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Diagnostic value of serum LRG1 and SFRP4 levels for early renal injury in patients with gestational diabetes mellitus

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Abstract: **Objective** To investigate the diagnostic value of serum leucine-rich-alpha-2-glycoprotein-1 (LRG1) and secreted frizzled-related protein 4 (SFRP4) for early renal injury in patients with gestational diabetes mellitus (GDM), and to provide a reference for the clinical prediction of GDM-related renal injury. **Methods** A total of 118 pregnant women with GDM and 112 normal pregnant women undergoing prenatal examination (control group) who visited the Seventh Medical Center of Chinese PLA General Hospital from January 2022 to December 2023 were selected as the study subjects. Clinical data were collected from all subjects. According to urinary albumin-to-creatinine ratio (UACR), the 118 pregnant women with GDM were divided into GDM without renal injury group (UACR<30 mg/g, n=72) and GDM with renal injury group (UACR≥30 mg/g, n=46). Pearson correlation analysis was used to explore the correlations of serum LRG1 and SFRP4 levels with serum creatinine, interleukin -6 (IL -6), blood urea nitrogen, glycosylated hemoglobin (HbA_{1C}), and estimated glomerular filtration rate (eGFR) in pregnant women with GDM. Multivariate logistic regression analysis was performed to analyze the influencing factors of early renal injury in patients with GDM. Receiver operating characteristic (ROC)curve was used to analyze the diagnostic value of serum LRG1 and SFRP4 levels for early renal injury in patients with GDM. **Results** The levels of IL-6, blood urea nitrogen, serum creatinine, HbA_{1C}, LRG1, and SFRP4 in the GDM with renal injury group were significantly higher than those in the GDM without renal injury group, while eGFR was significantly lower (P<0.05). Serum LRG1 and SFRP4 in GDM pregnant women with renal injury were significantly positively correlated with serum creatinine, IL-6, blood urea nitrogen, and HbA_{1C}, and significantly negatively correlated with eGFR (P<0.05). High IL-6 (OR=1.698, 95%CI: 1.261-2.287), HbA1C (OR=2.596, 95%CI: 1.284-5.247), LRG1 (OR=1.563, 95%CI: 1.214-2.013), and SFRP4 (OR=1.893, 95%CI: 1.185-3.024) were independent risk factors for renal injury in GDM, while high eGFR (OR=0.642, 95%CI: 0.515-0.800) was an independent protective factor (P<0.05). The area under the ROC curve of combined detection of LRG1 and SFRP4 for renal injury in GDM was 0.925, which was better than that of single detection ($Z_{combination-LRG1}$=2.221, P= 0.026; $Z_{combination-SFRP4}$=3.153, P=0.002). **Conclusion** Serum LRG1 and SFRP4 levels have certain diagnostic value for detecting early renal injury in pregnant women with GDM.

Keywords: Leucine-rich-alpha-2-glycoprotein-1; Secreted frizzled-related protein 4; Gestational diabetes mellitus; Renal injury; Glycosylated hemoglobin; Estimated glomerular filtration rate

Gestational diabetes mellitus (GDM) is a disorder of glucose metabolism occurring during pregnancy, which may lead to premature rupture of membranes and postpartum hemorrhage, seriously threatening maternal and fetal health [1-2]. As the disease progresses, GDM patients may develop renal injury [3-4]. Early renal injury often presents insidiously, with symptoms such as weight gain and peripheral edema. Due to individual variability and age-related factors, the early diagnosis rate of renal injury remains low. Once overt proteinuria or other obvious symptoms appear, optimal treatment timing is often missed, leading to progressive deterioration of renal function and, ultimately, renal failure. Therefore, identifying reliable and sensitive biomarkers associated with GDM-related renal injury is of great significance for improving pregnancy outcomes. Leucine-rich alpha-2-glycoprotein-1 (LRG1) is a proangiogenic factor predominantly expressed in vascular endothelial cells. Its expression is modulated by blood glucose levels. Previous studies have confirmed that LRG1 is associated with postpartum glucose dysregulation in pregnant women and is abundantly expressed in glomerular endothelial cells, making it a commonly used biomarker for assessing diabetic nephropathy [5-6]. Thus, LRG1 is hypothesized to serve as a potential biomarker for early diabetic renal injury. Secreted frizzled-related protein 4 (SFRP4) is an adipokine involved in glucose metabolism [7]. Studies have shown that SFRP4 can induce glomerular lesions and renal dysfunction, thereby promoting renal fibrosis and other pathologies [7-9]. Based on this, SFRP4 is speculated to have potential utility in evaluating diabetic renal injury. Currently, research on serum LRG1 and SFRP4 levels in early renal injury among GDM patients remains limited. Therefore, this study focuses on evaluating the levels of serum LRG1 and SFRP4 in GDM-associated early renal injury and assessing their diagnostic value, aiming to provide clinical reference for predicting renal injury in GDM patients.

1. Subjects and Methods

1.1 Study Population

From January 2022 to December 2023, 118 pregnant women with GDM who visited the Seventh Medical Center of Chinese PLA General Hospital were prospectively enrolled.

Inclusion criteria: ① Met the diagnostic criteria for GDM [10]; ② No prior diagnosis of diabetes before pregnancy; ③ Singleton pregnancy.

Exclusion criteria: ① Concomitant cardiovascular or cerebrovascular disease; ② Other pregnancy complications; ③ Malignant tumors; ④ Insulin treatment prior to diagnosis.

According to the urinary albumin-to-creatinine ratio (UACR) [11], the 118 GDM patients were divided into the no-renal-injury group (UACR < 30 mg/g, n = 72) and the renal-injury group (UACR ≥ 30 mg/g, n = 46). All patients in the renal-injury group had early renal injury—without typical clinical symptoms of renal disease, negative urinary protein on routine urinalysis, and urinary albumin > 20 mg/L. An additional 112 healthy pregnant women undergoing routine prenatal examination at the same center served as the control group. The study was approved by the Ethics Committee of the Seventh Medical Center, Chinese PLA General Hospital (approval no. [2021] Ethics Review No. 058), and all participants provided written informed consent.

1.2 Methods

1.2.1 Clinical Data Collection

Age, gestational week, gravidity, parity, and body mass index (BMI, kg/m²) were collected.

1.2.2 Laboratory Measurements

Fasting venous blood (5 mL) was collected on the day of admission and during late pregnancy (28–34 weeks) in the morning after an overnight fast, centrifuged, and stored at –20°C. Urine samples were collected simultaneously and stored at 4°C. Serum LRG1, SFRP4, and interleukin-6 (IL-6) levels were measured by enzyme-linked immunosorbent assay (ELISA). Commercial kits were purchased from: LRG1: Shanghai Keaibo Biological (CB10586-Hu); SFRP4: Huamei Biological (CSB-E13721h); IL-6: Shanghai Meilian Biological (ml038116). Serum urea nitrogen, creatinine, and total cholesterol were measured using an automatic biochemical analyzer (AS-800, Nanjing Yilanbei Biological). Urinary albumin and creatinine were measured, and eGFR was calculated using the CKD-EPI equation. HbA_1c was determined by a glycated hemoglobin analyzer (Vantage2000, Shaanxi Siboride Electronic Technology). Serum insulin was measured by an automatic immunoassay analyzer, and the homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as: HOMA-IR = (fasting insulin [μIU/mL] × fasting glucose [mmol/L]) / 22.5.

1.3 Statistical Analysis

SPSS 22.0 was used for statistical analysis. Normally distributed continuous variables are expressed as $\bar{x}\pm s$; intergroup comparisons used one-way ANOVA, with SNK-q test for pairwise comparisons. Categorical variables are expressed as numbers (%), and χ^2 tests were used for comparison. Pearson correlation analysis was used to assess associations between serum LRG1/SFRP4 and creatinine, IL-6, BUN, HbA_1c, and eGFR. Multivariate logistic regression analysis was performed to identify the influencing factors of early renal injury in patients with GDM. Receiver operating characteristic (ROC) curve analysis was adopted to evaluate the diagnostic value of serum LRG1 and SFRP4 levels for early renal injury in GDM patients, and the comparison of area under the curve (AUC) was conducted using the DeLong test. A P value less than 0.05 was considered statistically significant.

2. Results

2.1 Comparison of Baseline Characteristics and Laboratory Parameters Among Groups

No significant differences in age, gestational week, gravidity, parity, or BMI were observed among the three groups (P>0.05). Compared with the control group, both GDM groups showed significantly higher fasting glucose, 1-h and 2-h post-glucose load glucose, fasting insulin, IL-6, total cholesterol, HOMA-IR, HbA_1c, LRG1, and SFRP4 (P<0.05). Compared with the no-renal-injury group, the renal-injury group had significantly higher IL-6, BUN, creatinine, total cholesterol, HbA_1c, LRG1, and SFRP4, and significantly lower eGFR (P<0.05). See **Table 1**.

2.2 Correlation Analysis

Pearson correlation analysis showed that in GDM patients with renal injury, serum LRG1 and SFRP4 were significantly positively correlated with IL-6, BUN, creatinine, and HbA_1c, and significantly negatively correlated with eGFR (P<0.05). See **Table 2**.

2.3 Multivariate Logistic Regression Analysis

Using renal injury (yes = 1, no = 0) as the dependent variable, and variables with P<0.05 in univariate analysis (creatinine, IL-6, BUN, HbA_1c, LRG1, SFRP4, eGFR) as covariates, multivariate logistic regression (enter method) was performed. BUN and creatinine were excluded due to collinearity. The results indicated that IL-6, HbA_1c, eGFR, LRG1, and SFRP4 were independent predictors of renal injury (P < 0.05). See **Table 3**.

2.4 Diagnostic Value

ROC curve analysis showed that the combined detection of LRG1 and SFRP4 had superior diagnostic performance compared to either marker alone ($Z_{combination–LRG1}$ = 2.221, P = 0.026; $Z_{combination–SFRP4}$ = 3.153, P = 0.002). See **Table 4** and **Figure 1**.

Table 1 Comparison of General Clinical Data and Laboratory Indicators Among Groups ($\bar{x}\pm s$)

Variable	Control (n = 112)	No-renal-injury GDM (n = 72)	Renal-injury GDM (n = 46)	F value	P value
Age (years)	32.56 ± 5.26	32.89 ± 4.89	32.13 ± 5.10	0.311	0.733
Gestational week (weeks)	31.56 ± 5.62	31.25 ± 5.48	31.78 ± 5.84	0.134	0.874
Gravidity	1.46 ± 0.35	1.51 ± 0.41	1.57 ± 0.42	1.392	0.251
Parity	1.23 ± 0.26	1.31 ± 0.21	1.28 ± 0.27	2.393	0.094
BMI (kg/m²)	25.89 ± 4.59	25.46 ± 4.20	25.78 ± 4.89	0.200	0.819
Fasting glucose (mmol/L)	4.59 ± 0.62	8.28 ± 2.86[a]	8.49 ± 3.08[a]	88.475	<0.001
1-h glucose (mmol/L)	8.24 ± 0.85	11.43 ± 0.96[a]	11.57 ± 0.87[a]	382.429	<0.001
2-h glucose (mmol/L)	7.16 ± 0.77	9.25 ± 0.87[a]	9.12 ± 0.76[a]	186.727	<0.001
Fasting insulin (μIU/mL)	4.12 ± 0.58	18.98 ± 3.95[a]	19.82 ± 4.12[a]	789.203	<0.001
IL-6 (pg/mL)	13.59 ± 2.58	45.86 ± 5.26[a]	86.24 ± 9.87[ab]	2,854.200	<0.001
BUN (mmol/L)	6.58 ± 0.89	8.23 ± 2.58[a]	36.89 ± 4.26[ab]	2,678.694	<0.001
Creatinine (μmol/L)	66.52 ± 13.58	72.59 ± 18.28[a]	180.26 ± 29.23[ab]	629.023	<0.001
eGFR (mL·min⁻¹·1.73 m⁻²)	123.31 ± 15.89	122.78 ± 18.58	72.75 ± 8.82[ab]	189.001	<0.001
Total cholesterol (mmol/L)	3.56 ± 0.45	5.89 ± 0.74[a]	6.15 ± 1.08[ab]	340.541	<0.001
HOMA-IR	0.84 ± 0.17	2.36 ± 0.68[a]	2.48 ± 0.85[a]	234.215	<0.001
HbA_1c (%)	4.56 ± 1.28	6.58 ± 1.78[a]	8.49 ± 1.85[ab]	108.600	<0.001
LRG1 (ng/mL)	149.58 ± 33.56	258.79 ± 72.89[a]	332.89 ± 85.56[ab]	170.583	<0.001
SFRP4 (ng/mL)	139.56 ± 25.89	232.98 ± 65.54[a]	304.59 ± 88.59[ab]	153.372	<0.001

Note: Compared with the control group, [a] $P < 0.05$; compared with no-renal-injury GDM group, [b] $P < 0.05$.

Table 2 Correlation of Serum LRG1 and SFRP4 with IL-6, BUN, Creatinine, HbA_1c, and eGFR

Indicator	LRG1		SFRP4	
	r value	P value	r value	P value
IL-6	0.482	< 0.05	0.392	< 0.05
BUN	0.563	< 0.05	0.611	< 0.05
Creatinine	0.519	< 0.05	0.597	< 0.05
HbA_1c	0.327	< 0.05	0.386	< 0.05
eGFR	–0.439	< 0.05	–0.412	< 0.05

Table 3 Multivariate Logistic Regression Analysis of Factors Influencing Renal Injury in GDM

Variable	β	SE	$Wald\ \chi^2$	P value	OR (95%CI)
IL-6	0.529	0.159	12.133	<0.001	1.698 (1.261–2.287)
HbA_1c	0.954	0.359	7.061	0.008	2.596 (1.284–5.247)
eGFR	–0.443	0.112	15.657	<0.001	0.642 (0.515–0.800)
LRG1	0.447	0.129	11.986	<0.001	1.563 (1.214–2.013)
SFRP4	0.638	0.239	7.130	0.008	1.893 (1.185–3.024)

Table 4 Predictive Value of Serum LRG1 and SFRP4 for Early Renal Injury

Indicator	AUC	95%CI	Sensitivity (%)	Specificity (%)	Cut-off (ng/mL)	Youden Index
LRG1	0.862	0.786–0.981	56.52	97.22	329.586	0.537
SFRP4	0.817	0.736–0.882	54.35	98.61	295.482	0.530
Combined	0.925	0.862–0.965	82.61	86.11	–	0.687

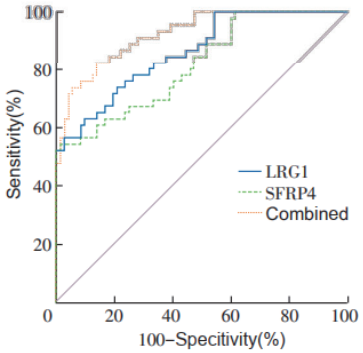

Figure 1. ROC curves of serum LRG1, SFRP4, and their combination for diagnosing renal injury in GDM patients

3. Discussion

The core pathophysiological alterations in GDM include glucose metabolism dysregulation and increased insulin resistance [12-13]. Although GDM is a transient metabolic disorder of pregnancy, renal injury is a common complication requiring close clinical monitoring [3-4]. Early renal injury is insidious and often lacks typical symptoms, leading to missed or delayed diagnosis. As the disease progresses, renal enlargement and reduced eGFR may occur, culminating in renal failure [14-16]. Thus, early identification, identification of sensitive and specific biomarkers, and development of individualized interventions are clinically critical for improving pregnancy outcomes.

LRG1 is primarily secreted by hepatocytes and neutrophils and participates in angiogenesis and inflammatory mediator release via the Smad pathway [17]. Its expression correlates with blood glucose levels and is associated not only with diabetic retinopathy and atherosclerotic cardiovascular disease, but also with progression to end-stage renal disease [6]. As a key mediator of the TGF-β1 signaling pathway, LRG1 is highly expressed in glomerular epithelial cells, and is thus considered a critical factor in diabetic nephropathy [18]. Studies have shown that LRG1 is significantly elevated in GDM women with poor glycemic control and correlates with early renal injury markers, supporting its utility as a biomarker for early renal injury in GDM [19]. In this study, serum LRG1 was significantly elevated in the renal-injury group compared to controls and the no-renal-injury group, and correlated significantly with creatinine, IL-6, BUN, HbA_1c, and eGFR. Multivariate logistic regression confirmed that elevated IL-6 is a risk factor, while elevated eGFR is protective, suggesting a mechanistic link between LRG1 and GDM-related renal injury. Zhang *et al.* [20] reported that in hypertensive mice with renal injury, serum LRG1 correlated positively with IL-6, consistent with our

findings. We hypothesize that microinflammation associated with renal damage induces LRG1 expression, and in turn, LRG1 may exacerbate insulin resistance and promote proinflammatory cytokine release (e.g., IL-1β, IL-6), thereby amplifying inflammation and contributing to renal injury [6,21].

SFRP4 is an adipokine that competitively binds to frizzled receptors and inhibits the Wnt signaling pathway [22]. Elevated serum SFRP4 has been reported in GDM patients, and increased early-pregnancy SFRP4 is associated with higher risk of developing GDM later in pregnancy [23]. Our study further demonstrates that serum SFRP4 is significantly elevated in GDM patients with renal injury and correlates significantly with creatinine, IL-6, BUN, HbA_1c, and eGFR. This suggests that SFRP4 may contribute to GDM pathogenesis by impairing β-cell function through interaction with inflammatory mediators and by inhibiting insulin secretion via Wnt and other signaling pathways, leading to inflammatory damage and β-cell dysfunction [7], thereby promoting renal injury.

In summary, serum LRG1 and SFRP4 levels are independent risk factors for early renal injury in GDM, with combined detection offering superior diagnostic performance over either marker alone. Limitations of this study include a relatively small sample size, which may introduce bias, and the need for further mechanistic studies on the roles of LRG1 and SFRP4 in GDM-related renal injury. Future studies will expand the cohort for validation and mechanistic exploration.

Conflict of Interest: None

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·论　著·

血清LRG1和SFRP4对妊娠期糖尿病患者早期肾损伤的诊断价值

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摘要：目的　探究血清富亮氨酸α-2糖蛋白-1（LRG1）与分泌型卷曲相关蛋白4（SFRP4）对妊娠期糖尿病（GDM）患者早期肾损伤的诊断价值，为临床GDM肾损伤的预测提供参考依据。**方法**　选择2022年1月到2023年12月中国人民解放军总医院第七医学中心就诊的118例GDM孕妇及同期产检的正常孕妇112例（对照组）为研究对象。收集所有研究对象的临床资料。根据尿白蛋白/肌酐比值（UACR）将118例GDM孕妇分为无肾损伤GDM组（UACR<30 mg/g，n=72）和肾损伤GDM组（UACR≥30 mg/g，n=46）。采用Pearson相关性分析探讨GDM孕妇血清LRG1、SFRP4水平与血肌酐、白细胞介素-6（IL-6）、血尿素氮、糖化血红蛋白（HbA_{1C}）、估算肾小球滤过率（eGFR）的相关性。采用多因素logistic回归分析发生GDM患者早期肾损伤的影响因素。采用受试者工作特征（ROC）曲线分析血清LRG1、SFRP4水平对GDM患者早期肾损伤的诊断价值。**结果**　肾损伤GDM组IL-6、血尿素氮、血肌酐、HbA_{1C}、LRG1、SFRP4均高于无肾损伤GDM组（P<0.05），eGFR低于无肾损伤GDM组（P<0.05）。肾损伤GDM孕妇血清LRG1、SFRP4分别与血肌酐、IL-6、血尿素氮、HbA_{1C}呈显著正相关（P<0.05），与eGFR呈显著负相关（P<0.05）。高IL-6（OR=1.698，95%CI：1.261~2.287）、HbA_{1C}（OR=2.596，95%CI：1.284~5.247）、LRG1（OR=1.563，95%CI：1.214~2.013）、SFRP4（OR=1.893，95%CI：1.185~3.024）是GDM发生肾损伤的独立危险因素（P<0.05），高eGFR（OR=0.642，95%CI：0.515~0.800）为其独立保护因素（P<0.05）。LRG1、SFRP4联合检测GDM发生肾损伤的曲线下面积为0.925，优于各自单独检测（$Z_{两者联合\text{-}LRG1}$=2.221，P=0.026；$Z_{两者联合\text{-}SFRP4}$=3.153，P=0.002）。**结论**　血清LRG1和SFRP4水平对GDM孕妇早期肾损伤有一定的诊断价值。

关键词：富亮氨酸α-2糖蛋白-1；分泌型卷曲相关蛋白4；妊娠期糖尿病；肾损伤；糖化血红蛋白；估算肾小球滤过率

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Abstract: Objective　To investigate the diagnostic value of serum leucine-rich-alpha-2-glycoprotein-1 (LRG1) and secreted frizzled-related protein 4 (SFRP4) for early renal injury in patients with gestational diabetes mellitus (GDM), and to provide a reference for the clinical prediction of GDM-related renal injury. **Methods**　A total of 118 pregnant women with GDM and 112 normal pregnant women undergoing prenatal examination (control group) who visited the Seventh Medical Center of Chinese PLA General Hospital from January 2022 to December 2023 were selected as the study subjects. Clinical data were collected from all subjects. According to urinary albumin-to-creatinine ratio (UACR), the 118 pregnant women with GDM were divided into GDM without renal injury group (UACR<30 mg/g, n=72) and GDM with renal injury group (UACR≥30 mg/g, n=46). Pearson correlation analysis was used to explore the correlations

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of serum LRG1 and SFRP4 levels with serum creatinine, interleukin-6 (IL-6), blood urea nitrogen, glycosylated hemoglobin (HbA_{1C}), and estimated glomerular filtration rate (eGFR) in pregnant women with GDM. Multivariate logistic regression analysis was performed to analyze the influencing factors of early renal injury in patients with GDM. Receiver operating characteristic (ROC) curve was used to analyze the diagnostic value of serum LRG1 and SFRP4 levels for early renal injury in patients with GDM. **Results** The levels of IL-6, blood urea nitrogen, serum creatinine, HbA_{1C}, LRG1, and SFRP4 in the GDM with renal injury group were significantly higher than those in the GDM without renal injury group, while eGFR was significantly lower (P<0.05). Serum LRG1 and SFRP4 in GDM pregnant women with renal injury were significantly positively correlated with serum creatinine, IL-6, blood urea nitrogen, and HbA_{1C}, and significantly negatively correlated with eGFR (P<0.05). High IL-6 (OR=1.698, 95%CI: 1.261-2.287), HbA_{1C} (OR=2.596, 95%CI: 1.284-5.247), LRG1 (OR=1.563, 95%CI: 1.214-2.013), and SFRP4 (OR=1.893, 95%CI: 1.185-3.024) were independent risk factors for renal injury in GDM, while high eGFR (OR=0.642, 95%CI: 0.515-0.800) was an independent protective factor (P<0.05). The area under the ROC curve of combined detection of LRG1 and SFRP4 for renal injury in GDM was 0.925, which was better than that of single detection ($Z_{combination-LRG1}$=2.221, P=0.026; $Z_{combination-SFRP4}$=3.153, P=0.002). **Conclusion** Serum LRG1 and SFRP4 levels have certain diagnostic value for detecting early renal injury in pregnant women with GDM.

Keywords: Leucine-rich-alpha-2-glycoprotein-1; Secreted frizzled-related protein 4; Gestational diabetes mellitus; Renal injury; Glycosylated hemoglobin; Estimated glomerular filtration rate

妊娠期糖尿病(gestational diabetes mellitus, GDM)是孕妇在妊娠期发生的糖代谢异常疾病,易引发胎膜早破、产后出血,严重危害母婴健康[1-2]。随着疾病的发展,GDM患者会出现肾损伤[3-4],而早期肾损伤发病隐匿,通常会表现为体质量增加、外周性水肿等症状,加之个体差异、年龄等因素的影响,肾损伤早期诊断率偏低,而一旦出现显性蛋白尿等明显症状,已延误最佳治疗时机,肾功能将进行性恶化,最终可导致肾功能衰竭。因此寻找可靠、敏感的与GDM患者肾损伤发病有关的因素,对提高妊娠质量有重要意义。血清富亮氨酸α-2糖蛋白-1(leucine rich-alpha-2-glycoprotein-1, LRG1)是一类内皮血管中促血管生成因子,其表达水平受血糖水平影响,已有研究证实LRG1与孕妇产后血糖异常有关,且LRG1还在肾小球内皮细胞中表达丰富,是判断、评估糖尿病诱导的肾功能障碍疾病的常用指标[5-6],因此推测其可作为糖尿病早期肾损伤的评价指标。分泌型卷曲相关蛋白4(secreted frizzled-related protein 4, SFRP4)是一种脂肪因子,与糖代谢有关[7]。研究发现,SFRP4能够诱导肾小球病变,引发肾功能障碍,进而促进肾脏纤维化等疾病的发生[7-9],据此推测其对糖尿病肾损伤也有一定的评估潜力。目前关于血清LRG1、SFRP4水平在GDM患者早期肾损伤的研究较少,因此本研究将围绕血清LRG1、SFRP4在GDM早期肾损伤中的水平以及二者的诊断价值展开讨论,旨在为临床GDM患者肾损伤的预测提供参考依据。

1 对象与方法

1.1 *研究对象* 随机选择2022年1月到2023年12月于中国人民解放军总医院第七医学中心就诊的GDM孕妇118例为研究对象。(1) 纳入标准:①符合GDM诊断标准[10];②孕前未确诊为糖尿病;③单胎妊娠。(2) 排除标准:①合并心脑血管疾病;②合并其他妊娠疾病;③合并恶性肿瘤;④确诊前进行胰岛素治疗。

根据尿白蛋白/肌酐比值(urinary albumin-tocreatinine ratio, UACR)[11],将118例GDM孕妇分为无肾损伤GDM组(UACR<30 mg/g, n=72)和肾损伤GDM组(UACR≥30 mg/g, n=46)。肾损伤GDM组均为早期肾损伤,无肾损伤典型症状,尿常规蛋白阴性,且尿白蛋白>20 mg/L。另纳入同期中国人民解放军总医院第七医学中心进行产检的正常孕妇112例作为对照组。本研究已征得中国人民解放军总医院第七医学中心伦理委员会批准[〔2021〕伦审第(058)号],所有患者均签署知情同意书。

1.2 *方法*

1.2.1 临床资料收集 收集研究对象年龄、孕周、孕次、产次、身体质量指数(body mass index, BMI)等一般临床资料。

1.2.2 检测指标 收集研究对象入院当日、孕晚期(28~34周)孕检当日清晨空腹静脉血5 mL,离心,-20 ℃保存备用。收集研究对象入院当日、孕检当日尿液,4 ℃保存备用。酶联免疫吸附法检测血清LRG1、SFRP4和白细胞介素(interleukin, IL)-6表达

水平，LRG1 检测试剂盒购自上海科艾博生物（CB10586-Hu），SFRP4 检测试剂盒购自华美生物（CSB-E13721h）；IL-6 检测试剂盒购自上海酶联生物（ml038116）。全自动生化分析仪（南京颐兰贝生物，AS-800）检测血清中尿素氮、肌酐及总胆固醇水平，检测尿液中白蛋白和肌酐水平，计算估算肾小球滤过率（estimated glomerular filtration rate，eGFR）。采用糖化血红蛋白分析仪（陕西斯博瑞德电子科技，Vantage2000）检测血清中糖化血红蛋白（glycosylated hemoglobin，HbA_{1C}）水平。全自动免疫分析仪检测血清中胰岛素水平，并计算稳态模型评估胰岛素抵抗指数（Homeostasis Model Assessment of Insulin Resistance，HOMA-IR）。

1.3　统计学方法　本研究采用 SPSS 22.0 软件进行数据分析。符合正态分布的计量资料用 $\bar{x}\pm s$ 表示，多组间比较采用单因素方差分析，两两比较采用 SNK-q 检验。计数资料以例（%）表示，比较行 χ^2 检验。采用 Pearson 相关性分析探讨 GDM 孕妇血清 LRG1、SFRP4 水平与血肌酐、IL-6、血尿素氮、HbA_{1C}、eGFR 的相关性。采用多因素 logistic 回归分析 GDM 早期肾损伤的影响因素。采用受试者工作特征（receiver operating characteristic，ROC）曲线分析血清 LRG1、SFRP4 水平对 GDM 患者早期肾损伤的诊断价值，曲线下面积（area under curve，AUC）比较采用 DeLong 检验。P<0.05 为差异有统计学意义。

2　结　果

2.1　不同组别一般临床资料及检测指标对比　三组年龄、孕周、孕次、产次、BMI 比较差异无统计学意义（P>0.05）。与对照组相比，无肾损伤 GDM 组与肾损伤 GDM 组空腹血糖、服糖后 1 h 血糖、服糖后 2 h 血糖、空腹胰岛素、IL-6、总胆固醇、HOMA-IR、HbA_{1C}、LRG1、SFRP4 显著升高（P<0.05），肾损伤 GDM 组 IL-6、血尿素氮、血肌酐、总胆固醇、HbA_{1C}、LRG1、SFRP4 均高于无肾损伤 GDM 组，eGFR 低于无肾损伤 GDM 组（P<0.05）。见表 1。

2.2　相关性分析　Pearson 相关分析显示，肾损伤 GDM 孕妇血清 LRG1、SFRP4 分别与 IL-6、血尿素氮、血肌酐、HbA_{1C} 呈显著正相关，与 eGFR 呈显著负相关（P<0.05）。见表 2。

2.3　多因素 logistic 回归分析 GDM 患者发生肾损伤的影响因素　以 GDM 患者是否存在肾损伤为因变量，以单因素分析中差异有统计学意义的指标（血肌酐、IL-6、血尿素氮、HbA_{1C}、LRG1、SFRP4、eGFR）为自变量，采用输入法筛选自变量纳入多因素 logistic 回归分析，排除有共线性的血尿素氮、血肌酐，结果显示 IL-6、HbA_{1C}、eGFR、LRG1、SFRP4 均是 GDM 患者发生肾损伤的独立影响因素（P<0.05）。见表 3。

表 1　不同组别一般临床资料及检测指标对比　（$\bar{x}\pm s$）

Tab.1　Comparison of general clinical data and detection indicators among different groups　（$\bar{x}\pm s$）

项目	对照组（n=112）	无肾损伤 GDM 组（n=72）	肾损伤 GDM 组（n=46）	F 值	P 值
年龄（岁）	32.56±5.26	32.89±4.89	32.13±5.10	0.311	0.733
孕周	31.56±5.62	31.25±5.48	31.78±5.84	0.134	0.874
孕次	1.46±0.35	1.51±0.41	1.57±0.42	1.392	0.251
产次	1.23±0.26	1.31±0.21	1.28±0.27	2.393	0.094
BMI（kg/m^2）	25.89±4.59	25.46±4.20	25.78±4.89	0.200	0.819
空腹血糖（mmol/L）	4.59±0.62	8.28±2.86[a]	8.49±3.08[a]	88.475	<0.001
服糖后 1 h 血糖（mmol/L）	8.24±0.85	11.43±0.96[a]	11.57±0.87[a]	382.429	<0.001
服糖后 2 h 血糖（mmol/L）	7.16±0.77	9.25±0.87[a]	9.12±0.76[a]	186.727	<0.001
空腹胰岛素（μIU/mL）	4.12±0.58	18.98±3.95[a]	19.82±4.12[a]	789.203	<0.001
IL-6（pg/mL）	13.59±2.58	45.86±5.26[a]	86.24±9.87[ab]	2 854.200	<0.001
血尿素氮（mmol/L）	6.58±0.89	8.23±2.58	36.89±4.26[ab]	2 678.694	<0.001
血肌酐（μmol/L）	66.52±13.58	72.59±18.28	180.26±29.23[ab]	629.023	<0.001
eGFR（$mL\cdot min^{-1}\cdot 1.73\ m^{-2}$）	123.31±15.89	122.78±18.58	72.75±8.82[ab]	189.001	<0.001
总胆固醇（mmol/L）	3.56±0.45	5.89±0.74[a]	6.15±1.08[ab]	340.541	<0.001
HOMA-IR	0.84±0.17	2.36±0.68[a]	2.48±0.85[a]	234.215	<0.001
HbA_{1C}（%）	4.56±1.28	6.58±1.78[a]	8.49±1.85[ab]	108.600	<0.001
LRG1（ng/mL）	149.58±33.56	258.79±72.89[a]	332.89±85.56[ab]	170.583	<0.001
SFRP4（ng/mL）	139.56±25.89	232.98±65.54[a]	304.59±88.59[ab]	153.372	<0.001

注：与对照组相比，[a]P<0.05；与无肾损伤 GDM 组相比，[b]P<0.05。

2.4　血清 LRG1、SFRP4 水平对 GDM 患者发生肾损伤的诊断价值　以无肾损伤 GDM 组和肾损伤 GDM 组血清 LRG1、SFRP4 水平进行 ROC 曲线分析，结果显示，二者联合检测 GDM 患者发生肾损伤的诊断价值优于各自单独检测（$Z_{两者联合\text{-}LRG1}$=2.221，P=0.026；$Z_{两者联合\text{-}SFRP4}$=3.153，P=0.002）。见表 4、图 1。

表 2　血清 LRG1、SFRP4 与 IL-6、血尿素氮、血肌酐、HbA_{1C}、eGFR 的相关性

Tab.2　Correlation of serum LRG1 and SFRP4 with IL-6, blood urea nitrogen, serum creatinine, HbA_{1C} and eGFR

指标	LRG1		SFRP4	
	r 值	*P* 值	*r* 值	*P* 值
IL-6	0.482	<0.05	0.392	<0.05
血尿素氮	0.563	<0.05	0.611	<0.05
血肌酐	0.519	<0.05	0.597	<0.05
HbA_{1C}	0.327	<0.05	0.386	<0.05
eGFR	−0.439	<0.05	−0.412	<0.05

表 3　多因素 logistic 回归分析 GDM 患者发生肾损伤的影响因素

Tab.3　Multivariate logistic regression analysis of influencing factors for renal injury in patients with GDM

指标	*β*	*SE*	Wald χ^2	*P* 值	*OR* 值	95%*CI*
IL-6	0.529	0.159	12.133	<0.001	1.698	1.261~2.287
HbA_{1C}	0.954	0.359	7.061	0.008	2.596	1.284~5.247
eGFR	−0.443	0.112	15.657	<0.001	0.642	0.515~0.800
LRG1	0.447	0.129	11.986	<0.001	1.563	1.214~2.013
SFRP4	0.638	0.239	7.130	0.008	1.893	1.185~3.024

表 4　血清 LRG1、SFRP4 水平对 GDM 患者肾损伤的预测价值

Tab.4　Predictive value of serum levels of LRG1 and SFEP4 for early renal injury in patients with GDM

指标	AUC	95%*CI*	灵敏度（%）	特异度（%）	截断值	约登指数
LRG1	0.862	0.786~0.981	56.52	97.22	329.586 ng/mL	0.537
SFRP4	0.817	0.736~0.882	54.35	98.61	295.482 ng/mL	0.530
联合检测	0.925	0.862~0.965	82.61	86.11		0.687

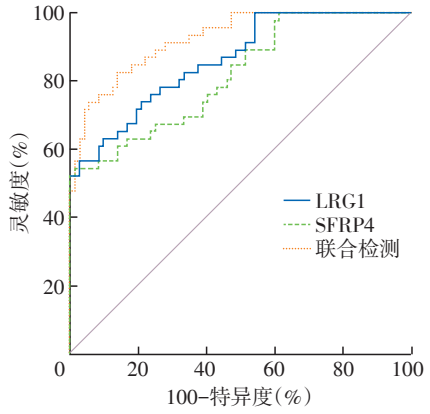

图 1　血清 LRG1、SFRP4 诊断 GDM 患者肾损伤的 ROC 曲线

Fig.1　ROC curves of serum LRG1 and SFRP4 in diagnosing renal injury in patients with GDM

3　讨　论

GDM 患者的核心病理生理改变为糖代谢异常、胰岛素抵抗增加等[12-13]。GDM 属于妊娠期暂时性糖代谢异常，肾损伤是 GDM 常见的并发症，临床需重点监测[3-4]。GDM 早期肾损伤起病隐匿，缺乏典型症状，容易造成漏诊、误诊；病情发展到后期会引起肾脏增大、肾小球滤过率降低等，最终导致肾衰竭[14-16]。因此早期识别 GDM 相关肾损伤、寻找敏感特异的生物学标志物，并制定个体化干预策略，对改善妊娠结局具有重要临床意义。

LRG1 在人体内主要由肝细胞和中性粒细胞分泌产生，通过 Smads 途径参与新血管生成、炎症介质释放等生理过程[17]。LRG1 的表达与血糖水平有关，不仅会引起糖尿病患者视网膜病变、冠状动脉粥样硬化及其他心血管疾病的发生，还是糖尿病患者病情进展为终末期肾病的危险因素[6]。LRG1 是 TGF-β1 信号通路的关键因子，在肾小球上皮细胞中表达较多，因此也被认为是引起糖尿病肾损伤的关键因素[18]。研究发现，LRG1 在血糖控制不良的 GDM 孕妇中显著升高，并且与早期肾脏损伤指标具有相关性，可作为 GDM 早期肾损伤的生物标志物[19]。本研究发现，与对照组和无肾损伤 GDM 组孕妇相比，LRG1 在肾损伤 GDM 组中显著升高，且与血肌酐、IL-6、血尿素氮、HbA_{1C}、eGFR 之间均存在显著相关性。多因素 logistic 回归分析结果显示，高 IL-6 是 GDM 患者肾损伤的危险因素，高 eGFR 是保护因素。以上结果说明 LRG1 与 GDM 发生肾损伤之间存在一定联系，可能参与 GDM 发病过程。张琳琳等[20]的研究结果也显示，在高血压所诱导的肾损伤小鼠血清中 LRG-1 与炎症因子 IL-6 等的水平均呈正相关，本研究结果与其一致，并推测是由于肾损害的微炎症状态会诱导 LRG-1 的表达，而 LRG-1 有可能反过来影响胰岛素抵抗、促进炎性介质（IL-1β、IL-6 等）的表达，加剧炎症反应，进而引发肾损伤[6,21]。本研究进一步分析显示 LRG1 对 GDM 患者发生肾损伤具有诊断价值，为临床提供了诊断参考指标。

SFRP4 作为脂肪因子，被发现其可通过与卷曲蛋白受体竞争性结合，从而抑制 Wnt 信号通路[22]。研究发现，SFRP4 在 GDM 患者血清中表达水平升高，且妊娠早期血清 sFRP4 浓度升高与妊娠后期罹患 GDM 的风险增加有关[23]，基于此推测其与 GDM 病情发展及并发症的发生有关。本研究结果显示，SFRP4 在 GDM 伴肾损伤孕妇血清中显著升高，与血肌酐、IL-6、血尿素氮、HbA_{1C}、eGFR 之间均显著相关，推测可能是

由于SFRP4能够与炎症因子发生作用影响胰岛β细胞功能，并且sFRP4还可以通过Wnt等信号通路抑制胰岛素的分泌，导致炎症损害及胰岛β细胞功能紊乱[7]，进而参与GDM的发生及发展，诱发肾损伤。

综上所述，血清中LRG1和SFRP4水平是GDM患者发生早期肾损伤的影响因素，二者对GDM患者发生肾损伤具有潜在诊断价值，联合检测诊断效能较单一检测更高。本研究尚有不足之处，纳入病例数较少，导致部分数据及统计结果可能存在偏倚，另外LRG1、SFRP4表达水平在GDM患者发生肾损伤过程中的作用需要进一步研究，后续将继续收集病例进行验证及探究。

利益冲突　无

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