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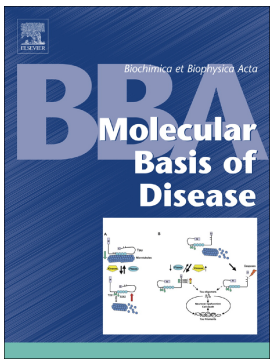

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The β-Cell Stress Continuum: Molecular Mechanisms Driving Diabetes Progression and Cellular Failure

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Abstract

Diabetes mellitus encompasses heterogeneous disorders in which β-cell dysfunction contributes to impaired glucose regulation. Although the causes and sequence of disease processes differ across diabetes subtypes, β-cell stress has emerged as a potential convergent mechanism that may contribute to disease progression in some contexts. However, current evidence does not establish β-cell stress as the initiating event in all forms of type 1 diabetes (T1D) or type 2 diabetes (T2D). In T1D, autoimmune injury is a defining disease process, whereas in T2D, insulin resistance, genetic susceptibility, and environmental factors may precede or interact with β-cell dysfunction.

This narrative review proposes the β-cell Stress Continuum as a testable conceptual framework for examining how β-cells may transition from adaptive responses to persistent dysfunction and, in some settings, loss of cellular identity or survival. The framework integrates immune, metabolic, oxidative, endoplasmic reticulum, mitochondrial, inflammatory, and genomic stress, while recognizing that their relative contributions and temporal sequence may vary among individuals and diabetes subtypes. It also considers interactions between islets and other organs, including the liver, adipose tissue, skeletal muscle, immune system, and nervous system.

The β-cell Stress Continuum is intended to organize research questions about β-cell adaptation and diabetes progression; it is not presented as a universal mechanism or as a replacement for disease-specific models. The proposed framework may help guide the investigation of biomarkers, disease staging, and therapeutic strategies, but its applicability and clinical utility require validation in subtype-specific, longitudinal studies.

Keywords: β -cell stress, Diabetes continuum, Endoplasmic reticulum stress, Oxidative stress, Molecular pathophysiology, Cellular stress adaptation

1. Introduction

Diabetes mellitus is commonly classified as type 1 diabetes (T1D), characterized by autoimmune β-cell destruction and absolute insulin deficiency, or type 2 diabetes (T2D), characterized primarily by insulin resistance and progressive β-cell dysfunction [1,2]. This classification remains clinically useful, but phenotypes such as latent autoimmune diabetes in adults (LADA), ketosis-prone diabetes, adult-onset autoimmune diabetes, and insulin-resistant autoimmune diabetes illustrate overlap between disease mechanisms [3–5].(**Figure 1**)

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Rather than representing two completely separate disease entities, diabetes is increasingly recognized as a biological continuum in which immune-mediated injury, metabolic overload, intrinsic β-cell vulnerability, and environmental influences contribute in varying proportions to disease initiation and progression [4,5]. Genetic and mechanistic studies likewise point to shared susceptibility factors and pathways alongside distinct disease-specific drivers [5,6]. Consequently, understanding the mechanisms that govern β-cell adaptation, decompensation, and failure has become one of the central challenges in contemporary diabetes research.

Diabetes pathogenesis involves interacting processes, including insulin resistance, autoimmunity, glucolipotoxicity, endoplasmic reticulum (ER) and oxidative stress, mitochondrial dysfunction, inflammation, and changes in β-cell identity. These processes are often studied separately, while clinical staging commonly relies on metabolic abnormalities that may emerge after β-cell functional reserve has declined. A framework connecting β-cell adaptation with disease progression may therefore help organize these mechanisms and their relationship to systemic metabolic changes [1–3].

Recent advances in single-cell transcriptomics, spatial biology, systems immunometabolism, and multi-organ communication have substantially expanded our understanding of β-cell biology. These studies suggest that β-cell dysfunction is not merely the consequence of chronic hyperglycemia but instead represents a dynamic systems-level process regulated by continuous interactions among intracellular stress pathways, immune activation, metabolic demand, and endocrine communication between the pancreas, liver, adipose tissue, skeletal muscle, gut, and nervous system [1–3]. Collectively, these findings indicate that β-cell stress should be viewed as

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a central biological hub integrating diverse pathogenic signals across the diabetes spectrum rather than as a downstream manifestation of established disease.

Here, we propose the **β-cell Stress Continuum**, a unified mechanistic framework that integrates immune, metabolic, and cellular stress pathways into a single systems-level model of diabetes progression. Rather than replacing the existing clinical classification, this framework complements it by explaining the substantial biological overlap among T1D, T2D, LADA, and intermediate phenotypes. Within this model, β-cell fate is determined by the cumulative burden of immune-mediated injury, metabolic overload, intracellular stress signaling, and inter-organ crosstalk, which together regulate the transition from adaptive compensation to maladaptive remodeling, progressive loss of β-cell identity, and ultimately irreversible metabolic decompensation.

The β-cell stress continuum proposed here is a **testable conceptual framework** for examining how β-cell responses to immune, metabolic, genetic, and environmental pressures may change over time. β-cells can initially adapt to increased secretory demand through mechanisms such as enhanced insulin biosynthesis, unfolded protein response (UPR) activation, and mitochondrial remodeling [7–9]. Importantly, increasing evidence indicates that these maladaptive mechanisms are shared across multiple diabetes phenotypes rather than representing disease-specific pathways [2,7,9].

β-cell dysfunction also occurs within a broader tissue and immune environment. Inflammatory mediators and chemokines, including IL-1β, TNF-α, CCL2, and CCL5, may contribute to inflammatory circuits in some diabetes phenotypes [10,11]. In autoimmune and mixed diabetes phenotypes, cytokines including IL-1β and TNF-α, together with chemokine networks such as CCL2 and CCL5, establish self-perpetuating inflammatory circuits that amplify β-cell stress and

accelerate functional decline [10,11]. Importantly, the tempo of disease progression varies according to the relative contributions of immune activation, metabolic overload, and intrinsic β-cell resilience, providing a biological explanation for the broad clinical heterogeneity observed across diabetes phenotypes [2,5].

Changes in insulin secretion can also interact with glucagon regulation, hepatic glucose production, signaling from adipose tissue and muscle, incretin pathways, and systemic insulin resistance. [1,2,4]. These reciprocal interactions establish a vicious cycle in which local β-cell dysfunction progressively evolves into systemic metabolic failure and ultimately contributes to the vascular and metabolic complications shared across the diabetes spectrum [1–3].

The framework does not propose β-cell stress as a universal initiating event or replace disease-specific explanations. In T1D, autoimmune processes remain central; in T2D, insulin resistance and genetic and environmental influences are also important [1,2,5]. Rather, the continuum provides a way to organize evidence about β-cell adaptation, dysfunction, and failure across overlapping but biologically diverse forms of diabetes [4,6].

The following sections examine the relevant cellular mechanisms, inter-organ interactions, clinical contexts, and translational questions. Although stress-targeted and β-cell-preserving approaches are of interest, their proposed effects on disease progression require evaluation against clinical evidence [3,8,9,12].

Limitations of a β-cell-centered interpretation

A β-cell-centered framework has important limitations. In T1D, autoreactive immune responses are central to disease pathogenesis and cannot be reduced to β-cell stress alone. In T2D, insulin

resistance in liver, skeletal muscle, and adipose tissue, together with genetic, developmental, and environmental factors, can shape disease risk and progression independently of—or in interaction with—β-cell dysfunction. Moreover, evidence that stress markers accompany disease progression does not by itself establish that stress is the initiating cause. β-cell stress may be a cause, a consequence, or an amplifier of injury, and these possibilities may differ among patients and diabetes subtypes. The proposed continuum should therefore be interpreted alongside disease-specific models and evaluated using longitudinal and causal studies.

Accordingly, this review integrates current evidence from cellular stress biology, immunometabolism, β-cell plasticity, inter-organ crosstalk, and emerging systems biology to establish the **β-cell Stress Continuum** as a unifying conceptual framework for diabetes pathophysiology. By connecting molecular mechanisms with disease heterogeneity and therapeutic vulnerability, we aim to provide a biologically coherent perspective that supports mechanism-based patient stratification, biomarker-guided precision medicine, and the development of interventions focused on preserving β-cell integrity rather than treating hyperglycemia alone.

Here, we use the term β-cell Stress Continuum to describe a proposed sequence in which β-cells may move from adaptive responses to persistent dysfunction and, in some settings, loss of cellular identity or survival. We present this sequence as a testable conceptual model, not as a demonstrated universal mechanism or a claim that β-cell stress initiates all forms of diabetes. In T1D, autoimmune injury is a defining upstream process, whereas in T2D, insulin resistance, genetic susceptibility, and environmental exposures may precede or interact with β-cell dysfunction. β-

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cell stress may therefore be an early contributor, a secondary response, an amplifier of ongoing injury, or a downstream consequence, depending on the disease context.

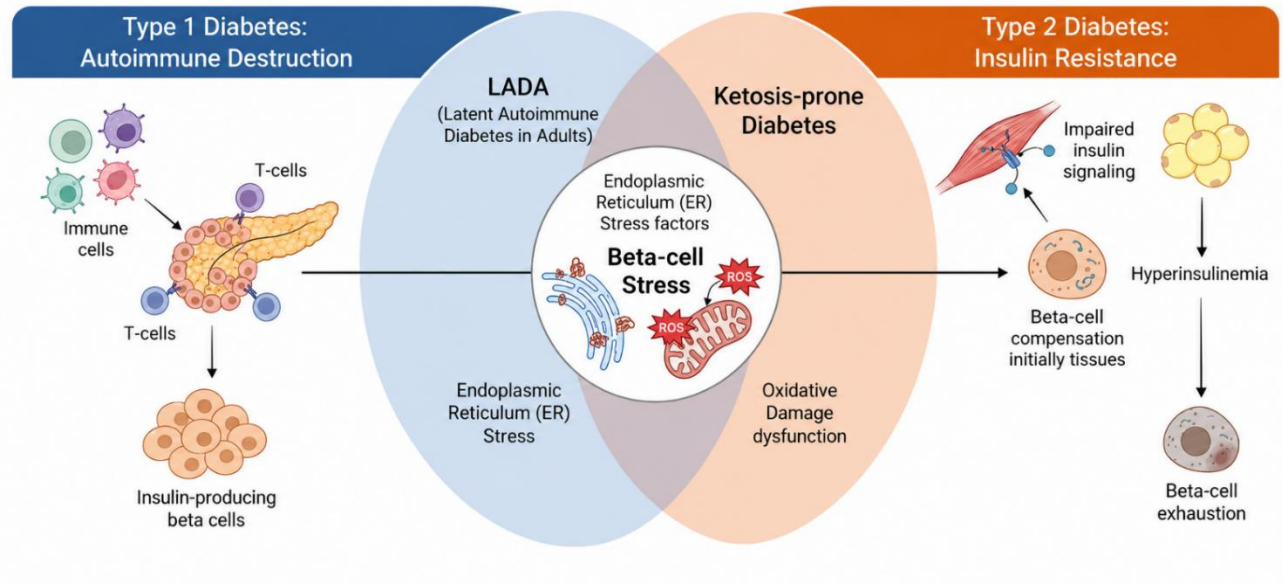

Figure 1. The Unified Continuum Model of Diabetes. *A schematic representation illustrating diabetes as a dynamic physiological spectrum rather than discrete clinical entities. The model highlights the phenotypic overlap between Type 1 Diabetes (T1D), Type 2 Diabetes (T2D), and Latent Autoimmune Diabetes in Adults (LADA), positioning β-cell stress as a context-dependent contributor to β-cell dysfunction and diabetes progression that connects localized islet dysfunction to systemic metabolic collapse.*

2. Search Strategy and Selection Criteria

This article is a narrative review of molecular and cellular mechanisms that may contribute to β-cell stress, dysfunction, and diabetes progression. Relevant literature was identified through

searches of PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar, alongside examination of the reference lists of relevant reviews and primary studies. Searches used combinations of terms related to β-cell stress and identity, including "β-cell stress," "β-cell dedifferentiation," "endoplasmic reticulum stress," "glucolipotoxicity," "β-cell identity," "islet inflammation," "senescence," "diabetes progression," "immunometabolic crosstalk," "extracellular vesicles," "β-cell rest," and mechanisms of type 1 and type 2 diabetes.

The literature search covered foundational and more recent publications available during manuscript preparation, including relevant work published through 2026. We selected sources for their relevance to the scope of the review, their contribution to understanding β-cell stress and diabetes pathophysiology, and their value in representing experimental, animal, and clinical evidence. Primary studies were considered alongside reviews and meta-analyses to provide context and to compare findings across evidence types. Because this is a narrative review, the search and selection process was not designed as a systematic review; no claim of exhaustive retrieval, formal risk-of-bias assessment, or systematic-review protocol is made. The evidence is synthesized thematically, with attention to differences in study models and to the limits of extrapolating experimental findings to human disease.

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Inclusion criteria

• Original research, reviews, or metanalyses involving molecular, cellular, or physiological mechanisms of β-cell stress.

• Studies examining ER stress, mitochondrial dysfunction, glucolipotoxicity, dedifferentiation, senescence, inflammation, or extracellular vesicle signaling in diabetes.

• Human, rodent, or in vitro studies providing mechanistic insight into β-cell failure.

• Articles published in English.

Exclusion criteria

• Non-mechanistic clinical reports lacking β-cell biology relevance.

• Case reports, conference abstracts, editorials, or narrative commentaries without primary data.

• Studies focused solely on glucose metabolism without β-cell or islet outcomes.

Ultimately, 176 high-quality, mechanism specific articles formed the scientific basis for developing the unified β-cell stress continuum model presented in this work.

3. β-Cell Stress as a Convergent Mechanism in Diabetes Progression

Pancreatic β-cells are the principal effectors of systemic glucose homeostasis through regulated synthesis, storage, and nutrient-stimulated secretion of insulin, and their specialized secretory machinery and metabolic coupling underpin glucose-responsive insulin release [13]. Because insulin production and secretion place unusually large proteostatic and bioenergetic demands on β-cells, these cells operate with limited reserve and are disproportionately susceptible to perturbations of protein folding, redox balance, and mitochondrial function; this intrinsic vulnerability places β-cell stress as a key node of pathogenic cascades that culminate in both type 1 and type 2 diabetes [20,21]. Importantly, β-cell dysfunction driven by cellular stress manifests well before clinical hyperglycemia (the 'prediabetic' phase), and longitudinal and histological human and experimental data link early stress signatures to later progressive loss of regulated insulin secretion across diabetes subtypes [22,23]. (the operational stages, key hallmarks, biomarkers, and reversibility characteristics across this continuum are summarized in Table 4).

3.1. Molecular and Cellular Sources of β-Cell Stress

The dominant ER folding load from proinsulin synthesis renders β-cells highly sensitive to proteostatic perturbations. Disruptions increasing unfolded proinsulin rapidly activate the unfolded protein response (UPR). UPR sensors (PERK, IRE1α, ATF6) mediate adaptation acutely by reducing translation and enhancing chaperones/ERAD, but chronic activation shifts to pro-apoptotic pathways (PERK→CHOP; IRE1α→JNK/RIDD; ATF6 remodeling), leading to ER dilation and early loss of β-cell fidelity [9,12]. Notably, prolonged IRE1 signaling can directly degrade proinsulin mRNA through its RNase domain as a defensive mechanism to reduce ER folding load, providing a molecular explanation for why stressed β-cells reduce insulin biosynthesis well before undergoing apoptosis [16].

β-cells express low levels of antioxidant enzymes (e.g., catalase, glutathione peroxidases, superoxide dismutases), impairing ROS neutralization during intense glucose and fatty-acid metabolism. This amplifies oxidative damage to proteins, lipids, and DNA [6]. Antioxidant and mitophagy-restoring strategies rescue function in preclinical models, highlighting ROS centrality [14]. Also, the heavy biosynthetic demand itself acts as an intrinsic source of oxidative stress, as the formation of oxidative disulfide bonds during proinsulin folding directly generates reactive oxygen species, compounding the vulnerability caused by low endogenous antioxidant defenses [17].

Chronic hyperglycemia drives glucotoxicity via increased mitochondrial ROS, glycation products, and post-translational modifications that impair transcriptional regulators and secretory machinery, reducing insulin biosynthesis and causing early loss of first-phase secretion [14].

Lipotoxicity from excess free fatty acids—common in obesity—accumulates ceramides, disrupting mitochondrial function, insulin secretion, ER calcium handling, and promoting inflammatory signaling [20,22,26]. Specifically, chronic nutrient stress and lipid accumulation

impair SERCA-dependent calcium uptake into the ER, depleting calcium stores and directly weakening calcium-dependent chaperone functions, which creates a vicious cycle of further proinsulin misfolding [18].

In T2D models and human islets, IAPP misfolding forms oligomeric aggregates that disrupt membranes, induce ER stress, local inflammation, and replicate diabetic transcriptomic features [19].

Nutrient excess causes mitochondrial hyperpolarization, ROS leakage, impaired ATP synthesis, and caspase activation, undermining granule exocytosis [20]. Mitophagy-enhancing interventions restore bioenergetics and secretion [20,21]. Beyond proteostatic and redox perturbations, accumulating evidence identifies DNA damage and activation of the DNA damage response as common early events across both type 1 and type 2 diabetes, establishing a self-reinforcing cycle in which oxidative and inflammatory stress induces genomic injury that, in turn, further compromises β-cell stress-resolution capacity [22].These insults converge early, producing morphological (ER/mitochondrial swelling) and molecular (UPR activation, TF suppression) changes before major mass loss [19]. (**Table 1**)

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Table 1. Molecular and Cellular Drivers of Pancreatic β-Cell Stress.

Stress Type	Molecular Mechanisms & Mediators	Cellular Consequences & Final Outcomes
Endoplasmic Reticulum (ER) Stress	• Heavy folding load from proinsulin synthesis. • Unfolded Protein Response (UPR) activation via PERK, IRE1α, and ATF6. • Prolonged IRE1 signaling degrades proinsulin mRNA via RNase domain (RIDD).	• Early reduction in insulin biosynthesis. • ER dilation and loss of cellular fidelity. • Shift from adaptation to pro-apoptotic pathways (PERK→CHOP; IRE1α→JNK).

	• Depleted ER calcium stores (impaired SERCA) weaken chaperone functions.	
Oxidative Stress	• Low endogenous antioxidant defenses (e.g., catalase, SOD). • High ROS generated from intense glucose/lipid metabolism. • ROS byproducts from forming oxidative disulfide bonds during proinsulin folding.	• Widespread oxidative damage to cellular proteins, lipids, and DNA. • Self-reinforcing cycle of genomic injury.
Glucotoxicity	• Chronic hyperglycemia driving mitochondrial ROS. • Accumulation of glycation products. • Harmful post-translational modifications.	• Impaired transcriptional regulators and secretory machinery. • Reduced insulin biosynthesis. • Early loss of first-phase insulin secretion.
Lipotoxicity	• Excess free fatty acids leading to ceramide accumulation. • Disruption of ER calcium handling. • Activation of inflammatory signaling pathways.	• Disrupted insulin secretion. • Impaired mitochondrial function. • Amplification of ER stress and functional decline.
IAPP Aggregation	• Misfolding of Islet Amyloid Polypeptide (IAPP). • Formation of toxic oligomeric aggregates.	• Physical disruption of cellular membranes. • Induction of localized inflammation and ER stress. • Transcriptomic shifts toward a diabetic phenotype.
Mitochondrial Dysfunction	• Nutrient excess leading to mitochondrial hyperpolarization. • ROS leakage and impaired ATP synthesis. • Caspase activation.	• Morphological changes (mitochondrial swelling). • Undermined insulin granule exocytosis (bioenergetic failure).
Genomic Stress (DNA Damage)	• Oxidative and inflammatory stress inducing genomic injury. • Activation of the DNA damage response (DDR).	• Compromised β-cell stress-resolution capacity. • Self-reinforcing cycle of cellular deterioration and vulnerability.

3.2. Adaptive Responses and Loss of β-Cell Identity

As described earlier, early stress favors adaptive UPR to temporarily restore proteostasis, where specific manipulations (e.g., XBP1) yield reversible functional changes [21,23]. However,

sustained stress drives pro-apoptotic pathways and identity repression, with genetic models demonstrating timing-dependent reversible or irreversible phenotypes [23,24].

β-cells remodel metabolism (glycolytic/mitochondrial adjustments) and activate selective autophagy (mitophagy, ER-phagy) to clear damage[25]. Autophagy enhancers reverse early dysfunction preclinically[19,25].

Initially, lineage transcription factors (PDX1, MAFA, NKX6.1) and anti-apoptotic genes are preserved, but persistent stress suppresses them, activating alternative programs [25,26].

Prolonged stress induces dedifferentiation: loss of mature markers (INS, GLUT2, MAFA, NKX6.1), re-expression of progenitor/"disallowed" genes, or trans differentiation—preserving survival but abolishing glucose-responsive secretion[26–29]. Observed in human T2D islets, metabolic/inflammatory models, and single-cell studies; microenvironmental/UPR/epigenetic cues collaborate [26,30].

Early consequences include lost first-phase secretion, impaired Ca^{2+} handling, and hyperproinsulinemia as ER dysfunction biomarkers [20,31,32].

Stress generates neoantigens, amplifying autoimmunity in susceptible hosts; intrinsic genes (e.g., TET2) determine elimination versus dedifferentiated survival [31–33]. Before the establishment of overt insulitis, stressed or dying β-cells actively release danger-associated molecular patterns (DAMPs) such as HMGB1 and heat shock proteins, which alert innate immune cells and initiate the transition from localized stress to active immune recruitment [34]. Beyond antigenic changes, emerging evidence further indicates that stressed β-cells actively remodel their microenvironment by contributing to peri-islet extracellular matrix degradation, including collagen IV breakdown,

which weakens pro-survival matrix signaling and facilitates immune cell infiltration into the islet [35].

A prolonged therapeutic window exists for dysfunctional but salvageable β-cells via reduced demand, proteostatic correction, or organellar quality control [21,24,36,37]. Effective strategies include chemical chaperones/UPR modulators, antioxidants/mitophagy inducers, and identity-preserving agents (GLP-1 agonists, TF/epigenetic targeting) [21,36,37].

Evidence supports β-cell stress (proteostatic, oxidative, and lipid insults; mitochondrial dysfunction; and inflammation) as a context-dependent contributor to β-cell dysfunction and diabetes progression. Depending on disease context, β-cell stress may precede, follow, or amplify other pathogenic processes; progression may involve a shift from adaptive to maladaptive responses, dedifferentiation, and immune amplification [22–24]. Priorities: early biomarkers (proinsulin: insulin ratio, UPR signatures); genetic/immunologic modifier stratification (TCF7L2, HLA, TET2); translation of stress-relieving/identity-restoring interventions (chaperones, mitophagy enhancers, GLP-1/gene therapies) to halt/reverse diabetes while β-cells remain viable [36–38].

Clarifying β-Cell States: Dysfunction, Dedifferentiation, Senescence, and Mass Loss

To establish operational precision across the continuum, distinct cellular fates must be delineated based on their physiological and physical status:

β-Cell Dysfunction: A functional deficit wherein the cellular identity and mass are preserved, but insulin secretion is blunted due to reversible metabolic or oxidative signaling derangements (e.g., impaired calcium handling or uncoupled mitochondrial respiration).

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β-Cell Dedifferentiation: A phenotype characterized by the regression to an immature, progenitor-like state with downregulation of mature identity markers (MAFA, NKX6.1, INS) and ectopic re-expression of disallowed genes (LDHA, ALDOB). Here, cell viability is maintained without immediate commitment to cell death, conferring potential reversibility upon stress alleviation.

β-Cell Senescence: A terminal state of proliferative arrest driven by persistent DNA damage and organelle stress, typified by $p16^{INK4\alpha}$ and SA-β-galactosidase activation. Senescent β-cells actively perpetuate local tissue dysfunction via the senescence-associated secretory phenotype (SASP).

β-Cell Apoptosis and Cell Death: Irreversible execution of cell termination programs (apoptosis, necroptosis, pyroptosis), leading to structural membrane breakdown and cell loss.

Loss of Functional β-Cell Mass: The cumulative clinical and physiological outcome of the preceding states. It reflects the net reduction in active, mature, and secretory-competent β-cell capacity, resulting from both genuine physical cell loss (death) and the functional silencing of surviving cells (dysfunction, dedifferentiation, or senescence).

4. Disrupted Endocrine Signaling and Inter-Organ Crosstalk

β-cell stress initiates a cascade that extends beyond the pancreas, disrupting coordinated endocrine signaling and inter-organ communication essential for metabolic homeostasis [31,32]. In health, insulin and glucagon act in concert to regulate nutrient storage and mobilization across liver, adipose tissue, skeletal muscle, and brain [20,32]. Building on this, our recent work highlights how such metabolic disruption extends profoundly into the central nervous system, driving region-specific brain insulin resistance and linking peripheral failure to neural circuit dysfunction

[21].Consequently, progressive loss of pancreatic function and altered secretory patterns—including reduced insulin amplitude, lost pulsatility, and relative hyperglucagonemia—severely perturb these systemic axes, amplifying hyperglycemia, dyslipidemia, and global insulin resistance [19,20,23].

4.1. Pancreas–Liver Axis

The pancreas-liver axis is central to glycemic control, with insulin suppressing hepatic glucose production (HGP) and glucagon stimulating it [45]. Early β-cell stress disrupts insulin pulsatility—high-frequency oscillations critical for portal vein signaling and hepatic insulin sensitivity [24]. Loss of pulsatile delivery, observed in prediabetes and both type 1 and type 2 diabetes progression, desensitizes hepatocytes, leading to unchecked gluconeogenesis and glycogenolysis even at modest insulin levels [47,51].

Concurrently, impaired intra-islet paracrine regulation allows unrestrained α-cell glucagon secretion. Stressed β-cells release fewer inhibitory signals (insulin, GABA, zinc), resulting in hyperglucagonemia that drives excessive HGP, particularly fasting hyperglycemia [33,40,41]. This bidirectional dysregulation forms a vicious cycle: elevated glucose and free fatty acids (FFAs) further stress β-cells while promoting hepatic insulin resistance via diacylglycerol accumulation and protein kinase C activation [20,40,41].

Altered lipid metabolism ensues. Reduced insulin signaling impairs SREBP-1c suppression, increasing de novo lipogenesis and VLDL secretion, contributing to dyslipidemia. Hepatic steatosis develops as FFAs from adipose lipolysis overwhelm oxidative capacity, with inflamed islets releasing cytokines that exacerbate Kupffer cell activation and fibrosis progression [19,30,41,42]. Longitudinal studies show that glucagon suppression tests reveal

hyperglucagonemia early in type 2 diabetes pathogenesis, correlating with NAFLD severity [19,25,42]. Importantly, this axis operates bidirectionally: recent work demonstrates that β-cell ER stress can broadcast outward to influence peripheral metabolism, and reducing the UPR mediator CHOP in β-cells improves not only insulin secretion but also systemic insulin sensitivity and vascular function, positioning the stressed β-cell as an active driver rather than a passive victim of systemic metabolic dysfunction [43].

4.2. Pancreas–Adipose Tissue Axis

Adipose tissue serves as an energy buffer, with insulin promoting glucose uptake, lipogenesis, and antilipolytic effects via HSL inhibition [25–27]. Declining β-cell function reduces insulin exposure, fostering adipose insulin resistance characterized by impaired GLUT4 translocation and unrestrained lipolysis [28,29].

Increased FFA release floods circulation, exacerbating lipotoxicity in β-cells and hepatocytes. Ectopic fat deposition in the pancreas further impairs islet function, creating a feed-forward loop. Beyond classical hormones and lipids, emerging evidence identifies extracellular vesicles as critical carriers of inter-organ stress signals; for instance, adipocyte-derived exosomes enriched in ANGPTL2 can activate the EIF2α/ATF4/CHOP stress pathway in β-cells, while β-cell-derived vesicles can propagate mitochondrial dysfunction to skeletal muscle, establishing a novel vesicle-mediated axis of metabolic deterioration [44]. Adipose hypertrophy and hypoxia drive crown-like structure formation, with macrophage infiltration releasing proinflammatory adipokines (leptin, resistin, TNF-α) that systemically amplify insulin resistance and β-cell apoptosis [36,37].

Leptin resistance emerges as insulin normally suppresses leptin; hypoinsulinemia disinhibits expression, yet central signaling fails amid inflammation. Adiponectin, an insulin-sensitizing

adipokine, declines with visceral fat expansion, reducing AMPK activation in liver and muscle [37,38,45]. This axis explains paradoxical hyperinsulinemia in early type 2 diabetes—compensatory β-cell effort against adipose-driven resistance—followed by decompensation as stress accumulates [46,47].

4.3. Pancreas–Skeletal Muscle and Neural Regulation

Skeletal muscle accounts for ~80% of insulin-stimulated glucose disposal. Impaired insulin signaling—via reduced PI3K/Akt activation—impairs GLUT4 translocation, decreasing glucose uptake and glycogen synthesis [48–50]. Early β-cell stress contributes indirectly: hypoinsulinemia limits muscle perfusion and substrate delivery, while hyperglucagonemia promotes proteolysis, releasing amino acids for gluconeogenesis [51–53].

Myokines (irisin, IL-6 post-exercise) normally enhances insulin sensitivity, but chronic inflammation blunts this. Ectopic intramuscular lipid accumulation activates PKCθ, inhibiting IRS-1 tyrosine phosphorylation [73–76].

Neural regulation integrates these axes through the autonomic nervous system (ANS). While vagal parasympathetic tone normally stimulates insulin and inhibits glucagon, this balance is reversed by sympathetic overactivity and hypothalamic inflammation driven by circulating metabolites and cytokines [57–59]. This central dysregulation is compounded by impaired brain-islet crosstalk, as the diminished incretin effect (e.g., GLP-1) weakens the vagal signaling that supports β-cell function [51,60]. Consequently, reduced insulin pulsatility disrupts central feedback, perpetuating hyperphagia and resistance, with autonomic neuropathy ultimately desynchronizing secretion in advanced disease [51,57,58].

These disrupted axes converge: the liver overproduces glucose, adipose tissue releases excess FFAs, muscle glucose uptake is impaired, and neural dysregulation may further amplify metabolic dysfunction. β-cell stress may interact bidirectionally with these processes, acting as a context-dependent contributor or amplifier while also arising downstream of systemic metabolic disturbances. Multi-organ models confirm that restoring β-cell function (e.g., via intensive insulin therapy early) partially reverses peripheral defects, supporting the continuum framework [61–63]. At the local tissue level, stressed β-cells can also propagate dysfunction to neighboring cells through bystander spread of ER stress via connexin-43-mediated gap junction coupling, amplifying the total islet stress burden even when the initial insult is focal, and further locking the pancreas into a self-sustaining state of metabolic injury [64].(**Table 2**)

Table 2: Disrupted Inter-Organ Crosstalk in the β-Cell Stress Continuum

Axis	Primary Signaling Molecules	Target Organ Effects	Physiological Consequences
Pancreas–Liver	• **Hormones:** Insulin (loss of pulsatility), Glucagon (excess) • **Metabolites:** Free Fatty Acids (FFAs) • **Cytokines/Other:** Inflammatory cytokines, UPR mediators (CHOP)	• **Liver:** Desensitized hepatocytes, impaired suppression of glucose production, increased *de novo* lipogenesis, Kupffer cell activation, steatosis.	• Unchecked hepatic glucose production (HGP) • Fasting hyperglycemia • Hepatic insulin resistance • Dyslipidemia (elevated VLDL) and NAFLD
Pancreas–Adipose	• **Hormones:** Insulin (reduced), Leptin, Resistin, Adiponectin (reduced) • **Metabolites:** FFAs • **Other:** Proinflammatory adipokines (TNF-α), Extracellular vesicles (e.g., with ANGPTL2)	• **Adipose Tissue:** Impaired GLUT4 translocation, unrestrained lipolysis, macrophage infiltration (crown-like structures), chronic low-grade inflammation.	• Elevated circulating FFAs leading to systemic lipotoxicity • Amplified systemic insulin resistance • Increased β-cell apoptosis • Ectopic fat deposition (pancreas, liver)
Pancreas–Skeletal Muscle	• **Hormones:** Insulin (reduced), Glucagon (excess)	• **Skeletal Muscle:** Impaired GLUT4 translocation and PI3K/Akt signaling, reduced glucose uptake and glycogen	• Failure to clear ~80% of postprandial glucose

	• **Metabolites:** Intramuscular lipids • **Myokines:** Blunted beneficial signaling (e.g., Irisin)	synthesis, increased proteolysis.	• Insulin resistance at the largest site of glucose disposal • Release of amino acid precursors for gluconeogenesis
Pancreas–Neural Regulation	• **Neurotransmitters:** Autonomic nervous system (ANS) imbalance (↓Parasympathetic, ↑Sympathetic) • **Hormones:** Incretins (e.g., reduced GLP-1 effect) • **Metabolites/Cytokines:** Central inflammation drivers	• **Brain/ANS:** Hypothalamic inflammation, impaired central feedback loops, reduced vagal signaling to the pancreas.	• Dysregulation of insulin and glucagon secretion • Perpetuation of hyperphagia and central insulin resistance • Eventual desynchronization of secretion due to autonomic neuropathy
Intra-Islet Paracrine	• **Local Signals:** Insulin, GABA, Zinc (reduced inhibitory signals) • **Intercellular:** Connexin-43 gap junctions	• **α-cells:** Disinhibition leading to unrestrained glucagon secretion. • **Neighboring β-cells:** Bystander spread of ER stress.	• Relative or absolute hyperglucagonemia, worsening hyperglycemia • Amplification of the total stress burden within the islet, creating a self-sustaining cycle of dysfunction

5.Transition from Islet-Restricted Injury to Systemic Metabolic Collapse: A Synthesized, Evidence-Based Framework

5.1. β-Cell Compensation and Collapse

In early insulin resistance, β-cells increase insulin output (hyperinsulinemia) through enhancements in secretory drive and mass, which temporarily preserves euglycemia. However, chronic nutrient and oxidative stress can lead to β-cell apoptosis, loss of functional mass, and phenotypic changes consistent with dedifferentiation and loss of glucose-stimulated insulin secretion. This collapse of insulin secretory reserve leads to progressive hyperglycemia [65–67]. Microvascular disturbances within islets and local oxidative stress amplify this vulnerability and may precede symptomatic hyperglycemia, thereby linking local vascular and cellular stress to subsequent endocrine failure [67,68]. Notably, this transition is marked by a reversal in inter-organ signaling: in prediabetes, circulating WNT3a activates islet Frizzled-Wnt signaling to support

compensatory insulin secretion and β-cell proliferation, but in established type 2 diabetes, the balance of Wnt ligands and inhibitors from adipose tissue, muscle, and plasma shifts toward suppression, converting pro-adaptive signals into drivers of dysfunction [69].

5-2. Unmasking and Entrenching Insulin Resistance: Molecular Pathways

Once insulin secretion falls below the compensatory threshold, pre-existing insulin resistance in the liver, skeletal muscle, and adipose tissue is unmasked and amplified by multiple mechanisms. Lipid overload (elevated circulating free fatty acids and diacylglycerols) and inflammatory adipokines activate serine/threonine kinases, such as classical PKCs, JNK, IKK/SAPK, and mTOR/S6K1, increasing serine phosphorylation of insulin receptor substrate proteins, thereby reducing PI3K→Akt signaling necessary for GLUT4 translocation [70–72]. Experimental and translational studies clarify that lipid overload is linked to increased IRS-1 serine phosphorylation and diminished downstream insulin signaling, accounting for much of the early reversible insulin resistance observed in obesity and prediabetes [70,71]. Importantly, inflammation itself undergoes a functional reversal during this transition: while beta cells from obese donors without diabetes show increased sensitivity to the insulin-secreting effects of IL-1β (suggesting a transient adaptive role), beta cells from obese donors with type 2 diabetes lose this responsiveness, indicating that the same inflammatory context becomes maladaptive as stress deepens [73].

5.3. From Reversible to Fixed Resistance: Lipotoxic, Mitochondrial, and Epigenetic Mechanisms

While early, signal-driven insulin resistance may improve with decreased substrate exposure, chronic nutrient excess and inflammation result in persistent cellular damage—including mitochondrial overload, sphingolipid accumulation, ROS-driven signaling, and epigenetic

reprogramming of metabolic genes—which heralds a more ingrained state of insulin resistance [68,74,75]. Ceramide synthesis and sphingolipid pathway activation have been implicated across diabetic complications and are mechanistically linked to mitochondrial dysfunction and insulin signaling blockade, thereby connecting chronic lipid dysmetabolism to irreversible defects in insulin action [74,75]. A critical organelle-level failure marking decompensation is the progressive decline in autophagic flux, which chronic metabolic stress impairs through LATS2 and MTORC1 signaling, reducing the β-cell's ability to clear damaged components and survive stress [76].

5.4. Organ-Level Consequences — Muscle, Liver, Adipose as Effectors of Systemic Dysfunction

The skeletal muscle, liver, and adipose tissue are key effectors of the systemic phenotype that follows β-cell decompensation. Impaired insulin signaling in muscle disrupts GLUT4 trafficking and postprandial glucose disposal. Concurrently, hepatic insulin resistance disinhibits gluconeogenesis, maintaining fasting and post-absorptive hyperglycemia despite hyperinsulinemia. Insulin-resistant adipose tissue fails to suppress lipolysis, which sustains elevated circulating free fatty acids that perpetuate lipotoxicity [65,70,77]. These processes are interrelated; circulating substrates from adipose tissue worsen hepatic and muscular insulin responses, and hepatic steatosis not only reflects but also enhances insulin resistance via increased lipogenesis and diacylglycerol accumulation [77,78].

5.5. Atherogenic Dyslipidemia as a Parallel and Proximate Consequence

Loss of insulin's anti-lipolytic and regulatory effects generates a typical dyslipidemic profile characterized by elevated triglyceride-rich particles and free fatty acids, reduced HDL cholesterol,

and increased hepatic VLDL production, resulting in small, dense, atherogenic LDL particles. This dyslipidemia is perpetuated by metabolic stress, with epidemiologic and mechanistic data linking NAFLD and metabolic dysfunction to increased atherosclerotic risk, which is sometimes independent of glycemic levels [70,75,78–80]. Consequently, macrovascular disease often develops in the context of the metabolic syndrome before overt biochemical diabetes is diagnosed [75,79].

5.6. Mitochondrial Bioenergetics, Metabolic Inflexibility, and Energy Sensing

Impaired mitochondrial bioenergetics is a common theme across tissues, where chronic nutrient excess and oxidative stress lead to reduced ATP production, increased ROS, and accumulation of incompletely oxidized lipid intermediates [81–84][8. Physiologically, this manifests as metabolic inflexibility—a diminished capacity to switch between carbohydrate and lipid oxidation, biased heavily toward fatty-acid oxidation [82,85,86]. This systemic failure is compounded by the dysregulation of key energy sensors: AMPK activity and SIRT1 are decreased, compromising adaptive responses, while mTOR/S6K pathways become overactive, promoting insulin-resistance signaling. Concurrently, central regulatory mechanisms, including hypothalamic inflammation, hinder satiety signals, encouraging persistent metabolic injury [85–88].

5-7. Bioenergetic Failure as a Unifying Substrate of Diabetic Complications

Organ complications of diabetes may be viewed as manifestations of tissue-specific energy dysregulation exacerbated by oxidative stress and inflammation: endothelial dysfunction and atherosclerosis can result from mitochondrial ROS production, reduced nitric oxide bioavailability,

and impaired vascular regulation [57,58,78]; diabetic nephropathy is linked to energy stress, mitochondrial ROS, and maladaptive immune responses contributing to fibrosis[59,60]; diabetic neuropathy correlates with impaired mitochondrial function and increased oxidative stress [89]; and diabetic retinopathy is exacerbated by lipid-driven ROS and ceramide signaling in retinal cells[74,90]. These diverse complications share a common mechanism—bioenergetic derangement under oxidative stress—stemming from the β-cell to peripheral vicious cycle [59,68,86].

5.8. Clinical Priorities and Therapeutic Implications

In summary, persistent β-cell stress initiates a multistep progression from compensatory hyperinsulinemia to systemic energy dysregulation and subsequent micro- and macrovascular complications [81,86,91]. Reconceptualizing diabetes as a systemic energy miscoordination broadens therapeutic goals beyond solely glycemic control to restoring substrate balance and mitochondrial health. This multipronged strategy includes lifestyle interventions that reduce substrate overload [92], alongside pharmacological agents that act at complementary pathways. For instance, metformin activates AMPK [87,92], SGLT2 inhibitors and incretin-based therapies confer vascular and mitochondrial benefits while reducing metabolic demand [93–95], and emerging therapeutics target ROS handling and biogenesis [96,97]. Together, early intervention during the metabolically flexible prediabetic stage is prioritized to tackle both proximal islet dysfunction and peripheral cycles perpetuating systemic disarray [96,98].

6. Immune Activation, Inflammation, and Redox Imbalance — Synthesis of Mechanistic Evidence and Therapeutic Implications

Progression from metabolic dysregulation to overt diabetes and complications involves amplification of endocrine/metabolic defects by chronic immune activation and redox imbalance. Metabolic overload (hyperglycemia, excess free fatty acids) triggers oxidative stress and damage-associated signals, activating innate immune pathways, recruiting/reprogramming myeloid cells, and initiating feed-forward inflammatory cycles that impair insulin signaling, damage mitochondria and β-cells, and promote vascular/end-organ pathology [96,99,100]. (**Figure 2**)

6.1. Islet and Systemic Chronic Inflammation

A state of chronic, low-grade inflammation is a critical link between obesity, insulin resistance, and T2D progression. This process begins locally within the pancreas, where β-cell stress itself triggers an inflammatory response. Islet inflammation intertwines with this stress, as cytokines (IL-1β, TNF-α), chemokines (e.g., CCL2, CCL5), and innate immune cell infiltration exacerbate β-cell dysfunction [10,11,101]. This local process is amplified by systemic inflammation originating from other metabolic tissues. In hypertrophic adipose tissue, for example, hypoxia and cellular stress recruit pro-inflammatory macrophages, which secrete cytokines like TNF-α, IL-1β, IL-6, and MCP-1 [102]. These factors circulate and impair insulin signaling systemically in muscle and liver via stress-activated pathways including JNK, IKK, and NF-κB, while also contributing to endothelial dysfunction and furthering β-cell demise [103–105].

In obese adipose, hypertrophy, hypoxia, and metabolic stress elevate oxidative burden, altering adipokine/chemokine output to recruit/activate macrophages, favoring pro-inflammatory phenotypes and secretion of TNF-α, IL-1β, IL-6, and MCP-1, propagating systemic inflammation [96,100,106]. NOX pathways and mitochondrial dysfunction in adipocytes/immune cells sustain ROS-driven chemokine/cytokine expression [102,103].

Released cytokines and lipid signals exert endocrine effects, impairing insulin signaling in muscle/liver via stress kinases, reducing β-cell secretion, and inducing endothelial dysfunction/prothrombotic states [96,99,104]. Inflammation-driven JNK/IKK/NF-κB pathways and redox modifications cause IRS serine phosphorylation, disrupting insulin receptor→PI3K→Akt signaling [113,114,119]. Notably, the β-cell itself is not exempt from insulin resistance; impaired insulin signaling within β-cells compromises their survival programs and amplifies lipotoxic vulnerability, establishing a cell-intrinsic positive feedback loop that further accelerates functional decline [98].

Islets actively contribute: β-cell metabolic stress/ROS increase chemokine/DAMP release, recruiting macrophages and causing low-grade insulitis that impairs function/survival [104,106] [116,119]. Infiltrating myeloid cells and IL-1β exacerbate ER stress/apoptosis via NF-κB, converting reversible dysfunction to progressive loss [106,107]. Beyond apoptosis, a subset of stressed β-cells enters a senescent state characterized by a senescence-associated secretory phenotype (SASP), through which they actively secrete pro-inflammatory cytokines and chemokines that harm neighboring cells and lock the islet into a self-perpetuating inflammatory loop [108]. In autoimmune-susceptible contexts, redox stress modulates antigen presentation/T-cell responses, accelerating adaptive injury [101,107].

Inflammation drives complications: vascular inflammation/oxidized lipids promote atherogenesis [109]; renal macrophage/NOX activation advances glomerulosclerosis/kidney disease [104]; neurovascular inflammation contributes to neuropathy [104]. Elevated biomarkers in prediabetes/early T2D highlight inflammation's temporal role [96,99,100]. Anti-inflammatory interventions (pharmacological/lifestyle) yield metabolic/organ benefits, supporting causality [99,105,110]. Ultimately, persistent exchange of inflammatory and metabolic signals can

transform the islet microenvironment into a self-sustaining immune niche in which cytokines amplify oxidative and ER stress, reactive oxygen and nitrogen species cause further tissue damage, and ongoing injury generates new antigens that help maintain and perpetuate the immune response [81].

6.2. Oxidative Stress and Mitochondrial Damage

ROS arise from mitochondrial leakage, NOX, xanthine oxidase, and uncoupled NOS, acting as messengers or cytotoxins in excess [106,111]. β-cells' low antioxidant capacity (glutathione, catalase/SOD/GPx) heightens vulnerability to ROS impairing insulin synthesis/folding, coupling, and survival [106,112]. Systemic stressors (hyperglycemia, FFAs, AGE-RAGE) boost NOX/mitochondrial ROS across tissues [103,113].

Excess ROS damage lipids/proteins/DNA, perturb bioenergetics; mitochondrial hyperpolarization increases superoxide, peroxidation products act as DAMPs, and DNA damage depletes NAD+ [104,111,114]. ER stress/UPR and redox perturbations reinforce mutually: PERK/ATF4/CHOP and IRE1α link to NF-κB/cytokine induction [104,107]. ROS activate kinases suppressing insulin signaling/mitochondrial biogenesis (PGC-1α) [96,104].

Damaged mitochondria amplify ROS/ATP deficit: compromising β-cell release, muscle GLUT4/oxidation, endothelial NO/adhesion [104,115,116]. Fragmentation, impaired mitophagy, mtDNA damage feature in chronic disease; mitophagy manipulation alters inflammation/progression preclinically [91].

Inflammation/redox crosstalk is bidirectional: cytokines induce NOX/iNOS, amplifying damage; ROS activate NLRP3/IL-1β [103,117]. Propagated signals (oxidized lipids/exosomes) extend focal inflammation systemically [104,117].

Broad antioxidants yield mixed results, as scavenging ignores upstream sources (mitochondrial/NOX dysfunction, immune signaling, glutathione deficit) [96,99,111,118]. Promising targets: upstream NOX inhibition, mitophagy/quality control restoration, Nrf2 activation, inflammation modulation [110,119]. NOX inhibitors reduce remodeling; Nrf2/glutathione enhancers mitigate damage; lifestyle lowers burden [117,128,123,134]. GLP-1/SGLT2/NOX/Nrf2 agents improve readouts [13,120].

Synthesis: Substrate overload/β-cell stress initiates oxidative/inflammatory perturbations, recruiting immune cells that amplify insulin resistance/mitochondrial dysfunction via cytokine/ROS loops, perpetuating pathology/complications [96,106,121]. Priorities: map ROS/NOX sources; test upstream interventions (mitophagy/UCP/mtDNA protection, pathologic NOX suppression); stage trials pairing metabolic (GLP-1 agonists, SGLT2 inhibitors) with anti-inflammatory/redox therapies in reversible windows to preserve β-cell/vascular health [13,118,120,122]. Immune/redox imbalances are mechanistic accelerants and actionable for disease modification.

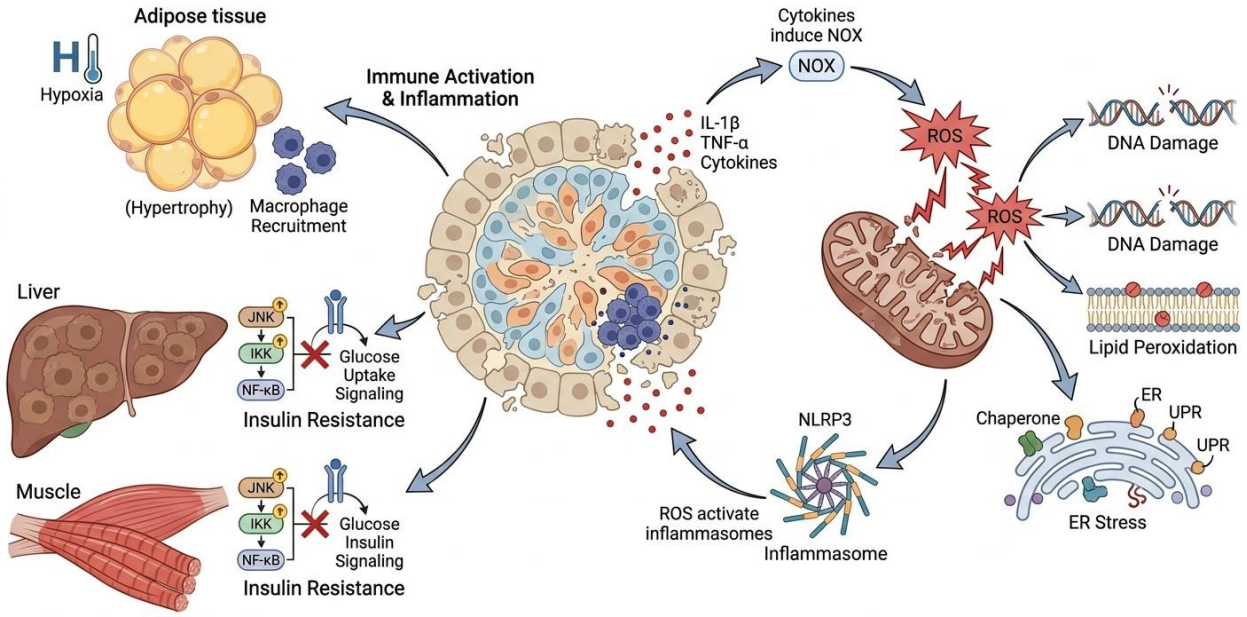

Figure 2. ***Immune–metabolic crosstalk linking oxidative stress, inflammation, and β-cell dysfunction across the diabetes continuum.*** *Hypoxia and adipose tissue expansion promote macrophage recruitment and inflammatory cytokine production, including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α). These mediators stimulate NADPH oxidase (NOX)-dependent generation of reactive oxygen species (ROS), resulting in DNA damage, lipid peroxidation, endoplasmic reticulum (ER) stress, and activation of the NLRP3 inflammasome. The resulting inflammatory and oxidative feedback loops contribute to insulin resistance and progressive β-cell dysfunction through signaling pathways such as NF-κB, JNK, and IKK, while the unfolded protein response (UPR) is activated as an adaptive response to ER stress*

7. Integrating Type 1 and Type 2 Diabetes within a Unified β-cell Stress Continuum

Traditional classifications separate type 1 diabetes (T1D) as an autoimmune β-cell–destructive disease and type 2 diabetes (T2D) as a metabolic disorder dominated by insulin resistance and progressive β-cell failure; however, accumulating molecular, cellular, and clinical evidence supports a β-cell–centric continuum in which shared mechanisms of β-cell stress, dysfunction, and loss underlie both conditions and determine phenotypic variation in timing, tempo, and dominant drivers of injury [82,92,97] . Single-cell and multi-omic analyses, genetic studies, and experimental models converge on a model in which endoplasmic reticulum (ER) stress/UPR activation, oxidative and mitochondrial dysfunction, inflammation, and β-cell dedifferentiation/senescence are common pathobiological nodes linking metabolic and immune pathways across the diabetes spectrum [123–125]. Recognizing diabetes as a continuum focused on β-cell stress reframes diagnosis, prognosis, and therapeutic prioritization toward interventions that reduce β-cell workload, limit cellular stress, and modulate pathogenic immunity across traditional diagnostic boundaries [97,126,127].

7.1. Rationale for a β-cell–centric continuum

The classical dichotomy that frames T1D as primarily autoimmune and T2D as primarily metabolic remains useful clinically, but it understates the mechanistic overlap documented across molecular, cellular, and clinical studies [92,97]. Reviews and conceptual pieces argue explicitly that both T1D and T2D share β-cell pathology and that strategies to protect β-cell are central to both diseases [82,97]. Empirical evidence supporting a continuum includes observations of autoimmune markers and β-cell autoimmunity in subsets of individuals with phenotypes otherwise resembling T2D, and of metabolic stress and insulin resistance in subsets of individuals with autoimmune diabetes and adult-onset presentations such as latent autoimmune diabetes in adults (LADA) or "double diabetes" [3,5,147]. Importantly, some β-cells may possess an intrinsic fragility independent of immune attack; experimental models demonstrate immune-independent β-cell vulnerability, suggesting that differences in β-cell resilience itself can modify both autoimmune and metabolic disease pathways and help explain partial overlap between T1D and T2D [22].

These cross-over clinical phenotypes and mechanistic overlaps motivate a model in which variation in timing, intensity, and the primary upstream stressor (immune versus metabolic) produce the clinically observed heterogeneity along a single path of progressive β-cell dysfunction and loss [84,85,97]. A more explicitly integrative proposal frames diabetes along immunoetiopathogenic lines, positioning T1D and T2D at opposite ends of a continuum where one pole is dominated by β-cell-targeting autoimmunity and the other by immune-sensitizing metabolic disruption, with mixed endotypes between those extremes where the two kinds of mechanisms blend [87].

7.2. Shared Mechanistic Vulnerabilities and Cellular End Points

As previously established, pancreatic β-cells are uniquely susceptible to ER stress, oxidative damage, and mitochondrial dysfunction due to their high metabolic throughput and secretory demands [129–131]. Rather than being exclusive to a single diabetes subtype, maladaptive UPR signaling and ROS generation form recurrent nodes of vulnerability in mechanistic studies of both autoimmune and metabolic diabetes [130–132]. Notably, even within shared stress pathways, the dominant branches may differ: while IRE1-mediated signaling appears more prominent in autoimmune contexts (T1D), PERK-eIF2α activation tends to dominate in metabolically driven β-cell failure (T2D), suggesting that overlapping mechanisms can still operate through distinct molecular routes depending on the primary upstream driver [88].

These chronic insults—whether driven by cytokines or glucolipotoxicity—converge on shared downstream endpoints [129,133]. Single-cell and multi-omic studies confirm this shared trajectory, revealing upregulation of stress pathways, progressive loss of canonical identity markers (e.g., MAFA and PDX1), and the acquisition of senescence-associated secretory phenotypes (SASP) across the diabetes spectrum [129,134–136]. Consequently, different upstream stressors (immune or metabolic) act through these convergent mechanisms to produce a similar downstream loss of β-cell competence [129,133,137].

7.3. Immune–metabolic crosstalk: bridging “autoimmune” and “metabolic” diabetes

The immune system figures centrally in T1D pathogenesis through autoreactive T cells and pro-inflammatory cytokines (e.g., IL-1β, IFN-γ, TNF-α) that contribute directly to β-cell dysfunction and death [138–140]. However, T2D is also characterized by chronic, low-grade inflammation driven by adipose tissue cytokines, innate immune activation (including NLRP3 inflammasome pathways), and islet macrophage infiltration, all of which exacerbate β-cell stress and impair insulin secretion [87,141,142]. Metabolic stress can therefore create a

pro-inflammatory islet milieu that promotes antigen modification and neo-epitope formation—mechanisms (for example, hybrid insulin peptides) that have been implicated in the generation and amplification of β-cell–directed adaptive immune responses in T1D and that illustrate a plausible route by which metabolic injury could initiate or amplify autoimmunity in susceptible hosts [82,143,144]. Conversely, β-cell–intrinsic stress responses and antigen presentation pathways can render β-cells more immunogenic and thereby link cell-intrinsic dysfunction to immune attack [93,139,145]. Thus, immune engagement should be viewed as a graded axis—intense and antigen-specific in classical T1D, lower-grade and innate-biased in many T2D cases—but continuous in mechanistic possibility across the spectrum [83,87,94].

7.4. Systemic modifiers: insulin resistance, genetics, and environment

Insulin resistance increases demand on β-cells and accelerates functional exhaustion and loss when compensatory capacity is exceeded, making β-cell workload a key systemic amplifier of intrinsic cellular stress across the diabetes continuum [87,97,126]. Insulin resistance is not exclusive to T2D; it can co-exist with autoimmunity (particularly in adult-onset cases and in overweight individuals), producing "double diabetes" phenotypes in which metabolic and immune processes interact to accelerate β-cell failure [3,9]. Genomic analyses identify pleiotropic loci and rare-variant associations that influence β-cell resilience, immune regulation, or both, supporting shared genetic susceptibility that can bias individuals toward different positions on the β-cell stress continuum depending on environmental exposures and life course events [124,145,146]. Environmental modifiers—obesity, viral exposures, gut microbiome, and fungal dysbiosis—alter systemic and islet-local immune tone and metabolic demand, shaping the clinical phenotype and tempo of β-cell decline across the continuum [96,99,100,106].

7.5. Natural history and heterogeneity along the continuum

Clinically, the continuum model accommodates the rapid, immune-driven β-cell loss and early insulin dependence typical of childhood-onset classical T1D and the prolonged, compensatory hyperinsulinemia followed by gradual decompensation characteristic of T2D, as different manifestations of a shared trajectory of progressive β-cell impairment whose pace and dominant mechanisms differ [82,103,126]. Intermediate and mixed phenotypes—LADA, latent autoimmune diabetes in youth (LADY), and double diabetes—illustrate how variation in autoantibody titers, immune cell signatures, and metabolic stress map onto intermediate clinical trajectories and prognoses, reinforcing the utility of a continuum perspective for individualized prognostication and treatment selection [83–85,102]. Longitudinal transcriptional and single-cell studies of at-risk individuals and of human islets show that progressive loss of β-cell identity and increases in stress/senescence programs precede overt hyperglycemia in many cases, providing mechanistic support for intervening earlier in the continuum to preserve or restore β-cell function [104,107,123].

7.6. Therapeutic implications: targeting shared nodes and personalizing intervention

Therapeutic implications. The β-cell stress continuum may help organize hypotheses about when β-cell-directed or systemic interventions could be relevant, but it does not establish that a particular intervention prevents β-cell failure or alters disease progression. Therapeutic evidence, clinical indications, and translational limitations are discussed in Section 8.

7.7 Applicability of the framework across diabetes subtypes

The applicability of the β-cell Stress Continuum differs across diabetes subtypes and should not be assumed from evidence in T1D or T2D alone **(Table 3)**. In monogenic diabetes, the primary defect may involve β-cell development, glucose sensing, insulin synthesis, or secretion; the specific mechanism varies by gene, and β-cell stress may be a primary mechanism in selected

disorders or a modifier in others [131,132]. In pancreatogenic diabetes, exocrine pancreatic disease or pancreatic injury is upstream, often affecting multiple islet cell types; β-cell stress is therefore better considered a possible secondary response or modifier, depending on the underlying disease and extent of pancreatic damage [147]. In gestational diabetes, pregnancy-related insulin resistance increases secretory demand, and inadequate β-cell compensation contributes to hyperglycemia; this does not establish β-cell stress as the sole initiating mechanism [148]. Ketosis-prone diabetes is heterogeneous, with β-cell functional reserve and autoantibody status varying across clinical subgroups; the timing and reversibility of β-cell dysfunction are not uniform [149]. Drug-induced diabetes also has drug-specific mechanisms, which can include insulin resistance, impaired insulin secretion, or immune-mediated β-cell injury; its pathogenesis should therefore be evaluated for the individual drug rather than attributed generally to β-cell stress [150].

Diabetes subtype	Likely upstream context	Possible role of β-cell stress	Evidence limitation	References
Monogenic diabetes	Gene-specific defects in β-cell development or function	Primary mechanism in selected disorders; possible modifier in others	Mechanism varies by gene and should not be generalized across monogenic diabetes	[151,152]
Pancreatogenic diabetes	Exocrine pancreatic disease, injury, or resection	Possible secondary response or modifier	Depends on the cause and extent of pancreatic damage; other islet cell types may also be affected	[147]
Gestational diabetes	Pregnancy-related insulin resistance and	Inadequate β-cell compensation contributes to	Evidence for impaired compensation does not establish stress as the	[148]

	increased insulin-secretory demand	hyperglycemia; stress may be a modifier	sole initiating mechanism	
Ketosis-prone diabetes	Heterogeneous metabolic and β-cell phenotypes	Possible contributor or modifier; dysfunction may be reversible in some subgroups	Clinical course varies with autoantibody status and β-cell functional reserve	[149]
Drug-induced diabetes	Drug-specific effects on insulin sensitivity, secretion, or immune regulation	May be secondary, modifying, or part of the drug-specific causal pathway	Mechanism depends on the drug and patient context	[150]

Table 3. Applicability of the β-cell Stress Continuum across diabetes subtypes. The table summarizes the likely upstream context of each subtype and the possible contribution of β-cell stress. These roles are context-dependent and should not be interpreted as evidence that β-cell stress is the universal initiating mechanism of diabetes.

8. Therapeutic Implications and Future Directions of a β-Cell Stress Continuum Model in Diabetes

Reconceiving type 1 (T1D) and type 2 diabetes (T2D) as points on a single β-cell stress continuum shifts therapeutic focus from mere hyperglycemia control to early reduction of β-cell stress, preservation of residual function, and restoration of functional β-cell mass. Human and experimental evidence links insulin resistance, metabolic overload, ER stress, oxidative damage, inflammation, and disrupted inter-organ signaling to progressive β-cell dedifferentiation and loss across both diabetes types [12,116,117]. This model prioritizes early interventions targeting shared pathways (ER stress, redox imbalance, inflammation, inter-cellular communication) while advancing regenerative, immunomodulatory, and biomarker-guided approaches [12,118,119].

Stage along Continuum	Functional Characteristics	Molecular & Cellular Hallmarks	Candidate Circulating & Translational Biomarkers	Reversibility Profile & Therapeutic Window
1. Adaptive Compensation	Insulin secretion may be preserved or increased to meet higher metabolic demand. Glucose tolerance can remain normal for a time; first-phase secretion is context-dependent.	Adaptive ER-stress responses support increased insulin biosynthesis and folding capacity. BiP/GRP78, XBP1s and ATF6 are relevant UPR components, but their activation alone does not establish β-cell injury. Mature identity markers such as INS, MAFA and PDX1 may be retained [152].	Fasting insulin and C-peptide are influenced by insulin sensitivity, clearance and disease context. A normal proinsulin: C-peptide ratio does not exclude early β-cell stress.	Compensation may improve if metabolic demand falls, but the extent and timing of recovery vary. Avoid describing the stage as "fully reversible" or assuming a return to a defined baseline.
2. Maladaptation & Early Dysfunction	First-phase or glucose-stimulated insulin secretion may become impaired, sometimes before fasting glucose becomes abnormal. Secretory defects vary among individuals and disease types.	Persistent ER stress and metabolic load can disrupt proinsulin folding and processing, mitochondrial function and stimulus–secretion coupling. CHOP/DDIT3 is a stress-associated pathway marker, not a stand-alone clinical staging test [152,153].	The fasting proinsulin: C-peptide ratio has been studied as a marker of β-cell stress, including before clinical T1D onset; interpretation depends on assay and clinical context. Stimulated C-peptide is a functional measure. Circulating miR-375 has been studied in acute islet injury, especially after transplantation, but is not an established routine marker of early dysfunction [153].	Some functional impairment may improve when metabolic stress is reduced, but evidence does not support a universal "golden therapeutic window" or guarantee that proposed ER-targeted or glucose-lowering treatments restore normal β-cell function.
3. Dedifferentiation (Identity Loss)	β-cells may lose mature secretory function while remaining present; dysfunction should not be equated with cell death. Findings vary across	Reported features include reduced expression of mature β-cell factors such as MAFA, PDX1 and NKX6-1, with altered expression of progenitor-associated or non-β-cell genes. These markers are model- and context-dependent; no single	Stimulated C-peptide measures residual secretory function but cannot by itself distinguish dedifferentiation from reduced β-cell mass or other causes. There is currently no validated circulating test that directly	Redifferentiation has been reported in experimental models, and recovery of β-cell function may occur in some clinical settings after metabolic improvement. The evidence does not justify saying that clinical unloading or epigenetic treatment

	experimental models and human tissue studies.	marker establishes dedifferentiation [154].	quantifies β-cell dedifferentiation in routine care.	has been shown to redifferentiate β-cells in patients [154].
4. Senescence	Senescence-like β-cell states have been associated with reduced function and inflammatory signaling in experimental studies. Senescence should not be treated as a single, uniformly irreversible stage identifiable by one marker.	Studies report combinations of p16^INK4a/CDKN2A, p21^CIP1/CDKN1A, senescence-associated β-galactosidase and SASP-related signals. These findings are mainly tissue- and model-based; individual markers are not specific on their own [108].	Circulating SASP factors are nonspecific and are not validated β-cell-specific clinical biomarkers. Islet tissue profiling remains a research approach; "senescent-cell-specific exosomal surface markers" should be removed unless a specific validated source is supplied.	Senolytic approaches have shown effects in preclinical models. Clinical benefit and safety for diabetes treatment are not established. Replace "irreversible at the cellular level" with "often persistent, although reversibility and fate may depend on context [108].
5. Apoptosis & Functional Mass Loss	Severe β-cell loss can reduce endogenous insulin secretion and stimulated C-peptide, but insulin dependence or brittle diabetes does not map uniquely to a specific amount of β-cell loss.	Cleaved caspase-3 and PARP are apoptosis-associated tissue markers. Other forms of cell death require their own evidence and should not be listed as established features of every case [152].	Stimulated C-peptide is used to assess residual endogenous secretion. Circulating miR-375 and unmethylated INS DNA have been investigated as injury/death biomarkers, including in islet transplantation; they are not interchangeable, and neither should be described as a routine, definitive measure of β-cell mass π [155].	Lost β-cells are not assumed to regenerate sufficiently to restore function. Islet or stem-cell-derived replacement and immunomodulation remain specialized or investigational approaches whose use depends on indication; they should not be presented as an inevitable requirement for every patient at this stage.

Table 4. Operational stages, hallmarks, biomarkers, and reversibility across the beta-cell stress continuum

Abbreviations: ATF, activating transcription factor; BiP, binding immunoglobulin protein; CHOP, C/EBP homologous protein; GCK, glucokinase; GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; GSIS, glucose-stimulated insulin secretion; IL, interleukin; MMTT, mixed-meal tolerance test; OGTT, oral glucose tolerance test; ROS, reactive oxygen species; SA-β-gal,

senescence-associated beta-galactosidase; SASP, senescence-associated secretory phenotype; SGLT2, sodium-glucose cotransporter-2; UPR, unfolded protein response.

8-1. Targeted Clinical Strategies for Shared Pathogenic Pathways

A foundational strategy informed by the continuum model is **early metabolic unloading** to reduce secretory demand, glucolipotoxicity, and β-cell dedifferentiation. This is achieved through lifestyle interventions, exercise, and therapies like GLP-1 receptor agonists and SGLT2 inhibitors, which reduce systemic metabolic load and provide indirect β-cell benefit [129,156].

Building on this, several shared molecular nodes can be targeted directly. Since ER stress and defects in proinsulin processing are key vulnerabilities, proteostasis enhancers and ER modulators (e.g., MANF) are promising for preserving function and protecting against cytokine-induced apoptosis [20, 23]. Concurrently, modulating redox imbalance and oxidative stress, for example by inhibiting TXNIP or activating Nrf2, can improve β-cell resilience and prevent stress-induced senescence [133]. Further, therapies targeting islet amyloid formation and lipotoxicity can directly address sources of mitochondrial and membrane stress. Translating these stress-targeting concepts into clinical practice is already underway through drug repurposing; for instance, verapamil and imatinib have demonstrated the capacity to preserve residual C-peptide and blunt stress-linked apoptosis in recent-onset type 1 diabetes, proving that modulating intracellular stress pathways can yield tangible disease-modifying benefits in humans [157,158].

Stage-dependent immunomodulation is also critical. In early or at-risk T1D, antigen-specific therapies or agents like teplizumab can delay progression, whereas in T2D with an inflammatory component, modulating innate immunity is more relevant [84,112]. Crucially, this continuum model dictates that immunotherapy alone is unlikely to durably halt type 1 diabetes if the β-cell

remains highly stressed and immunogenic; therefore, combining immune tolerance strategies with β-cell stress relievers is essential to simultaneously lower autoantigen presentation and preserve secretory capacity [13]. For advanced disease with significant β-cell loss, **regenerative strategies**—such as proliferation inducers or stem cell-derived islets—are being pursued, though they face scalability and immunosuppression hurdles [114,137].

Ultimately, the model supports a shift toward **rational combination therapies**, pairing metabolic unloading with pathway-specific protective agents and adding immunomodulation or regenerative approaches as dictated by disease stage and patient phenotype [115].

Therapeutic evidence and development status. Therapies discussed in this review are distinguished by their regulatory status and level of evidence. Approved therapies should be described in relation to their established indications and demonstrated clinical outcomes. Off-label use should be identified explicitly and supported by evidence relevant to the population discussed. Agents undergoing clinical investigation should be labeled as investigational, with the trial population and study phase specified when available. Interventions supported only by cell-based or animal studies should be identified as preclinical. Mechanistic plausibility or improvement in experimental readouts does not, by itself, establish clinical efficacy or disease modification.

8-2. Biomarkers and Monitoring

Circulating miRNAs, extracellular vesicle cargo, and redox/ER markers are currently being investigated as **candidate biomarkers** for early detection and pharmacodynamic monitoring [11,117,118]. While promising, these candidates remain in the research stage; their standardization, clinical validity, and sensitivity as measures of β-cell stress or mass require further validation in longitudinal human studies, as detailed in Table 4.

8-3. Translational Priorities and Challenges

Priorities include early mechanism-guided combination trials with biomarker endpoints, adaptive platform designs, regeneration pipeline maturation, and precision stratification using genetics, autoantibodies, and multi-omics [12,114,119,121]. Major translational challenges encompass demonstrating long-term durability of β-cell rest and functional recovery, managing potential proliferative or oncogenic risks associated with regenerative strategies, achieving durable immunoprotection in autoimmune settings, and ensuring equitable clinical access [114,119].

To contextualize these translational priorities, Table 5 synthesizes the evolving therapeutic paradigms in diabetes management, illustrating the shift from conventional reactive glycemic control toward proactive, disease-modifying β-cell preservation. Specifically, Table 5 delineates interventions across key functional categories—ranging from incretin-based metabolic unloading and endoplasmic reticulum/oxidative stress mitigation to immunomodulation, cellular identity restoration, and regenerative replacement. For each class, the table summarizes proposed molecular mechanisms, target disease stages along the stress continuum, current regulatory and developmental status, and critical translational barriers. Integrating these therapeutic strategies with stage-specific biomarker stratification represents a pivotal step toward precision intervention before irreversible β-cell mass loss occurs.

Table 5. Evolving therapeutic paradigms in diabetes management: Transitioning from reactive glycemic control to proactive β-cell preservation.

Therapeutic Paradigm	Specific Agents / Interventions	Mechanism and Evidence Relevant to eta-Cell Biology	Target Disease Stage & Context	Regulatory & Clinical Status	Key References
1. Metabolic Risk Reduction & Incretin-Based Therapy	**GLP-1 receptor agonists** (e.g., semaglutide,	Potentiate glucose-dependent insulin secretion, suppress	Type 2 diabetes across early to advanced stages requiring glycemic control, weight management, or	**FDA- & EMA-Approved** for type 2 diabetes, chronic weight	[159,160]

	liraglutide); **dual GIP/GLP-1 receptor agonists** (tirzepatide)	inappropriate glucagon release, slow gastric emptying, and reduce body weight. Preclinical models indicate enhanced β-cells survival pathways and reduced ER stress, but direct preservation of human β-cells mass or identity is not an established primary clinical indication.	cardiovascular/kidney risk reduction; not indicated as disease-modifying β-cells therapy in T1D or prediabetes.	management, and specific cardiorenal risk reduction indications. Direct β-cells preservation" is not a labeled indication.	
2. Alleviation of Glucotoxicity & Secretory Workload	**Short-term intensive insulin therapy (IIT)**	Rapidly corrects overt hyperglycemia, alleviating glucotoxicity, oxidative stress, and excessive secretory demand on remaining β-cells. Transient restoration of first-phase insulin response and temporary clinical remission observed in subsets of patients.	Selected patients with newly diagnosed type 2 diabetes presenting with severe hyperglycemia/glucotoxicity.	**Clinical Intervention Strategy** utilizing approved insulin preparations. Long-term disease-modifying β-cells rest is not a discrete labeled indication.	[161]
3. Pharmacological Modulation of Secretory Activity	**Diazoxide**	Opens ATP-sensitive potassium K_{ATP} channels in β-cells, hyperpolarizing the membrane and suppressing endogenous insulin exocytosis to induce temporary resting states.	Investigational / exploratory protocols in recent-onset autoimmune diabetes or specialist research settings.	**Investigational for Diabetes Modification.** Diazoxide is approved for hyperinsulinemic hypoglycemia, but not approved for diabetes treatment or β-cell preservation.	[162]
4. Repurposed Molecular Stress &	**Verapamil** (TXNIP inhibitor); **Imatinib** (c-Abl tyrosine	**Verapamil:** Blocks L-type calcium channels, downregulating thioredoxin-	Recent-onset type 1 diabetes (within 3–6 months of clinical	**Investigational in Diabetes.** Off-label in diabetes; neither agent is	[157,158]

Kinase Inhibitors	kinase inhibitor)	interacting protein (TXNIP) and reducing β-cells apoptosis. **Imatinib:** Inhibits c-Abl and platelet-derived growth factor receptor pathways, decreasing oxidative and inflammatory stress in islets.	diagnosis with residual β-cells function).	FDA/EMA-approved for preserving β-cells function or altering diabetes progression.	
5. Direct ER-Stress & Senescence Modulation	**Chemical chaperones** (e.g., TUDCA, 4-PBA); **Senolytics** (e.g., Dasatinib + Quercetin, Bcl-2 family inhibitors)	**TUDCA / 4-PBA:** Enhance protein folding capacity in the endoplasmic reticulum and mitigate maladaptive UPR pathways. **Senolytics:** Selectively eliminate senescent β-cells displaying senescence-associated secretory phenotypes (SASP).	Exploratory / preclinical models; pilot biomarker-driven translational trials.	**Experimental.** Not approved for the treatment of diabetes or β-cellsfunctional decline.	[163,164]
6. Secretory Augmentation via Secretagogues	**Sulfonylureas** (e.g., glimepiride, gliclazide); **Meglitinides** (e.g., repaglinide)	Bind to the SUR1 subunit of the K_{ATP} channels, stimulating glucose-independent insulin secretion. While lowering blood glucose effectively, continuous forced exocytosis does not mitigate underlying cellular stress and is associated with progressive secondary failure.	Type 2 diabetes without absolute endogenous insulin deficiency; monogenic neonatal diabetes (activating K_{ATP} channels mutations).	**FDA- & EMA-Approved** for glycemic management in type 2 diabetes and specific monogenic diabetes subtypes.	[165,166]
7. Exogenous Hormone Replacement	**Insulin formulations** (basal, prandial, ultra-rapid	Directly replaces or supplements endogenous insulin deficiency to restore glucose	Absolute β-cells loss in Stage 3 Type 1 diabetes; advanced/decompensated Type 2 diabetes; pancreatectomy;	**FDA- & EMA-Approved Standard of Care.** Provides	[167]

	analogs, concentrated regimens)	uptake, suppress hepatic gluconeogenesis, and prevent ketoacidosis.	secondary endocrine failures.	physiological metabolic substitution rather than β-cells rescue.	
8. Cardiorenal Protection & Hemodynamic Unloading	**SGLT2 inhibitors** (e.g., empagliflozin, dapagliflozin); **non-steroidal MRAs** (finer none)	**SGLT2i:** Inhibit renal proximal tubule glucose and sodium reabsorption, promoting glycosuria, reducing intraglomerular pressure, and improving cardiac energetics. **Finer none:** Blocks mineralocorticoid receptor overactivation, suppressing downstream inflammation and fibrosis.	Type 2 diabetes with diabetic kidney disease (DKD), chronic kidney disease (CKD), or cardiovascular disease / heart failure across glycemic stages.	**FDA- & EMA-Approved** for type 2 diabetes glycemic control, CKD progression reduction, and heart failure management. Off-target organ protection, not β-cells targeted therapy.	[168–170]

9. Future Perspectives and Research Priorities

The β-cell stress continuum model provides a transformative framework for diabetes research, yet its full clinical translation depends on resolving several fundamental knowledge gaps. Foremost among these is the need to define the molecular checkpoints that separate adaptive β-cell stress from irreversible decompensation. Although compensation and failure are widely described, the signaling networks governing the switch between protective and pathological unfolded protein response (UPR) programs remain poorly understood, and it is unclear whether progression reflects failure of adaptive UPR, early susceptibility to decompensated ER stress, or context-dependent trajectories shaped by genetics, immune tone, and metabolic exposure [120,156]. Temporal multi-omics and spatiotemporal mapping offer promising avenues to reconstruct these trajectories, but such datasets remain limited and challenging to integrate [129,171].

A second major frontier lies in understanding β-cell heterogeneity and plasticity. Multiple subpopulations have been described at the transcriptional and functional level, yet it remains unresolved whether these represent stable functional classes, dynamic interchangeable states, or a continuum of transitional phenotypes [134]. This distinction is critical because if apparent subpopulations reflect fluid states, then part of the stress continuum may represent impaired transitions between productive and recovery programs rather than unidirectional deterioration. Importantly, much of the existing heterogeneity literature relies on dissociated cells, which strip away the local islet environment that shapes β-cell behavior; advancing intact-tissue analyses, in situ RNA and protein measurements, and longitudinal reporters will be essential to connect molecular identity with spatial position, cell–cell signaling, and coordinated islet output [130].

Beyond cell-autonomous programs, the fate decisions that stressed β-cells make—among dedifferentiation, apoptosis, and alternative death pathways such as pyroptosis, necroptosis, or ferroptosis—represent a largely unmapped layer of the continuum. These branching decisions may define stage boundaries not as a matter of degree but as distinct endpoints with different reversibility profiles. Equally important is the emerging recognition that stressed β-cells do not fail in isolation; ER stress can propagate to neighboring cells through connexin-mediated gap junction coupling, while extracellular vesicles, exocrine–endocrine crosstalk, vascular remodeling, and extracellular matrix degradation collectively reshape the islet microenvironment into a self-sustaining injury niche [122,133]. Extending this network view to gut–pancreas axes, neural circuits, and microbiome-derived signals will be necessary to capture the full extra-pancreatic dimension of β-cell stress [172].

Translating this systems-level understanding into clinical practice will require a new generation of biomarkers and computational tools. Current measures largely capture β-cell function rather than

mass or stress state, making it difficult to place patients along the continuum or to distinguish reversible dysfunction from committed failure [173,174]. Future biomarker strategies should move beyond single analytes toward stage-specific panels that integrate molecular indicators of β-cell exocytosis, ER stress, senescence, extracellular vesicle cargo, and systemic redox or immune tone [131,132]. Spatial and temporal multi-omics, including spatial transcriptomics and multiplex imaging of intact islets, will be instrumental in identifying master regulators and microenvironment-dependent stress patterns that bulk assays cannot resolve [135]. Complementing these experimental advances, mechanism-based mathematical models and machine learning approaches—trained on longitudinal cohorts and validated against human outcomes—could forecast individual β-cell survival trajectories, detect early dysfunction, and guide patient selection for mechanism-matched interventions [135,136].

Therapeutically, the continuum model calls for a fundamental shift from one-size-fits-all glycemic management toward stage-matched, mechanism-guided combination strategies. Early stages may respond best to interventions that lower metabolic and cellular stress, whereas later stages may require coordinated rescue of function, protection from death, and, where appropriate, immune control or cell replacement [137].A central design challenge is the replication-versus-function tradeoff: regenerative approaches must be judged not only by whether β-cell number increases, but by whether expanded cells remain functionally mature, stress-resilient, and durable within a hostile metabolic environment [137]. This implies a rational therapy sequencing—first calming the stress environment, then supporting recovery or regeneration, and finally maintaining survival and function—paired with endpoints that capture shifts toward more stable, less stress-sensitive β-cell states rather than short-term glycemic improvement alone [137].

Ultimately, the next phase of the continuum model must move from cataloging stress pathways to constructing causal, stage-aware maps of how they interact in human disease. Closing the loops between spatial and single-cell mapping, precise perturbation tools such as RNA therapies and gene editing, stress-conditioned human islet multi-omics, and functional readouts of secretion, survival, senescence, and recovery will be essential [175,176]. If these priorities are met, β-cell stress can evolve from a conceptual organizing principle into a practical framework for staging disease, selecting mechanism-matched therapies, and ultimately reshaping diabetes care from reactive glucose control to proactive preservation of β-cell identity and function.

10. Conclusion

The β-cell Stress Continuum redefines diabetes as a disorder of progressive failure in cellular stress adaptation rather than a collection of independent pathogenic pathways or two biologically distinct diseases **(Figure 3)**.

Within this framework, immune activation, metabolic overload, oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, inflammatory signaling, and inter-organ communication should not be viewed as isolated mechanisms but as interconnected components of a unified stress network governing β-cell fate.

Progressive accumulation of unresolved β-cell stress drives the transition from adaptive compensation to irreversible loss of cellular identity, senescence, apoptosis, and systemic

metabolic collapse. Consequently, the severity and tempo of diabetes progression primarily reflect the capacity—or failure—of β-cells to maintain stress resilience.

This stress-centered paradigm extends beyond conventional diabetes classification by establishing β-cell stress as a potentially important integrative framework for selected disease mechanisms heterogeneity, progression, and therapeutic responsiveness. Accordingly, future therapeutic strategies should prioritize restoration of stress resilience, preservation of adaptive β-cell function, and early interruption of maladaptive stress signaling before irreversible decompensation occurs.

More broadly, positioning β-cell stress at the center of diabetes biology provides a conceptual bridge between cellular stress research and clinical diabetology, thereby expanding opportunities for biomarker development, mechanism-based precision medicine, and stress-directed therapeutic innovation.

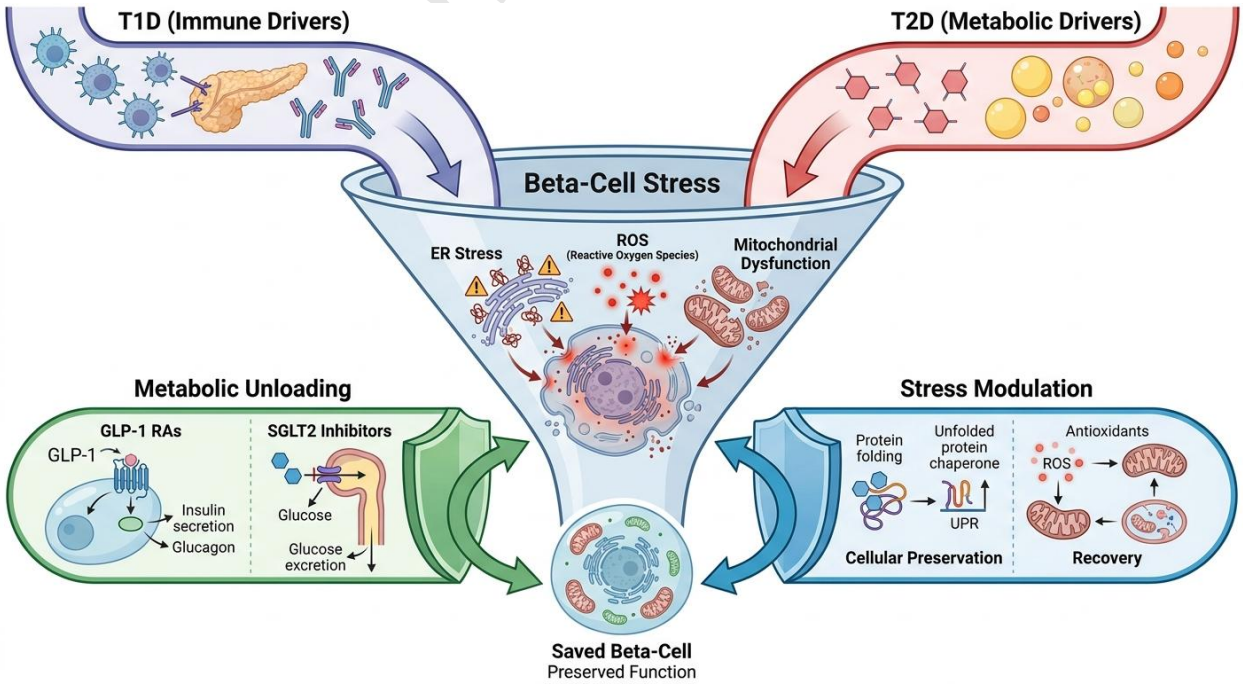

Figure 3. The β-cell stress continuum model and therapeutic implications. This model illustrates T1D and T2D as overlapping conditions converging on shared cellular failure mechanisms (e.g., ER stress and inflammation). It highlights proactive, stage-specific interventions—such as metabolic unloading and stress modulation—aimed at preserving β-cell identity and preventing systemic metabolic decompensation.

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Journal Pre-proof

Highlights:

1. A unified continuum model integrates T1D, T2D, and LADA via β-cell stress.
2. Glucolipotoxicity and ER stress drive β-cell identity loss and senescence.
3. Immune-metabolic crosstalk amplifies systemic dysfunction across organs.
4. Therapeutic focus shifts from glycemic control to β-cell preservation.
5. Biomarker-guided staging supports precision medicine in diabetes care.

Journal Pre-proof