the mechanisms underlying the link of IGF-I to GDM were not well established, we found that specific ucOC might be the intermediates in the association between IGF-I and GDM through mediation analysis. Several studies have demonstrated that IGF-I interacts with OC to regulate serum OC levels. IGF-I promotes OC synthesis and increases ucOC content by promoting forkhead box O1 (Foxo1) phosphorylation and nuclear exclusion and activating osteocalcin gene 2 promoter activity. Cellular osteocalcin mRNA concentration increased in a dose-dependent and time-dependent manner after the treatment of osteosarcoma cells with IGF-I [40]. During pregnancy, the need for fetal growth and metabolic disorders in the body lead to an increase in the secretion of IGF-I, which elevates the level of OC via negative feedback. The synergistic effect of IGF-I and ucOC promotes increased adipogenesis and impairs insulin β-cell function, culminating the development of GDM. And a population experiment also proved that the insulin response is weakened in the co-presence of OC and IGF-I, which also confirms our hypothesis [41]. In summary, IGF-I not only has its own effects but also impacts the risk of GDM and indirectly affects islet β-cell function by modulating serum OC levels, potentially leading to the onset of GDM. There was no change in the ratio of ucOC/OC, which signals a uniform decrease in insulin. This effect may result from compensatory mechanisms in response to experimental hyperinsulinemia, wherein pregnant women downregulate their endogenous production of ucOC to avert additional rises in plasma insulin via OC-stimulated β-cell insulin secretion. In response, individuals downregulate their endogenous production of ucOC to prevent further increases in plasma insulin through OC-stimulated β-cell secretion of insulin [42].

According to subgroup analysis the higher serum IGF-I, OC, ucOC levels and ucOC/OC could elevate the risk of GDM when BMI>24 kg/m^2. Postpartum overweight or obesity may lead to insulin resistance and reduce insulin sensitivity, which promotes the development of GDM. Recent studies shows that the adiponectin level decreases with the increase of central adiposity, which causes obesity [43, 44], and IGF-I and ucOC might regulate adiponectin secretion. Adiponectin is a hormone secreted by adipocytes and controls the metabolism of lipids by decreasing gluconeogenesis and stimulating glycolysis and fatty acid oxidation [45]. Congenital deletion of adiponectin impairs glucose tolerance and reduces insulin sensitivity in mice [46, 47]. Adiponectin was a potential T2DM predictor for Swedish healthy women, and lower serum adiponectin increases the risk of abnormal blood glucose metabolism in women [48]. Kanazawa et al. discovered a significant inverse association between IGF-I and adiponectin levels in Japanese males with T2DM. This correlation was not influenced by factors such as age, duration of diabetes, BMI, and renal function, indicating that IGF-I may directly inhibit serum adiponectin levels [49]. However, our investigation revealed that elevated serum IGF-I and ucOC levels also raised the risk of GDM for women whose BMI < 24 kg/m2, which may be due to the smaller sample size, and one possible reason is that the majority of participants were normal weight.

The current investigation possesses numerous advantages. Firstly, this study is the first to evaluate the effect of ucOC on the associations between IGF-I and the risk of GDM using mediation analyses, which provides important clues for further mechanism research. Secondly, RCS analyses were used to evaluate the non-linear relationship between IGF-I, ucOC, and the odds ratio of GDM. Thirdly, a thorough analysis was conducted to account for and correct some potential confounding factors. Inevitably, several limitations should also be noted. Above all, our study collected serum time points that were limited to a certain gestational age in the second (24–28 gestational weeks), which may not reflect the serum IGF-I and OC levels throughout pregnancy or the correlation between IGF-I and OC and perinatal outcomes. We need to enroll pregnant women in all three trimesters in the future study. In addition, small sample size participants in this study were only recruited from Henan Province, China, and more and larger sample pregnancy women should be further expanded to support our results. Residual confounding cannot be excluded due to the absence of data on factors such as weight gain during pregnancy, dietary patterns, exercise habits. Last, mediation analyses for the association between IGF-I and GDM were conducted in a subset of the study population with a limited sample size; hence the findings should be validated in large prospective studies.

To summarise, our investigation confirmed a positive association between the serum level of IGF-I and ucOC and the risk of GDM. The association between IGF-I and GDM might be partially mediated by ucOC. The current findings may offer forceful epidemiological evidence for the pathogenesis and mechanism of GDM. However, further research with larger a sample size and more mechanism studies are still expected to verify the correlation between IGF-I, ucOC, and GDM in the future. What's more, serum IGF-I concentration has potential to aid in diagnosing GDM.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2: Figure S1. Difference of serum IGF-I,ucOC and OC level and ucOC/uc between two groups

Supplementary Material 3: Figuer S2. Mediation model of the relationship between IGF-I and GDM for ucOC

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Author contributions

Lingling Cui and Yuting Gao carried out the analysis of data and interpretation of data and drafted the manuscript. Luying Qin participated in the study design and preparation of the manuscript. Hua Ye revised critically for the manuscript and reviewed the manuscript. Zhiqian Li, Ruijie Sun, Zhengya Zhang, Yibo Wang and Linpu Ji participated in the acquisition of data and coordination of the research.

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Data availability

The derived data generated in this research will be shared with corresponding authors upon reasonable request.

Declarations

Ethics approval and consent to participate

Our research adheres to the Declaration of Helsinki. The study was approved by the Clinical Trial Ethics Committee of the Third Afliated Hospital of Zhengzhou University in January 04, 2020, and the study had been registered with the Chinese Clinical Trial Registry (ChiCTR2000028811). Informed consent was provided by all participants before they were recruited for the study, and data were analyzed anonymously.

Consent to participate

The participant has consented to the submission of the case report to the journal.

Competing interests
The authors declare no competing interests.

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