The impact of malnutrition on secondary diabetes and calcific pancreatitis: A comprehensive review

Ashraf Soliman 1, *, Fawzia Alyafei 1, Nada Soliman 2, Sohair Elsiddig 1, Nada Alaaraj 1, Noor Hamed 1 and Shayma Ahmed 1

1 Department of Pediatrics, Hamad General Hospital, Doha, Qatar.
2 Department of Public Health, North Dakota State University, ND, USA.

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Abstract

Introduction: Malnutrition in low- and middle-income countries significantly impacts the development of secondary diabetes and calcific pancreatitis.

Aim and Methods: This review summarizes the prevalence, characteristics, and findings from key studies over the past decade on the link between malnutrition and secondary diabetes, focusing on protein-deficient pancreatic diabetes (PDPD) and fibro-calcific pancreatic diabetes (FCPD). A comprehensive literature search was conducted in PubMed, Scopus, and Google Scholar for articles published between 1995 and 2023. Studies included were peer-reviewed articles focusing on the link between malnutrition and secondary diabetes, conducted in LMICs, and discussing the prevalence, clinical characteristics, and outcomes of PDPD and FCPD. Both observational and interventional studies were considered.

Results: The review of studies revealed several key findings:

- PDPD is characterized by lower C-peptide levels and varied responses to glibenclamide post-nutritional rehabilitation.
- FCPD patients show rapid calcification, diminished exocrine and beta-cell function, and more severe exocrine deficiency compared to PDPD.
- Both PDPD and FCPD patients often present with lower BMI and significant renal involvement.
- Recent studies indicate improved nutritional status and prognosis of FCPD patients with enhanced medical care.
- Insulin-requiring diabetes in Ethiopia is strongly linked with poor education, poverty markers, and childhood malnutrition.
- Lean diabetes, linked to childhood malnutrition, is characterized by low-normal BMI, early onset, and rapid beta-cell failure.

Discussion: The development of diabetes following early malnutrition can be attributed to several interconnected mechanisms involving metabolic, endocrine, and epigenetic factors. Early nutritional intervention trials are crucial to prevent glucose abnormalities and diabetes later in life. Studies highlight that improving early-life nutrition can enhance beta-cell function, reduce insulin resistance, and mitigate long-term metabolic dysfunction. Lean diabetes, linked to childhood malnutrition, presents unique challenges but can be addressed through targeted nutritional support.

*Corresponding author: Ashraf Soliman

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Conclusion: The review underscores the significant impact of malnutrition on the development of secondary diabetes and calcific pancreatitis in LMICs. Addressing malnutrition through early nutritional interventions is crucial to mitigate the risk of chronic conditions and improve metabolic health outcomes. Continued research and targeted public health strategies are essential to break the cycle of malnutrition and disease in vulnerable populations.

Keywords: Malnutrition; Secondary diabetes; Protein-deficient pancreatic diabetes (PDPD); Fibro-calculous pancreatic diabetes (FCPD); Calcific pancreatitis.

1. Introduction

Malnutrition remains a critical public health issue, particularly in low- and middle-income countries (LMICs), where it significantly impacts the development of various diseases, including secondary diabetes and calcific pancreatitis. Malnutrition, characterized by deficiencies in essential nutrients, leads to impaired growth and development, weakened immune function, and increased susceptibility to infections and chronic diseases. The global prevalence of malnutrition highlights the urgent need for comprehensive research and intervention strategies to address this multifaceted problem. Secondary diabetes, a condition that arises due to other primary diseases or conditions, has been increasingly linked to malnutrition. (1,2,3)

In recent years, there has been growing interest in understanding the relationship between malnutrition and the onset of secondary diabetes, particularly protein-deficient pancreatic diabetes (PDPD) and fibro-calculous pancreatic diabetes (FCPD). These forms of diabetes are prevalent in regions with high rates of malnutrition and are characterized by unique clinical features distinct from primary types of diabetes. Studies have shown that chronic undernutrition and micronutrient deficiencies can lead to significant pancreatic dysfunction, contributing to the development of these secondary diabetes forms (4-7)

The impact of malnutrition on pancreatic health extends beyond diabetes to include conditions such as calcific pancreatitis. Calcific pancreatitis, often seen in conjunction with FCPD, involves the formation of calcium deposits in the pancreas, leading to chronic inflammation and progressive pancreatic damage. This condition is particularly common in tropical regions, where dietary factors and socioeconomic conditions contribute to high rates of malnutrition and subsequent pancreatic disease. The interplay between malnutrition, pancreatic dysfunction, and the development of diabetes and calcific pancreatitis underscores the complexity of managing these conditions in affected populations. (8-12)

Given the significant public health implications, this review aims to synthesize the current literature on the prevalence, characteristics, and clinical outcomes of secondary diabetes and calcific pancreatitis in malnourished populations. (7,13-15) By examining studies from diverse regions and populations, this review seeks to highlight the critical link between early-life nutritional deficiencies and long-term metabolic health. Understanding these relationships is essential for developing targeted interventions and healthcare strategies to mitigate the impact of malnutrition on chronic disease outcomes.

1.1. Aim

This review summarizes the prevalence, characteristics, and findings from key studies over the past decade on the link between malnutrition and secondary diabetes, focusing on protein-deficient pancreatic diabetes (PDPD) and fibro-calculous pancreatic diabetes (FCPD).

2. Materials and Methods

This review was conducted through a comprehensive literature search to gather relevant studies examining the relationship between malnutrition and the development of secondary diabetes, particularly protein-deficient pancreatic diabetes (PDPD) and fibro-calculous pancreatic diabetes (FCPD). The literature search included several key databases and followed a structured approach to ensure a thorough and systematic collection of data.

2.1. Literature Search Strategy

The primary databases searched were PubMed, Scopus, and Google Scholar. The search was conducted for articles published between 1995 and 2023 to capture both historical and recent perspectives on the topic. The search terms used included combinations of keywords such as "malnutrition," "secondary diabetes," "protein-deficient pancreatic

2.2. Inclusion and Exclusion Criteria
Studies were selected based on the following inclusion criteria:

- Peer-reviewed articles focusing on the link between malnutrition and secondary diabetes.
- Studies discussing the prevalence, clinical characteristics, and outcomes of PDPD and FCPD.
- Research conducted in low- and middle-income countries, given the higher prevalence of malnutrition in these regions.
- Both observational and interventional studies were considered.

Exclusion criteria included:

- Studies not published in English.
- Articles focusing solely on primary diabetes types without reference to malnutrition.
- Case reports with insufficient data on the broader population impact.

2.3. Data Extraction and Synthesis
From the selected studies, data were extracted on the study population, key findings, and conclusions regarding the relationship between malnutrition and secondary diabetes. The extracted data were organized chronologically to identify trends and changes over time. Studies were categorized based on their focus, such as clinical characteristics, biochemical profiles, and intervention outcomes.

2.4. Quality Assessment
The quality of the included studies was assessed using standard criteria for observational and interventional research. This included evaluating the study design, sample size, methodology, and the robustness of the conclusions drawn. Any potential biases or limitations within the studies were noted and considered when synthesizing the overall findings.

2.5. Ethical Considerations
As this review involved the analysis of previously published data, there were no direct ethical implications. However, ethical standards were maintained by accurately citing all sources and ensuring that interpretations were based on the presented data.

By following these methods, this review aimed to provide a comprehensive and accurate synthesis of the current knowledge on the impact of malnutrition on the development of secondary diabetes and calcific pancreatitis, highlighting the importance of early nutritional interventions in mitigating these health outcomes.
3. Results

The main findings of the studies are summarized in table 1.

Table 1 Summary of Research on glucose and pancreatic abnormalities in relation to malnutrition.

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>Patients</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. Abdulkadir</td>
<td>Diabetologia</td>
<td>1990</td>
<td>39</td>
<td>Comparison of PDPD and type 1 diabetes in Ethiopian patients found lower C-peptide levels in PDPD, similar glucagon patterns, and varying responses to glibenclamide post-nutritional rehabilitation.</td>
</tr>
<tr>
<td>G. Premalatha</td>
<td>Diabetes Res Clin Pract</td>
<td>1994</td>
<td>2</td>
<td>First reported cases of FCPD in infancy, suggesting rapid calcification.</td>
</tr>
<tr>
<td>E. Bhatia</td>
<td>Diabetes Care</td>
<td>1995</td>
<td>91</td>
<td>Both FCPD and PDPD patients had diminished exocrine and beta-cell function, with FCPD showing more severe deficiency.</td>
</tr>
</tbody>
</table>
### 3.1. Comments on Main Findings

Tropical chronic pancreatitis (TCP) diabetes in South India exhibits heterogeneity concerning nutritional levels, severity of glucose intolerance, beta-cell function, response to therapy, and occurrence of microvascular complications. This complexity is further underscored by the findings that PDPD in Ethiopian patients presents with lower C-peptide levels compared to type 1 diabetes, yet both conditions show similar glucagon patterns. The responses to glibenclamide post-nutritional rehabilitation vary significantly, indicating different underlying metabolic mechanisms (17, 27).

In early-onset cases, rapid progression of pancreatic calcification is notable. Both FCPD and PDPD patients show diminished exocrine and beta-cell function, with FCPD patients experiencing more severe exocrine deficiency. Autoimmunity may play a role in PDPD but not in FCPD. FCPD patients often present with lower BMI and significant renal involvement, alongside evidence of oxidative damage. Improvements in nutritional status and prognosis of FCPD patients have been noted in recent years, suggesting better outcomes with enhanced medical care (18, 19, 20).

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Journal</th>
<th>Year</th>
<th>Reference</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. A. Khan (20)</td>
<td>J Gastroenterol Hepatol</td>
<td>1997</td>
<td>Not specified</td>
<td>FCPD patients present with lower BMI and significant renal involvement and oxidative damage.</td>
</tr>
<tr>
<td>N. Mittal (21)</td>
<td>Natl Med J India</td>
<td>2002</td>
<td>80</td>
<td>Improved nutritional status and prognosis of FCPD patients compared to earlier reports.</td>
</tr>
<tr>
<td>A. Saraya (4)</td>
<td>Trop Gastroenterol</td>
<td>2003</td>
<td>20</td>
<td>Pancreatic ductal changes are more frequent in FCPD compared to PDPD.</td>
</tr>
<tr>
<td>Viswanathan Mohan (5)</td>
<td>J Gastroenterol Hepatol</td>
<td>2005</td>
<td>73</td>
<td>TCP subjects without diabetes showed progressive deterioration of endocrine pancreatic function, with 50% developing diabetes over 5 years.</td>
</tr>
<tr>
<td>S. Fekadu (22)</td>
<td>Eur J Clin Nutr</td>
<td>2010</td>
<td>107</td>
<td>Insulin-requiring diabetes in Ethiopia strongly linked with poor education, poverty markers, and childhood malnutrition. Men with the disease showed disproportionate skeletal growth.</td>
</tr>
<tr>
<td>Charlotte Bavuma (7)</td>
<td>J Glob Health</td>
<td>2019</td>
<td>22 articles</td>
<td>Identified two atypical diabetes phenotypes in thin young individuals from poor backgrounds, requiring lifelong insulin, and another resembling type 1 diabetes but responding to oral hypoglycemics.</td>
</tr>
<tr>
<td>S. Alemu (16)</td>
<td>Curr Diab Rep</td>
<td>2018</td>
<td>Not specified</td>
<td>Type 1 diabetes in Ethiopia presents later, more often in males, and is associated with undernutrition. The role of autoimmunity may be modified by malnutrition.</td>
</tr>
<tr>
<td>Eric Lontchi-Yimagou (24)</td>
<td>Diabetes Care</td>
<td>2022</td>
<td>Not specified</td>
<td>Low BMI diabetes in LMICs has unique metabolic characteristics, distinct from type 1 and type 2 diabetes, suggesting a distinct entity possibly related to malnutrition.</td>
</tr>
<tr>
<td>V. Mohan (25)</td>
<td>Diabetologia</td>
<td>1985</td>
<td>33</td>
<td>Tropical pancreatic diabetes in South India is heterogeneous with respect to level of nutrition, severity of glucose intolerance, beta-cell function, response to therapy, and occurrence of microvascular complications.</td>
</tr>
</tbody>
</table>
Pancreatic ductal changes are more frequent in FCPD compared to PDPD. Progressive deterioration of endocrine pancreatic function is observed in TCP subjects without diabetes, with 50% developing diabetes over five years. Insulin-requiring diabetes in Ethiopia is strongly linked to poor education, poverty markers, and childhood malnutrition. Men with this condition also showed disproportionate skeletal growth, indicating long-term developmental impacts (4, 21, 22).

Lean diabetes, linked to childhood malnutrition, is characterized by low-normal BMI, early onset, and rapid beta-cell failure. Type 1 diabetes in Ethiopia tends to present later, more frequently in males, and is associated with undernutrition. The role of autoimmunity in type 1 diabetes may be modified by malnutrition, highlighting the interaction between nutritional status and immune function (5, 23, 15).

Two atypical diabetes phenotypes have been identified in thin young individuals from poor backgrounds: one requiring lifelong insulin and another resembling type 1 diabetes but responding to oral hypoglycemics. Low BMI diabetes in LMICs has unique metabolic characteristics, suggesting it is a distinct entity possibly related to malnutrition. This highlights the need for further research and targeted interventions to address these unique forms of diabetes and their underlying causes (7, 13, 24, 26).

4. Discussion

The development of diabetes later in life following infantile and childhood malnutrition can be attributed to several interconnected mechanisms involving metabolic, endocrine, and epigenetic factors. These mechanisms highlight how early nutritional deficits can set the stage for long-term metabolic dysfunction. These possible mechanisms include the following: (fig 2)

4.1. Impaired Beta-Cell Function
Malnutrition during critical periods of growth can lead to impaired development and function of pancreatic beta cells, which are responsible for insulin production. Studies have shown that protein-energy malnutrition reduces beta-cell mass and insulin secretion capacity, thereby predisposing individuals to glucose intolerance and diabetes in later life. This is exacerbated by the increased demand for insulin during periods of catch-up growth, which often follows malnutrition (26, 27).

4.2. Insulin Resistance
Early malnutrition is associated with increased insulin resistance, a hallmark of type 2 diabetes. Malnourished individuals often experience changes in body composition, such as increased visceral fat, which is more metabolically active and contributes to insulin resistance. Additionally, chronic undernutrition can lead to alterations in muscle mass and function, further impairing glucose metabolism and insulin sensitivity (28, 29).

4.3. Epigenetic Changes
Malnutrition can induce epigenetic modifications, such as DNA methylation and histone modification, which can alter gene expression related to metabolic pathways. These epigenetic changes can persist into adulthood, influencing the risk of developing diabetes. For example, genes involved in insulin signaling and glucose metabolism may be permanently modified, leading to a predisposition to diabetes even after nutritional rehabilitation (30, 31).

4.4. Inflammatory Pathways
Chronic malnutrition can lead to a persistent low-grade inflammatory state, which is a key factor in the development of insulin resistance and type 2 diabetes. Malnutrition alters the production of cytokines and adipokines, such as TNF-alpha and leptin, which are involved in the regulation of insulin sensitivity and glucose homeostasis. This pro-inflammatory milieu can damage pancreatic beta cells and impair insulin action (32, 33).

4.5. Hormonal Imbalance
Nutritional deficiencies during early life can disrupt the hormonal balance necessary for normal growth and metabolism. Deficiencies in essential nutrients, such as zinc, magnesium, and vitamins, can impair the function of hormones like insulin and growth hormone, further contributing to the risk of diabetes. Hormonal imbalances during critical periods of development can have long-lasting effects on metabolic regulation (34, 35).
Figure 2 Possible mechanisms that link childhood malnutrition with dysglycemia later in life.

The importance of early nutritional intervention trials to prevent glucose abnormalities and diabetes later in life cannot be overstated. Studies have consistently shown that early-life malnutrition significantly impacts the development of glucose intolerance and diabetes, particularly in low- and middle-income countries (LMICs). For instance, Fekadu et al. (2010) found that insulin-requiring diabetes in Ethiopia is strongly linked with poor education, poverty markers, and childhood malnutrition, indicating that improving nutritional status during childhood could mitigate these risks (22).

Malnutrition during critical growth periods can lead to developmental delays and stunted growth, which are associated with an increased risk of metabolic diseases, including diabetes. The work of Abdulkadir et al. (1990) in Ethiopian patients demonstrates that protein-deficient pancreatic diabetes (PDPD) is characterized by lower C-peptide levels and similar glucagon patterns to type 1 diabetes, but with varying responses to glibenclamide post-nutritional rehabilitation. This suggests that improving nutrition early on could enhance beta-cell function and overall metabolic health (16).

Additionally, studies by Mohan et al. (2005) on tropical chronic pancreatitis (TCP) without diabetes found progressive deterioration of endocrine pancreatic function, with 50% of subjects developing diabetes over five years. This underscores the potential for early nutritional interventions to preserve endocrine function and prevent the onset of diabetes. The findings highlight that improving early-life nutrition can have long-term benefits in maintaining pancreatic health and preventing diabetes (25).

Lean diabetes, as described by George et al. (2015), linked to childhood malnutrition, presents with low-normal BMI, early onset, and rapid beta-cell failure. This type of diabetes is becoming increasingly recognized in the context of the global obesity epidemic. Early nutritional interventions could help prevent the onset of lean diabetes by ensuring adequate nutrition during childhood, thereby supporting normal metabolic function and growth (14).

The findings from Bavuma et al. (2019) also support the notion that improving early-life nutrition can prevent diabetes. They identified two atypical diabetes phenotypes in thin young individuals from poor backgrounds, one requiring lifelong insulin and another resembling type 1 diabetes but responding to oral hypoglycemics. This suggests that early nutritional support could alter the trajectory of these atypical diabetes phenotypes, reducing the need for lifelong insulin therapy and improving quality of life (7,13).
5. Conclusion

The review highlights the significant impact of malnutrition on the development of secondary diabetes and calcific pancreatitis, particularly in low- and middle-income countries. Early-life nutritional deficiencies are closely linked to long-term metabolic dysfunction, including protein-deficient pancreatic diabetes (PDPD) and fibro-calcious pancreatic diabetes (FCPD). The mechanisms underlying this link include impaired beta-cell function, increased insulin resistance, epigenetic changes, inflammatory pathways, and hormonal imbalances. Addressing malnutrition through early nutritional interventions is crucial to mitigate the risk of these chronic conditions and improve metabolic health outcomes. Continued research and targeted public health strategies are essential to break the cycle of malnutrition and disease in vulnerable populations.

Recommendations

Implement Comprehensive Nutritional Programs: Governments and health organizations should prioritize nutritional intervention programs targeting pregnant women, infants, and young children to prevent malnutrition and its long-term health impacts.

Enhance Public Health Education: Increase efforts to educate communities about the importance of proper nutrition and the risks associated with malnutrition, utilizing schools, community centers, and healthcare providers for effective dissemination.

Strengthen Healthcare Systems: Improve healthcare systems to provide accessible and quality care, including early recognition and treatment of malnutrition-related conditions and integration of nutritional assessments into routine healthcare visits.

5.1. What this study adds

The review article thoroughly synthesizes findings from various studies spanning multiple decades, providing a holistic understanding of the relationship between malnutrition and secondary diabetes, including protein-deficient pancreatic diabetes (PDPD) and fibro-calcious pancreatic diabetes (FCPD). By concentrating on the prevalence and characteristics of these conditions in LMICs, the review highlights the unique challenges and the urgent need for tailored interventions in these regions.
5.2. Limitation of the study
The review includes several older studies, some dating back to the 1990s, which may not fully reflect the current epidemiological trends and advancements in understanding malnutrition-related diabetes. While the review effectively outlines the link between malnutrition and diabetes, it falls short in discussing recent intervention trials and their outcomes, which are crucial for forming actionable recommendations and policy changes.

Compliance with ethical standards

Disclosure of conflict of interest
There is no conflict between the authors regarding the study. All authors have participated, reviewed, and approved the publication of the study.

Author Contributions
AS was responsible for the conceptualization of the review study, setting the stage for the research with a clear outline of the scope and objectives. All authors actively participated in the data collection, screening, and analysis process, ensuring a comprehensive and meticulous evaluation of the research findings. All authors have given their final approval of the version to be published, collectively ensuring the manuscript’s accuracy and integrity, and have agreed to the published version, thus upholding rigorous scholarly standards, and ensuring the work’s credibility and reliability.

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References

[1] Malnutrition. WHO Malnutrition Facts. Available at: https://www.who.int/news-room/fact-sheets/detail/malnutrition?gad_source=1&gclid=Cj0KCQjwu8uyBhC6ARIsAKwBgpQW5_mm1Bw97p1bETk4kG2_DartTIVQ8q466ZeSRQFC_1UVDz1_0aAm70EALw_wcB# Accessed March 1, 2024.


