Original Article

DOI: 10.4274/haseki.galenos.2024.9475
Med Bull Haseki 2024;62:128-135

Investigation of Gasdermin-D and Pannexin-1 in Omental Adipose and Placental Tissues in Obese Pregnant Women

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Abstract

Aim: Gasdermin-D (GSDMD) and pannexin-1 (PANX1), which are proinflammatory proteins, may be involved in the pathogenesis of complications in pregnant women with obesity. We aimed to investigate the expression of GSDMD and PANX1 biochemically in samples of maternal omental and placental tissue obtained from pregnant women with or without obesity, and their correlation with maternal, obstetric, and fetal/neonatal variables.

Methods: The prospective observational study included 79 pregnant women who underwent elective cesarean sections with a pregnancy between 37 and 41 weeks from December 2021 to April 2022. They were divided into three study groups according to their body mass index (BMI): normal weight (with a BMI <25) (n=25), overweight (BMI between 25 and 30) (n=28), and obese (with a BMI >30) (n=26). Omental and placental GSDMD and PANX1 levels were measured by enzyme-linked immunosorbent assay between the groups.

Results: In the homogenate of omental tissue, the median levels of GSDMD and PANX1 protein in the overweight and obese groups were significantly lower than those in the normal weight groups (p=0.0154 and p=0.0184, respectively). In the placental tissue samples, the median levels of GSDMD and PANX1 proteins in the normal weight, overweight, and obese groups were similar.

Conclusion: GSDMD and PANX1 expressions were shown for the first time in the omentum and placenta together; which has the potential to be used as a predictive and diagnostic test panel after further studies in obese pregnant women.

Keywords: Gasdermin-D, pannexin-1, placenta, omental tissue, obesity, inflammation

Introduction

An increased prevalence of obesity in pregnant women may lead to an increased risk of pregnancy-related problems such as gestational diabetes, cesarean birth, hypertensive disorders, preeclampsia, neonatal hypoglycemia, shoulder dystocia, and macrosomia in newborns (1), as well as a long-term rise in the risk of obesity, diabetes, and cardiovascular diseases in children (2). However, the pathogenesis of the condition that affects the health of the mother and offspring caused by obesity during pregnancy remains elusive.

Adipose tissue is a dynamic endocrine organ that participates in a variety of processes, including inflammation (3). Because of the unfavorable secretion pattern of obesity, proinflammatory adipokine stimulates the production of reactive oxygen species, leading to increased oxidative stress (4). Additionally, the placenta secretes a variety of chemicals to sustain the physiology

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Received: 27.10.2023 **Accepted:** 31.05.2024

of pregnancy. Inflammation levels in the placenta could impact the health condition of the mother and her risk of developing gestational diabetes mellitus (GDM), along with the negative effects of obesity and GDM on the fetus (5). Pyroptosis is a rapid, proinflammatory form of cell death in which the pathways of gasdermin-D (GSDMD) and pannexin-1 (PANX1) proteins intersect through their interactions in cellular functions. These novel proteins are produced in cells from both adipose tissue and the placenta (6,7). GSDMD is a pore-forming protein that plays a critical role in inflammation, autoimmunity, and/or cell death. GSDMD is cleaved by activated caspase, releasing its N-terminal domain, which forms pores at the plasma membrane and induces pyroptosis (8). PANX1 hemichannels are expressed by a variety of cell types and form pores in the plasma membrane that allow the penetration of nonviable stains. In this manner, their signaling governs many physiological functions, but they have also been implicated in numerous pathological processes (9).

Understanding and preventing the underlying mechanisms can help prevent long-term pathologies caused by obesity in the mother and infant. Therefore, it is important to conduct further research to understand the etiology of pregnancy-related events in obese women. The expression of the proteins GSDMD and PANX1 has not been adequately investigated in maternal omental adipose tissue and placental tissue samples. We hypothesized that combining these proteins would enhance our understanding of their role in obesity-related pregnancy and perinatal outcomes. Therefore, we biochemically assessed the expression of GSDMD and PANX1 in samples of maternal omental adipose tissue and placental tissue obtained from pregnant women, dividing them into groups based on their body mass index (BMI).

Materials and Methods

Compliance with Ethical Standards

In this prospective observational study, omental adipose tissue and placental samples from mothers who delivered by cesarean section were examined histologically, and ELISA was performed. Ethical approval was obtained from the Institutional Ethics Committee of the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (dated: 24.11.2021, approval no.: 116-2021) and was registered in the ClinicalTrials.gov database (Registry no: NCT05475951, dated: 25.07.2022) according to the Helsinki Declaration and its later amendments or comparable ethical standards. Each woman was asked for written consent after being fully informed of the nature and intended use of the procedures. There was nothing about the study that could harm the health of the mother or the baby. The inclusion of mothers who underwent cesarean sections facilitated the collection of research materials.

Study Design

This study was conducted in accordance with appropriate clinical and experimental ethical guidelines between December 2021 and April 2022 at the Obstetrics and Gynecology Service. The study included 79 pregnant women, and they were divided into three study groups according to their BMI: normal weight (with a BMI<25) (n=25), overweight (BMI between 25 and 30) (n=28), and obese (with a BMI >30) (n=26) (Figure 1). The inclusion criteria were as follows: being between the ages of 20 and 35 years, having a term pregnancy (37-41 weeks), absence of abnormalities during pregnancy follow-up, having a planned cesarean section, absence of complications during surgery, being an appropriate gestational age newborn, and placenta with an anterior or posterior wall. Multiple pregnancies, pregnancies with oligohydramnios or polyhydramnios, preeclampsia, fetal growth restriction or premature birth, and intrauterine surgical procedures were all exclusion criteria.

The study included the basic clinical characteristics, sociodemographic properties, anthropometric measurements, cigarets, and comorbidities of the groups classified according to their BMI. The study also included the birth weight, APGAR values, pH values at birth, and gestational age of the infants born by cesarean section.

Sample Collection and Analysis

Following uterine repair during cesarean section, pieces of omental tissues were taken as adipose tissue, and placental samples were collected from four quadrants of the placentas, including the decidua and chorionic sides, 4-5 cm away from the umbilical cord entrance site for *in vitro* analyses in accordance with prior studies (10,11). Homogenization was applied to the omental and placental tissues collected for biochemical analysis. With ELISA tests, the expressions of GSDMD (12) and PANX-1 (13) proteins in omental and placental homogenates were measured, and the results were used in statistical analysis. The remaining omental tissue samples and placental tissues were fixed with 4% paraformaldehyde for more than 24 h; consequently, they were embedded to prepare wax blocks and cut into slices with a thickness of approximately 4 µm. The sections were stained with hematoxylin and eosin (H&E). Lastly, under-microscope images were collected and analyzed (12,13).

Statistical Analysis

IBM SPSS V26.0 (IBM, USA) software was used for statistical analysis. Graphical presentations were prepared using GraphPad Prism v9.x (GraphPad Software, USA).

Descriptive statistics are presented as average ± standard deviation, median value, 25-75 percentiles, frequency distribution, and percentage. The Kolmogorov-Smirnov test was used to determine whether the distribution of continuous variables obtained is normal or not. Continuous variables are analyzed by parametric ANOVA and Tukey's test if they fit into the normal distribution and by non-parametric Kruskal-Wallis and Mann-Whitney U test if they do not. For comparisons of categorical data, the chi-square test was used for categorical variables. The correlation among continuous variables was examined by Spearman correlation analysis. When the p-value was less than 0.05, the differences were considered significant.

Results

Table 1 presents the maternal and perinatal clinical characteristics of normal-weight, overweight, and obese pregnant women. There were no significant differences among the study groups regarding women's age, blood pressure, smoking status, economic status, gestational age at delivery, number of gravidities, parity, vaginal birth and cesarean birth, newborn's birth weight, Apgar scores at 1 and 5 min, cord blood pH, or the ratio of neonatal intensive care unit admission. Weight, height, and BMI measurements varied because the research groups were created based on the level of obesity.

In Figure 1, the omental tissue homogenate gasdermin-D and pannexin-1 levels of pregnant women

Table 1. Baseline clinical characteristic of study population

	Normal weight (n=25)	Overweight (n=28)	Obese (n=26)	p-value
Age (years)	26 (20-35)	31 (20-35)	28.5 (21-35)	0.163
Blood pressure (mmHg) Systolic Diastolic	 110 (90-150) 60 (60-80)	 110 (90-120) 65 (60-80)	 110 (100-140) 70 (60-80)	 0.51 0.661
Smoking, n (%) Yes No	 2 (8%) 23 (92%)	 0 (0%) 28 (100%)	 1 (3.8%) 25 (96.2)	 0.314
Weight (kg)	62 (48-74)	75 (66-89)	89 (74-123)	0.001
Height (cm)	160 (150-175)	162 (154-177)	158 (150-170)	0.015
Body mass index (kg/m²)	24.09 (20.5-24.8)	28.35 (26.56-29.53)	33.9 (30.9-43.07)	0.001
Comorbidities, n (%) Gestatitonal diabetes Gestatitonal hypertension Kidney diseases Asthma Hypothyroidism	 1 (4%) 1 (4%) 0 (0%) 1 (4%) 5 (20%)	 4 (60.7%) 1 (3.6) 0 (0%) 2 (7.1%) 4 (14.3%)	 3 (11.5%) 0 (0%) 1 (3.8%) 2 (7.7%) 1 (3.8%)	 0.645
Economic status, n (%) Low Low-medium Medium Medium-high High	 4 (16%) 11 (44%) 9 (36%) 1 (4%) 0 (0%)	 6 (21.4%) 13 (46.4%) 8 (18.6%) 1 (3.6%) 0 (0%)	 5 (19.2%) 16 (61.5%) 5 (19.2%) 0 (0%) 0 (0%)	 0.755
Gestational age (weeks)	38 (37-41)	39 (37-40)	39 (37-41)	0.419
Gravidity	3 (1-8)	3 (1-7)	3.5 (2-7)	0.246
Parity	2 (1-5)	3 (1-7)	3 (1-4)	0.408
Number of births Vaginal birth Cesarean	 1 (1-4) 0 (0-3)	 2 (1-4) 0 (0-4)	 2 (1-4) 0 (0-3)	 0.382 0.958
Birth weight (gr)	3240 (2235-4600)	3390 (2375-4410)	3545 (2150-4120)	0.105
Apgar score At 1 min. At 5 min.	 9 (4-9) 9 (5-10)	 9 (5-9) 10 (7-10)	 9 (5-9) 10 (6-10)	 0.997 0.969
Cord blood pH	7.33 (7.09-7.43)	7.36 (7.27-7.42)	7.32 (7.20-7.41)	0.233
NICU admission, n (%) Yes No	 11 (44%) 14 (56%)	 4 (14.3%) 24 (85.7%)	 8 (32%) 17 (68%)	 0.057

The presentation of the data in the table was made as median (minimum-maximum) and number (%). The comparisons of numerical variables were made by the Kruskal-Wallis ANOVA test. The analysis of the nominal data in this table was performed by the chi-square test
NICU: Newborn intensive care unit

with normal weight, overweight, and obesity are shown. The median levels of GSDMD protein in the overweight and obese groups were significantly lower than those in the normal weight groups (p=0.0116 and p=0.0154); however, the median levels of GSDMD in the overweight and obese groups were not comparable. The median levels of PANX1 protein in the overweight and obese groups were also significantly lower than those in the normal weight group (p=0.0101 and p=0.0184); however, no significant difference was found between the overweight and obese groups regarding the median levels of PANX1 protein.

The placental GSDMD and PANX1 levels of pregnant women with normal weight, overweight, and obesity are presented in Figure 2. There were no significant differences among the groups' placental GSDMD levels. In addition, the median levels of placental PANX1 proteins in the normal weight, overweight, and obese groups were similar.

In Figure 3, the serum lipid levels of the normal weight, overweight, and obese groups are shown. There were no significant differences among the groups' median serum levels of high-density lipoprotein, low-density lipoprotein, triglycerides, and cholesterol.

Histological examinations were also performed on placental and omental biopsy samples collected from pregnant women who participated in the study during a cesarean section. During the placental tissue tests, H&E staining revealed that four patients (one of them was normal weight, two of them were overweight, and one of them was obese) had a focal calcification infarction area in their placental tissue, and there were two cases of inflammatory placental tissue (a person was normal weight, a person was obese). All omental biopsy samples were found to be free of any pathological abnormalities.

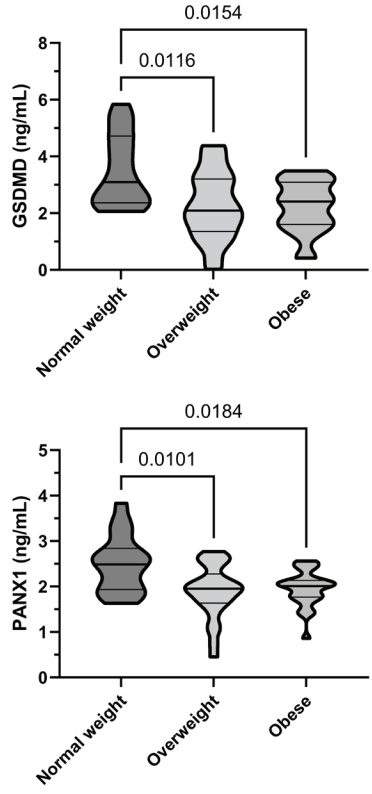

Figure 2. In the omental tissue samples, median levels of GSDMD and PANX1 proteins in the normal weight, overweight, and obese groups. Non-parametric data were presented as a median (dark line) with minimum and maximum values (smallest-largest limits), and comparisons were analyzed using the Kruskal-Wallis test. P-values representing significant differences are expressed on the graphs

GSDMD: Gasdermin-D, PANX1: Pannexin-1

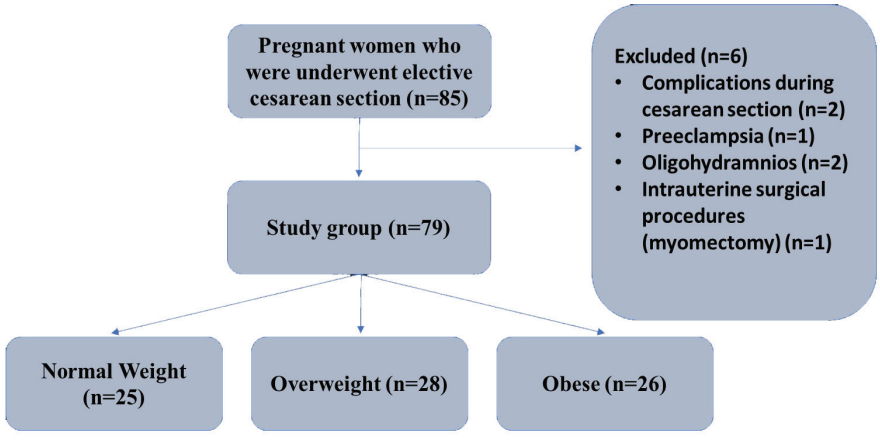

Figure 1. Flow diagram of the study design

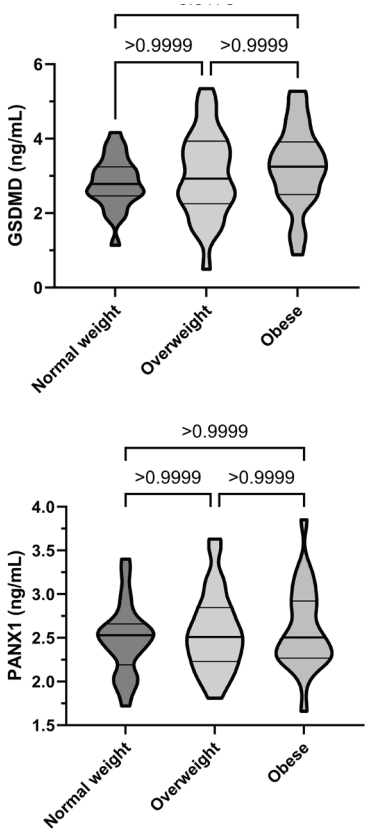

Figure 3. In the placental tissue samples, median levels of GSDMD and PANX1 proteins in the normal weight, overweight and obese groups. Non-parametric data were presented as a median (dark line) with minimum and maximum values (smallest-largest limits), and comparisons were analyzed using the Kruskal-Wallis test
GSDMD: Gasdermin-D, PANX1: Pannexin-1

Discussion

In this study, biochemical and histological changes in omental and placental tissues were observed to investigate the pathogenesis and impact of obesity on pregnancy. GSDMD and PANX1 proteins in omental tissue and the placenta were used to identify inflammation associated with maternal obesity. There was no significant difference in the concentrations of GSDMD and PANX1 in placental tissue among the study groups, although the concentrations of GSDMD and PANX1 in the overweight and obese groups were noticeably lower than those in the normal weight group in the omental tissue. These results would be expected to indicate higher levels of GSDMD and PANX1 in obese and overweight individuals. Obesity modifies metabolic states and may affect the expression of proteins implicated in pathways leading to cell death and signaling. Regarding the involvement of GSDMD and PANX1 proteins in pathways such as inflammation and cell death, their reduced levels may result from metabolic adaptations seen in women with obesity. Additionally, hormone levels are considerably altered during pregnancy, which can impact protein expression. Pregnancy hormones and obesity may interact differently in obese women compared with normal-weight women. The correlation of our findings in humans will be aided by additional clinical and epidemiological studies.

GSDMD and PANX1 proteins are linked to inflammation associated with maternal obesity. The pathogenesis of morbidities affecting mother and baby health caused by obesity during pregnancy is not well known. According to studies, if the stress in the adipose tissue's endoplasmic reticulum increases, obese pregnant women have increased inflammatory processes, which cause obesity and gestational diabetes to form morbidities during pregnancy (13). Studies that examined the pathophysiology of several pregnancy-related morbidities separately included GSDMD and PANX1. The extrinsic pathway of GSDMD is affected by caspase-1 and caspase-8, which also create pores in the cell membrane and result in lytic cell death. The cell membrane glycoprotein structure is triggered by PANX1 with the activation of caspase-3 and caspase-7, creating a channel (7). PANX1 and GSDMD are involved in various body parts. Lower levels of intracellular pyroptosis-related inflammatory factors, such as GSDMD, mitigate hippocampal neuronal injury (14). In a study, it was observed that spontaneous labor at term resulted in greater GSDMD levels in the amniotic fluid than delivery without labor. These findings offer proof that proptosis plays a role in the mechanisms that trigger the sterile inflammatory process of term parturition (12). GSDMD and other proptosis indicators were investigated in placental samples from pregnant women who had preeclampsia and participated in the study. Hypoxia intensifies stress in trophoblasts, considering the multifactorial structure of preeclampsia. Consequently, the GSDMD of the endoplasmic reticulum found in trophoblasts was much higher (15). In this study, according to the results of GSDMD in the homogenate of placental tissue, there was no significant difference in the expression of GSDMD. The underlying reason for this result may be that mothers with any complications, such as GDM and preeclampsia, were not included. On the other hand, when compared with GSDMD expression in the groups, omental adipose tissue was observed to be statistically significant. Although it was not observed beyond the placental tissue, the damage associated with obesity was detectable in the omental tissue. To better comprehend alterations in the placenta due to increased stress, conducting new studies that include pregnant women with complications will be beneficial.

PANX1 is located in many parts of the body; the brain and placenta are some places where it is located. They are found in the cell membrane and share structural similarities with connexins. The results of this study

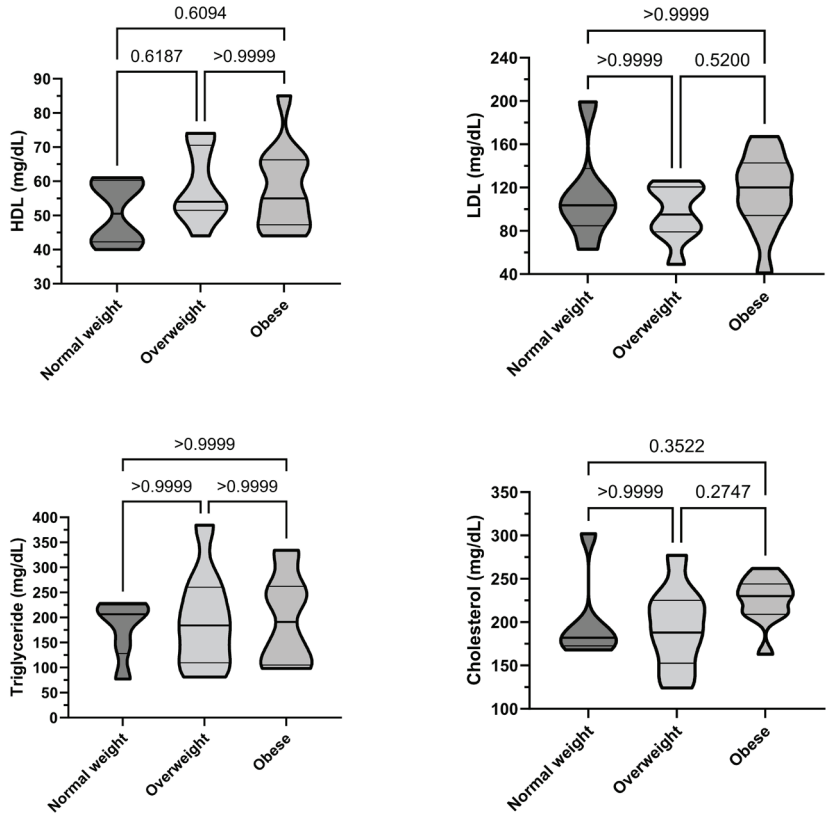

Figure 4. In the serum samples, median levels of HDL, LDL, triglyceride, and cholesterol in the normal weight, overweight and obese groups. Non-parametric data were presented as median (dark line) with minimum and maximum values (smallest-largest limits) and analyzed with the Kruskal-Wallis ANOVA test
HDL: High-density lipoprotein, LDL: Low-density lipoprotein

indicated that PANX1 is continually expressed within various cell types. Moreover, neuroepithelial growth is impeded in the absence of PANX1. This compromise stems from the dysregulation of both cell-cell and cell-matrix adhesion mechanisms, disruption of intracellular signaling pathways, and alterations in gene regulation. These findings highlight the crucial role of PANX1 in the coordination of important processes that regulate early brain development (16). According to some research, neurodevelopmental impairment in children caused by infection or vitamin D deficiency in mothers is linked to an increase in PANX1 suppression in infants (17). Another study was conducted to better understand the role of the PANX-1 protein in ensuring cell migration and purinergic communication. It has been claimed that PANX1 acts as a positive or negative regulator in various inflammatory events (18). It has been acknowledged that the insulin-pannexin-1-purinergic signal was activated with each other in adipocyte cell culture and that this path caused adipose tissue inflammation and type 2 diabetes (19). P2YX7 receptor and PANX1 synthesis in beta cells were shown to be affected by increased glucose levels in the environment in mice and rats. Increased purinergic signals regulate cell function and cell life (20). In this study, PANX1 and Toll-Like Receptor 4 were examined because they correspond to the inflammatory mechanisms involved in preeclampsia pathogenesis. PANX1 channels play a role in inhibiting ferroptosis, which is the reversal of cell death caused by reactive oxygen species produced by NADPH oxidase. Serum Panx1 has a high diagnostic power for ferroptosis in preeclampsia and correlates well with its placental expression (21). The PANX1 glycoprotein is crucial to cell type demise. Human placental cell culture was used to study the death mechanism of syncytiotrophoblasts, and it was discovered that the PANX1 glycoprotein was crucial to the cell type's death (22). There was not a significant difference in PANX1 protein expression within the groups in placental tissue homogenates, according to our data. This could be because the study groups did not include patients with preeclampsia, gestational diabetes, or other diseases. Past studies have revealed that PANX1 channels regulate the absorption of glucose by adipocytes

in response to insulin. Humans with obesity have higher levels of Panx1 expression in adipose tissue (23). An additional investigation revealed interactions within the purinergic and pannexin-1 signaling pathways in adipose tissue, and it was hypothesized that the dysregulation of this signaling may be a factor in type 2 diabetes and inflammation of the adipose tissue (19). The study results regarding the expression of PANX1 protein among the groups in omental tissue were consistent with prior studies; though there was a statistically significant difference.

Study Limitations

The results are more reliable because a prospective observational cohort study design was used. Comparative analysis was made possible by including a control group (normal weight) alongside the overweight and obese groups. Moreover, this study examines an essential relationship between pregnancy outcomes, inflammation, and maternal obesity. The emphasis on the inflammatory processes linked to GSDMD and PANX1 provides new insights into the pathophysiology of complications related to obesity during pregnancy. However, inflammatory processes involve numerous pathways and substances. One of the study's limitations is that additional inflammatory parameters like IL-6 and C-reactive protein were not evaluated. Additionally, due to a lack of adequate funding, immunohistochemical staining could not be performed, and research proteins were only biochemically evaluated by ELISA. Although we conducted the study in a single location, the generalizability of these findings may be limited. Larger, multicenter studies are necessary to generalize the results. Pregnant women with comorbidities such as GDM or preeclampsia were excluded from the study, which may restrict the ability to comprehend the distinctions in GSDMD and PANX1 expressions in these comorbidities.

Conclusion

We observed that maternal obesity during pregnancy increased proptosis, which may impact the health of the mother and infant. The results of this research contributed to the relevant literature in basic science. For both the mother and the newborn, obesity is a major contributor to the development of many problems and comorbidities during pregnancy. GDMD and PANX1 have the potential to be used as predictive and diagnostic test panels after further studies in obese pregnant women.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Institutional Ethics Committee of the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital (dated: 24.11.2021, approval no.: 116-2021).

Informed Consent: Each woman was asked for written consent after being fully informed of the nature and intended use of the procedures.

Authorship Contributions

Concept: F.K., B.A.S., B.S.A., M.T.O., F.Y.G., A.C., Design: F.K., B.A.S., B.S.A., M.T.O., F.Y.G., A.C., Data Collection or Processing: F.K., B.A.S., B.S.A., M.T.O., F.Y.G., A.C., Analysis or Interpretation: F.K., B.A.S., B.S.A., M.T.O., F.Y.G., A.C., Literature Search: F.K., B.A.S., B.S.A., M.T.O., F.Y.G., A.C., Writing: F.K., B.A.S., B.S.A., M.T.O., F.Y.G., A.C.

Conflict of Interest: No conflicts of interest were declared by the authors.

Financial Disclosure: This study received no financial support.

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