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Fibrinogen-Albumin Ratio: A Potential New Marker for Gestational Diabetes Severity?

Fibrinojen-Albümin Oranı: Gestasyonel Diyabet Şiddeti için Potansiyel Yeni Bir Belirteç Olabilir mi?

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Abstract

Objectives: Approximately 15% of all pregnancies result in gestational diabetes mellitus (GDM). GDM is a common metabolic disease that is associated with significant changes in inflammatory markers and insulin sensitivity. Higher fibrinogen and lower albumin levels are observed during pregnancy. In addition, since GDM is also an inflammatory process, the fibrinogen-albumin ratio (FAR) may increase more than that in normal pregnancies, suggesting a potential role as an indicator of disease severity. The article aims to investigate the relationship between the severity of gestational diabetes (GDM) and the FAR.

Materials and Methods: A prospective observational study was conducted at the Giresun Maternity and Children Training and Research Hospital. This study included 87 pregnant women, 41 women with GDM, and 46 women in the control group. Demographic, clinical, and biochemical parameters were collected, and FAR was computed. Statistical analyses were conducted to evaluate the diagnostic efficacy of FAR and compare the groups.

Results: Compared to the control group, the GDM group had significantly higher fibrinogen levels (440±73.8 mg/dL vs. 403±57.9 mg/dL, p=0.012), lower albumin levels (36.61 vs. 38.80 g/L, p<0.001), and a higher FAR (12.28 vs. 10.07, p<0.001). A weak positive correlation was found between estimated fetal weight and FAR (p=0.04, r=0.22). ROC analysis demonstrated that FAR had an area under the curve of 0.810, a sensitivity of 78%, and a specificity of 71.7%, indicating acceptable diagnostic accuracy for GDM.

Conclusion: In this study, pregnant women with GDM showed a significant increase in FAR, and this elevation correlated with fetal growth. The results of the study support the potential of FAR as a new biomarker in the management of GDM. However, further research is needed for these findings to translate into clinical applications.

Keywords: Gestational diabetes mellitus (GDM), fibrinogen-to-albumin ratio (FAR), inflammatory markers, insulin resistance, pregnancy complications

Öz

Amaç: Tüm gebeliklerin yaklaşık %15'i gestasyonel diabetes mellitus (GDM) ile sonuçlanabilmektedir. GDM enflamatuvar belirteçlerde ve insülin duyarlılığında önemli değişikliklerle ilişkili, yaygın bir metabolik hastalıktır. Gebelikte daha yüksek fibrinojen ve daha düşük albümin seviyeleri görülmektedir. Buna ek olarak GDM de enflamatuvar bir süreç olduğundan fibrinojen-albümin oranının (FAR) normal gebelere oranla daha fazla artabileceği, hastalığın şiddetinin göstergesi olarak potansiyel bir rol oynayabileceğini düşündürmektedir. Bu çalışmanın amacı, hamile kadınlarda GDM şiddeti ile FAR arasındaki bağlantıyı araştırmaktır.

Gereç ve Yöntem: Giresun Kadın Doğum ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi'nde prospektif gözlemsel bir çalışma yürütüldü. Çalışmaya GDM (n=41) ve kontrol (n=46) gruplarına ayrılan 87 gebe kadın dahil edildi. Demografik, klinik ve biyokimyasal parametrelere ilişkin veriler toplandı ve FAR hesaplandı. Grupları karşılaştırmak ve FAR'ninn tanısal performansını değerlendirmek için istatistiksel analizler yapıldı

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Bulgular: GDM grubunda kontrol grubuna kıyasla anlamlı olarak daha yüksek fibrinojen düzeyleri (440±73,8 mg/dL'ye karşılık 403±57,9 mg/dL, p=0,012) ve FAR (12,28'e karşılık 10,07, p<0,001) ve daha düşük albümin düzeyleri (36,61'e karşılık 38,80 g/L, p<0,001) vardı. FAR ile tahmini fetal ağırlık arasında pozitif yönde, zayıf derecede bir korelasyon bulundu (p=0,04, r=0,22). ROC analizi, FAR'nin 0,810 eğri altında kalan alan, %78 duyarlılık ve %71,7 özgüllük ile GDM için iyi bir tanısal doğruluğa sahip olduğunu gösterdi.

Sonuç: Bu çalışmada FAR, GDM olan gebelerde önemli ölçüde yükselmekte ve fetal büyüme ile korelasyon göstermektedir. Çalışmanın sonuçları, GDM yönetiminde yeni bir biyobelirteç olarak FAR'nin potansiyelini desteklemektedir. Ancak, bu bulguların klinik uygulamalara dönüşmesi için daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: Gestasyonel diabetes mellitus (GDM), fibrinojen-albümin oranı (FAR), enflamatuvar belirteçler, insülin direnci, gebelik komplikasyonları

Introduction

Gestational diabetes mellitus (GDM) is characterized by glucose intolerance that is first recognized during pregnancy and is categorized into two types: A1GDM, controlled through diet, and A2GDM, which requires medication for glycemic control. During pregnancy, metabolic changes, particularly insulin action and sensitivity, increase owing to insulin resistance and hyperglycemia, peaking in the second half of pregnancy (1-3).

GDM management begins with non-pharmacological methods including dietary modifications, exercise, and glucose monitoring. The American Diabetes Association (ADA) recommends nutritional counseling and regular physical activity. Insulin therapy is introduced if glucose levels remain high despite lifestyle changes, with specific dosing strategies based on the trimester and blood glucose targets (2).

GDM is associated with increased levels of inflammatory markers, including pro-inflammatory cytokines (IL-1, IL-6, and TNF-α), and reduced anti-inflammatory cytokines (IL-4 and IL-10). This inflammatory dysregulation is more pronounced in women with GDM than in those without non-GDM pregnancies (4-6).

The fibrinogen-to-albumin ratio (FAR) is a novel marker of inflammation and has been associated with various adverse outcomes, including myocardial infarction, stroke, and cancer. Fibrinogen levels increase during pregnancy, whereas albumin levels decrease because of the inflammatory response. Given that GDM is an inflammatory process, FAR could be higher in GDM patients than in non-GDM pregnancies, potentially serving as a marker of GDM severity. However, no studies have investigated whether FAR can predict disease progression in pregnant women with GDM (7-14).

This study aimed to investigate the relationship between the severity of GDM and FAR. This topic encompasses an important area in both clinical practice and the scientific literature. Identifying new biomarkers for the management of GDM and prevention of complications could provide valuable contributions to the field.

Materials and Methods

Study Design and Setting

Giresun Maternity and Children Training and Research Hospital served as the study site. Pregnant women receiving standard prenatal care at obstetrics and perinatology clinics constituted the study population. This study had a prospective observational design.

Women aged 18-40 years with GDM diagnosed by 75 g oral glucose tolerance test (OGTT) and women who were pregnant but not diagnosed with GDM were included in the study.

Women with several pregnancies were excluded from the study. Women who declined to participate in the research,

women suffering from mental illnesses, and comorbidities included recurrent spontaneous abortions, immunological disorders, hematological disorders, chronic hypertension, chronic nephropathy, liver disease, heart disease and smoking.

Patients diagnosed with GDM were enrolled in the dietary group. However, patients with fasting blood glucose >95 mg/dL and postprandial blood glucose >140 in the 1st hour and >120 in the 2nd hour were included in the insulin treatment. The daily insulin dose was divided as follows: Half was administered as long-acting insulin (detemir) as basal insulin at bedtime, and the other half as rapid-acting insulin (aspart) before meals.

Sample Size

Using the G*Power program (version 3.1.9.4 Heinrich-Heine-Universitat, Düsseldorf, Germany) with similar publications in the literature, Cohen's d effect size was 0.80, alpha(α) value was 0.05, power (1-β) value was 0.80, and the minimum sample size required for statistical significance was 72, including 36 patients from the GDM group and 36 patients from the non- GDM (NGDM) group.

GDM Diagnostic Standards

A 75 g OGTT was used to diagnose GDM according to the ADA guidelines (OGTT). Following a minimum 8- hour overnight fast, plasma glucose levels were assessed at one and two hours

after glucose consumption (12). The diagnostic thresholds were as follows:

- Plasma glucose at fasting: ≥92 mg/dL (5.1 mmol/L);
- Plasma glucose after one hour: ≥180 mg/dL (10.0 mmol/L);
- Plasma glucose after two hours: ≥153 mg/dL (8.5 mmol/L).

Data Collection

Both Direct patient interviews and medical records were used to gather data. The subsequent variables were noted: Age, gender, body mass index, number of pregnancies, gestational age, consanguinity, number of stillbirths, presence of other disorders, and usage of medication are among the demographic and clinical variables.

The following parameters were measured in the laboratory: Levels of creatinine, calcium, albumin, glucose, platelets, white blood cells, neutrophils, and lymphocytes, and complete blood count. Individuals with GDM were treated with insulin as necessary in addition to dietary changes. The treatment plan was documented for all the patients.

Biochemical Analysis

Venous blood samples were collected in BD Vacutainer Sodium Citrate Tube (3.2%=0.109M) and centrifuged at 1500 x g for 15 min to obtain plasma samples. Plasma Fibrinogen levels (mg/dL) were measured based on the fibrinogen clotting time using the Clauss method by Diagon Coag XL (Diagon Ltd., Budapest, Hungary).

Venous blood samples were collected in a BD Vacutainer SST II Advance. It was centrifuged at 1500 x g for 10 min to obtain serum samples. Serum albumin levels (g/L) were measured using the Colorimetric Bromocresol Green method using Cobas c501 (Roche Diagnostics GmbH, Mannheim, Germany).

Statistical Analysis

IBM Corp., Armonk, New York, USA, SPSS version 26.0 was used for all statistical analyses. The normality of the data was evaluated using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Mean ± standard deviation was used to report normally distributed (parametric) data, whereas the median (25^{th}-75^{th} percentile) was used to report non-normally distributed (non-parametric) data. To compare demographic, biochemical, and clinical data between the GDM and control groups, the Mann-Whitney U test was used for non-parametric variables and Student's t-test for parametric variables. GDM subgroups were compared based on treatment modality using the same assays. The associations between FAR and biochemical and demographic factors were assessed using the Spearman's correlation test. The diagnostic sensitivity, specificity, accuracy, and area under the curve (AUC) of the tests were assessed using receiver operating characteristic (ROC) analysis. The Youden index was used to establish a proper cut-off value. Statistical significance was attained when the p-value was less than 0.05.

This study was conducted in accordance with the principles of the Declaration of Helsinki. The Giresun Training and Research Hospital Local Ethics Committee granted clearance (decision number April 07 3, 2024). Before inclusion in the study, each participant provided informed consent.

Results

The participants consisted of 41 GDM pregnancies and 46 controls. Biochemical results and clinical and demographic data are presented in Table 1. The average age There were no statistically significant differences between the GDM and control groups regarding gravidity, parity, estimated fetal weight (EFW), or gestational week at blood sampling (p>0.05).

The fibrinogen and FAR levels were significantly higher in the GDM group than in the control group (p<0.05). Albumin levels were significantly lower in the GDM group (p<0.05) (Table 1).

Pregnancies with GDM were divided into two groups according to the treatment method: those treated with insulin

Table 1: Comparing demographic, biochemical and clinical data of the GDM between control group

	GDM (n=41)	Control (n=46)	p-value*
Age (year)	30.93±4.76	31.07±5.47	0.910
Gravidity	2.15±1.15	2.12±1.12	0.448
Parity	0.92±0.87	0.73±0.97	0.185
Gestational week	31 (29-33)	29 (26-32)	0.06
EFW (gram)	1766±914	1521±761	0.069
Fibrinogen (mg/dL)	440±73.8	403±57.9	**0.012**[a]
Albumin (g/L)	36.31 (33.75-37.77)	38.80 (36.97-40.35)	**<0.001**[b]
FAR	12.28 (10.74-13.69)	10.07 (9.33-11.01)	**<0.001**[b]

*: p=0.05 statistical significance. Paremetric data are presented mean ± standard deviation. [a]: Student's t-test was utilised. Non-parametric data are presented median (25^{th}-75^{th} percentile), [b]: Mann-Whitney U test was utilised, GDM: Gestational diabetes mellitus, EFW: Estimated fetal weight, FAR: Fibrinogen albumin ratio

Table 2: Comparison of demographic, biochemical and clinical data of the GDM group according to treatment method			
	Diet (n=20)	**Insulin (n=21)**	**p-value***
Age (year)	31.11±5.19	30.78±7.22	0.832
Gravidity	2.13±1.07	2.16±1.18	0.418
Parity	0.97±0.86	0.85±0.79	0.217
Gestational week	33.5 (29 -35)	31 (27.5-32.5)	0.236
EFW (gram)	1687±650	1821±713	0.148
Fibrinogen (mg/dL)	441.4±76.31	438.7±73.22	0.548[a]
Albumin (g/L)	36.70 (33.32-37.60)	36.58 (33.95-38.10)	0.296[b]
FARs	11.99 (10.78-13.31)	12.37 (10.63-13.88)	0.639[b]

*: p=0.05 statistical significance. Parametric data are presented mean ± standard deviation, [a]: Student's t-test was utilised. Non-parametric data are presented median (25^{th}-75^{th} percentile), [b]: Mann-Whitney U test was utilised, EFW: Estimated fetal weight, FAR: Fibrinogen albumin ratio

Table 3: Correlations between FAR and demographic, biochemical parameters		
In all groups (n=87)	**Correlation coefficient (r)**	**p-value**
Age (year)	-0.110	0.308
Gravidity	-0.073	0.399
Parity	-0.010	0.924
Gestational week	0.197	0.066
EFW **(gram)**	0.220	**0.040***

*: Spearman Correlation analysis was utilized, FAR: Fibrinogen albumin ratio, EFW: Estimated fetal weight

Table 4: Receiver operating curve analysis of biochemical marker						
Parameter	**AUC**	**95% CI**	**Cut-off value**	**Sensitivity**	**Specificity**	**p-value**
Fibrinogen (mg/dL)	0.659	0.544-0.774	>434	53.7%	76.1%	<0.001
Albumin (g/L)	0.767	0.669-0.865	>37.25	69.6%	65.9%	<0.001
FAR	**0.810**	0.718-0.903	**>10.69**	**78%**	**71.7%**	<0.001

AUC: Area under curve, CI: Confidence interval, FAR: Fibrinogen albumin ratio

(n=21) and those treated with diet (n=20). The two subgroups were analyzed. However, the Mann-Whitney U test and Student's t-test showed that gravidity, parity, EFW, gestational week at blood sampling, fibrinogen, albumin, and FAR between the different treatment methods were not statistically significant (p>0.05) (Table 2).

The correlations between FAR levels and biochemical and demographic variables are shown in Table 3. The FAR levels were positively and weakly correlated with EFW (p=0.04, r=0.22). No significant correlations were found between FAR levels and age, gravidity, parity, or gestational week at blood sampling.

According to the ROC analysis, FAR had the highest AUC value compared to fibrinogen and albumin at 0.810, 0.659, and 0.767, respectively (p<0.001) (Figure 1, Table 4). According to ROC analysis and Youden index FAR level was 10.69 to differentiate GDM pregnancies from controls with 78% sensitivity and 71.7% specificity [95% confidence interval= (0.718-0.903), p<0.001].

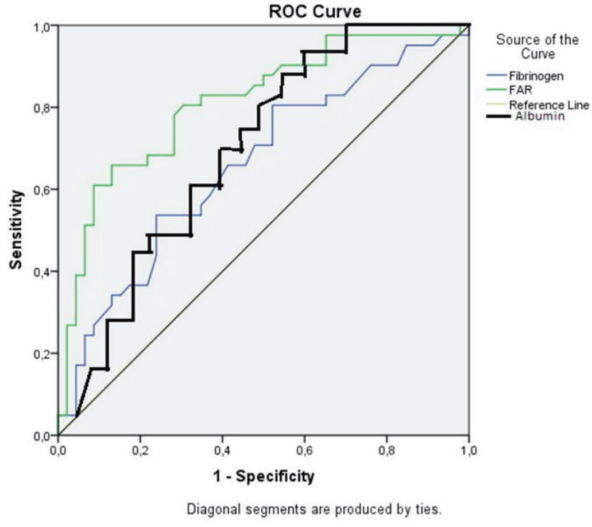

Figure 1: ROC analysis

ROC: Receiver operating characteristic

Discussion

This study aimed to investigate the relationship between the severity of GDM and FAR. Compared to the control group, the GDM group had significantly higher fibrinogen levels (440±73.8 mg/dL vs. 403±57.9 mg/dL, p=0.012), lower albumin levels (36.61 vs. 38.80 g/L, p<0.001), and a higher FAR (12.28 vs. 10.07, p<0.001). A weak positive correlation was found between EFW and FAR (p=0.04, r=0.22). ROC analysis demonstrated that FAR had an AUC of 0.810, a sensitivity of 78%, and a specificity of 71.7%, indicating acceptable diagnostic accuracy for GDM.

The FAR levels were positively and weakly correlated with EFW. This is particularly important, as GDM is associated with an increased risk of macrosomia and related complications.

Interestingly, no significant differences were found in FAR, fibrinogen, or albumin levels between GDM patients treated with insulin and those managed with a diet alone. This may be because glycemic control is achieved with diet or insulin, and FAR is related to glycemic control. In our study, glycemic control was achieved using both diet and insulin. To explain this situation, studies in which an uncontrolled blood glucose group was also included are required.

Previous studies have identified inflammation as a key determinant in the development of GDM. Kansu-Celik et al. (16) reported that high CRP levels in the first trimester are risk factors for the later development of GDM during pregnancy. Ureyen Ozdemir et al. (17) studied the C-reactive protein/albumin ratio (CAR), a recently emerging marker of inflammation, in patients with GDM. Their findings indicated that CAR levels in pregnant women with GDM were significantly higher compared to those in healthy pregnant women (17).

Yilmaz et al. (18) investigated the relationship between the neutrophil-lymphocyte ratio (NLR), another inflammatory marker, and GDM. They concluded that inflammation plays a central role in the pathogenesis of GDM and that NLR is a reliable marker for the disease (18).

Previous studies have linked inflammation to insulin resistance. Elevated levels of advanced glycation end-products in circulation are associated with inflammation and GDM, suggesting that this may play a key role in the underlying pathology of GDM (18).

Fibrinogen is mostly produced by the liver and is a good indicator of coagulation status and inflammation, especially after vascular injury. In the presence of tissue injury and an inflammatory response, its concentration rises dramatically (20-22), linked to microvascular issues in patients with type 2 diabetes (23). In addition, albumin plays a crucial role in extracellular antioxidant activity and immune defense, shows protective anti-inflammatory effects, and is linked to microvascular complications in type 2 diabetes mellitus. The FAR has been found to more accurately reflect inflammation than fibrinogen or albumin alone (24).

Generally, during pregnancy, a series of physiological changes occur in the human hemostatic system as hormones change rapidly, including elevation of coagulation factors, reduction of anticoagulant substances, and decrease in fibrinolytic activity, which finally results in the formation of a hypercoagulable state (25,26). Compared to women who are not pregnant, fibrinogen levels rise sharply in the first trimester of pregnancy and remain elevated in the third trimester (13,27).

Underlying mechanism of FAR increase in GDM patient; fibrinogens also play a role in the development of insulin resistance and impaired glucose control. In contrast, low albumin levels worsen inflammation by increasing the synthesis of molecules that bind cells to one another and reducing the elimination of free radicals (8). The production of hepatic fibrinogen may be stimulated by elevated free fatty acid release during the pathophysiology of insulin resistance and type II diabetes. Visceral fat quantity is strongly correlated with high plasminogen activator inhibitor-1 levels, indicating that insulin resistance syndrome, which predates type II diabetes, may have a greater influence than diabetes itself (8,24). TNF-α is known to increase the synthesis of hepatic fibrinogen and has been implicated in the insulin resistance observed in human obesity, according to recent investigations. Thus, hyperfibrinogenemia may result from specific pathogenic conditions linked to the insulin resistance syndrome (8).

FAR in pregnant women has been studied in conditions such as preeclampsia (28), recurrent pregnancy loss (29), early pregnancy loss (30), and venous thrombosis (31) with FAR found to be elevated FAR. In a study by Ren et al. (28), it was found that the FAR increased in proportion to the severity of preeclampsia, with higher FAR observed in severe preeclampsia compared to mild preeclampsia and the control group.

However, FAR has not yet been studied in pregnant women with diabetes. To the best of our knowledge, this is the first study to investigate FAR in GDM.

Our results align with those of previous research indicating elevated fibrinogen levels in GDM patients. Fibrinogen, an acute-phase reactant, increases in response to inflammation and tissue injury, which are common in GDM. Compared to healthy pregnant women, women with GDM have a greater incidence of thrombophilia, which has been linked to elevated fibrinogen levels.

Study Limitations

This study has several limitations. Conducted at a single center with a small sample size, the generalizability of the results may be constrained. In addition, the cross- sectional

design limits the ability to establish causality. Future research should involve larger, multicenter cohorts, employ longitudinal designs to validate these findings, and further investigate the potential of FAR as a prognostic marker for complications associated with GDM.

Conclusion

The study concluded that pregnant patients with GDM have a significantly higher FAR. These findings support the potential of FAR as a novel biomarker for GDM management. However, further research is required to translate these results into clinical applications.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the principles of the Declaration of Helsinki. The Giresun Training and Research Hospital Local Ethics Committee granted clearance (decision number April 07 3, 2024).

Informed Consent: Before inclusion in the study, each participant provided informed consent.

Footnotes

Authorship Contributions

Concept: M.A., Design: M.A., H.F.A., Data Collection or Processing: M.A., H.F.A., Analysis or Interpretation: M.A., H.F.A., Literature Search: M.A., H.F.A., Writing: M.A., H.F.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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