PATHOPHYSIOLOGICAL AND CLINICAL CONSEQUENCES OF IMPAIRED INSULIN SECRETION IN THE HUMAN BODY

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Introduction. Insulin is a peptide hormone secreted by pancreatic β-cells and plays a fundamental role in maintaining glucose homeostasis. Dysregulation of insulin secretion has been recognized as a central pathogenic factor in the onset and progression of metabolic disorders, particularly type 2 diabetes mellitus (T2DM), which currently affects more than 537 million people worldwide and is projected to reach 783 million cases by 2045 (International Diabetes Federation, 2022). Insulin secretory defects precede clinical manifestations and contribute to systemic metabolic imbalance, increasing the risk of cardiovascular diseases, obesity, metabolic syndrome, and microvascular complications. Despite significant therapeutic progress, the global burden of T2DM continues to rise, indicating the urgent need for deeper understanding of the molecular and cellular mechanisms underlying β-cell dysfunction.

Aim and objectives. The aim of this study was to review recent literature (2010–2025) on the mechanisms of insulin secretory impairment and to assess its role in the development and progression of human diseases. The specific objectives were:

1. To identify molecular and cellular pathways leading to β-cell dysfunction.
2. To analyze the systemic consequences of impaired insulin secretion on human physiology.
3. To evaluate the potential strategies for early detection and prevention of secretory decline.

Materials and methods. A narrative literature review methodology was employed, focusing on articles published between 2010 and 2025 in PubMed, Scopus, and Web of Science. Key search terms included *"insulin secretion," "β-cell dysfunction," "glucotoxicity," "lipotoxicity,"* and *"type 2 diabetes."* Selected studies included genetic, molecular, and clinical investigations, as well as epidemiological data on insulin-related disorders. Statistical models from meta-analyses were referenced, such as Ballena-Caicedo et al. (2025), who reported a global prevalence of insulin resistance of 31.4% (95% CI: 27.2–35.8) among adults. Clinical trials addressing early intervention strategies were also analyzed.

Results. The synthesis of data revealed multiple mechanisms underlying impaired insulin secretion:

1. **Glucotoxicity and lipotoxicity**: Chronic hyperglycemia and elevated free fatty acids induce β-cell apoptosis and impair insulin granule exocytosis.

2. **Mitochondrial and ER stress**: Dysfunction in oxidative phosphorylation and unfolded protein response (UPR) pathways reduces insulin biosynthesis.

3. **Genetic and epigenetic alterations**: Variants in *TCF7L2, KCNJ11,* and DNA methylation patterns alter β-cell sensitivity to glucose.

4. **Reduced β-cell mass and impaired intercellular coupling**: Loss of β-cell synchrony disrupts pulsatile insulin release, worsening metabolic control.

Clinically, impaired secretion results in:

- Persistent hyperglycemia, a hallmark of prediabetes and T2DM.
- Accelerated insulin resistance, particularly in obese individuals.
- Increased cardiovascular morbidity (relative risk ~2.1 in T2DM patients compared to healthy individuals).
- Microvascular complications such as nephropathy (up to 30% of patients), neuropathy (40–50%), and retinopathy (25–35%).

Our analysis confirms that β-cell secretory failure is not only a byproduct of insulin resistance but a primary driver of metabolic disease. The traditional "disposition index" model describing the inverse relationship between insulin secretion and sensitivity requires expansion, as demonstrated by Vazquez Arreola et al. (2022), who highlighted nonlinear dynamics in β-cell compensation. Importantly, β-cell adaptation occurs in early prediabetes, but progressive glucotoxicity and lipotoxicity overwhelm compensatory mechanisms, leading to irreversible dysfunction.

Moreover, global epidemiological trends emphasize the urgency of preventive interventions. The systematic review by Ballena-Caicedo et al. (2025) demonstrated alarming increases in insulin resistance prevalence, particularly in low- and middle-income countries. These findings suggest that without early preservation of β-cell function, the global diabetes epidemic will escalate further. Emerging therapeutic strategies such as incretin-based therapies, sodium–glucose cotransporter 2 inhibitors, and gene/epigenetic modulation offer promising avenues for delaying or reversing early β-cell dysfunction.

Conclusion. Insulin secretory defects play a pivotal role in the development and progression of T2DM and other metabolic diseases. The mechanisms are multifactorial, involving glucotoxicity, lipotoxicity, oxidative and ER stress, genetic susceptibility, and impaired β-cell communication. Early detection of β-cell dysfunction and implementation of preventive strategies are essential to mitigate disease burden. Targeted interventions aimed at preserving β-cell function could significantly reduce the risk of long-term complications and alleviate the global health impact of T2DM.

References

1. Ballena-Caicedo, J., Zuzunaga-Montoya, F. E., Loayza-Castro, J. A., Bustamante-Rodríguez, J. C., Vásquez Romero, L. E. M., Tapia-Limonchi, R., Gutierrez De Carrillo, C. I., & Vera-Ponce, V. J. (2025). Global prevalence of insulin resistance in the adult population: A systematic review and meta-analysis. *Frontiers in Endocrinology*, *16*, 1646258. https://doi.org/10.3389/fendo.2025.1646258

2. Galderisi, A., Carr, A. L. J., Martino, M., Taylor, P., Senior, P., & Dayan, C. (2023). Quantifying beta cell function in the preclinical stages of type 1 diabetes. *Diabetologia, 66*(11), 2045–2058. https://doi.org/10.1007/s00125-023-05923-4

3. International Diabetes Federation. (2022). *IDF Diabetes Atlas* (10th ed.). Brussels, Belgium: International Diabetes Federation. Retrieved from https://diabetesatlas.org

4. Vazquez Arreola, E., Hanson, R. L., Bogardus, C., & Knowler, W. C. (2022). Relationship between insulin secretion and insulin sensitivity and its role in development of type 2 diabetes: Beyond the disposition index. *Diabetes, 71*(1), 128–141. https://doi.org/10.2337/db21-0416

5. Prentki, M., & Nolan, C. J. (2022). Islet β cell failure in type 2 diabetes. *The Journal of Clinical Investigation, 132*(3), e154520. https://doi.org/10.1172/JCI154520

6. Henquin, J. C. (2021). Regulation of insulin secretion: A matter of phase control and amplitude modulation. *Diabetologia, 64*(10), 2147–2160. https://doi.org/10.1007/s00125-021-05538-3

7. Wang, Y., Sun, X., & Zhang, Y. (2020). Mechanisms of pancreatic β-cell dysfunction in type 2 diabetes mellitus: Oxidative stress, endoplasmic reticulum stress, and beyond. *Frontiers in Endocrinology, 11*, 119. https://doi.org/10.3389/fendo.2020.00119

8. Kahn, S. E., Cooper, M. E., & Del Prato, S. (2014). Pathophysiology and treatment of type 2 diabetes: Perspectives on the past, present, and future. *The Lancet, 383*(9922), 1068–1083. https://doi.org/10.1016/S0140-6736(13)62154-6