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Placental expression of inflammatory Galectin-12 is associated with gestational diabetes

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ABSTRACT

Objectives: Gestational diabetes mellitus (GDM) is a growing health concern. Since members of the galectin-family are identified to play a role in the pathogenesis of GDM, we determined galectin-12 as an essential protein due to its influence in lipolysis and inflammation processes. This study investigates the expression of galectin-12 in the placentas of women with GDM.

Study design: The study population includes 40 expectant women suffering from GDM and 40 healthy controls. The expression of galectin-12 in the syncytiotrophoblast (SCT) and the extra villous trophoblast (EVT) of the placenta was analyzed by immunohistological staining and double immunofluorescence. Immunoreactivity Score (IRS) was used for evaluation.

Results: The results demonstrate a significant overexpression of galectin-12 in the nucleus of the SCT and the EVT of placentas with GDM compared to the healthy control group.

Additionally, double immunofluorescence visualizes corresponding results with an overexpression of galectin-12 in the extra villous trophoblast of GDM placentas representing maternal cells.

Conclusion: This study identifies galectin-12 to be associated with the process of gestational diabetes mellitus. These findings are in correspondence with the involvement of galectin-12 in inflammatory processes. Maternal BMI and male sex seem to be confounder for the expression of galectin-12 in the nuclear syncytiotrophoblast, but not in other parts of the investigated placental areas. Further investigations are necessary to verify the correlation between gestational diabetes mellitus and the expression of galectin-12 in the placenta and to further elucidate its distinct role.

1. Introduction

Gestational diabetes is defined as hyperglycemia first detected at any time during pregnancy. The WHO criteria from 2006 describe one of the following conditions to diagnose gestational diabetes mellitus (GDM): fasting plasma 5.1 – 6.9 mmol/l (92–125 mg/dl), 1-h plasma glucose ≥ 10.0 mmol/l (180 mg/dl) following a 75 g oral glucose load and 2-h plasma glucose 8.5–11.0 mmol/l (153–199 mg/dl) following a 75 g oral glucose load (World Health Organization Guideline, 2014). As a growing health concern, the global prevalence of GDM is 14% with the highest prevalence in high income countries (Wang et al., 2022; Sweeting et al., 2022). Risk factors for developing GDM are well-known: advanced maternal age, overweight or obesity, previous GDM, family history of diabetes and cigarette smoking (Zhang et al., 2016). GDM

Abbreviations: BMI, Body Mass Index; CK7, Cytokeratin 7; Cm, centimeter; Dl, deciliter; EVT, Extra-Villous-Trophoblast cell; GDM, Gestational Diabetes Mellitus; H, hours; IRS, Immunoreactivity Score; IUGR, Intrauterine Growth Restriction; Kg, Kilogramm; M, Meter; Mmol, Millimol; OGTT, oral Glucose Tolerant Test; PP-13, Placenta Protein 13; SCT, Syncytiotrophoblast; WHO, World Health Organization.

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Table 1
Epidemiological and clinical data of the study population.

	GDM		Control		*p*-value
gender	n	%	n	%	
male	20	50.0	20	50.0	
female	20	50.0	20	50.0	
maternal BMI prior to pregnancy (kg/m²)					
Underweight (BMI < 18.5 kg/m²)	0	0	4	10.0	0.116
Normal BMI (18.5 – 24.9 kg/m²)	16	40.0	25	62.5	0.044
Overweight (25.0 – 29.9 kg/m²)	10	25.0	3	7.5	0.034
Obese (≥ 30.0 kg/m²)	12	30.0	5	12.5	0.056
Insulin therapy	30	75.0	0	0	
Delivery mode					
vaginal	27	67.5	32	80.0	0.310
C-section	13	32.5	8	20.0	0.310
Fetal birthweight (g)					
Low birthweight (< 3000 g)	1	2.5	2	5.0	0.556
Normal birthweight (3000 g - 4000 g)	30	75.0	33	82.5	0.412
High birthweight (> 4000 g)	9	22.5	5	12.5	0.239

results in an increased number of peripartum short-term complications and long-term consequences for mother and child. These include macrosomia, shoulder dystocia, developing type 2 diabetes, cardiovascular diseases and metabolic syndromes (Sweeting et al., 2022; Ye et al., 2022; Chiou et al., 2022).

Galectins are proteins of the lectin-family, which are characterized by an amino acid sequence and the affinity to ß-galactoside sugars. Its various functions are reported to play a role as positive and negative regulators in cell proliferation, migration, adhesion, differentiation and defense (Barondes et al., 1994; Kasai et al., 1996; Wan et al., 2016).

In this study we investigated the expression of galectin-12. Galectin-12 consists of a ß-galactoside-binding protein and a carbohydrate recognition domain. It is expressed in adipocytes and peripheral blood leukocytes. Yang et al. described that galectin-12 localizes to lipid droplets in adipocytes. It is a major regulator of adipose tissue development depending on the induction of adipogenic factors by hormone stimulation. Furthermore, galectin-12 functions as a negative regulator of lipolysis leading to an increased mitochondrial respiration for reduced adiposity and improved insulin resistance when suppressed (Yang et al., 2004; Yang et al., 2011). This points to the fact that galectin-12 plays a nonredundant role in fat tissue. However, the mechanisms and necessary interactions for controlling lipolysis triggered by galectin-12 are not completely detected so far (Wan et al., 2016).

As galectin-12 was found to be expressed in macrophages, an influence on inflammation processes could be assumed in correlation with a higher level of interleukins (Baum et al., 2011).

In previous studies, evidence could be provided for the involvement of members of the galectin-family in the syncytiotrophoblast and the cytotrophoblast of the placenta in patients suffering from GDM (Hepp et al., 2020; Unverdorben et al., 2015).

Assuming a correlation between inflammation, lipolysis processes and gestational diabetes mellitus, this study focusses on the expression patterns of galectin-12 in placentas with GDM.

2. Material and methods

2.1. Study design and tissue samples

This study was approved by the LMU ethical committee. Written consent was received by participants. The study group included 80 expectant women divided into 40 patients suffering from GDM (study group) and 40 healthy women (control group). Fetal gender was balanced in both groups.

The diagnosis of gestational diabetes was based on the criteria of the German Society of Diabetes Mellitus which are defined as one of the following pathological measurements of oral glucose tolerant test (oGTT) between 24 and 28 weeks of pregnancy: fasting glucose serum level > 92 mg/dl, after one hour > 180 mg/dl and after two hours > 153 mg/dl.

Furthermore, clinical end epidemiological data like maternal BMI, insulin therapy, birth mode and fetal birthweight were obtained in the study cohort.

Placenta tissue samples sizing 2 ×2×2 cm^3 from a central placenta cotyledon containing maternal decidua, fetal syncytiotrophoblast and amniotic epithelia was collected directly after delivery. Areas with signs of ischemia and calcification were avoided. Samples were fixated in 4% buffered formalin solution for 24 h and embedded in paraffin for further analyzes.

2.2. Immunohistochemical staining

For immunohistochemical staining, a detailed protocol published by Hutter et al. (Hutter et al., 2015) was applied. First, paraffin was removed from the samples in a Roticlear bath (Carl Roth, Karlsruhe, Germany) followed by blocking endogenous peroxidase activity with a 3% H_2O_2-solution. Second, high-pressure sodium citrate treatment (pH 6) was used to demask protein epitopes. To avoid unspecific antigen-antibody interaction, the samples were edited with a blocking solution (ZytoChem Plus HRP Polymer System, Zytomed Systems GmbH, Berlin, Germany). Next, samples were treated with primary antibodies-anti-galactin-12-antibody (polyclonal rabbit IgG, concentrate 0,05 mg/mL, NBP1–89690, Novus Biologicals, Minneapolis, USA), washed in PBS at 1:200 dilution for 16 h at 4 °C and incubated with Post Block (Reagent 2, ZytoChem Plus HRP Polymer System mouse/rabbit, Zytomed) for 20 min followed by HRP Polymer (Reagent 3, ZytoChem Plus HRP Polymer System mouse/rabbit, Zytomed) for 30 min. Visualizing of detected Galectin-12 was guaranteed by applying chromogen 3, 3`-diaminoenzidine (DAB; Dako; Glostrup, Denmark).

Positive and negative control staining were carried out with human colon tissue. All Samples were evaluated using a Leitz Diaplan microscope with 10-fold and 40-fold objectives.

The Immunoreactivity Score (IRS) was used for a detailed description and interpretation of the slides. Therefore, staining intensity (0: none; 1: weak; 2: moderate; 3: strong) and the percentage of positively stained cells (0: no staining; 1: <10% of the cells; 2: 11–50%; 3: 51–80%; 4: >80) was calculated and multiplied in an IRS between 0 and 12 for each slide. All samples were assessed by two different observers counting a minimum of 100 cells.

Table 2
Immunoreactivity Scores IRS.

	GDM			Control			*p*-value
IRS	Mean	Median	Modus	Mean	Median	Modus	
Nuclear expression SCT	2.175	2	2	1.128	1	1	0.004
Cytoplasmatic expression SCT	2.575	3	4	2	2	0	0.297
Nuclear expression Decidua	3.026	3	4	2.436	2	2	0.045
Cytoplasmatic expression Decidua	2.821	3	3	2.360	2	3	0.258

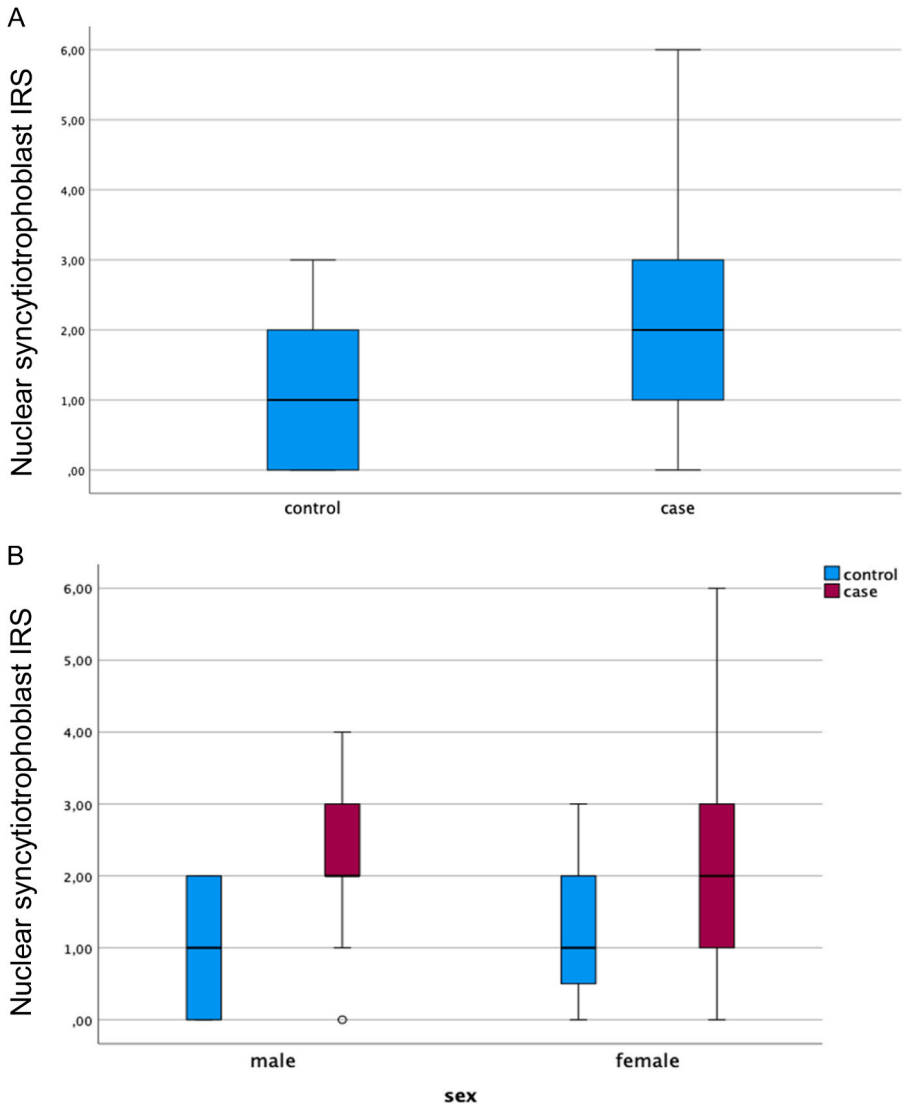

Fig. 1. A: Nuclear Galectin-12 expression in syncytiotrophoblast of GDM placentas (case) and healthy controls (p = 0.004). 1B: gender-specific galectin-12 expression. Boxplots show IRS for nuclear galectin-12 expression by fetal gender in the syncytiotrophoblast.

2.3. Double Immunofluorescence

As Cytokeratin 7 (CK7) is a marker for extra villous trophoblast cells (EVT) (Maldonado-Estrada et al., 2004), it was used in this study to differentiate between fetal and maternal cells within this double immunofluorescence staining method. Again, the paraffin was removed and protein epitopes were demasked following by treatment with a blocking solution (Ultra V-Block, Thermo Scientific, Lab Vision, Fremont, CA, USA) for 15 min to prevent unspecific antigen-antibody interactions. After incubation with primary antibody mixtures (Table 3), the samples were treated with secondary fluorescent antibody mixtures for 30 min. Mounting buffer (Vector Laboratories, Burlinghame, USA), which contains DAPI, was applied for nuclear counterstaining. The slides were evaluated with the fluorescent Axioskop photomicrocope (Zeiss, Oberkochen, Germany) pictured by a digital Axiocam camera system (Zeiss, Oberkochen, Germany) under a 63-fold objective.

2.4. Statistical analysis

IBM SPSS Statistics (Version 26 for MAC, Armonk, NY; USA) was used for data collection and statistical analysis. The non-parametric Mann-Whitney-U-Test was performed for categorial data, the Kruskal Wallis Test was used to analyze continuous variables. Statistical significance was considered to be at $p < 0.05$.

3. Results

A systematic immunohistochemical and immunofluorescent analysis was performed within this study population concerning the expression pattern of galectin-12. Furthermore, we analyzed epidemiological and clinical data and ruled out expected confounding factors.

3.1. Study population

The study cohort included 80 expectant women divided into 40 women diagnosed GDM and 40 healthy controls. Fetal gender was balanced with 20 male and 20 female in each group.

Expectant mothers in the case group where more often overweight than in the control group. Analyzing the average of maternal BMI as a continuous variable in the case group (28.13 kg/m^2) compared to the control group (23.35 kg/m^2) showed significance ($p = 0.002$). Furthermore, the difference of fetal birthweight was also significant with an increased average birthweight of 3611 g in the case group compared to 3317 g in the control group ($p = 0.013$).

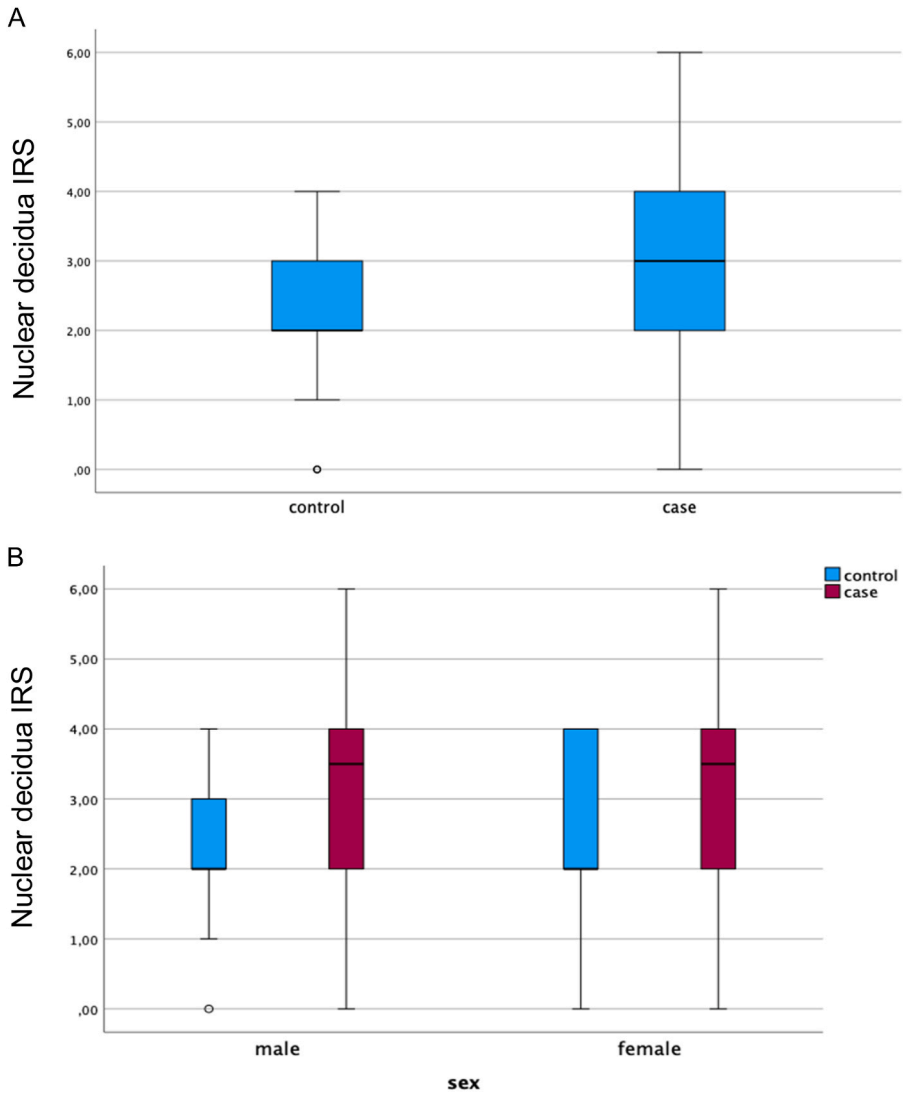

Fig. 2. A: Nuclear Galectin-12 expression in decidua of GDM placentas (case) and healthy controls (p = 0.045) 2B: gender-specific galectin-12 expression. Boxplots show IRS for nuclear galectin-12 in the decidua.

There was no significant difference of delivery mode within the groups.

75% of patients in the case group received insulin therapy. Further known risk factors for gestational diabetes were not detected within the study population.

These epidemiological a clinical data is illustrated in Table 1.

3.2. Galectin-12 is increased in fetal syncytiotrophoblast and EVT of GDM placentas

This study analyzed the expression of galectin-12 in the syncytiotrophoblast, representing the fetal part of the placenta and the decidua, representing the maternal part of the placenta using IRS. An overview of IRS is illustrated in Table 2.

The results show a significant overexpression of galectin-12 in the nucleus of the syncytiotrophoblast ($p = 0.004$) in GDM placentas, whereas the expression of galectin-12 in the cytoplasmatic syncytiotrophoblast is not significant ($p = 0.297$).

In the EVT of GDM placentas our results indicate significance for the upregulated nuclear expression of galectin-12 in the decidua ($p = 0.045$). No significance is seen in the cytoplasmatic decidua ($p = 0.258$). This is highlighted in Figs. 1 and 2.

Representative pictures of the immunohistological staining are presented in Fig. 3.

3.3. Multiple regression analysis

Broere-Brown et al. identified fetal sex as risk factors for pregnancy-associated diseases like preeclampsia and gestational diabetes (Broere-Brown, 2020). For this reason, we performed a regression analysis to describe the influence of these factors on the expression of galectin-12. The linear regression model was used to discover confounding and interaction.

The linear regression model for the nuclear SCT IRS was significant (p = 0.013). The results showed that BMI ($p = 0.008$) and male sex ($p = 0.05$) have to be seen as confounders of the galectin-12 expression in the nuclear SCT.Table 3

However, no significance regarding BMI and male sex could be described for the cytoplasmatic SCT, the nuclear decidua and the cytoplasmatic decidua. These results are depicted in Tables 4 and 5.

3.4. Galectin-12 overexpression is visualized by immunofluorescence double staining

The expression of galectin-12 was visualized by using the immunofluorescence double staining method. Here, Cytokeratin 7 (CK7) was

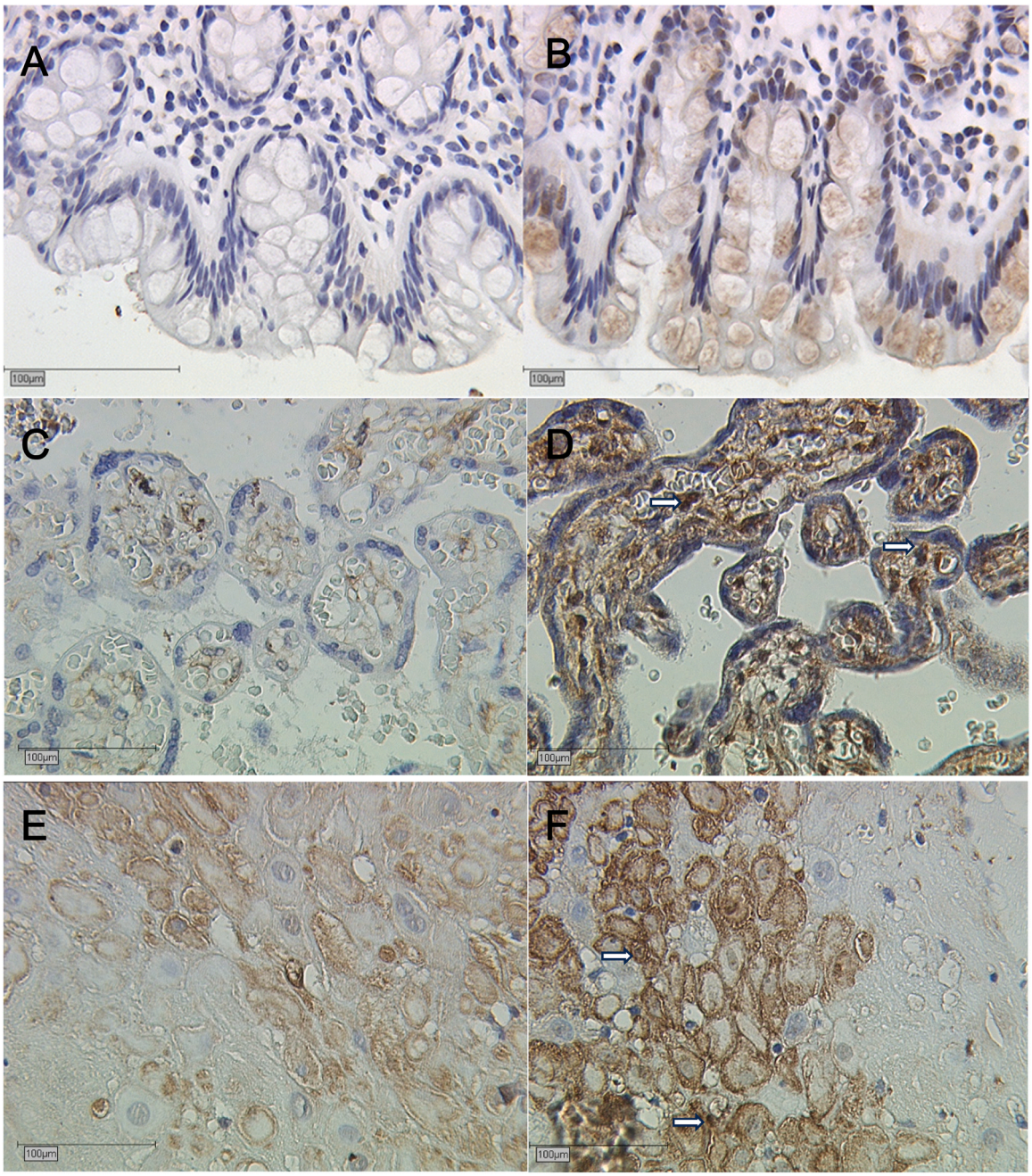

Fig. 3. Immunohistochemical staining of galectin-12, positive expressions are marked with arrows. A: negative control of human colon tissue. B: positive control of human colon tissue. C: Nuclear Galectin-12 staining in the syncytiotrophoblast of control placentas. D: Nuclear Galectin-12 staining in the syncytiotrophoblast of GDM placentas ($p = 0.004$). E: Nuclear Galectin-12 staining in the decidua of control placentas. F: Nuclear Galectin-12 staining in the decidua of GDM placentas ($p = 0.045$).

Table 3
Antibody features used for double immunofluorescence.

Antibody	Incubation	Manufacturer
Galectin-2—polyclonal Rabbit IgG	16 h at 4°C	Novus Biologicals—NBP1–89690
CK7—Clone OVTL Mouse IgG	16 h at 4°C	Novocastra—NCL-L-CK7-OVTL
CD31—Clone JC/70 A Mouse IgG	16 h at 4°C	Abcam—ab9498
Cy-2-labelled goat-anti-rabbit	30 min at RT	Dianova—115–226–062
Cy-3-labelled goat-anti-mouse	30 min at RT	Dianova—111–165–144

Table 4
Multivariate Model of nuclear SCT in placenta tissues.

	Regression coefficient B	Standard deviation	p-value
GDM	0.866	0.553	0.108
Male sex	0.781	0.322	0.05
Maternal BMI	1.365	0.951	0.008

Table 4: Multivariate Model of nuclear SCT placenta tissues. IRS was identified as the depended variable. GDM, male sex and maternal BMI were added as independent variables to the model.

Table 5
Multivariate Model of cytoplasmatic decidual placenta tissues.

	Regression coefficient B	Standard deviation	p-value
GDM	1.573	0.366	0.100
Male sex	0.157	0.737	2.855
Maternal BMI	1.5	1.516	0.526

Table 5: Multivariate Model of cytoplasmatic decidual placenta tissues. IRS-Score was identified as the depended variable. GDM, male sex and maternal BMI were added as independent variables to the model.

used as marker for the extra-villous trophoblast cells (EVT). In this study, CK7 is stained in green. Microscopic evaluation verified the overexpression of galectin-12 in the EVT.

Fig. 4 illustrates these findings.

4. Discussion

Gestational diabetes mellitus is a growing global health concern. Early detection and intervention are mandatory to reduce short-term and long-term complications for mother and child. Nevertheless, there are differences in screening, diagnostic tests and therapeutic options worldwide (Reece et al., 2009; Schneider et al., 2011). However, in 2016 the World Health Organization WHO published a guideline with classification, screening and treatment criteria. Here, a 75 g oral Glucose Tolerant Test (oGTT) is recommended to detect GDM between 24 and 28 weeks of pregnancy (1. World Health Organization Guideline, 2014).

Suffering from GDM requires a multidisciplinary approach including diet management, physically activity, blood-glucose monitoring and medication. In up to 30% of patients diagnosed with GDM treatment with medications is necessary (Lende et al., 2020; Chiou et al., 2022). Since risk factors like obesity and an advanced maternal age are rising within the last decades, the prevalence of GDM is also growing (2). This demonstrates the need of researching pathophysiological and characteristic factors of GDM to provide diagnostic options and reduce severe outcomes.

As galectins are known to be relevant in the inflammation process of GDM, this study focusses on the expression of galectin-12 in placental tissue.

We investigated the expression of galectin-12 in the syncytiotrophobast (SCT), representing the fetal part and the decidua, representing the maternal part of the placenta by immunohistochemical staining and double immunofluorescence.

Our findings showed a significant overexpression of galectin-12 in the nucleus of the SCT and the EVT of GDM placentas compared to the control group.

In previous studies the overexpression of various members of the galectin family could be demonstrated for GDM placentas. For galectin-1, which is known to be involved in inflammatory processes, immunosuppression and regulation on cell proliferation (Blois et al., 2014; Jeschke et al., 2006), Blois et al. described a dysregulation of galectin-1 locally in the placenta and peripherally in the circulation in pregnancies complicated by GDM (Blois et al., 2014).

Galectin-2, another member of the galactoside-binding galectin family, was also detected to be upregulated in GDM placentas. It is predominately expressed in the gastrointestinal tract and is linked to coronary artery diseases, rheumatic arthritis and inflammatory bowel diseases (Negedu et al., 2022; Hepp et al., 2020).

Galectin-13 and galectin-14 are only expressed by the placenta and induce the apoptosis of activated T lymphocytes leading to an imbalance of immune response. For these types of galectins a decreased expression

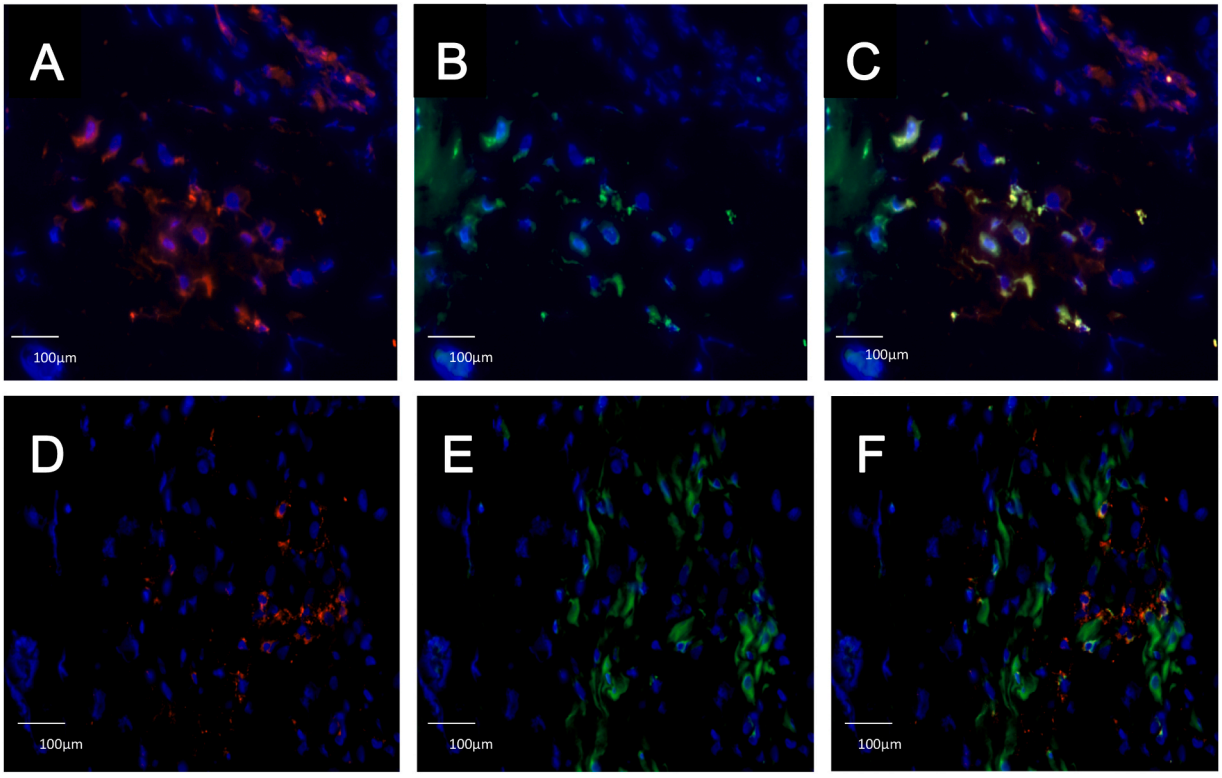

Fig. 4. Double immunofluorescence phenotyping of decidual cells of the placenta in 40x magnification. Nuclei are stained with DAPI (blue). Galectin-12 is stained red. CK7 is stained green, marking the extra-villous trophoblast (EVT). A: Galectin-12 expression in GDM placenta. Nuclei are stained with DAPI (blue), Galectin-12 is stained in red. B: Galectin-12 expression in GDM placenta. Nuclei are stained with DAPI (blue), CK7 is stained in green. C: Galectin-12 expression in GDM placenta. Nuclei are stained with DAPI (blue), CK7 is stained in green and Galectin −12 is stained in red. D: Galectin-12 expression in control group. Nuclei are stained with DAPI (blue), Galectin-12 is stained in red. E: Galectin-12 expression in control group. Nuclei are stained with DAPI (blue), CK7 is stained in green. F: Galectin-12 expression in control group. Nuclei are stained with DAPI (blue), CK7 is stained in green and Galectin Galectin-12 is stained in red.

could be identified for preeclampsia and miscarriages in the first trimester (Balogh et al., 2019). These findings could be strengthened by Unverdorben et al. The study group investigated the expression of galectin-13 in GDM placentas and demonstrated downregulated levels compared to the healthy control group. This confirms an anti-inflammatory function of galectin-13 in the pathogenesis of gestational diabetes (Unverdorben et al., 2015).

Summarizing the results of previous studies, the expression of galectins is correlated to the presence of pregnancy associated diseases like preeclampsia, gestational diabetes mellitus and miscarriages and could influence its pathogenesis. The expression varies depending on the type of galectin and might play an important role in inflammatory and immunomodulatory processes of GDM.

Focusing on galectin-12, we detected an overexpression in the syncytiotrophobast und the EVT of GDM placentas. In 2001 Hotta et al. identified the beta-galactoside protein galectin-12 in adipose tissue of human and mouse adipocytes, localized in the nucleus (Hotta et al., 2001).

The work by Yang et al. reports an insulin resistance and glucose intolerance in galectin-12-profecient mice whereas galectin-12-deficiency improved insulin sensitivity and glucose tolerance. This could be a result of reduced adiposity or improved adipose tissue function (Yang et al., 2011). These facts raise the question if the insulin sensitivity and glucose tolerance differ depending on the BMI of mothers with GDM.

Our observations are limited by the finding that maternal BMI and male sex can be regarded as confounders for the expression of galectin-12 in the nuclear SCT. However, the factors mentioned above could be ruled out as confounders concerning the findings in all other investigated areas of the placentas. Fasshauer et al. illustrated a down-regulation of galectin-12 by various insulin resistance-inducing hormones like tumor necrosis factor alpha and dexamethasone (Fasshauer et al., 2002). Due to a variety of hormonal changes during pregnancy, further investigations are required to figure out the influence of hormones on the expression of galectin-12 in pregnant and non-pregnant situations. As GDM is known to be a state of low-grade inflammation, increased levels of pro-inflammatory cytokines in the syncytiotrophoblast and the extra villous trophoblast could be shown (Keckstein et al., 2020). If there is an interaction between cytokines and galectins will be interesting to evaluate in the future. Changes in the gene or protein expression of galactosin-12 in the placenta was not investigates in this study population and might be an interesting questioning to convince the presenting results.

This study identified the upregulation of galectin-12 in GDM placentas. Maternal BMI and fetal male sex have to be considered as potential confounders in this situation. Further investigation is necessary to understand the impact of galectins and the dependence to other proteins in pregnancy related diseases and to implement these findings in the management of gestational diabetes mellitus.

Disclosure of ethical statements

The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. Ethics committee of the faculty of medicine of the LMU Munich on January 26th, 2010. Approval No. 337–06. All informed consent was obtained from the subjects and/or guardians.

Animals were not involved in this study.

CRediT authorship contribution statement

Udo Jeschke: Writing – original draft, Formal analysis, Conceptualization. **Christina Buschmann:** Investigation, Formal analysis, Data curation. **Sarah Meister:** Visualization, Validation, Data curation. **Susanne Beyer:** Validation, Software, Formal analysis. **Thomas Kolben:** Validation, Software, Resources. **Julia Knabl:** Writing – review & editing, Validation, Conceptualization. **Franziska Ganster:** Writing – original draft, Visualization, Validation. **Stefan Hutter:** Supervision, Resources, Conceptualization. **Elisa Schmöckel:** Software, Resources, Methodology. **Mirjana Kessler:** Writing – original draft, Methodology, Funding acquisition. **Maximiliane Burgmann:** Visualization, Software, Resources. **Alaleh Zati zehni:** Writing – review & editing, Validation, Data curation. **Tanja Kristina Eggersmann:** Resources, Methodology, Formal analysis. **Sven Mahner:** Validation, Software, Resources. **Laura Unverdorben:** Resources, Methodology, Investigation.

Declaration of Competing Interest

Thomas Kolben: holds stock of Bayer AG. Sven Mahner: Research support, advisory board, honoraria and travel expenses from AbbVie, AstraZeneca, Clovis, Eisai, GlaxoSmithKline, Medac, MSD, Novartis, Olympus, PharmaMar, Pfizer, Roche, Sensor Kinesis, Teva, Tesaro. The other authors declare no conflict of interest.

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