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COMMENTARY

Exploring the Autoimmune Hypothesis of Type 1 Diabetes: Investigating the Potential Role of Peritoneal Membrane Defects in the Pancreatic Tail and Revisiting Alternative Theories of Disease Etiology

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Abstract

Type 1 Diabetes Mellitus (T1DM) has traditionally been understood through the lens of autoimmune destruction of pancreatic beta cells. However, emerging evidence suggests that defects in the peritoneal membrane, particularly in the pancreatic tail, may play a significant role in the disease's pathogenesis. This study explores the "Peritoneal Protection Hypothesis," which posits that the integrity of the peritoneal membrane is crucial in maintaining pancreatic beta cell function and preventing autoimmune-mediated destruction. We review the biochemical and immunological mechanisms through which peritoneal membrane defects could contribute to beta-cell dysfunction and T1DM onset. By integrating novel insights into peritoneal membrane biology with current autoimmune theories, we provide a comprehensive framework that may redefine the understanding of T1DM etiology and highlight potential therapeutic avenues.

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1. Introduction

Type 1 Diabetes Mellitus (T1DM) is a chronic autoimmune disorder characterized by the selective destruction of pancreatic beta cells, leading to an absolute deficiency of insulin. This condition typically manifests during childhood or adolescence, with a sudden onset of symptoms such as polyuria, polydipsia, and unexplained weight loss. It is one of the most common endocrine disorders in children, with the peak incidence occurring between the ages of 5 and 7, and another spike during puberty [1]. Although T1DM primarily affects younger individuals, it can also present in adults, often with a delayed diagnosis due to its atypical presentation. The autoimmune hypothesis remains the predominant theory explaining the pathogenesis of T1DM, suggesting that an aberrant immune response, possibly triggered by genetic and environmental factors, targets and destroys insulin-producing beta cells within the pancreatic islets of Langerhans [2].

Although significant evidence supports this theory, several aspects of T1DM pathophysiology remain unresolved, suggesting the need for alternative or complementary hypotheses to better understand disease onset and progression [3]. In this context, the peritoneal membranes serve as crucial protective barriers that prevent immune-mediated damage to internal organs. The peritoneum, a serous membrane that lines the abdominal cavity and covers the visceral organs, plays a critical role in regulating immune responses and maintaining tissue homeostasis [4]. Biologically and immunologically, the peritoneal membrane contains mesothelial cells that secrete anti-inflammatory cytokines and modulate immune cell trafficking. Furthermore [5], Major Histocompatibility Complex (MHC) proteins expressed on these membranes aid in distinguishing self from non-self, thereby reducing the likelihood of immune-mediated tissue damage [6].

The pancreatic tail, which is enveloped by the peritoneum in the retroperitoneal space, may be particularly vulnerable to defects in this protective barrier [7]. The pancreatic tail is a critical site for endocrine function, housing approximately 25-30% of the pancreas's beta cells, which are responsible for insulin secretion [8]. This region also has a relatively higher density of GLP-1 receptors, which play a significant role in enhancing insulin secretion and beta-cell proliferation [9]. A potential defect in the peritoneal membrane or its associated immune-regulatory [10] mechanisms could allow autoreactive immune cells or antibodies to access and destroy beta cells specifically in this region, leading to the onset of T1DM [11].

The aim of this study is to gather and analyze evidence supporting a novel hypothesis that links peritoneal membrane dysfunction in the pancreatic tail to the etiology of T1DM. We propose that defects in the structure or function of the

peritoneal barrier may predispose individuals to beta-cell destruction by autoimmune mechanisms, particularly in the pancreatic tail. This study seeks to reassess the current understanding of T1DM pathogenesis and explore the possibility that impaired peritoneal defenses against immune attack might be a primary contributing factor in the development of this disease.

2. Methodology

This review employs a comprehensive and systematic approach to evaluate and propose a novel hypothesis regarding the pathogenesis of Type 1 Diabetes Mellitus (T1DM). An extensive literature search was conducted across multiple databases, including PubMed, Scopus, and Web of Science, to gather relevant studies on the autoimmune hypothesis of T1DM, pancreatic anatomy, peritoneal membrane defects, and related immunological processes. The search included both primary research articles and review papers, covering a range of studies from clinical trials to animal models, with a focus on those that directly contribute to the understanding of T1DM etiology. The collected literature was critically analyzed to identify gaps in the current understanding of T1DM pathogenesis, particularly in the context of immune responses and structural abnormalities in the pancreas. Special attention was given to studies that explore the relationship between the peritoneum, pancreatic function, and immune system interactions, which formed the basis for developing the new hypothesis that defects in the peritoneal membrane of the pancreatic tail might play a crucial role in initiating or exacerbating the autoimmune destruction of beta cells. The autoimmune hypothesis of T1DM was compared with the proposed hypothesis regarding peritoneal membrane defects, evaluating the strengths and limitations of each theory and assessing how well each explains the clinical manifestations and progression of T1DM. This evaluation also considered existing experimental data and clinical observations that could support or refute the new hypothesis. Based on this analysis, a conceptual framework was developed to illustrate how peritoneal membrane defects could influence pancreatic immune tolerance and beta-cell survival, integrating insights from immunology, anatomy, and cellular biology to propose a new model of T1DM pathogenesis that accounts for both structural and immune-related factors. In light of the findings, specific research directions were proposed to test the validity of the new hypothesis, including experimental designs to verify the impact of peritoneal defects on beta-cell autoimmunity and clinical studies aimed at identifying potential biomarkers related to peritoneal integrity in T1DM patients. This methodology ensures a thorough and balanced exploration of the novel hypothesis, providing a strong foundation for future investigations into alternative mechanisms underlying T1DM.

3. Anatomical and Physiological Characteristics of the Pancreas with a Focus on the Tail Region

The pancreas is a vital organ located in the abdominal cavity, playing dual roles in both the digestive and endocrine systems. Anatomically, it is divided into four main regions: the head, neck, body, and tail. The pancreas is a retroperitoneal organ, meaning that it is located behind the peritoneum, except for a small portion of the tail, which is intraperitoneal and

covered by the peritoneal membrane [Figure 1].

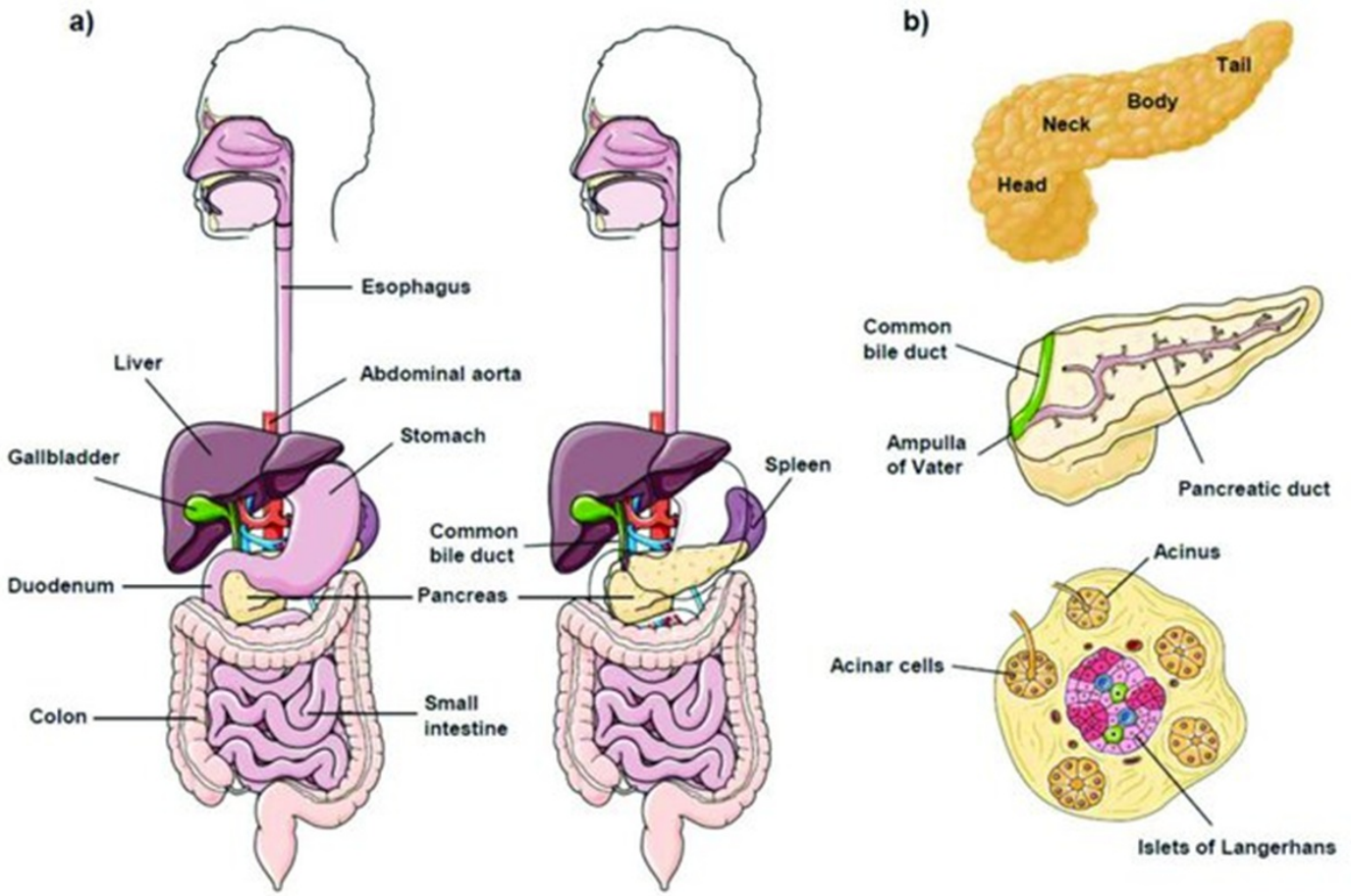

Figure 1. Pancreas anatomy. (a) Location and anatomical relationships between the pancreas and organs surrounding it in the abdomen. The pancreas is located behind the stomach, and the head of the pancreas is surrounded by the C-loop of the duodenum. (b) (Upper) The pancreas is divided into four major anatomical regions: head, neck, body, and tail. (Middle) The pancreatic duct extends from the tail to the head and collects juices from all of the branches of the pancreatic stream. The pancreatic duct joins the common bile duct in the head of the pancreas to form the ampulla of Vater, which empties into the duodenum. (Lower) Most of the pancreas consists of exocrine tissue, producing pancreatic enzymes for digestion. The cells that synthesize and secrete digestive enzymes are clustered in grape-like bunches called acini (acinus, singular). These pancreatic acinar cells of the acinus synthesize, store, and secrete digestive enzymes that are drained into the pancreatic duct. The remaining tissue consists of endocrine cells called islets of Langerhans, which are clusters of pancreatic endocrine cells that produce and release hormones (such as insulin and glucagon) into the bloodstream regulating glucose levels [12].

This distinction in location has important implications for both the structural integrity of the organ and its vulnerability to autoimmune attacks. The pancreas measures approximately 12-20 cm in length, with the tail representing the narrow, leftmost portion, tapering off near the spleen [13]. The tail of the pancreas is embedded within the splenorenal ligament and is unique in that it is the only part of the pancreas that lies intraperitoneally, specifically within the interperitoneum [14].

This location allows the tail to be more accessible to potential peritoneal defects, making it a key focus in understanding the etiological factors contributing to diseases like Type 1 Diabetes Mellitus (T1DM).

Physiologically, the pancreas is composed of both exocrine and endocrine tissues. The exocrine tissue, comprising acinar

cells, is responsible for secreting digestive enzymes into the duodenum. In contrast, the endocrine tissue is organized into the islets of Langerhans, which are dispersed throughout the pancreas and contain various cell types, including alpha cells (producing glucagon), beta cells (producing insulin), delta cells (producing somatostatin), and PP cells (producing pancreatic polypeptide) [15].

The tail of the pancreas is particularly significant from an endocrine perspective, as it contains a higher concentration of islets of Langerhans compared to other regions of the pancreas. It is estimated that approximately 25-30% of the pancreas's beta cells reside in the tail region, which is responsible for insulin production [16]. This higher density of beta cells in the tail suggests that it plays a crucial role in maintaining glucose homeostasis. Furthermore, the tail region has a relatively higher expression of Glucagon-Like Peptide-1 (GLP-1) receptors, which are critical in enhancing insulin secretion and beta-cell proliferation. These receptors modulate the insulinotropic effects of incretins and are thus vital in glucose regulation, particularly postprandially [17].

The intraperitoneal location of the pancreatic tail makes it unique in that it is enveloped by the peritoneal membrane, a serous membrane that acts as a protective barrier. This membrane plays a pivotal role in preventing the immune system from mistakenly attacking the pancreatic tissue. The peritoneal membrane's anti-inflammatory properties and regulation of immune cell trafficking are essential in maintaining the immunological privilege of the pancreas [18]. However, any defects in this membrane, particularly in the tail region, could potentially expose the beta cells to autoimmune destruction, leading to conditions such as T1DM.

The tail region of the pancreas, including its intraperitoneal portion, constitutes approximately 15-20% of the total pancreatic mass. Given that the tail harbors a significant proportion of the pancreas's beta cells, its functional integrity is paramount in preserving endocrine function. The interperitoneal coverage of the tail, while offering a layer of protection, also presents a potential vulnerability; a breach in this protective barrier could allow immune cells or antibodies to target the beta cells within the tail. This potential vulnerability underscores the importance of understanding the structural and immunological characteristics of the pancreatic tail in the context of autoimmune diseases like T1DM.

4. Potential Causes of Interperitoneal Membrane Dysfunction in the Pancreatic Tail: Biological Mechanisms and Genetic Influences

The interperitoneal membrane surrounding the tail of the pancreas plays a crucial role in maintaining the immune privilege of the organ by shielding it from immune system attacks. However, several factors can contribute to the weakening, inflammation, or temporary failure of this protective barrier, leading to a heightened vulnerability of the pancreatic beta cells to autoimmune destruction. Understanding the mechanisms behind such dysfunction is critical for elucidating the pathogenesis of Type 1 Diabetes Mellitus (T1DM) and other autoimmune conditions.

One of the primary factors that can compromise the interperitoneal membrane's integrity is chronic inflammation. Persistent inflammatory stimuli within the abdominal cavity, such as peritonitis or chronic inflammatory conditions like Crohn’s disease, can lead to the disruption of the mesothelial cell layer that lines the peritoneum [19][20]. These cells are

essential for maintaining the anti-inflammatory environment and regulating immune cell trafficking. When inflamed, mesothelial cells can lose their ability to produce anti-inflammatory cytokines, such as IL-10 and TGF-β, which are critical for suppressing local immune responses [21]. This inflammatory milieu can lead to increased permeability of the interperitoneal membrane, allowing immune cells to infiltrate the pancreatic tail and potentially target beta cells [22].

Another contributing factor to interperitoneal membrane dysfunction is oxidative stress. Reactive oxygen species (ROS) generated during chronic inflammation or metabolic disturbances can damage cellular components, including lipids, proteins, and DNA within the mesothelial cells [23]. Oxidative damage can lead to apoptosis of these cells and disrupt the structural integrity of the interperitoneal membrane [24]. Additionally, oxidative stress can activate signaling pathways such as NF-κB, which promotes the expression of pro-inflammatory cytokines and further exacerbates inflammation [25]. This vicious cycle of inflammation and oxidative stress can ultimately lead to the breakdown of the protective barrier around the pancreatic tail.

From a genetic perspective, polymorphisms or mutations in genes involved in the regulation of immune responses and barrier integrity could predispose individuals to interperitoneal membrane dysfunction. One such gene is the NOD2 (Nucleotide-binding oligomerization domain-containing protein 2) gene, which plays a critical role in the innate immune system by recognizing bacterial components and activating inflammatory pathways [26]. Mutations in NOD2 have been associated with a defective immune response and increased susceptibility to chronic inflammatory diseases, particularly those affecting the gastrointestinal tract, such as Crohn's disease. Given the proximity of the pancreas to the intestines and the shared embryological origin, it is plausible that NOD2 dysfunction could contribute to a weakened interperitoneal membrane in the pancreatic tail, increasing the risk of immune-mediated damage to beta cells [27].

Another gene of interest is the IL-6 gene, which encodes the Interleukin-6 (IL-6) cytokine, a key mediator of the inflammatory response. Elevated levels of IL-6 are often found in chronic inflammatory conditions and have been implicated in disrupting the epithelial-mesenchymal transition (EMT) process, which is essential for tissue repair and barrier integrity [28]. Overexpression of IL-6 can lead to a sustained inflammatory environment, further compromising the protective function of the interperitoneal membrane. In the context of T1DM, elevated IL-6 levels may exacerbate the immune attack on the pancreatic tail, particularly in individuals with a genetic predisposition to inflammatory diseases [29].

From a pharmacological standpoint, certain medications, particularly nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, can affect the integrity of the interperitoneal membrane. Long-term use of NSAIDs can lead to gastric and intestinal mucosal damage, which may extend to the peritoneal lining, resulting in increased membrane permeability and inflammation [30]. While corticosteroids are typically used to suppress inflammation, chronic use can impair tissue repair mechanisms, making the interperitoneal membrane more susceptible to damage.

Moreover, autoimmune conditions themselves can directly target the peritoneal membrane. In conditions like systemic lupus erythematosus (SLE), autoantibodies against nuclear antigens can lead to immune complex deposition in various tissues, including the peritoneum, leading to immune-mediated damage. This can compromise the barrier function of the interperitoneal membrane, allowing autoreactive immune cells to access the pancreatic tail and attack beta cells [31].

5. Mechanisms of Peritoneal Repair and Beta-Cell Regeneration Induced by GLP-1 Agonists in Type 1 Diabetes

The hypothesis that GLP-1 receptor agonists can induce both peritoneal membrane repair and beta-cell regeneration in the context of Type 1 Diabetes Mellitus (T1DM) is grounded in several interconnected biological mechanisms. These mechanisms primarily revolve around the GLP-1 receptor (GLP-1R), a G-protein-coupled receptor that exerts its effects through the activation of intracellular signaling pathways critical for cellular growth, differentiation, and survival [32].

5.1. *GLP-1 Receptor Activation and Cellular Signaling*

Upon binding of GLP-1 (glucagon-like peptide-1) to GLP-1R, the receptor undergoes a conformational change, triggering the activation of adenylyl cyclase through the Gαs protein. This leads to an increase in cyclic adenosine monophosphate (cAMP) levels within the cell. Elevated cAMP then activates protein kinase A (PKA), which phosphorylates downstream targets, including CREB (cAMP response element-binding protein), a transcription factor that promotes the expression of genes involved in cell survival and growth. In pancreatic beta cells, GLP-1R activation enhances glucose-stimulated insulin secretion (GSIS), thereby reducing the metabolic burden on these cells. By lowering the demand for insulin production, GLP-1 allows beta cells to enter a more quiescent state, reducing oxidative stress and apoptosis, which are common in the hyperglycemic environment of T1DM [33].

5.2. *Anti-Inflammatory Effects and Peritoneal Membrane Repair*

The peritoneal membrane, particularly in the tail of the pancreas, plays a critical role in preventing autoimmune attacks on beta cells. In T1DM, chronic inflammation can compromise the integrity of the peritoneal barrier, allowing immune cells to infiltrate and attack the pancreatic tissue. GLP-1R activation has been shown to exert potent anti-inflammatory effects, mediated through the inhibition of nuclear factor-kappa B (NF-κB), a key transcription factor that regulates the expression of pro-inflammatory cytokines such as TNF-α (tumor necrosis factor-alpha) and IL-1β (interleukin-1 beta) [34].

By inhibiting NF-κB, GLP-1 reduces the production of these cytokines, thereby alleviating local inflammation and protecting the peritoneal membrane from further damage. Moreover, GLP-1R activation promotes the expression of anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta (TGF-β), which further contribute to the resolution of inflammation and the restoration of tissue homeostasis [35].

5.3. *Promotion of Cellular Proliferation and Tissue Regeneration*

GLP-1R signaling also plays a role in promoting the proliferation of mesothelial cells, which are the primary cells of the peritoneal membrane. This proliferation is driven by the activation of mitogen-activated protein kinase (MAPK) pathways, particularly ERK1/2 (extracellular signal-regulated kinases 1/2). ERK1/2 activation leads to the transcription of genes involved in cell cycle progression, such as cyclin D1, promoting the growth and repair of the peritoneal membrane [36].

In addition to direct effects on mesothelial cells, GLP-1 enhances the secretion of growth factors like insulin-like growth factor-1 (IGF-1) and epidermal growth factor (EGF). These growth factors are crucial for the repair of damaged tissues, including the peritoneal membrane. IGF-1, in particular, has been shown to promote the survival and proliferation of beta cells, suggesting that GLP-1 may indirectly support beta-cell regeneration by fostering a more supportive microenvironment within the pancreas [37].

5.4. *Interaction with the Immune System and Antigen Presentation*

The peritoneal membrane, and by extension the pancreatic tail, plays a key role in immune surveillance and antigen presentation. In T1DM, the failure of the peritoneal membrane may allow for the presentation of beta-cell antigens to autoreactive T cells, thereby exacerbating the autoimmune response. GLP-1R activation may help to mitigate this by promoting the upregulation of anti-apoptotic proteins such as Bcl-2, which protect beta cells from immune-mediated destruction [38].

Additionally, GLP-1 has been shown to influence the function of dendritic cells and macrophages, key players in antigen presentation. By modulating the activation state of these cells, GLP-1 may reduce the likelihood of beta-cell antigens being presented to autoreactive T cells, thus dampening the autoimmune response and allowing for beta-cell preservation and regeneration [39].

5.5. *Genetic Factors and the Role of HLA*

A critical genetic component in the context of T1DM and peritoneal membrane integrity is the HLA (human leukocyte antigen) system. HLA genes, particularly HLA-DR3 and HLA-DR4, are strongly associated with T1DM susceptibility. These HLA molecules are involved in the presentation of beta-cell antigens to the immune system, and mutations or polymorphisms in these genes can lead to aberrant immune responses. The integrity of the interperitoneal membrane, especially in the tail of the pancreas, may also be influenced by genetic factors that regulate extracellular matrix composition and cellular adhesion. Mutations in genes encoding collagen or fibronectin, for instance, could impair the structural integrity of the peritoneal membrane, making it more susceptible to inflammatory damage and immune cell infiltration [40].

6. Evidence Supporting the Hypothesis

A recent study provides compelling evidence supporting the hypothesis that GLP-1 receptor agonists, such as semaglutide, may contribute to both peritoneal membrane repair and beta-cell regeneration in Type 1 Diabetes Mellitus (T1DM). The study analyzed 10 newly diagnosed T1DM patients, aged 21 to 39, who initiated semaglutide treatment within three months of diagnosis. The findings revealed that all patients were able to discontinue prandial insulin within three months, and seven of the ten patients discontinued basal insulin within six months. Additionally, there was a significant reduction in glycated hemoglobin (HbA1c) levels from 11.7% at diagnosis to 5.7% after 12 months, coupled with

an increase in fasting C-peptide levels, indicating improved endogenous insulin secretion and beta-cell function.

These outcomes suggest that semaglutide, a GLP-1 receptor agonist, may reduce the metabolic burden on beta cells, allowing them to recover and function more effectively. By decreasing the need for exogenous insulin and enhancing endogenous insulin production, semaglutide may alleviate the stress on remaining beta cells, thereby protecting them from further autoimmune destruction. This aligns with the hypothesis that GLP-1 agonists can promote beta-cell preservation and regeneration through their anti-inflammatory effects, reduction in oxidative stress, and enhancement of cellular proliferation pathways.

The study also highlights the concept of the "honeymoon phase" in T1DM, where a residual population of functioning beta cells remains post-diagnosis. During this phase, the peritoneal membrane may play a crucial protective role by shielding beta cells from autoimmune attacks. The ability of GLP-1 receptor agonists to stabilize or even improve beta-cell function during this critical period further supports their potential role in repairing the peritoneal barrier and fostering beta-cell regeneration. By mitigating immune-mediated damage and promoting a more favorable microenvironment for beta-cell survival, GLP-1 receptor agonists offer a promising therapeutic approach for early T1DM intervention.

This study underscores the importance of further research through prospective, randomized clinical trials to validate the long-term benefits of GLP-1 receptor agonists in T1DM, particularly in preserving beta-cell function and minimizing the need for insulin therapy [41].

7. Biological and Immunological Rationale for the Proposed Treatment Approach

The hypothesis suggesting that a compromised peritoneal membrane of the pancreatic tail (the intraperitoneum) contributes to Type 1 Diabetes Mellitus (T1DM) offers a novel framework for understanding the disease's pathology and guiding therapeutic interventions. This hypothesis posits that an impaired peritoneal membrane could disrupt the protective environment around pancreatic beta cells, exacerbating autoimmune damage and impeding the maintenance of residual beta-cell function.

The proposed therapeutic approach, combining GLP-1 receptor agonists with degludec basal insulin, leverages the biological and immunological insights derived from this hypothesis. GLP-1 receptor agonists are known for their insulinotropic effects, stimulating insulin secretion from beta cells in response to meals. Beyond this, GLP-1 has been shown to promote beta-cell proliferation and survival, which could be particularly beneficial in the context of the compromised peritoneal membrane. By enhancing beta-cell function and potentially aiding in beta-cell regeneration, GLP-1 agonists address the residual beta-cell activity that might be preserved during the "honeymoon phase" of T1DM.

Degludec basal insulin, with its extended pharmacokinetic profile, provides stable and prolonged insulin delivery. Its reversible binding to albumin ensures consistent insulin levels, reducing the risk of nocturnal hypoglycemia and maintaining effective glucose control. This stability is crucial when addressing the compromised peritoneal membrane hypothesis, as it may help mitigate the disruptions in insulin delivery and efficacy caused by the impaired membrane.

Immunologically, the hypothesis of peritoneal membrane dysfunction aligns with the understanding of autoimmune processes in T1DM. The peritoneal membrane's role in shielding beta cells from autoimmune attack could be compromised, leading to increased exposure of beta cells to self-reactive T cells. By promoting beta-cell survival and function, GLP-1 receptor agonists may reduce the impact of autoimmune destruction. Additionally, the enhanced glycemic control achieved with degludec insulin could reduce the overall metabolic stress on beta cells, potentially diminishing the autoimmune attack's intensity [42].

8. Discussion

The autoimmune hypothesis of Type 1 Diabetes Mellitus (T1DM) posits that the destruction of pancreatic beta cells is driven by self-reactive T cells targeting beta-cell antigens. This well-established theory highlights the role of autoantibodies against key beta-cell proteins, such as insulin, glutamic acid decarboxylase (GAD), and islet antigen-2 (IA-2), in the disease's pathogenesis. However, emerging evidence suggests that this traditional autoimmune model may be complemented by alternative mechanisms, such as defects in the peritoneal membrane of the pancreatic tail, which warrant further exploration. Our hypothesis introduces the concept of peritoneal membrane defects within the pancreatic tail as a contributing factor to T1DM. This theory posits that abnormalities in the peritoneal membrane—particularly in the interperitoneal space—could compromise the protective environment surrounding pancreatic beta cells, facilitating autoimmune destruction. Such defects might result in an increased exposure of beta cells to autoimmune triggers or facilitate the infiltration of pathogenic immune cells into the pancreatic tissue.

The potential efficacy of this new hypothesis lies in its capacity to address limitations of the autoimmune model. While the autoimmune hypothesis provides a framework for understanding beta-cell destruction, it does not fully explain why some individuals with autoimmune markers do not develop T1DM. By incorporating the concept of peritoneal membrane defects, we can better account for variability in disease onset and progression. This integrated approach offers a more nuanced understanding of the pathogenesis of T1DM, recognizing that both autoimmune and structural factors may interplay in disease development.

The strength of this hypothesis is supported by preliminary observations suggesting that defects in the peritoneal membrane could lead to increased beta-cell vulnerability. These findings are consistent with the notion that structural alterations in the pancreatic environment might influence autoimmune activity and beta-cell destruction. Moreover, this hypothesis opens new avenues for research, potentially leading to novel therapeutic strategies aimed at correcting peritoneal membrane defects or mitigating their impact on pancreatic beta cells.

In conclusion, the integration of peritoneal membrane defects into the existing autoimmune framework of T1DM represents a significant shift in our understanding of the disease. By addressing the interplay between immune and structural factors, this hypothesis could refine our approach to T1DM pathogenesis and treatment. Future research should focus on validating this hypothesis through experimental studies and clinical trials, which will be crucial for confirming its validity and exploring its potential impact on T1DM management and therapy.

9. Conclusion

The "Peritoneal Protection Hypothesis" offers a groundbreaking perspective on the pathogenesis of Type 1 Diabetes Mellitus. By emphasizing the role of peritoneal membrane integrity, particularly in the pancreatic tail, this hypothesis presents a novel explanation for beta-cell dysfunction and autoimmune destruction. The proposed link between peritoneal membrane defects and the onset of T1DM could shift the focus of research towards exploring protective strategies for the peritoneal membrane as a means of preventing or mitigating the disease. Further experimental validation of this hypothesis is essential, as it may lead to innovative therapeutic approaches that target peritoneal membrane health and offer new strategies for managing or even preventing T1DM. The integration of this hypothesis with existing autoimmune theories provides a more holistic view of T1DM etiology and opens up exciting avenues for future research and clinical applications.

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References

1. ^*Katsarou, A., Gudbjörnsdottir, S., Rawshani, A., Dabelea, D., Bonifacio, E., Anderson, B. J., Jacobsen, L. M., Schatz, D. A., & Lernmark, Å. (2017). Type 1 diabetes mellitus. Nature reviews. Disease primers, 3, 17016. https://doi.org/10.1038/nrdp.2017.16.*
2. ^*Giwa, A. M., Ahmed, R., Omidian, Z., Majety, N., Karakus, K. E., Omer, S. M., Donner, T., & Hamad, A. R. A. (2020). Current understandings of the pathogenesis of type 1 diabetes: Genetics to environment. World journal of diabetes, 11(1), 13–25. https://doi.org/10.4239/wjd.v11.i1.13.*
3. ^*Bluestone, J. A., Herold, K., & Eisenbarth, G. (2010). Genetics, pathogenesis and clinical interventions in type 1 diabetes. Nature, 464(7293), 1293–1300. https://doi.org/10.1038/nature08933.*
4. ^*Liu, M., Silva-Sanchez, A., Randall, T. D., & Meza-Perez, S. (2021). Specialized immune responses in the peritoneal cavity and omentum. Journal of leukocyte biology, 109(4), 717–729. https://doi.org/10.1002/JLB.5MIR0720-271RR.*
5. ^*Yung, S., & Chan, T. M. (2012). Pathophysiological changes to the peritoneal membrane during PD-related peritonitis: the role of mesothelial cells. Mediators of inflammation, 2012, 484167. https://doi.org/10.1155/2012/484167.*
6. ^*Nakamura, T., Shirouzu, T., Nakata, K., Yoshimura, N., & Ushigome, H. (2019). The Role of Major Histocompatibility Complex in Organ Transplantation- Donor Specific Anti-Major Histocompatibility Complex Antibodies Analysis Goes to the Next Stage. International journal of molecular sciences, 20(18), 4544. https://doi.org/10.3390/ijms20184544.*
7. ^*Brandon Michael Henry, Bendik Skinningsrud, Karolina Saganiak, Przemysław A. Pękala, Jerzy A. Walocha, Krzysztof A. Tomaszewski. Development of the human pancreas and its vasculature An integrated review covering*

anatomical, embryological, histological, and molecular aspects, Annals of Anatomy - Anatomischer Anzeiger. doi.org/10.1016/j.aanat.2018.09.008.

8. ^*Ravi, P. K., Singh, S. R., & Mishra, P. R. (2021). Redefining the tail of pancreas based on the islets microarchitecture and inter-islet distance: An immunohistochemical study. Medicine, 100(17), e25642. https://doi.org/10.1097/MD.0000000000025642.*
9. ^*Christ, E., Antwi, K., Fani, M., & Wild, D. (2020). Innovative imaging of insulinoma: the end of sampling? A review. Endocrine-related cancer, 27(4), R79–R92. https://doi.org/10.1530/ERC-19-0476.*
10. ^*Yung, S., & Chan, T. M. (2011). Pathophysiology of the peritoneal membrane during peritoneal dialysis: the role of hyaluronan. Journal of biomedicine & biotechnology, 2011, 180594. https://doi.org/10.1155/2011/180594.*
11. ^*Zhu B. T. (2022). Pathogenic Mechanism of Autoimmune Diabetes Mellitus in Humans: Potential Role of Streptozotocin-Induced Selective Autoimmunity against Human Islet β-Cells. Cells, 11(3), 492. https://doi.org/10.3390/cells11030492.*
12. ^*Mollinedo F, Gajate C. Direct Endoplasmic Reticulum Targeting by the Selective Alkylphospholipid Analog and Antitumor Ether Lipid Edelfosine as a Therapeutic Approach in Pancreatic Cancer. Cancers. 2021; 13(16):4173. https://doi.org/10.3390/cancers13164173.*
13. ^*pancreas from a surgical perspective: an illustrated overview. Annals of Surgery, 6, 1. https://doi.org/10.21037/aos-21-2.*
14. ^*Mahadevan, V. (2019). Anatomy of the pancreas and spleen. Surgery (Oxford), 37(6). https://doi.org/10.1016/j.mpsur.2019.04.008.*
15. ^*Da Silva Xavier G. (2018). The Cells of the Islets of Langerhans. Journal of clinical medicine, 7(3), 54. https://doi.org/10.3390/jcm7030054.*
16. ^*Wang, X., Misawa, R., Zielinski, M. C., Cowen, P., Jo, J., Periwal, V., Ricordi, C., Khan, A., Szust, J., Shen, J., Millis, J. M., Witkowski, P., & Hara, M. (2013). Regional differences in islet distribution in the human pancreas--preferential beta-cell loss in the head region in patients with type 2 diabetes. PloS one, 8(6), e67454. https://doi.org/10.1371/journal.pone.0067454.*
17. ^*Lehrstrand, J., Davies, W.I.L., Hahn, M. et al. Illuminating the complete ß-cell mass of the human pancreas- signifying a new view on the islets of Langerhans. Nat Commun 15, 3318 (2024). https://doi.org/10.1038/s41467-024-47686-7.*
18. ^*Takahashi, K., et al. (2022). Altered intraperitoneal immune microenvironment in patients with peritoneal metastases from gastric cancer. Frontiers in Immunology, 13. https://doi.org/10.3389/fimmu.2022.969468.*
19. ^*Aufricht, C., Neuhofer, W., Topley, N., & Wörnle, M. (2012). Peritoneal infection and inflammation. Mediators of inflammation, 2012, 456985. https://doi.org/10.1155/2012/456985.*
20. ^*Baroni, G., Schuinski, A., de Moraes, T. P., Meyer, F., & Pecoits-Filho, R. (2012). Inflammation and the peritoneal membrane: causes and impact on structure and function during peritoneal dialysis. Mediators of inflammation, 2012, 912595. https://doi.org/10.1155/2012/912595.*
21. ^*Taylor, A., Verhagen, J., Blaser, K., Akdis, M., & Akdis, C. A. (2006). Mechanisms of immune suppression by interleukin-10 and transforming growth factor-beta: the role of T regulatory cells. Immunology, 117(4), 433–442. https://doi.org/10.1111/j.1365-2567.2006.02321.x*

22. ^Toren, E., Burnette, K. S., Banerjee, R. R., Hunter, C. S., & Tse, H. M. (2021). Partners in Crime: Beta-Cells and Autoimmune Responses Complicit in Type 1 Diabetes Pathogenesis. Frontiers in immunology, 12, 756548. https://doi.org/10.3389/fimmu.2021.756548.
23. ^Yu, W., Tu, Y., Long, Z., Liu, J., Kong, D., Peng, J., Wu, H., Zheng, G., Zhao, J., Chen, Y., Liu, R., Li, W., & Hai, C. (2022). Reactive Oxygen Species Bridge the Gap between Chronic Inflammation and Tumor Development. Oxidative medicine and cellular longevity, 2022, 2606928. https://doi.org/10.1155/2022/2606928.
24. ^Bhattacharyya, A., Chattopadhyay, R., Mitra, S., & Crowe, S. E. (2014). Oxidative stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases. Physiological reviews, 94(2), 329–354. https://doi.org/10.1152/physrev.00040.2012.
25. ^Lingappan K. (2018). NF-κB in Oxidative Stress. Current opinion in toxicology, 7, 81–86. https://doi.org/10.1016/j.cotox.2017.11.002.
26. ^Trindade, B. C., & Chen, G. Y. (2020). NOD1 and NOD2 in inflammatory and infectious diseases. Immunological reviews, 297(1), 139–161. https://doi.org/10.1111/imr.12902.
27. ^Walia, J., & Mujahid, R. (2023). Clinical Disease States Related to Mutations of the NOD2 Gene: A Case Report and Literature Review. Cureus, 15(5), e38584. https://doi.org/10.7759/cureus.38584.
28. ^Tanaka, T., Narazaki, M., & Kishimoto, T. (2014). IL-6 in inflammation, immunity, and disease. Cold Spring Harbor perspectives in biology, 6(10), a016295. https://doi.org/10.1101/cshperspect.a016295.
29. ^Dadgar, N., Sherry, C., Zimmerman, J. et al. Targeting interleukin-6 as a treatment approach for peritoneal carcinomatosis. J Transl Med 22, 402 (2024). https://doi.org/10.1186/s12967-024-05205-8.
30. ^Sohail, R., Mathew, M., Patel, K. K., Reddy, S. A., Haider, Z., Naria, M., Habib, A., Abdin, Z. U., Razzaq Chaudhry, W., & Akbar, A. (2023). Effects of Non-steroidal Anti-inflammatory Drugs (NSAIDs) and Gastroprotective NSAIDs on the Gastrointestinal Tract: A Narrative Review. Cureus, 15(4), e37080. https://doi.org/10.7759/cureus.37080.
31. ^Pan, L., Lu, M. P., Wang, J. H., Xu, M., & Yang, S. R. (2020). Immunological pathogenesis and treatment of systemic lupus erythematosus. World journal of pediatrics: WJP, 16(1), 19–30. https://doi.org/10.1007/s12519-019-00229-3.
32. ^Reed, J., Bain, S., & Kanamarlapudi, V. (2020). Recent advances in understanding the role of glucagon-like peptide 1. F1000Research, 9, F1000 Faculty Rev-239. https://doi.org/10.12688/f1000research.20602.1
33. ^Marzook, A., Tomas, A., & Jones, B. (2021). The Interplay of Glucagon-Like Peptide-1 Receptor Trafficking and Signalling in Pancreatic Beta Cells. Frontiers in endocrinology, 12, 678055. https://doi.org/10.3389/fendo.2021.678055.
34. ^Alharbi S. H. (2024). Anti-inflammatory role of glucagon-like peptide 1 receptor agonists and its clinical implications. Therapeutic advances in endocrinology and metabolism, 15, 20420188231222367. https://doi.org/10.1177/20420188231222367.
35. ^Lee, Y. S., & Jun, H. S. (2016). Anti-Inflammatory Effects of GLP-1-Based Therapies beyond Glucose Control. Mediators of inflammation, 2016, 3094642. https://doi.org/10.1155/2016/3094642.
36. ^Smith, N. K., Hackett, T. A., Galli, A., & Flynn, C. R. (2019). GLP-1: Molecular mechanisms and outcomes of a complex signaling system. Neurochemistry international, 128, 94–105. https://doi.org/10.1016/j.neuint.2019.04.010.
37. ^Fesler, Z., Mitova, E., & Brubaker, P. L. (2020). GLP-2, EGF, and the Intestinal Epithelial IGF-1 Receptor Interactions in the Regulation of Crypt Cell Proliferation. Endocrinology, 161(4), bqaa040. https://doi.org/10.1210/endocr/bqaa040.

38. ^*Chen, S., Saeed, A. F. U. H., Liu, Q., Jiang, Q., Xu, H., Xiao, G. G., Rao, L., & Duo, Y. (2023). Macrophages in immunoregulation and therapeutics. Signal transduction and targeted therapy, 8(1), 207. https://doi.org/10.1038/s41392-023-01452-1.*
39. ^*Chen, J., Mei, A., Wei, Y., Li, C., Qian, H., Min, X., Yang, H., Dong, L., Rao, X., & Zhong, J. (2022). GLP-1 receptor agonist as a modulator of innate immunity. Frontiers in immunology, 13, 997578. https://doi.org/10.3389/fimmu.2022.997578.*
40. ^*Lee, H. S., & Hwang, J. S. (2019). Genetic aspects of type 1 diabetes. Annals of pediatric endocrinology & metabolism, 24(3), 143–148. https://doi.org/10.6065/apem.2019.24.3.143.*
41. ^*Semaglutide in Early Type 1 Diabetes Paresh Dandona, The New England Journal of Medicine on September 7, 2023 N Engl J Med 2023; 389:958-959 DOI: 10.1056/NEJMc2302677.*
42. ^*Ahmed A, Akl MM. Exploring a Synergistic Approach: Dual GLP1 Agonist Combined with Degludec Basal Insulin for Early Type 1 Diabetes Treatment and its Impact on Albumin-Insulin Producing Cells Expression. Advanced Pharmaceutical Bulletin, https://doi.org/10.34172/apb.2024.040.*