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MORPHOLOGICAL CHANGES OF THE PANCREAS IN CHILDREN BORN TO MOTHERS WITH DIABETES MELLITUS. (IN AN EXPERIMENT)

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Abstract

Diabetes mellitus (DM) in the mother is a serious metabolic disorder that profoundly affects fetal development, in particular, the morphogenesis and functional maturation of the pancreas.

This review summarizes the experimental data of studies investigating the morphological and functional state of the pancreas in the offspring of diabetic rat mothers. Using alloxan citrate buffered diabetic rat models, the researchers demonstrated that maternal hyperglycemia impairs pancreatic development, resulting in structural abnormalities such as reduced β-cell mass, disorganized islet architecture, and impaired endocrine function in the offspring. Histopathological analyses reveal marked changes including reduced islet density, fibrosis, and irregular vascularization, which may contribute to long-term metabolic dysfunction., suggesting impaired adaptive mechanisms in glucose homeostasis. Mechanistically, these effects are attributed to intrauterine oxidative stress, epigenetic modifications, and altered expression of critical developmental genes. The results highlight the importance of glycemic control during pregnancy to mitigate the adverse effects of programming on pancreatic health in the offspring. Furthermore, this review highlights gaps in current research, such as the long-term consequences of these changes in adulthood and potential therapeutic interventions. Understanding these mechanisms may inform strategies to prevent metabolic disorders in individuals exposed to a diabetic intrauterine environment.

Keywords

maternal diabetes mellitus, offspring pancreatic development, pancreatic morphology, β-cell mass, islet architecture.

Introduction. Maternal diabetes mellitus (DM) during pregnancy has been extensively studied to have profound and long-lasting effects on fetal

organogenesis, particularly on pancreatic development and function. Offspring of diabetic mothers are at increased risk of metabolic disorders including impaired glucose tolerance, insulin resistance and type 2 diabetes later in life, as demonstrated by Plagemann et al. (2010) and Aerts & Van Assche (2006). The pancreas, as a key regulator of glucose homeostasis, undergoes critical developmental changes during pregnancy that make it highly susceptible to the adverse intrauterine environment induced by maternal hyperglycemia. Early experimental work by Aerts & Van Assche (1979, 2006) first established that maternal diabetes in rats results in β-cell hyperplasia in the fetal pancreas, followed by β-cell depletion and dysfunction in adulthood. Subsequent studies by Gauguier et al. (1991) further characterized these effects, showing that the offspring of diabetic rats exhibit impaired insulin secretion and glucose intolerance, suggesting long-term metabolic programming. Morphological

studies have revealed significant structural changes in the pancreatic islets of offspring exposed to maternal diabetes. Blondeau and all. (2001) reported disorganized islet architecture and reduced β-cell mass associated with oxidative stress induced by maternal hyperglycemia, while Srinivasan et al. (2008) identified fibrosis and decreased vascularity in pancreatic tissue, contributing to endocrine dysfunction. At the mechanistic level, Ericsson et al. (2003) demonstrated that intrauterine hyperglycemia increases oxidative stress in fetal pancreatic tissue, leading to DNA damage and β-cell apoptosis. More recent work by Pinney et al. (2011) and Thompson et al. (2017) has provided compelling evidence that epigenetic modifications, including DNA methylation and histone changes, alter the expression of genes critical for pancreatic development, such as Pdx1 and Glut2. This review summarizes the available experimental data from these key studies and examines the molecular and cellular mechanisms underlying pancreatic maldevelopment in the offspring of diabetic mothers, with the aim of identifying critical knowledge gaps and future research directions in this important area of developmental metabolic programming.

Purpose of the study. The primary objective of this review is to systematically analyze and synthesize existing experimental data on morphological and functional alterations in the pancreas of offspring born to diabetic mothers. By examining structural alterations in pancreatic islets, β-cell dysfunction, and associated metabolic abnormalities, this study aims to elucidate the mechanisms linking maternal diabetes to impaired pancreatic development in the offspring.

To provide a basis for future research aimed at developing preventive or therapeutic strategies to improve metabolic outcomes in offspring exposed to a diabetic intrauterine environment. This comprehensive analysis aims to link

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experimental findings to clinical implications, offering insights that could aid in better management of diabetic pregnancy and reduce intergenerational transmission of metabolic diseases.

Materials and Methods. This comprehensive review systematically analyzed experimental studies investigating morphological and functional changes in the pancreas in the offspring of diabetic rat models, primarily focusing on studies using diabetic dams induced with alloxan in citrate buffer at a rate of 11 mg/100 g of animal weight. The methodological analysis focused on studies reporting quantitative morphometric data (islet size, β-cell mass, vessel density), immunohistochemical methods

Results. Systematic analysis of experimental studies revealed consistent evidence that maternal diabetes causes significant morphological and functional changes in pancreatic tissue in the offspring. Morphometric analysis in several studies demonstrated a 25-40% reduction in β-cell mass, accompanied by disruption of islet architecture characterized by irregular distribution of α- and β-cells and decreased islet vascularization. Immunohistochemical studies showed a marked reduction in the number of PDX-1-positive cells (38.7 ± 5.2% vs. 62.3 ± 6.8% in the control group, $p < 0.01$) and an increase in apoptotic markers in pancreatic islets. Functional assessments revealed impaired glucose homeostasis in the offspring, with intraperitoneal glucose tolerance tests showing 25-30% higher peak glucose levels and a delayed insulin response (2.1 ± 0.3 vs. 3.4 ± 0.4 ng/mL/min in controls, $p < 0.05$) during critical developmental windows.

The study suggests that these early developmental changes predispose the offspring to metabolic dysfunction in adulthood, with 60% of exposed animals developing glucose intolerance by 6 months of age. The combination of maternal diabetes and obesity exacerbated these effects, resulting in more severe pancreatic fibrosis and earlier onset of insulin resistance. The overall results consistently support the conclusion that maternal diabetes programs long-term pancreatic dysfunction in the offspring through interacting mechanisms.

Tab. 1

Morphological changes in the pancreas of offspring

Parameter	Conclusions	Measurement method	Meaning	Links
β-cell mass	25-40% reduction compared to control samples	Immunohistochemistry (insulin+)	Impaired ability to produce insulin	Blondeau et al. (2001)
The architecture	Disorganized distribution of α/β	Confocal microscopy	Disruption of paracrine	Srinivasan et

of the island	cells; irregular islet shape		signaling in the islets	al. (2008)
PDX-1+ cell	38,7±5,2% versus 62,3±6,8% in the control group (p<0,01)	IHC (antibody to PDX-1)	Decreased differentiation of progenitor cells	Eriksson et al. (2003)
Apoptosis markers	↑ Caspase-3 activity (2,5 times)	Analysis TUNEL/Western blot	Increased β-cell death	

Quantified by the area of insulin-positive cells/total pancreatic area, indicating a decreased capacity to produce insulin. α-cells (glucagon+) are usually localized to the periphery of the islets; impaired distribution impairs glucose counterregulation. The master regulator of pancreatic development; its decrease suggests impaired β-cell maturation.

Tab. 2

Functional and long-term metabolic outcomes

Assessment	**Results**	**Experimental method**	**Interpretation**	**Links**
Glucose tolerance	Peak glucose ↑ 25-30%; AUC ↑ 1,8 times	IPGTT (2 g/kg)	Impaired glucose clearance	Pinney et al. (2011)
Insulin secretion	2.1±0.3 vs 3.4±0.4 ng/mL/min (p<0.05)	Hyperglycemia cystic clamp	Slowed first phase insulin response	
Adult onset dysfunction	60% developed glucose intolerance by 6 month	Longitudinal IPGTT	Programming the development of diabetes	Plagemann et al. (2010)
Fibrosis	Collagen deposition 1 to 3 times in offspring with obesity and diabetes	Coloring trichrome Masson	Structural damage that worsens functional decline	Zambrano et al. (2016)
Effects of interventions	↓ MDA antioxidants by 40%; glycemic control normalized β-cell mass	Treatment N-acetylcystein	Reversible component programming development	(Multiple studies)

An intraperitoneal glucose tolerance test (2 g/kg) showed delayed glucose clearance (AUC = area under the curve). Defective kinetics of insulin secretion (the first phase of the insulin response, critical for glucose homeostasis) were detected. Excessive collagen deposition (quantified by image analysis of stained sections) correlated with progressive pancreatic dysfunction. Antioxidant therapy (e.g., N-acetylcysteine) and strict maternal glycemic control partially reversed the phenotypes, suggesting modifiable mechanisms.

Discussion. The results of this systematic review demonstrate that maternal diabetes causes profound and long-lasting changes in pancreatic morphology and function in the offspring, mediated through multiple interconnected biological pathways. The observed 25–40% reduction in β-cell mass (Table 1) is consistent with previous reports of hyperglycemia-induced β-cell apoptosis (Blondeau et al., 2001), suggesting that intrauterine oxidative stress may trigger caspase-dependent cell death pathways. This is further supported by a 2.5-fold increase in apoptotic markers, which correlates with clinical studies showing reduced β-cell area in human infants of diabetic mothers (Pasek & Gannon, 2013). Disruption of islet architecture, in particular the abnormal distribution of α- and β-cells, may impair intra-islet paracrine signaling, a critical mechanism for glucose-stimulated insulin secretion (Brissova et al., 2018). These structural changes likely contribute to the blunted insulin response (2.1 ± 0.3 vs. 3.4 ± 0.4 ng/mL/min) observed during hyperglycemic clamps (Table 2). This creates a vicious cycle in which oxidative stress and epigenetic changes mutually reinforce pancreatic dysfunction. 60% of cases of glucose intolerance in adults (Plagemann et al., 2010) highlight the developmental origin of metabolic diseases. In particular, a 3-fold increase in pancreatic fibrosis in obese diabetic offspring (Zambrano et al., 2016) suggests accelerated organ aging, potentially via TGF-β-mediated stellate cell activation (Apte et al., 2019). This is consistent with clinical observations of early β-cell failure in adolescents with prenatal diabetes exposure (Petry et al., 2020). However, partial restoration of β-cell mass with antioxidant therapy implies modifiability of these pathways, opening up opportunities for targeted interventions.

The vulnerability of pancreatic progenitor cells in late pregnancy (Thompson et al., 2017) suggests the need for time-dependent interventions.

The 40% reduction in MDA levels with N-acetylcysteine (Table 2) warrants trials with mitochondria-targeted antioxidants.

Animal data indicate that glucose levels >11.1 mM cause irreversible changes (Pinney et al., 2011), allowing for the development of clinical monitoring protocols.

These findings fundamentally advance our understanding of developmental metabolic programming, highlighting the need for precision approaches to pregnancy management in diabetic patients to reduce risk to offspring.

Conclusion. This comprehensive review brings together compelling experimental evidence demonstrating that maternal diabetes causes significant and long-lasting morphological and functional abnormalities in offspring pancreatic tissue mediated through interrelated mechanisms involving oxidative stress, epigenetic modifications, and altered gene expression. Consistent findings of reduced β-cell mass (25-40%), disrupted islet architecture, and impaired glucose homeostasis across multiple studies highlight the profound impact of intrauterine hyperglycemia on pancreatic development. Molecular characterization of these alterations, in particular Pdx1 promoter hypermethylation and elevated oxidative stress markers, provides mechanistic insight into how maternal diabetes programs the offspring for metabolic dysfunction, as evidenced by 60% of cases of glucose intolerance in adulthood. Importantly, partial reversibility of these effects through antioxidant therapy or strict glycemic control during pregnancy offers promising intervention strategies, suggesting that adverse programming effects are not completely irreversible but rather modifiable during critical periods of development.

These findings have important clinical implications, highlighting the need for optimized glycemic control in diabetic pregnancy and warranting further exploration of targeted therapeutic approaches to reduce the risk of transgenerational metabolic diseases. However, the limitations of existing animal models, particularly their inability to fully recapitulate the progressive nature of human type 2 diabetes, highlight the need for additional studies in human cohorts and advanced molecular techniques such as single-cell sequencing to fully elucidate the cellular and epigenetic dynamics underlying these observations. Future research should prioritize longitudinal studies to assess the transgenerational robustness of these effects and explore novel interventions including antioxidants and mitochondria-targeted epigenetic modulators to break the cycle of metabolic disease transmission. Collectively, this work not only advances our understanding of developmental programming but also provides a scientific basis for developing preventive strategies to improve metabolic health outcomes in offspring exposed to a diabetic intrauterine environment.

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