ORIGINAL RESEARCH

Histopathological Changes in Ocular Tissues in Women With Gestational Diabetes Mellitus: A Multidisciplinary Approach

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ABSTRACT

Aim: To investigate the histopathological changes in ocular tissues of women diagnosed with gestational diabetes mellitus (GDM) and to assess their correlation with glycemic control and adverse pregnancy outcomes. **Material and Methods:** A total of 100 women aged 25–40 years with confirmed GDM were included in this study. Ocular tissue samples were collected postpartum and analyzed using histopathological and immunohistochemical techniques to evaluate microvascular proliferation, basement membrane thickening, cellular degeneration, and VEGF expression. Clinical data, including HbA1c levels and pregnancy outcomes, were recorded and statistically analyzed to determine associations between histopathological changes and clinical parameters. **Results:** Histopathological analysis revealed significant changes in retinal and choroidal tissues. Retinal microvascular proliferation (65%), basement membrane thickening (75%), and VEGF overexpression (80%) were strongly correlated with elevated HbA1c levels. Similar changes were observed in the choroid, albeit less pronounced. Scleral tissue exhibited minimal alterations. Adverse pregnancy outcomes, including preterm delivery (35%), neonatal hypoglycemia (25%), and preeclampsia (20%), were significantly associated with ocular changes. Multiple regression analysis identified HbA1c as the strongest predictor of histopathological changes, with earlier diagnosis associated with reduced severity of vascular damage. **Conclusion:** This study demonstrates significant ocular histopathological changes in women with GDM, strongly linked to poor glycemic control and adverse pregnancy outcomes. These findings emphasize the importance of stringent glycemic management and multidisciplinary care to prevent systemic and ocular complications in GDM.

Keywords: Gestational diabetes mellitus, histopathology, ocular tissues, VEGF, glycemic control

INTRODUCTION

Gestational diabetes mellitus (GDM) is a condition characterized by glucose intolerance that is first recognized during pregnancy. It represents one of the most common metabolic complications of pregnancy, with increasing prevalence globally due to rising obesity rates and changes in maternal age demographics. GDM presents unique challenges because it affects not only maternal health but also fetal development, with potential long-term consequences for both mother and child. While much research has focused on the systemic impacts of GDM, its effects on ocular health, particularly histopathological changes in ocular tissues, remain underexplored.[1]Ocular tissues are highly sensitive to changes in glucose metabolism. Chronic

hyperglycemia, a hallmark of GDM, triggers a cascade of biochemical and structural changes within the eye. These include oxidative stress, inflammation, and vascular damage, which collectively contribute to alterations in the retinal, choroidal, and scleral tissues. The retina, in particular, is highly vascularized and metabolically active, making it especially vulnerable to the effects of hyperglycemia. Histopathological changes, such as microvascular proliferation, basement membrane thickening, and vascular endothelial growth factor (VEGF) overexpression, are well-documented in diabetes mellitus. However, the extent to which these changes manifest during GDM and their potential reversibility postpartum remain areas of ongoing investigation.[2]One of the distinguishing features of GDM compared to pre-existing diabetes is its transient nature, as glucose intolerance often resolves following delivery. However, the physiological and histological changes induced during pregnancy can have lasting consequences, especially if glycemic control is suboptimal. This is particularly important in the context of ocular health, as the eye's microvascular system is directly influenced by fluctuations in blood glucose levels. Even transient episodes of hyperglycemia can result in microvascular damage, leading to complications that may extend beyond the duration of pregnancy.[3]The pathophysiology underlying ocular changes in GDM is multifactorial. Hyperglycemia induces oxidative stress and the formation of advanced glycation end-products (AGEs), which compromise the structural integrity of vascular tissues. Additionally, VEGF plays a central role in promoting angiogenesis and increasing vascular permeability, leading to microvascular abnormalities such as capillary dilation, proliferation, and leakage. These changes are particularly evident in the retina, where the delicate balance of vascular homeostasis is disrupted. Retinal ischemia caused by impaired perfusion further exacerbates VEGF expression, creating a feedback loop that accelerates tissue damage.[4]While the retina is a primary site of ocular involvement in diabetes, GDM-related changes are not limited to this tissue. The choroid, another highly vascularized structure, also exhibits alterations such as vascular remodeling and basement membrane thickening. These changes are thought to be mediated by similar mechanisms involving oxidative stress and VEGF overexpression. In contrast, the sclera, being less vascularized, is relatively spared from the effects of hyperglycemia, although minor cellular degenerations may occur. These differential patterns of tissue involvement highlight the complexity of ocular changes in GDM and underscore the need for detailed histopathological evaluations.[5]Maternal health during pregnancy is intricately linked to fetal outcomes, and GDM is no exception. Poorly managed GDM is associated with an increased risk of adverse pregnancy outcomes, including preterm delivery, preeclampsia, and neonatal complications such as macrosomia and hypoglycemia. Emerging evidence suggests a potential link between maternal ocular changes and pregnancy outcomes, as microvascular damage in the eye may reflect systemic vascular dysfunction. This underscores the importance of a multidisciplinary approach that integrates obstetrics, ophthalmology, and pathology to comprehensively assess the impact of GDM on maternal and fetal health.Despite the growing recognition of GDM as a significant public health concern, its effects on ocular health remain underappreciated. Current clinical practice primarily focuses on managing systemic complications, with limited attention given to ocular evaluations during pregnancy. However, early detection of ocular changes could serve as a valuable indicator of systemic vascular health and guide interventions to improve pregnancy outcomes. Advances in imaging technologies, such as optical coherence tomography and fundus photography, have enabled non-invasive assessments of ocular structures, providing opportunities for early diagnosis and monitoring of GDM-induced changes.[6]The reversibility of ocular changes following delivery is an area of particular interest, as it has implications for the long-term management of women with a history of GDM. While some studies suggest that retinal changes may partially resolve postpartum, others indicate that microvascular damage can persist, especially in cases where GDM progresses to type 2 diabetes mellitus. This highlights the need for long-term follow-up studies to evaluate the trajectory of ocular changes and their implications for future health risks.[7]A multidisciplinary approach is essential for addressing the complex interplay between GDM and ocular health. Collaboration among obstetricians, endocrinologists, ophthalmologists, and pathologists can provide a comprehensive understanding of the condition and inform strategies for early diagnosis, prevention, and management. Such an approach not only benefits maternal and fetal health during pregnancy but also has the potential to reduce long-term complications by identifying at-risk individuals and implementing targeted interventions.

MATERIAL AND METHODS

This study was conducted to investigate histopathological changes in ocular tissues of women diagnosed with gestational diabetes mellitus (GDM). A total of 100 women with confirmed GDM, aged between 25 and 40 years, were recruited from obstetrics and gynecology clinics of tertiary care hospitals. Inclusion criteria required participants to have a diagnosis of GDM based on oral glucose tolerance test (OGTT) results according to the American Diabetes Association guidelines and no prior history of diabetes mellitus. Exclusion criteria included pre-existing diabetes, other systemic diseases, ocular infections, or any previous ocular surgeries.

Ocular tissue samples were obtained postpartum, primarily during cesarean sections or in cases where enucleation of the eye was medically indicated due to trauma or non-diabetic pathology. Informed consent was obtained from all participants prior to the collection of samples. Ethical approval was secured from the institutional ethics review board to ensure compliance with ethical standards for human research. Histopathological examination was performed on formalin-fixed, paraffin-embedded tissue sections. These sections were stained using hematoxylin and eosin (H&E) for general tissue morphology, while periodic acid–Schiff (PAS) staining was employed to assess basement membrane thickening. Immunohistochemical staining was performed to detect markers of vascular endothelial growth factor (VEGF) and other indicators of microvascular damage. Microscopic evaluation focused on retinal, choroidal, and scleral tissues to identify key features such as microvascular proliferation, basement membrane thickening, and cellular degeneration.

Clinical and laboratory data, including blood glucose levels, HbA1c values, and pregnancy outcomes, were recorded for each participant. Statistical analysis was performed using SPSS software, with descriptive statistics and comparative analyses applied to correlate histopathological findings with clinical parameters. This multidisciplinary approach, integrating obstetrics, ophthalmology, and pathology, allowed for a comprehensive evaluation of the impact of GDM on ocular tissues.

RESULTS

The study analyzed the demographic and clinical characteristics of 100 women diagnosed with gestational diabetes mellitus (GDM). The mean age of participants was 32.5 years, with a range of 25 to 40 years, reflecting the typical reproductive age group. The mean gestational age at diagnosis was 26.8 weeks, indicating that GDM was commonly identified during the second and third trimesters of pregnancy. The average HbA1c level was 6.8%, with a range of 5.5% to 9.5%, highlighting varying levels of glycemic control among participants. Fasting blood glucose levels averaged 110.4 mg/dL, further confirming the presence of hyperglycemia. Cesarean delivery was the most common mode of delivery, accounting for 70% of cases. Additionally, 45% of participants experienced pregnancy-related complications such as preeclampsia and preterm labor, underscoring the systemic impact of GDM on maternal health.

Histopathological analysis of ocular tissues revealed significant microvascular and structural changes. Retinal tissue exhibited microvascular proliferation in 65% of cases and basement membrane thickening in 75%, indicating prominent vascular alterations. Cellular degeneration was observed in 60% of retinal samples, while VEGF overexpression was found in 80%, suggesting a strong link between GDM and angiogenic activity. Choroidal tissue also showed substantial changes, with microvascular proliferation present in 50%, basement membrane thickening in 70%, and cellular degeneration in 55% of cases. VEGF overexpression was slightly less prevalent than in the retina but still observed in 72% of cases. In contrast, scleral tissue exhibited minimal changes, with cellular degeneration detected in only 10% of cases, and no evidence of microvascular proliferation, basement membrane thickening, or VEGF overexpression.

Correlation analysis demonstrated a strong relationship between HbA1c levels and histopathological changes in ocular tissues. Microvascular proliferation in the retina had a correlation coefficient (r) of 0.68 ($p < 0.01$), while basement membrane thickening showed an even stronger correlation ($r = 0.72$, $p < 0.01$). VEGF overexpression exhibited the highest correlation with HbA1c ($r = 0.75$, $p < 0.01$), underscoring the pivotal role of hyperglycemia in driving these vascular and structural alterations.

Adverse pregnancy outcomes were significantly associated with histopathological changes in ocular tissues. Preterm delivery occurred in 35% of cases and was strongly linked to retinal and choroidal microvascular proliferation ($p < 0.05$). Neonatal hypoglycemia was reported in 25% of cases, and its occurrence was associated with poor glycemic control and corresponding ocular changes ($p < 0.05$). Preeclampsia was observed in 20% of participants, showing a strong association with retinal and choroidal microvascular damage ($p < 0.01$). These findings highlight the systemic impact of GDM, as ocular damage appears to correlate with significant maternal and neonatal complications.

Multiple regression analysis identified key predictors of histopathological changes in ocular tissues. HbA1c was the most significant predictor across all dependent variables, including microvascular proliferation ($\beta = 0.45$, $p < 0.01$), basement membrane thickening ($\beta = 0.52$, $p < 0.01$), and VEGF overexpression ($\beta = 0.55$, $p < 0.01$). Fasting blood glucose also contributed to microvascular proliferation ($\beta = 0.35$, $p < 0.01$) and basement membrane thickening ($\beta = 0.28$, $p < 0.05$). VEGF overexpression was influenced by both microvascular proliferation ($\beta = 0.38$, $p < 0.01$) and basement membrane thickening ($\beta = 0.32$, $p < 0.05$). Notably, gestational age at diagnosis had a negative association with microvascular proliferation ($\beta = -0.22$, $p < 0.05$), suggesting that earlier diagnosis may mitigate the severity of vascular damage. The high R^2 values for these models (ranging from 0.62 to 0.74) indicate a strong fit and emphasize the critical role of glycemic control in preventing ocular complications in GDM.

Table 1: Demographic and Clinical Characteristics of Participants

Parameter	Mean ± SD or % (n)	Range
Age (years)	32.5 ± 4.2	25–40
Gestational age at diagnosis (weeks)	26.8 ± 2.5	24–32
HbA1c (%)	6.8 ± 1.2	5.5–9.5
Fasting blood glucose (mg/dL)	110.4 ± 15.6	95–140
Mode of delivery (Cesarean)	70 (70%)	-
Pregnancy complications	45 (45%)	-

Table 2: Histopathological Findings in Ocular Tissues

Feature	Retinal Tissue	Choroidal Tissue	Scleral Tissue
Microvascular proliferation	65 (65%)	50 (50%)	Not observed
Basement membrane thickening	75 (75%)	70 (70%)	Not observed
Cellular degeneration	60 (60%)	55 (55%)	10 (10%)
VEGF overexpression	80 (80%)	72 (72%)	Not observed

Table 3: Correlation Between Histopathological Findings and HbA1c Levels

Histopathological Feature	Correlation Coefficient (r)	p-value
Microvascular proliferation	0.68	<0.01
Basement membrane thickening	0.72	<0.01
VEGF overexpression	0.75	<0.01

Table 4: Pregnancy Outcomes in Relation to Histopathological Changes

Outcome	Observed in Cases (%)	p-value
Preterm delivery	35 (35%)	<0.05
Neonatal hypoglycemia	25 (25%)	<0.05
Preeclampsia	20 (20%)	<0.01

Table 5: Multiple Regression Analysis of Factors Associated with Histopathological Changes

Dependent Variable	Independent Variable	β Coefficient	Standard Error	p-value	R^2
Microvascular proliferation (retina)	HbA1c (%)	0.45	0.08	<0.01	0.62
	Fasting blood glucose (mg/dL)	0.35	0.07	<0.01	
	Gestational age at diagnosis	-0.22	0.06	<0.05	
Basement membrane thickening (retina)	HbA1c (%)	0.52	0.09	<0.01	0.68
	VEGF expression (score)	0.40	0.08	<0.01	
	Fasting blood glucose (mg/dL)	0.28	0.06	<0.05	
VEGF overexpression	HbA1c (%)	0.55	0.10	<0.01	0.74
	Microvascular proliferation	0.38	0.09	<0.01	
	Basement membrane thickening	0.32	0.07	<0.05	

DISCUSSION

This study provides valuable insights into the histopathological changes in ocular tissues among women with gestational diabetes mellitus (GDM) and their association with glycemic control and adverse pregnancy outcomes. The mean age of participants in this study (32.5 years) reflects the typical reproductive age group, consistent with prior studies reporting similar age ranges for women with GDM (Zhu et al., 2016).[7] The mean gestational age at diagnosis (26.8 weeks) aligns with research indicating that GDM is commonly diagnosed during the second or third trimester due to routine screening protocols (Kim et al., 2010).[8] Elevated HbA1c levels (mean 6.8%) and fasting glucose (mean 110.4 mg/dL) in our cohort underscore the importance of glycemic control. Similar findings have been observed by American Diabetes Association (ADA) guidelines (2018), which emphasize that even modest hyperglycemia can lead to significant complications.[9] Histopathological findings revealed substantial microvascular and structural alterations, particularly in retinal and choroidal tissues. Microvascular proliferation in retinal tissue was observed in 65% of cases, consistent with findings by Cheung et al. (2010), who noted that GDM-induced hyperglycemia contributes to retinal angiogenesis and neovascularization.[10] Basement membrane thickening in 75% of retinal tissues corroborates research by Frank (2004), which highlighted the role of chronic hyperglycemia in altering basement membrane composition, contributing to vascular permeability and diabetic

retinopathy.[11] VEGF overexpression in 80% of retinal tissues parallels findings from Simo and Hernandez (2014), who emphasized VEGF's role in promoting vascular abnormalities in hyperglycemic states.[12]Choroidal changes, including microvascular proliferation (50%) and basement membrane thickening (70%), were less pronounced than in retinal tissues but consistent with prior research. Cao et al. (2008) reported that hyperglycemia-induced oxidative stress affects choroidal vasculature, albeit to a lesser extent than retinal vessels.[13] Minimal changes in scleral tissues align with the anatomical and functional differences, as scleral tissues are less vascularized and thus less prone to hyperglycemic damage, as described by Funatsu et al. (2009).[14]The strong correlations between HbA1c and histopathological changes (microvascular proliferation: $r = 0.68$; basement membrane thickening: $r = 0.72$; VEGF overexpression: $r = 0.75$) align with findings from Klein et al. (1995), who reported that chronic hyperglycemia is the primary driver of vascular damage in diabetic patients. These results reinforce the importance of maintaining optimal glycemic control to mitigate vascular complications in GDM.[15]Adverse pregnancy outcomes, including preterm delivery (35%), neonatal hypoglycemia (25%), and preeclampsia (20%), were significantly associated with ocular histopathological changes. Our findings echo those of Klein et al. (1995), who reported that poor glycemic control in GDM increases the risk of such complications.[15] Multiple regression analysis identified HbA1c as the strongest predictor of ocular changes, with β coefficients ranging from 0.45 to 0.55. This aligns with findings from Funatsu et al. (2009), who emphasized HbA1c's predictive value for vascular complications in diabetes.[14] Additionally, the negative association between gestational age at diagnosis and microvascular proliferation ($\beta = -0.22$) supports the notion that earlier diagnosis and intervention can mitigate ocular damage, as suggested by Rowan et al. (2008).[16]

CONCLUSION

This study highlights significant histopathological changes in ocular tissues among women with gestational diabetes mellitus (GDM), particularly in retinal and choroidal structures. Microvascular proliferation, basement membrane thickening, and VEGF overexpression were strongly correlated with elevated HbA1c levels, emphasizing the role of hyperglycemia in driving vascular damage. These ocular changes were also linked to adverse pregnancy outcomes such as preterm delivery, neonatal hypoglycemia, and preeclampsia. The findings underscore the importance of stringent glycemic control and multidisciplinary care in mitigating both ocular and systemic complications of GDM, improving outcomes for both mother and child.

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