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ARAŞTIRMA MAKALESİ

Serum XBP-1 as a Novel Biomarker for Sensitive Prediction of Gestational Diabetes

Gestasyonel Diyabetin Duyarlı Öngörüsünde Yeni Bir Biyobelirteç Olarak Serum XBP-1

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ABSTRACT

Aim: We investigated serum X-box binding protein 1 (XBP-1) as a diagnostic biomarker for gestational diabetes mellitus (GDM).

Material and Methods: This study included 88 gravidae, aged 18–45 years, who underwent GDM screening via 75-g 2-h Oral Glucose Tolerance Test (OGTT) at Bakırköy Dr. Sadi Konuk Training and Research Hospital. The serum XBP-1 was determined through enzyme-linked immunosorbent assay concurrent with OGTT. We determined the relation of serum XBP-1 with physiological parameters, including anthropometric measurements and cardiovascular indices. The value of XBP-1 was assessed in the diagnosis of GDM.

Results: Serum XBP-1 levels were significantly higher in women with GDM compared to those with normal glucose tolerance (5.12±1.65 vs. 2.05±0.40 ng/mL, p<0.001). Subgroup analysis revealed that even early-stage GDM patients had elevated XBP-1 levels (4.36±1.05 ng/mL) compared to controls (p<0.001). XBP-1 showed strong positive correlations with fasting and postprandial glucose levels and BMI (all p<0.001). ROC analysis demonstrated excellent diagnostic performance with area under the curve of 0.99, achieving 100% sensitivity and 99% specificity at a cutoff value of 2.71 ng/mL.

Conclusions: Serum XBP-1 represents a promising biomarker for early GDM detection, potentially complementing OGTT. Further validation studies in diverse populations are needed to establish its clinical utility.

Keywords: Gestational diabetes mellitus; X-box binding protein 1; Biomarker; Endoplasmic reticulum stress; Oral glucose tolerance test; Unfolded protein response

ÖZET

Amaç: Bu araştırmanın amacı gestasyonel diyabetes mellitus (GDM) için tanısal bir biyobelirteç olan serum X-box bağlayıcı protein 1'i (XBP-1) araştırmaktır.

Materyal ve Metodlar: Bu çalışma, Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi'nde 75-g 2-saatlik Oral Glukoz Tolerans Testi (OGTT) ile GDM taraması yapılan 18-45 yaş aralığındaki 88 gebeyi kapsadı. Serum XBP-1, OGTT ile eş zamanlı olarak enzim bağlı immünosorbent assay yöntemiyle belirlenmiştir. Serum XBP-1'in antropometrik ölçümler ve kardiyovasküler indeksler dahil olmak üzere fizyolojik parametrelerle ilişkisini belirlenmiştir. XBP-1'in GDM tanısındaki değeri değerlendirilmiştir.

Bulgular: Serum XBP-1 düzeyleri, GDM'li kadınlarda normal glukoz toleransı olan kadınlara kıyasla anlamlı derecede yüksekti (5,12±1,65'e karşı 2,05±0,40 ng/mL, p<0,001). Alt grup analizi, erken evre GDM hastalarının bile kontrollere kıyasla yüksek XBP-1 düzeylerine (4,36±1,05 ng/mL) sahip olduğunu ortaya koydu (p<0,001). XBP-1, açlık ve tokluk glukoz düzeyleri ve BMI ile güçlü pozitif korelasyonlar gösterdi (tümü p<0,001). ROC analizi, eğri altında kalan alan 0,99 ile mükemmel tanısal performans göstermektedir ve 2,71 ng/mL kesme değerinde %100 duyarlılık ve %99 özgüllük elde edilmiştir.

Sonuçlar: Serum XBP-1, erken GDM tespiti için umut vadeden bir biyobelirteç olarak ortaya çıkmakta ve potansiyel olarak OGTT'yi tamamlayabilmektedir. Klinik faydasını belirlemek için farklı popülasyonlarda daha fazla doğrulama çalışmasına ihtiyaç vardır.

Anahtar Kelimeler: Gestasyonel diabetes mellitus; X-box bağlayıcı protein 1; Biyobelirteç; Endoplazmik retikulum stresi; Oral glukoz tolerans testi; Katlanmamış protein yanıtı

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INTRODUCTION

"Gestational diabetes mellitus (GDM)", is a prevalent metabolic condition characterized by glucose intolerance that develops during pregnancy. Its impact extends beyond metabolic regulation, posing significant risks to both maternal and fetal health, underscoring the importance of early detection and management [1]. This condition is associated with higher rates of maternal complications like miscarriage, preterm birth, cesarean delivery, preeclampsia and gestational hypertension, in addition to fetal complications such as macrosomia, congenital malformations, and perinatal mortality [2]. In addition, infants born to mothers with a GDM diagnosis undergo a higher rate of hypoglycemia at birth, as well as a greater risk being diagnosed with metabolic pathways such as obesity and "type 2 diabetes (T2DM)" later in life [3]. Although GDM typically resolves after delivery, women with GDM experience an increased risk of developing T2DM and cardiometabolic disease, highlighting the need for effective early detection and preventative approaches [4].

Current screening and diagnostic protocols for GDM differ substantially between healthcare systems. The standardized detection and management protocols for GDM align precisely with the authoritative guidelines established by "The International Association of Diabetes and Pregnancy Study Groups (IADPSG)" and "American Diabetes Association (ADA)", which unequivocally endorse the implementation of "oral glucose tolerance testing (OGTT)" during the gestational interval spanning weeks 24-28, a critical developmental epoch for metabolic surveillance as the definitive screening and diagnostic paradigm [5]. Nevertheless, the OGTT is widely used for diagnosis, but not without limitations, including the time taken for tests, discomfort to patients and variability in results, prompting a search for alternative diagnostic approaches [6]. These limitations have led to an increased interest in searching for novel biomarkers that could improve early identification of GDM and facilitate more personalized care of pregnant women.

Recent studies have focused on identifying biomarkers having relation with "endoplasmic reticulum (ER)" stress and the "unfolded protein response (UPR)" given their important roles during both glucose metabolism and insulin mediated signaling pathways important to GDM pathogenesis [7]. One such biomarker, "X-box binding protein 1 (XBP-1)", is an important transcription factor activated by the UPR to relieve the stress of protein folding in the ER [8]. In addition to its classical role in cellular stress conditions to modulate cellular homeostasis, XBP-1 is also important for metabolic regulation including lipid biosynthesis, insulin sensitivity and glucose homeostasis [9,10]. XBP-1 orchestrates complex modulation of insulin signaling pathways via sophisticated transcriptional regulation of glucose metabolism-related genes, enabling fundamental control of glucose uptake and glycogenic processes in cells. Furthermore, this central molecular mediator has a significant influence on bioenergetic homeostasis through dual mechanisms of regulation: the coordination of mitochondrial function and the modulation of cellular responses to oxidative stress, both forming crucial molecular frameworks for the maintenance of glucose homeostatic mechanisms [11]. Furthermore, disturbances in XBP-1 function have been connected to metabolic diseases and thus implicates a potential role of XBP-1 dysregulation in the pathogenesis of GDM by affecting homeostasis of glucose and insulin. Given its established role in ER stress and metabolic regulation, XBP-1 emerges as a candidate biomarker for GDM. Emerging evidence indicates that circulating XBP-1 levels may reflect the underlying molecular pathway of GDM and show promise as a non-invasive diagnostic target for the early detection of GDM [12]. This study investigated the diagnostic value of serum XBP-1 levels as a biomarker for GDM in pregnant women undergoing OGTT. Although numerous studies have examined GDM, research specifically evaluating XBP-1 as a biomarker in this context remains limited, making our study a valuable contribution to the literature. By examining the relationship between serum XBP-1 levels and key metabolic parameters, including fasting and postprandial glucose levels, our study aims to provide a reliable and noninvasive approach to early GDM diagnosis. Additionally, we seek to improve on existing diagnostics, offering a more patient-specific alternative to the OGTT, while also characterizing novel aspects of XBP-1 in pregnant women.

MATERIALS AND METHODS

This research was conducted as "a prospective observational cohort study" to assess the diagnostic potential of serum XBP-1 levels in identifying GDM among pregnant women. The study took place at the Antenatal Care Center of Bakırköy Dr. Sadi Konuk Training and Research Hospital between July 2017 and February 2019. Approval was obtained from the Clinical Research Ethics Committee of the institution (Registry number 2017/151) before the study commenced. "Written informed consent" was obtained from all participants prior to their enrolment. The study adhered strictly to "the ethical principles outlined in the Declaration of Helsinki."

Study Population

The study subjects were pregnant women between 18 and 45 years of age who routinely attended our outpatient unit between 24 and 28 weeks of gestation and agreed to undergo a 75 g OGTT as part of GDM screening. Inclusion criteria included women with a singleton pregnancy, no prior history of diabetes, and no known chronic diseases such as hypertension, cardiovascular disease, or thyroid dysfunction. Participants with multiple pregnancies, preexisting diabetes, or any condition affecting glucose metabolism as well as pregnant women with metabolic disorders (like Cushing's syndrome or adrenal insufficiency), autoimmune diseases, or those undergoing cancer treatment for any reason were excluded from participation in the study.

Sample Size Calculation

By utilizing G*Power software (www.psychologie.hhu.de/) for our a priori power analysis, we determined that a total of 84 participants, with 28 participants per group, would provide sufficient statistical power for our study. Possible dropouts were considered, and the target sample size was increased to 88 participants, aiming for approximately 29-30 participants per group. This sample size was determined to detect a medium effect size (f = 0.35) in XBP-1 protein

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serum levels across our three study groups, considering power and significance values of 0.80 and 0.05, respectively, while also accommodating for potential participant attrition.

Grouping of Study Population

In this study, participants were divided into three groups based on their OGTT results:

Normal Glucose Tolerance (NGT) Group: This control population comprised gravidae demonstrating optimal glycemic regulation, characterized by normal glucose values throughout the standardized "OGTT": fasting, 1-hour, and 2-hour post-glucose challenge measurements.

GDM Subgroup 1: This cohort encompasses gravidae with elevated fasting and/or 1-hour postprandial glucose levels, while maintaining normal glucose values at the 2-hour measurement point of "OGTT". This phenotype represents an early manifestation of impaired glucose regulation during standardized tolerance testing.

GDM Subgroup 2: This subset comprises gravidae with elevated 2-hour postprandial glucose values during "OGTT", irrespective of their fasting and 1-hour glucose measurements. This phenotype represents the classical presentation of "GDM", characterized by impaired late-phase glucose clearance.

This three-group classification was utilized to apply for a detailed analysis of XBP-1 levels with reference to different glycemic status during pregnancy. It enables the evaluation of XBP-1 as a potential biomarker not only for the classic presentation of GDM but also for earlier stages of dysglycemia.

Data Collection

Venous specimens were obtained during "OGTT" administration following overnight fasting. Glucose levels were measured at three time points: fasting (baseline), followed by sequential measurements at 60-minute and 120-minute intervals after administration of a standardized 75-gram glucose challenge. Blood sampling procedures were performed according to validated metabolic assessment protocols. "Enzyme-linked immunosorbent assay (ELISA)" was used to detect serum XBP-1 concentrations level on the same time as measurement of glucose. Participants' additional clinical data, such as maternal age, "body mass index (BMI)", "blood pressure (BP)", and obstetric history were also documented. Systematic collection and analysis were performed on the data for fasting glucose, postprandial glucose, BP, and other important metabolic parameters

Biochemical Analysis

Quantification of serum "XBP-1" was accomplished utilizing a high-sensitivity "ELISA" methodology (BT LAB, China). The analytical protocol encompassed a calibrated series of standards (ranging 0-10 ng/ml) alongside serum specimens, each examined in duplicate. The procedural workflow involved sequential application of conjugate solution to antibody-functionalized microwells, followed by precise thermal conditioning (37°C, 60 minutes). Post-incubation processing incorporated automated washing protocols (Thermo Scientific WellWash), chromogenic development under controlled ambient conditions (20-25°C, 15 minutes), and spectrophotometric analysis (Multiskan FC, 450 nm). "XBP-1" concentrations were derived through logarithmic transformation of absorbance-concentration relationships, yielding a detection threshold of 0.1 ng/mL across a dynamic range of 0.5-10 ng/mL. Concurrent metabolic parameters were assessed via enzymatic glucose oxidation methodology, while cardiovascular indices were obtained through standardized sphygmomanometry.

Statistical Analysis

Descriptive and inferential statistical analyses were performed using IBM SPSS Statistics (version 26.0). Baseline characteristics of the study population were thoroughly described using descriptive statistical analysis. Quantitative variables were summarized as mean values with associated standard deviations, while categorical variables were presented as absolute numbers and relative frequencies. Normality of quantitative variables was tested by the Kolmogorov-Smirnov test. For variables that met assumptions of the normal distribution, one-way analysis of variance (ANOVA) was used for multi-group comparisons, and then the post-hoc procedures of Tukey were used to define specific differences between groups. Non-parametric data were analyzed across several groups using the Kruskal-Wallis test, followed by the Mann-Whitney U test with a multiple comparison correction using the Bonferroni test. The relationships between continuous variables were measured using Pearson's correlation coefficients in case of parametric data and by Spearman's rank correlation in case of non-parametric data. Receiver Operating Characteristic (ROC) curve analyses were conducted to determine optimal cutoff values for GDM prediction. Statistical significance was set at an alpha value of 0.05.

RESULTS

The personal and clinical characteristics of pregnant women with or without GDM revealed distinct differences in key health metrics (Table 1). The women with GDM exhibited significantly higher BMI values (30.2±3.9 vs. 26.2±3.5 kg/m², p<0.001), as well as elevated systolic and diastolic BP measurements. Specifically, the mean systolic pressure in the women with GDM was recorded at 113.8±13.2 mmHg, compared to 101.8±10.4 mmHg in the women without GDM (p<0.001). Similarly, diastolic pressure was higher in the women with GDM (71.7±8.5 mmHg) than in the women without GDM (63.9±7.1 mmHg, p<0.001).

OGTT results highlighted significantly higher glucose concentrations in the women with GDM at all measured time points. Fasting glucose levels (0-hour) were 92.8±17.4 mg/dL in the women with GDM compared to 78.1±6.5 mg/dL in the healthy participants (p<0.001). The one-hour postprandial glucose concentration in the women with GDM reached 193.3±29.4 mg/dL, markedly exceeding the 129.4±21.9 mg/dL observed in the healthy cohort (p<0.001). Similarly, the two-hour postprandial glucose level was 153.2±31.8 mg/dL in the women with GDM, significantly higher than the 111.4±20.3 mg/dL observed in the women without GDM (p<0.001). Furthermore, serum XBP-1 levels were found to be substantially elevated in the women with GDM (5.12±1.65 ng/mL) relative to the healthy

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participants (2.05±0.4 ng/mL, p<0.001; Figure 1). No significant intergroup differences were detected in the maternal age, gravida, parity, gestational age, gestational week at birth, or smoking history (p>0.05).

The clinical and laboratory values of the subgroups based on OGTT results are presented in Table 2. The analysis revealed an absence of statistically significant differences among the groups regarding age, gravidity, parity, gestational age at the time of OGTT, or gestational week at delivery. Systolic and diastolic BP values were significantly elevated in both GDM subgroups when compared to the NGT group (p<0.001). Additionally, BMI values were considerably higher in GDM Subgroup 1 (30.4±4.4 kg/m²) and GDM Subgroup 2 (30.0±3.4 kg/m²) relative to the NGT group (26.1±3.4 kg/m²; p<0.001).

The glucose levels across the three groups demonstrated clear and significant differences (all p<0.001). Fasting glucose concentrations were highest in the GDM Subgroup 2 (97.9±19.6 mg/dL), followed by the GDM Subgroup 1 (87.7±13.3 mg/dL), and the NGT group (78.1±6.5 mg/dL; p<0.001). Similarly, one-hour postprandial glucose levels were recorded as 196.1±27.5 mg/dL in Subgroup 2, 190.4±31.4 mg/dL in the Subgroup 1, and 129.4±21.9 mg/dL in the NGT group (p<0.001). This trend continued in the two-hour postprandial measurements, with the Subgroup 2 showing the highest values (177.4±19.5 mg/dL), followed by the Subgroup 1 (128.9±21.4 mg/dL) and the NGT group (111.4±20.3 mg/dL; p<0.001).

The serum XBP-1 levels displayed a significant gradient, with the highest levels observed in the GDM Subgroup 2 (5.89±1.80 ng/mL), followed by the Subgroup 1 (4.36±1.05 ng/mL), and the lowest levels in the NGT group (2.05±0.4 ng/mL; p<0.001). These findings suggest that the serum XBP-1 may serve as an effective biomarker for the early identification of GDM.

Correlation analysis revealed moderate positive associations between the serum XBP-1 levels and systolic (r=0.24, p=0.02) and diastolic BP (r=0.28, p=0.008), as well as BMI (r=0.29, p=0.006). Stronger correlations were identified between the XBP-1 and fasting glucose (r=0.55, p<0.001), one-hour glucose (r=0.51, p<0.001), and two-hour glucose levels (r=0.59, p<0.001) (Table 3).

The ROC curve analysis of serum XBP-1 levels demonstrated an area under the curve (AUC) of 99%, with a cutoff value of 2.71 ng/mL yielding 100% sensitivity and 99% specificity. This highlights the diagnostic value of XBP-1 for GDM, and possibly prediabetic stages

Table 1: *Demographic findings of healthy and pregnant women with gestational diabetes mellitus.*

	NGT (n=30)	GDM (n=58)	P-value
Age	28.6±6.2 (19-43)	31.0±4.6 (21-44)	0.060
Gravida	2.3±1.5 (0-6)	2.7±1.5 (1-8)	0.160
Parity	1.0±1.0 (0-3)	1.3±1.0 (0-5)	0.170
Gestational week	25.9±1.3 (24-28)	25.9±1.3 (24-28)	0.600
BMI	26.2±3.5 (17-32)	30.2±3.9 (23-40)	0.001
Week of birth	37.9±1.1(36-40)	38.4±1.2(36-40)	0.130
Smoking history	0.5±2.0 (0-10)	0.4±1.8 (0-12)	0.820
Blood Pressure	101.8±10.4 (80-130)	113.8±13.2 (80-163)	0.001
Systole	63.9±7.1 (51-88)	71.7±8.5 (50-106)	0.001
Diastole			
OGTT	78.1±6.5 (61-90)	92.8±17.4 (67-171)	0.001
0-h	129.4±21.9 (68-159)	193.3±29.4 (101-275)	0.001
1-h	111.4±20.3 (62-153)	153.2±31.8 (74-233)	0.001
2-h			
XBP-1	2.05±0.4 (1.56-3.48)	5.12±1.65 (2.73-9.64)	0.001

NGT: Normal Glucose Tolerance; GDM: Gestational Diabetes Mellitus, BMI: Body Mass Index; OGTT: Oral Glucose Tolerance Test; h: hour; XBP-1: X-Box Binding Protein 1.

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Table 2: Comparison of demographic characteristics and laboratory values according to groups.

	NGT	GDM Subgroup 1	GDM Subgroup 2	P-value
Age (y)	28.6±6.2 (19-43)	31.6±4.3 (21-41)	30.3±4.8 (24-44)	0.080
Gravidity (n)	2.3±1.5 (0-6)	2.7±1.7 (1-8)	2.6±1.2 (1-6)	0.510
Parity (n)	1.0±1.0 (0-3)	1.3±1.1 (0-5)	1.3±0.9 (0-4)	0.500
Gestational age	26.0±1.5 (24-28)	25.9±1.3 (24-28)	25.9±1.3 (24-28)	0.880
At admission (w)	37.9±1.1 (36-40)	38.3±1.3 (36-40)	38.4±1.1 (36-40)	0.230
At delivery (w)				
Blood pressure	101.8±10.4 (80-130)	116.1±16.2 (93-163)a,b	111.5±9.2 (80-120)	0.001
Systolic	63.9±7.0 (51-88)	73.1±9.4 (59-106)c,d	70.4±7.4 (50-83)	0.001
Diastolic				
Number of smoked cigarettes	0.5±2.0 (0-10)	0.7±2.4 (0-12)	0.1±0.5 (0-3)	0.510
BMI	26.2±3.5 (17-32)	30.4±4.4 (23.72-40.5)e,f	30±3.5 (23-34)	0.001
OGTT	78.1±6.5 (61-90)	87.7±13.3 (68-115)	97.9±19.6 (67-171)g,h,i	0.001
0-h	129.4±21.9 (68-159)	190.4±31.4 (109-275)	196.1±27.5 (101-232)j,k	
1-h	111.4±20.3 (62-153)	128.9±21.4 (74-149)	177.4±19.5 (156-233)l,m,n	
2-h				
XBP-1	2.05±0.4 (1.56-3.48)	4.36±1.05 (2.76-7.64)	5.89±1.80 (2.73-9.64)o,p,r	0.001

a,c,e,g,j,l,oSignificantly different vs. Group NGT and GDM Subgroup 1.

b,d,f,h,k,m,pSignificantly different vs. Group NGT and GDM Subgroup 2.

l,n,r Significantly different vs. GDM Subgroup 1 and GDM Subgroup 2.

NGT: Normal Glucose Tolerance; GDM: Gestational Diabetes Mellitus;

BMI: Body Mass Index; OGTT: Oral Glucose Tolerance Test;

XBP-1: X-Box Binding Protein-1.

Table 3: Correlation of serum X-box binding protein 1 (XBP-1) levels with various metabolic parameters. Pearson correlation coefficients (r) and significance levels are shown. XBP-1 was significantly correlated with all metabolic parameters (p<0.05), with particularly strong correlations observed for FBG, 1-hour, and 2-hour postprandial glucose (p<0.001).

	Systolic		Diastolic		BMI		FBG		1-hour		2-hour	
XBP-1	r	p	R	p	r	P	r	p	r	p	r	p
	0.24	0.02	0.28	0.008	0.29	0.006	0.55	<0.001	0.51	<0.001	0.59	<0.001

XBP-1: X-Box Binding Protein-1; BMI: Body Mass Index; FBG: Fasting Blood Glucose.

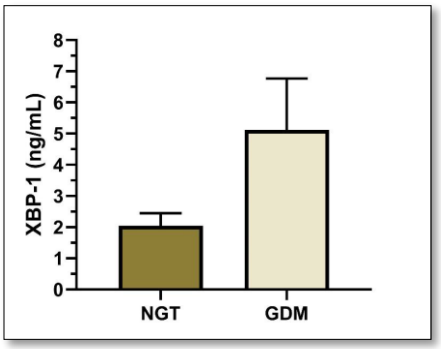

Figure 1: Comparison of serum X-box binding protein 1 (XBP-1) levels in pregnant women with normal glucose tolerance (NGT) and gestational diabetes mellitus (GDM). The bar graph displays the mean serum XBP-1 concentrations (ng/mL) in each group. Error bars represent standard deviations. Serum XBP-1 levels were significantly higher in the GDM group compared to the NGT group (p < 0.001). This finding indicates that elevated serum XBP-1 levels are associated with GDM and may serve as a potential biomarker for the condition.

Maltepe Tıp Derg. Cilt: 17 Sayı: 3/2025
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DISCUSSION

In this study, we investigated serum XBP-1 levels as a diagnostic biomarker for GDM in 88 pregnant women undergoing OGTT. Our findings demonstrated significantly elevated XBP-1 levels in women with GDM compared to those with normal glucose tolerance, with strong correlations observed between XBP-1 and key glycemic parameters. ROC analysis revealed excellent diagnostic performance (AUC: 0.99) with 100% sensitivity and 99% specificity at a cutoff value of 2.71 ng/mL.

XBP-1 has been well-recognized for its critical role in metabolic regulation and recent study showed that serum XBP-1 correlated well with GDM. Further, the higher XBP-1 level observed in pregnant persons with GDM in our analysis indicates involvement in disrupted glucose metabolism and insulin pathways—both of which have been associated with GDM, albeit with conflicting findings. Other than being a biomarker of metabolic dysregulation, this biomarker is also a key mediator between cellular stress pathways and the development of pathological conditions. XBP-1 is activated as a central mediator of the unfolded protein response (UPR), a cell state which is increasingly linked to the development of insulin resistance and systemic metabolic disease [13]. The observed upregulation of XBP-1 in the GDM cohort supports findings from previous studies with elevated ER stress markers in adipose tissue of subjects with obesity and insulin resistance [14]. Our results demonstrate that ER stress is not a bystander but an active contributor to the metabolic perturbations characteristic of GDM, and, therefore, emphasize its role in the underlying metabolic pathophysiology.

These findings have potential clinical implications. UPR pathways and ER stress regulation are potential targets for the development of diagnostic and therapeutic tools. This line of investigation opens the way to the elaboration of strategies aimed at targeting molecular triggers of gestational diabetes mellitus for proactive disease management, thereby improving maternal-fetal health outcomes.

In addition, there was strong correlation of the XBP-1 levels with several metabolic parameters such as FBG, postprandial glucose, and BMI. These correlations are consistent with a well defined metabolic function for XBP 1 in glucose homeostasis and insulin sensitivity [9,11]. These relationships suggest that XBP1 is a strong biomarker of GDM, and of metabolic derangements common to GDM in which ER stress and inflammation are superimposed on metabolic imbalance. Understanding the association between ER stress and inflammatory responses is particularly relevant, since inflammation exacerbates insulin resistance, as highlighted by recent studies [15,16]. These data support a role for XBP-1 as more than a passive sensor of metabolic imbalance, but as an active participant in its causation, thus providing a molecular basis for the clinical observations. That knowledge is the essential first step to targeted diagnostic and therapeutic strategies.

The serum XBP-1 exhibit exceptional diagnostic prowess, with an area under the curve (AUC) of 99% for GDM prediction. Such high sensitivity and specificity indicates that this parameter is a very good biomarker of early GDM detection. Beyond diagnostic accuracy, XBP-1 does a good job discriminating GDM from non GDM patients, and is therefore an attractive bedside biomarker to combine with other recently identified biomarkers for clinical practice. [15,17]. This evidence adds to evidence that can be attributed to a more general understanding of XBP-1 in metabolic regulation, such as its role in ER stress and metabolic disease mechanisms. XBP-1 helps to identify the molecular disruptions that characterize GDM and provides potential directions for diagnostic as well as intervention approaches. Its dual utilitarian role as a marker and participant in metabolic pathways further validates its potential as a cornerstone in advancing the management of GDM.

XBP-1 has potential as a predictor of GDM earlier and more reliably than currently available diagnostic methods, including the oral glucose tolerance test (OGTT). Although standard, the OGTT is commonly criticized for its limitations of patient discomfort, time consuming, and variable results and thereby that it is not the ideal screening tool for widespread or routine GDM screening [18]. On the other hand, it is advantageous to use XBP-1 as a noninvasive biomarker through a simple blood test. First, it may increase patient compliance; second, it can help with regular, repeatable early detection and early intervention, reducing the risk of complications of late diagnosis. It follows the emerging demand for more practical and more precise GDM screening tools, especially in resource limited settings where access to conventional testing is restricted [19]. Rising prevalence of GDM and strong established links with adverse maternal and infant outcomes, also make this robust urgent [1]. XBP-1 based diagnostics could transform maternal and neonatal health outcomes on a much broader scale by addressing these challenges.

Recognizing serum XBP-1 as a biomarker for GDM lays the foundation for innovative therapeutic approaches. Targeting the UPR and lowering ER stress are promising approaches, especially for high-risk populations for GDM [20]. This study reinforces the critical need to unravel XBP-1's mechanistic role in GDM and explore its viability as a target for therapeutic intervention. Potential avenues for future investigation include the development of pharmacological treatments and lifestyle adjustments aimed at XBP-1 and its associated UPR pathways. These approaches could effectively improve insulin sensitivity and restore glucose homeostasis. Translational regulation within the UPR, such as eIF2α phosphorylation and XBP-1 signaling, represents an essential component of glucose regulation. Addressing these molecular targets could alleviate ER stress and enhance insulin functionality, paving the way for impactful treatments for GDM and other metabolic disorders [21]. This growing body of evidence underscores the promise of XBP-1 as a cornerstone in advancing both therapeutic and preventive strategies for metabolic health.

Taking into account the data of the current study, the authors reached important clinical findings. This is among

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the first studies to evaluate serum XBP-1 as a biomarker for GDM, providing a foundation for future research in this domain. This prospective design improves the reliability of data collection because all participants were screened and monitored in standardized clinical conditions. Collecting several important metabolic features based on fasting and postprandial glucose levels in addition to the XBP-1 data contributes solid evidence as to the importance of the biomarker in the GDM related metabolic disorder. Furthermore, in addition to ROC curve analysis, the study applies stringent statistical tests to corroborate the diagnostic utility of XBP-1, with a high sensitivity and specificity. Our results highlight the utility of XBP-1 as a non-invasive and reliable alternative to traditional techniques for GDM diagnosis, enabling further progression towards patient-centred diagnostics. This opens up new avenues for further research and may serve as the basis for new diagnostics and/or treatments targeted towards this understudied area of GDM pathophysiology.

Although insightful, this study is limited in a number of respects. The first limitation is that the relatively small sample size hinders generalizability of findings, since the population studied may not be representative of broader demographic and clinical variations. Second, the cross-sectional design of the study precludes the ability to assess longitudinal outcomes, such as the progression of metabolic disturbances post pregnancy. However, without follow-up data on participants' metabolic health beyond delivery, there is no complete knowledge of serum XBP-1's potential as a prognostic marker for postpartum diabetes mellitus (T2DM) or other long term metabolic complications. Furthermore, no confounding factors such as dietary habits, physical activity levels or genetic predisposition were examined in the possibility that the observed XBP-1 levels might be due to them. Lastly, the mechanistic role of XBP-1 in GDM pathogenesis is incompletely characterized, and further experimental and clinical studies will be needed to identify the pathways in which it functions, and to evaluate its potential as a therapeutic target.

This study introduces XBP-1 as a potential biomarker for advancing non-invasive screening methods in GDM. Serum XBP-1 levels offer a scientific basis for improving early detection processes, emphasizing accuracy and ease of use. If validated through further research, this approach could address existing limitations in traditional methods, providing a modern solution that aligns with patient-centered care principles. Additionally, understanding the link between XBP-1, ER stress, and metabolic regulation may open up new avenues for therapeutic interventions aimed at reducing the burden of GDM and its associated long-term health risks.

CONCLUSION

This study highlights the potential of serum XBP-1 as a novel and highly sensitive biomarker for the early detection of gestational diabetes mellitus (GDM). Our findings demonstrate that XBP-1 levels are significantly elevated in pregnant women with GDM and strongly correlate with key metabolic parameters, including fasting and postprandial glucose levels. The exceptional sensitivity and specificity of XBP-1 (100% and 99%, respectively) underscore its diagnostic accuracy, offering a promising alternative to conventional oral glucose tolerance testing (OGTT). Serum XBP-1 shows powerful diagnostic ability together with a non-invasive testing method which makes it potentially revolutionary for GDM screening because it allows prompt interventions that benefit both mother and fetus. Large-scale validation studies are needed before XBP-1 can be accepted as a clinical tool for universal application among different populations. Future studies should investigate the underlying mechanisms through which XBP-1 contributes to GDM development to facilitate the development of targeted therapies for preventing GDM complications in mothers and newborns

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Working Concept/Design: CK
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Data Analysis /Interpretation: ST, AÇ
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Critical Review of Content: ST
Final approval and accountability: CGÖS, CK, AÇ
Material and technical support: CGÖS
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REFERENCES

1. McIntyre HD, Catalano P, Zhang C, Desoye G, Mathiesen ER, Damm P. Gestational diabetes mellitus. Nat Rev Dis Primer 2019;5:47. https://doi.org/10.1038/s41572-019-0098-8.
2. Ferrara A. Increasing Prevalence of Gestational Diabetes Mellitus. Diabetes Care 2007;30:S141–6. https://doi.org/10.2337/dc07-s206.
3. Agha-Jaffar R, Oliver N, Johnston D, Robinson S. Gestational diabetes mellitus: does an effective prevention strategy exist? Nat Rev Endocrinol 2016;12:533–46. https://doi.org/10.1038/nrendo.2016.88.
4. Sweeting A, Wong J, Murphy HR, Ross GP. A Clinical Update on Gestational Diabetes Mellitus. Endocr Rev 2022;43:763–93. https://doi.org/10.1210/endrev/bnac003.
5. Agarwal MM, Dhatt GS, Shah SM. Gestational Diabetes Mellitus. Diabetes Care 2010;33:2018–20. https://doi.org/10.2337/dc10-0572.
6. Jagannathan R, Neves JS, Dorcely B, Chung ST, Tamura K, Rhee M, Bergman M. The Oral Glucose Tolerance Test: 100 Years Later. Diabetes Metab Syndr Obes Targets Ther 2020;Volume 13:3787–805. https://doi.org/10.2147/DMSO.S246062.
7. Xu W, Wang C, Hua J. X-box binding protein 1 (XBP1) function in diseases. Cell Biol Int 2021;45:731–9. https://doi.org/10.1002/cbin.11533.
8. Hetz C, Martinon F, Rodriguez D, Glimcher LH. The Unfolded Protein Response: Integrating Stress Signals Through the Stress Sensor IRE1α. Physiol Rev 2011;91:1219–43. https://doi.org/10.1152/physrev.00001.2011.

9. Acosta-Alvear D, Zhou Y, Blais A, Tsikitis M, Lents NH, Arias C, Lennon CJ, Kluger Y, Dynlacht BD. XBP1 Controls Diverse Cell Type- and Condition-Specific Transcriptional Regulatory Networks. Mol Cell 2007;27:53–66. https://doi.org/10.1016/j.molcel.2007.06.011.
10. Hotamisligil GS. Endoplasmic Reticulum Stress and the Inflammatory Basis of Metabolic Disease. Cell 2010;140:900–17. https://doi.org/10.1016/j.cell.2010.02.034.
11. Bravo R, Parra V, Gatica D, Rodriguez AE, Torrealba N, Paredes F, Wang ZV, Zorzano A, Hill JA, Jaimovich E, Quest AFG, Lavandero S. Endoplasmic Reticulum and the Unfolded Protein Response. Int. Rev. Cell Mol. Biol., vol. 301, Elsevier; 2013, p. 215–90. https://doi.org/10.1016/B978-0-12-407704-1.00005-1.
12. Lu W, Hu C. Molecular biomarkers for gestational diabetes mellitus and postpartum diabetes. Chin Med J (Engl) 2022;135:1940–51. https://doi.org/10.1097/CM9.0000000000002160.
13. Cnop M, Foufelle F, Velloso LA. Endoplasmic reticulum stress, obesity and diabetes. Trends Mol Med 2012;18:59–68. https://doi.org/10.1016/j.molmed.2011.07.010.
14. Boden G, Duan X, Homko C, Molina EJ, Song W, Perez O, Cheung P, Merali S. Increase in Endoplasmic Reticulum Stress–Related Proteins and Genes in Adipose Tissue of Obese, Insulin-Resistant Individuals. Diabetes 2008;57:2438–44. https://doi.org/10.2337/db08-0604.
15. Ma K, Zhang Y, Zhao J, Zhou L, Li M. Endoplasmic reticulum stress: bridging inflammation and obesity-associated adipose tissue. Front Immunol 2024;15:1381227. https://doi.org/10.3389/fimmu.2024.1381227.
16. Xu C, Zhou L, Wu K, Li Y, Xu J, Jiang D, Gao L. Abnormal Glucose Metabolism and Insulin Resistance Are Induced via the IRE1α/XBP-1 Pathway in Subclinical Hypothyroidism. Front Endocrinol 2019;10:303. https://doi.org/10.3389/fendo.2019.00303.
17. Bertolotti A, Zhang Y, Hendershot LM, Harding HP, Ron D. Dynamic interaction of BiP and ER stress transducers in the unfolded-protein response. Nat Cell Biol 2000;2:326–32. https://doi.org/10.1038/35014014.
18. Bogdanet D, O'Shea P, Lyons C, Shafat A, Dunne F. The Oral Glucose Tolerance Test—Is It Time for a Change?—A Literature Review with an Emphasis on Pregnancy. J Clin Med 2020;9:3451. https://doi.org/10.3390/jcm9113451.
19. Metzger BE, Buchanan TA, Coustan DR, De Leiva A, Dunger DB, Hadden DR, Hod M, Kitzmiller JL, Kjos SL, Oats JN, Pettitt DJ, Sacks DA, Zoupas C. Summary and Recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. Diabetes Care 2007;30:S251–60. https://doi.org/10.2337/dc07-s225.
20. Glimcher LH, Lee A-H, Iwakoshi NN. XBP-1 and the unfolded protein response (UPR). Nat Immunol 2020;21:963–5. https://doi.org/10.1038/s41590-020-0708-3.
21. Wang M, Kaufman RJ. Protein misfolding in the endoplasmic reticulum as a conduit to human disease. Nature 2016;529:326–35. https://doi.org/10.1038/nature17041.

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