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Beta cell hibernation and stanning as special survival states of the pancreatic insulin-producing apparatus in type 2 diabetes mellitus

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KEYWORDS

Type 2 diabetes mellitus,
Beta cell failure.
Beta cell hibernation and stunning.
Glucosolipotoxicity.

Abstract:
This article aims to analyze the notion of stunned and hibernating beta cells and explore their involvement in beta cell failure. The onset of classic type 2 diabetes mellitus (T2D) typically begins with insulin resistance, leading to a gradual rise in the demand for beta cell to produce insulin. Glucolipotoxicity is a complex pathologic process leading to beta cell dysfunction. This process is reversible and depends on the severity and duration of exposure. Stunning and hibernation are among the forms of beta cell dysfunction that led to the failure of their function. This relationship is currently only partially understood. Glucolipotoxicity does not always kill beta cells, but they become temporarily silent (hibernated). In this way, there is an opportunity, on the one hand, to keep the beta cell in a hibernated state until better times (normoglycemia), and on the other hand, to restore beta cell differentiation and their normal biological activity, i.e., there is an actual escape of beta cells from their death. This article proposes the concept of stunned and hibernating beta cells and their role in beta cell failure.

PALABRAS CLAVE

Diabetes mellitus tipo 2.
Fallo de células beta.
Hibernación y aturdimiento de células beta.
Glucosolipotoxicidad.

La hibernación y el estancamiento de las células beta como estados especiales de supervivencia del aparato productor de insulina pancreática en la diabetes mellitus tipo 2

Resumen:
Este artículo tiene como objetivo analizar la noción de células beta aturdidas e hibernantes y explorar su implicación en el fallo de las células beta. La aparición de la diabetes mellitus tipo 2 (DT2) clásica suele comenzar con una resistencia a la insulina, lo que lleva a un aumento gradual en la demanda de células beta para producir insulina. La glucolipotoxicidad es un proceso patológico complejo que conduce a la disfunción de las células beta. Este proceso es reversible y depende de la gravedad y duración de la exposición. El aturdimiento y la hibernación son formas de disfunción de las células

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beta que llevaron al fracaso de su función. Esta relación se comprende actualmente sólo parcialmente. La glucolipotoxicidad no siempre mata las células beta, pero se vuelven temporalmente silenciosas (hibernadas). De esta manera, existe la oportunidad, por un lado, de mantener la célula beta en estado hibernado hasta tiempos mejores (normoglicemia), y por otro lado, para restaurar la diferenciación de las células beta y su actividad biológica normal, es decir, hay una escape real de las células beta de su muerte. Este artículo propone el concepto de células beta aturdidas e hibernantes y su papel en la falla celular beta.

Beta zelulen hibernazioa eta geldialdia, 2 motako diabetes mellitusean intsulina pankreatikoa sortzen duen aparatuaren biziraupen-egoera berezi gisa

Laburpena:
Artikulu honek beta zelula zorabiatuen eta hibernatzaileen nozioa aztertzea eta beta zelulen akatsean duten inplikazioa esploratzea du helburu. 2 motako mellitus diabetes klasikoa (DT2) intsulinarekiko erresistentziarekin hasi ohi da, eta, horren ondorioz, pixkanaka handitzen da intsulina sortzeko beta zelulen eskaera. Glukolipotoxikotasuna beta zelulen disfuntziora eramaten duen prozesu patologiko konplexua da. Prozesu hori itzulgarria da, eta esposizioaren larritasunaren eta iraupenaren araberakoa. Zorabioa eta hibernazioa beta zelulen disfuntzio-formak dira, eta funtzioaren porrotera eraman zuten. Gaur egun, erlazio hori zati batean baino ez da ulertzen. Glukolipotoxikotasunak ez ditu beti beta zelulak hiltzen, baina aldi baterako isilak bihurtzen dira (hibernatuak).
Horrela, aukera dago, batetik, beta zelula garai hobeagoetara arte (normoglizemia) egoera hibernatuan mantentzeko, eta, bestetik, beta zelulen desberdintzea eta haien jarduera biologiko normala berrezartzeko, hau da, haien heriotzatik benetako ihesbidea dago beta zeluletatik. Artikulu honek beta zelula zorabiatuen eta hibernatzaileen kontzeptua proposatzen du, baita zelula horiek beta failan duten eginkizuna ere.

GILTZA-HITZAK

2. motako diabetes mellitusa.
Beta zelulen akatsa.
Beta zelulak hibernatzea eta zorabiatzea.
Glukosolipotoxikotasuna.

Introduction

The World Health Organization (WHO) report states that approximately 422 million individuals worldwide are affected by diabetes, and 90–95 % of these cases are attributed to T2D. A study by Yokomichi, Nagai, and Hirata reported that mortality due to diabetes was up to 10.7%. T2D is characterized by a progressive decline in beta cell function and chronic insulin resistance[1]. While target organs exhibit an impaired response to insulin, commonly referred to as insulin resistance, beta cells in individuals with diabetes display a diminished and poorly timed reaction to nutrients. Unlike insulin resistance, which seems to persist relatively unchanged during the progression of diabetes, beta cell function undergoes a steep decline over time in a manner that is resistant to, and potentially exacerbated by, current treatments.
In general, it is influenced by lifestyle elements such as age, pregnancy, and obesity. However, its etiology includes a significant genetic aspect. Numerous genes are believed to play a role, each exerting a modest impact on the risk of developing T2D, impacting beta cell differentiation, functions, and survival[2]. Additionally, a growing number of uncommon monogenic forms of diabetes, resulting from mutations in a single gene, have been identified. These account for approximately 1%–2% of all diabetes cases in Europe, with the majority characterized by diminished insulin secretion.
There is also mounting evidence linking impaired insulin release to the development of T2D[3].

Over time, long-term hyperglycemia can lead to severe complications in various organ systems. Once chronic complications manifest, they prove challenging to reverse through drug treatment[4].
Chronic hyperglycemia damages the ability of beta cells to produce insulin and release it when blood glucose levels rise5. This suggests that prolonged hyperglycemia triggers a vicious spiral, in which elevated blood glucose levels lead to beta cell damage and decreased insulin secretion, causing blood glucose to rise even more and a further decline in beta cell function.

The physiological control of insulin secretion from pancreatic beta cells is now quite well comprehended. The exocytosis of insulin granules necessitates an elevation in intracellular calcium, primarily stemming from calcium influx through plasma membrane voltage-gated calcium channels. The opening of these channels is regulated by the adenosine triphosphate the ATP-sensitive potassium (KATP) channel, a key regulator of insulin secretion. When plasma glucose levels are low, the KATP channel remains open, facilitating K+ efflux and maintaining membrane hyperpolarization. This, in turn, prevents insulin secretion. An elevation in plasma glucose enhances glucose uptake and metabolism by the beta cell, leading to a

rise in metabolically produced ATP. These alterations in adenine nucleotide levels close KATP channels, thus triggering insulin secretion[6].

One of the most significant shifts in the field over the past decade has been the widespread acknowledgment that impaired beta cell function is the central issue in T2D. Until recently, the decrease in insulin production was attributed to the death of beta cells[7]. Although beta cell death may be the final common pathway in the natural course of type 2 DM, newer evidence points to a more complex situation, in which beta cells can initiate multiple alternative responses to prevent an irreversible loss, suggesting the possibility of early intervention[8,9]. First of all, we are talking about the disruption of beta cell identity as a result of dedifferentiation and transdifferentiation into other cell types[10]. The key implication from this finding is that beta cells can be rejuvenated through suitable treatments. Deterioration in metabolic function increases the likelihood of dedifferentiation. Noteworthy discoveries in this realm reveal that, as beta cells lose their distinct identity, they begin to mimic endocrine progenitor cells.

Analyzing the data obtained, we can assume that stanning represents the most labile (dynamic) state of the diabetic beta cell. Another, no less important, circumstance, in our opinion, is that the hibernated beta cell can be restored to normal. The hibernated beta cell recovers within a time frame of up to several months after normoglycemia is achieved and elimination of glucolipotoxicity and more slowly (compared to stanning). Repeated episodes of glucolipotoxicity cause reversible transient beta cell dysfunction with subsequent recovery. Although these brief episodes of glucolipotoxicity cause only transient beta cell dysfunction, alternating them can lead to more permanent dysfunction. Repetitive stanning can lead to chronic stanning, inducing a state of long-term beta cell dysfunction. According to the literature, in most cases it takes a few days to a few weeks for a stunned beta cell to fully recover. Hibernation represents the most severe and far-advanced form of beta cell dysfunction with complete cessation of insulin-producing function; it can be hypothesized that it thus promotes beta cell survival after prolonged exposure to glucolipotoxicity.

Thus, this article introduces the notion of stunned and hibernating beta cells and explores their involvement in beta cell failure. The definitions of these states are provided, and the data accumulated from studies over the past decades on this topic are summarized.

Specific beta cell states in hyperglycemia

The initial phase in the progression of T2D involves insulin resistance, prompting beta cells to increase insulin secretion to maintain normal glucose levels. By the time T2D is identified, approximately 40–50% of beta cell function has already diminished, and a continual loss of 4–5% is anticipated each year thereafter11. Consequently, gaining a deeper understanding of the pathophysiology of T2D carries significant

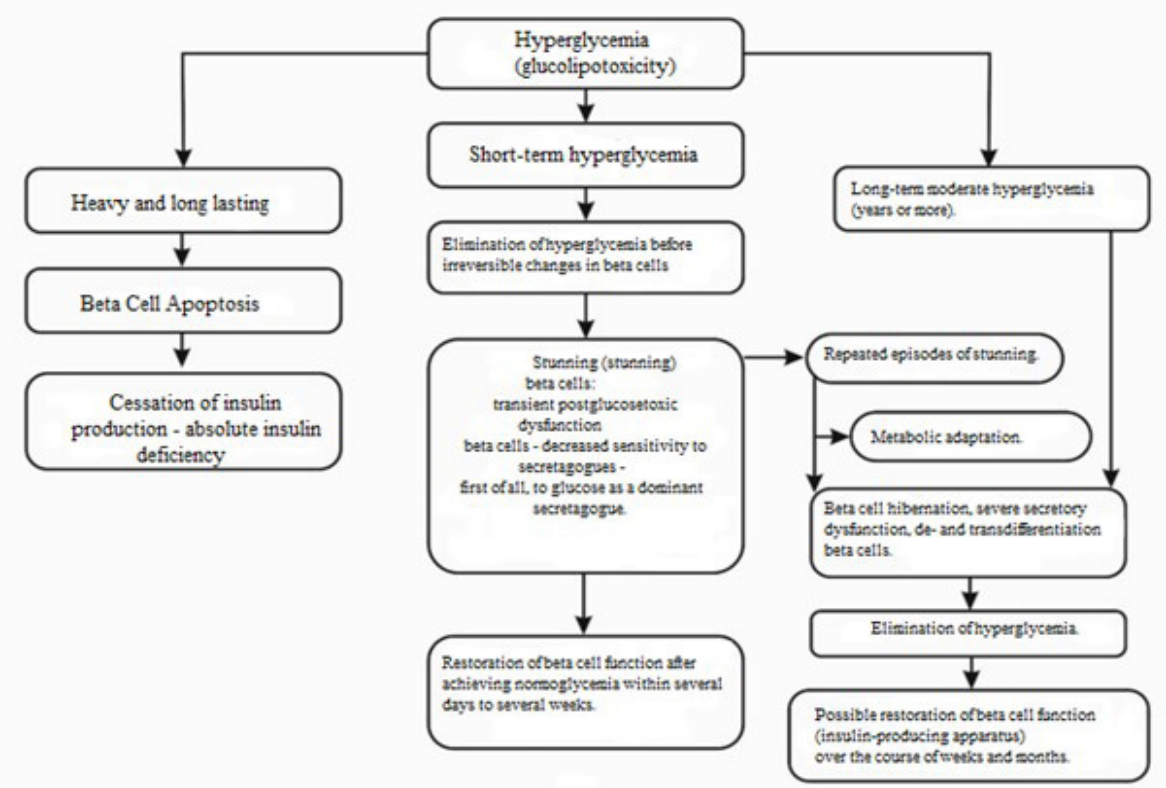

Figure 1. Model of the beta cell failure process and possible outcomes.

therapeutic implications for timely implementation of treatments targeting insulin resistance and the ongoing decline in beta cell function.

The etiology of beta cell dysfunction in T2D remains contentious. The beta cells in individuals with diabetes exhibit inadequate responsiveness to a glucose challenge and do not generate a timely and appropriate response[12]. Adaptation of beta cells to hyperglycemic conditions can be divided into two stages: a short-term "defense" reaction and a long-term "survival" phase (Figure 1). This short-term reaction could be stunned beta cells.

The second stage is the survival stage (hibernation) that ensures self-preservation of beta cells for an extended period. Hyperglycemia activates several intracellular signaling systems that trigger genetically determined defense mechanisms. This metabolic defense is evident in hyperglycemic states: stunning, hibernation, and, under certain conditions, can ultimately result in beta cell death (apoptosis).

If beta cells are not undergoing apoptosis or experiencing significant distress, such as autophagy, endoplasmic reticulum stress, or unfolded protein response, but are instead in a dormant state as undifferentiated cells that can be re-differentiated for insulin production, there is potential for restoring beta cell function and enhancing insulin secretion even after the onset of hyperglycemia[13-15].

The concept outlines three possible outcomes of hyperglycemia (glucolipotoxicity):

1. On the left, there is a scenario of severe and prolonged hyperglycemia. beta cells undergo apoptosis, insulin production stops, absolute insulin deficiency occurs, and the need for insulin replacement therapy arises[16].
2. In the middle, there is the scenario in which the duration and severity of hyperglycemia are not sufficiently long or severe to cause beta cell death. When hyperglycemia is eliminated by insulin therapy or other therapies and normoglycemia is achieved, there is eventually a recovery of beta cell function within days or weeks. The situation involves a stunning and transient post-glucotoxic beta cell dysfunction[17].
3. The third scenario of chronic moderate hyperglycemia is shown on the right. In this case, metabolic adaptation occurs, allowing beta cells to survive, but these cells do not synthesize insulin and display the typical morphology of de- and trans-differentiation. After elimination of glucolipotoxicity, beta cells eventually restore function, but it could take anywhere from a few weeks to a few months[18].

The resolution of hyperglycemia does not signify an instantaneous recovery of beta cell function; instead, it requires time for differentiation and complete restoration of the insulin-producing machinery[19,20].

Reversal or remission of type 2 DM after elimination of glucolipotoxicity suggests that at least a critical mass of beta cells is not permanently damaged but merely metabolically inhibited20,21. Additionally, another theory of the hibernating beta cell is presented, suggesting that recurrent episodes of glucolipotoxicity and beta cell stunning occur continuously. These recurrent episodes lead to severe secretory dysfunction and de- and transdifferentiation.

Stunned beta cell

Beta cell dysfunction is sufficient to cause hyperglycemia, and the loss of beta cells is not mandatory. With the progression of hyperglycemia, the beta cell experiences gradual deterioration, leading to a decrease in insulin secretion and becoming part of a descending spiral of functional loss. This continuous decline in cell function, induced by continual exposure to elevated concentrations of glucose, is referred to as glucose toxicity. Longitudinal and cross-sectional studies show that beta cell insensitivity to glucose (stunning) is closely associated with hyperglycemia and is partially reversible[22].

The most well-studied and impressive change is the precipitation of glucose-stimulated insulin secretion (GSIS). Nowadays, the loss of GSIS is explained by the glucolipotoxicity hypothesis, which leads to desensitization of insulin secretion[23]. The combined exposure to elevated glucose levels (glucotoxicity) following the onset of impaired glucose tolerance is believed to have synergistic toxic effects with free fatty acids (FFAs), giving rise to the concept of glucolipotoxicity. This concept describes a state of decreased secretory reactivity of pancreatic beta cells caused by prolonged exposure to multiple stimuli. These include the major physiologic stimulant glucose, as well as other nutrients, such as SJW and virtually all pharmacological stimulants, acting through depolarization and inflow Ca2+ to the beta cell. Impairment of insulin secretion appears to be a critical step in the development of type 2 diabetes and subsequent failure of oral antidiabetic treatment. GSIS has been shown to remain normal as long as glycemic levels remain <5.6 mmol/L.

However, the decrease in GSIS begins to manifest dramatically at levels above 5.6 mmol/L, and at levels above 6.4 mmol/L, GSIS disappears completely24. At the same time, despite the loss of GSIS (phase 1), the 2nd phase of insulin secretion in response to glucose is preserved, and the acute response to the so-called non-glucose stimulus (for example, arginine). Regarding glucose-induced desensitization, two fundamentally conflicting concepts have emerged. First, desensitization results from functional changes in beta cells that impair glucose sensing[25].

Second, prolonged increases in secretory activity led to depleted release, often despite increased insulin synthesis[26]. The latter concept is more accurately termed beta cell depletion. The same dichotomy applies to desensitization induced by pharmacological stimuli: once more, the debate over the role of

decreased insulin versus alterations in signal transduction persists. The impact of glibenclamide on beta cells could exemplify desensitization in beta cell dysfunction resulting from insufficient insulin release, as the signaling mechanisms remain largely unchanged. In contrast, phentolamine's action induces significant desensitization without reducing insulin levels or secretory granules, likely due to the influx of Ca2+. With pharmacological agents, both alterations in signal transduction and reduced availability of released insulin seem to play a role in inducing a desensitized state in beta cells, with their relative contributions varying depending on the type of secretory stimulus[24].

In vitro studies have significantly contributed to our present comprehension of the factors governing the beta cell's secretory response to glucose stimulation. Four principal factors have emerged as major contributors: 1) glucose sensitivity, representing the beta cell's capacity to react to variations in plasma glucose concentration (in absolute terms); 2) rate responsiveness, indicating the capacity to react to fluctuations in the rate of plasma glucose concentration; 3) potentiation, elucidating the well-established phenomenon where the insulin secretory response to a glucose challenge is enhanced in the presence of potentiating factors; and 4in an in vivo setting, insulin resistance and components of the insulin secretory response are impacted by the severity of the underlying insulin resistance.

The critical role of the duration of hyperglycemic exposure is also evidenced by in vivo data in patients with diabetes, where beta cell glucose sensitivity shows an inverse association with disease duration, even after accounting for the severity of hyperglycemia. This gives rise to the concept that a relatively frequent pathophysiological element in hyperglycemic syndromes is the so-called stunned beta cell: a cell that is temporarily unable to adequately restore competence, at least partially[24]. It can be assumed that each patient has a group of stunned cells that can be returned to function, and each person at risk of developing diabetes for various reasons has beta cells that can be restored by eliminating the stun[27]. Muscle insulin resistance, arising from both genetic and environmental factors, promotes the occurrence of fatty liver in conditions of positive energy balance. Upon its establishment, the heightened insulin secretion necessary for sustaining plasma glucose levels exacerbates the accumulation of fat in the liver. Fatty liver induces resistance to insulin's suppression of hepatic glucose output and results in elevated plasma triacylglycerol levels. The exposure of beta cells to elevated levels of fatty acids, originating from both circulating and locally deposited triacylglycerol, hampers glucose-induced insulin secretion. While this effect is initially reversible, it eventually becomes permanent over time.

In these conditions, the key target of treatment and prevention is hyperglycemia itself. Normalizing glycemic levels and, therefore, improving insulin sensitivity with insulin sensitizer drugs will reduce the burden on the endangered beta cell population, thereby providing sustainable glycemic control.

Hypothesis of increased glucose toxicity

To comprehend the advancement of type 2 diabetes in the context of the secretory activity of beta cells, the so-called hypothesis of increased glucose toxicity deserves attention[28]. The primary conjecture is that lingering hyperglycemia, particularly following meals, produces reactive oxygen species (ROS), lea-

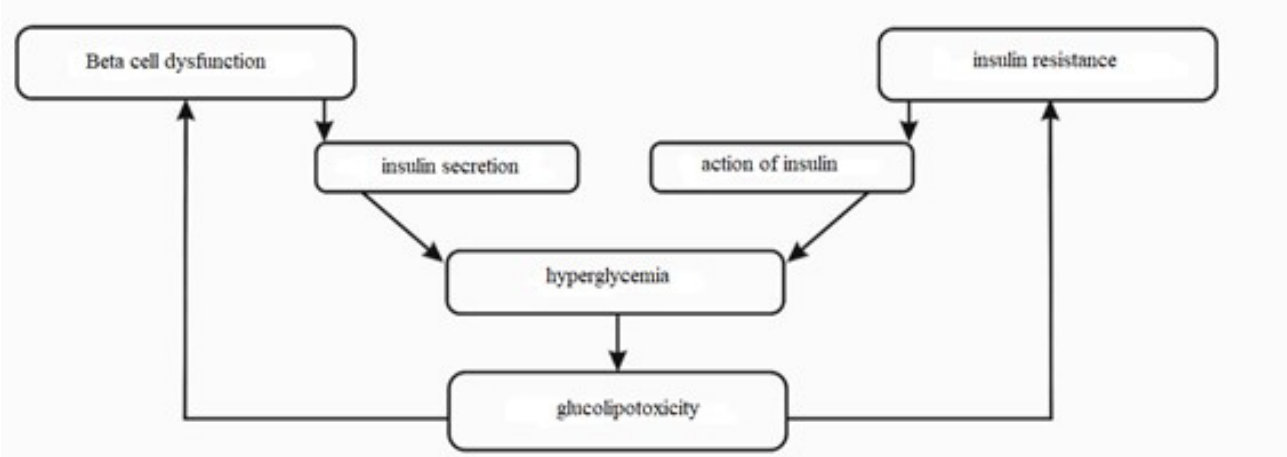

Figure 2. Amplification hypothesis.
Source: developed by the author according to Poitout and Robertson[29]

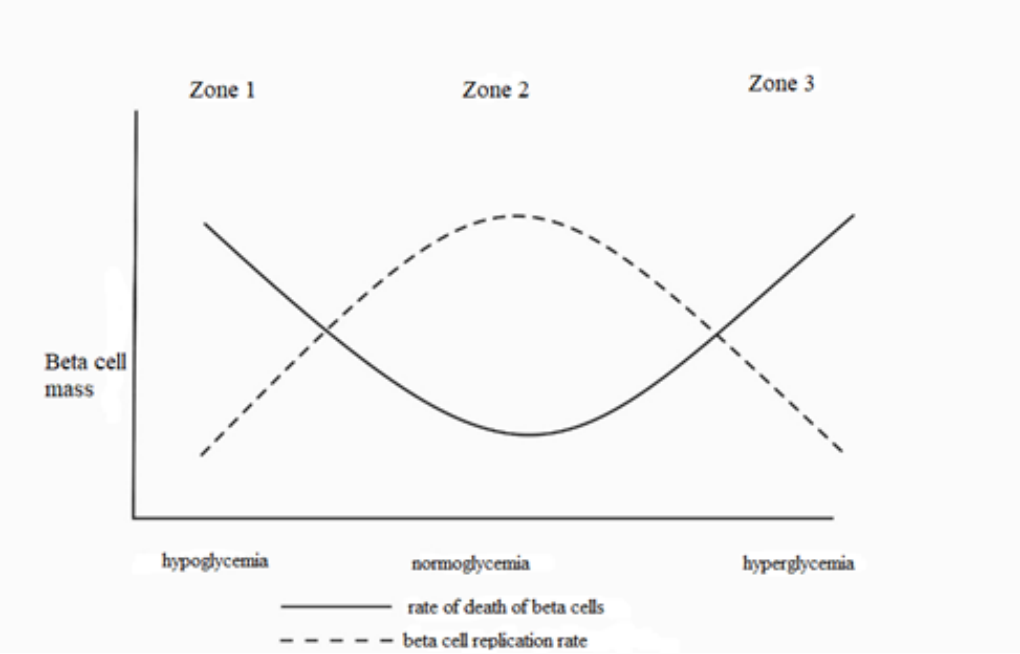

Figure 3. Effect of glycemic level on the dynamics of pancreatic beta cell mass.
Source: developed by the author according to Topp, Mc Arthur, and Finegood[4]

ding to persistent oxidative stress on the beta cell. As depicted in **Figure 2**, the insulin resistance and the malfunction of pancreatic beta cells, initially developing independently of each other, eventually combine and contribute to the development of hyperglycemia and, associated with it, acute and chronic glucose toxicity. In turn, glucotoxicity increases insulin resistance and contributes to the formation of insulin secretion deficiency.

Topp, Mc Arthur, and Finegood developed a three-component mathematical model to estimate beta cell mass in relation to serum insulin glucose levels[4]. The authors of this model assumed that the rate of beta cell replication and the rate of their apoptosis depend on blood glucose levels. It has been established that within range of normal physiological values, an elevation in glucose levels stimulates the replication processes of beta cells and suppresses the processes of their death (**Figure 3**).Simultaneously, when glucose levels rise to values considered glucotoxic, the replication rate of beta cells begins to decline, and the rate of beta cell death increases. Glucose toxicity should be considered not merely as a simple effect of glucose causing apoptosis of beta cells or disrupting replication, but as an effect that upsets the balance between replication and beta cell death[30]. Glucose toxicity primarily manifests itself at the level of pancreatic beta cells, with the critical threshold at a glucose concentration above 8 mmol/l16.

Currently, acute and chronic glucose toxicity are distinguished. Normally, beta cells are extremely sensitive to blood glucose levels. An acute increase in glucose levels increases insulin secretion, leading to an equalization of homeostatic equilibrium.

In contrast, chronic glucose toxicity suppresses insulin secretion[2]. The main factors associated with insulin resistance, impaired insulin secretion due to beta cell stunning and decreased mass of functioning beta cells include:

- glucolipotoxicity.
- oxidative stress.
- endoplasmic reticulum stress.
- disorders of remodeling of the islets of Lan gerhans.
- dysregulation of incretins.
- accumulation of islet amyloid polypeptide.

Considering the above, attention is drawn to the fact that the constant progression of type 2 diabetes is driven by hyperglycemia. Genetic predisposition, influenced by environmental factors, induces the development of type 2 diabetes, and subsequent hyperglycemia causes a second wave of deterioration in beta cell function and possibly insulin resistance. Additionally, the treatment of insulin resistance shows better results than stimulation of insulin secretion[18]. One plausible interpretation for these observations is that agents stimulating insulin secretion may inadvertently contribute to dedifferentiation by depleting insulin in beta cells. Conversely, treating insulin resistance reduces the demand for insulin production, thereby alleviating the strain on beta cells. Clinical experience in managing individuals with type 2 diabetes mellitus aligns with the enduring notion that allowing beta cells to “rest” supports the preservation of their function[19].

Constant hyperglycemia leads to the development of oxidative stress in many organs and tissues, resulting in complications. Beta cells are at greater risk due to their low levels of antioxidant protection. Elevated glucose levels increase the level of free radicals (ROS) inside the cell, a manifestation of glucose toxicity28,29. Molecular mechanisms of glucotoxicity are carried out through pdx-1 proteins, the main transcription factor of beta cell differentiation[31].
Consequently, damage to beta cells under the influence of high glycemia is considered a complication of diabetes, similar to retinopathy, nephropathy, neuropathy, etc.[32]. The vicious circle of impaired sensitivity to both glucose and insulin, along with defects in insulin secretion, develops over a long period. Chronic elevated blood glucose adversely affects insulin secretion, insulin gene expression, and is partly mediated by chronic oxidative stress. Chronically elevated FFA levels do not harm beta cells as long as blood glucose levels remain normal, but significantly impact beta cell function when hyperglycemia is present[28].

Therefore, glucotoxicity and lipotoxicity are closely interrelated, as lipotoxicity does not occur without chronic hyperglycemia. Furthermore, the impact of glucose on lipid metabolism is significant, suggesting that lipotoxicity can be viewed as one of the mechanisms of glucose toxicity. The generation of reactive oxygen species could be an alternative mechanism for both glucotoxicity and lipotoxicity. Exposure of islets to palmitate leads to the production of reactive oxygen species, and treatment of islets with the antioxidant metformin protects against the harmful effects of FFAs[29].

It is possible that glucose and lipotoxicity interdependently converge to produce deleterious effects on beta cell function. Prolonged hyperglycemia initiates a vicious spiral in which rising blood glucose levels lead to beta cell damage and decreased insulin secretion, further increasing glycemic levels and reduces beta cell function. High blood glucose levels reprogram beta cell metabolism in diabetes[33]. The metabolites of glucose, and not glucose itself, are the key to the progression of type 2 diabetes. Beta cells become glucose blind (stunned) and no longer respond to changes in blood glucose by secreting insulin.

Hibernating beta cell

The term “hibernation” is borrowed from zoology and denotes an adaptive reduction in energy consumption in conditions of reduced energy supply. This term was first used in relation to the myocardium[34]. However, it is very likely that hibernation and everything that precedes it (stunning) are general biological phenomena that occur and develop in a wide range of pathological processes, including beta cell failure. Beta cell hibernation is a persistent inhibition of the insulin-producing function of the beta cell of the islets of Langerhans, resulting from chronic moderate hyperglycemia. The most important manifestation of hibernation is the preservation of beta cell viability at the cellular level. There are three main mechanisms behind this phenomenon:

1. Metabolic adaptation of beta cells, which consists in maintaining the balance of glucose and lipids in the formation of acetyl-CoA for mitochondrial oxidation.
2. Activation of the genetic program for beta cell survival.
3. Programmed cell death, i.e., autophagy and beta cell apoptosis.

FOXO and beta cell refusal

A special role in the process of regulating the secretion of insulin and other hormones is played by FOXO - transcription factors belonging to an extensive group of proteins distinguished by a conserved DNA-binding domain35. FOXO 1, 3a, and 4 are three genes encoding forkhead-type transcription factors. Distinguished from other proteins containing the forkhead domain, FOXO proteins change their subcellular localization and, consequently, their activity in response to Akt-dependent phosphorylation and NAD+-dependent acetylation. Representatives of the FOXO family take an active part in the implementation of many cellular processes, ranging from cell death to, on the contrary, cell survival. These proteins are conserved in evolution and control the expression of many genes involved in various processes in the human body - response to external stress, proliferation, differentiation and apoptosis. The primary physiological function of FOXO is to facilitate metabolic flexibility, allowing for the ability to transition from utilizing glucose to lipids based on nutrient availability.

The intrinsic tendency of beta cells to become functionally depleted, called “beta cell failure”, distinguishes those people who develop diabetes from those people who, with the same level of insulin resistance, do not develop it. Clinical experience shows that beta cell deficiency can be reversed, albeit partially, despite the presence of hyperglycemia for many years[13]. There is a significant body of evidence that chronic hyperglycemia impairs glucose-induced insulin secretion and insulin gene expression[36,37]. The toxic effects of chronic hyperglycemia on beta cell function include three distinct phenomena:

- desensitization to glucose, i.e., disruption of the insulin response to glucose stimulus (stunning of beta cells);
- de- and transdifferentiation of beta cells, i.e., change in cell identity (hibernation);
- death of beta cells (autophagy and apoptosis)[8,38].

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- de- and transdifferentiation of beta cells, i.e., change in cell identity (hibernation);
- death of beta cells (autophagy and apoptosis)[8,38].

Now I will talk about beta cell hibernation, the next stage of survival of insulin-producing cells. Prolonged hyperglycemia and associated glucolipotoxicity cause profound changes in the function and structure of beta cells, including dedifferentiation and apoptosis. The observation that these related defects are reversible up to a certain point in time and become irreversible thereafter suggests a continuum between beta cell depletion and glucotoxicity, with the latter stage becoming predominant after prolonged exposure39,40. Besides functional changes, chronic hyperglycemia can reduce the mass of beta cells, inducing apoptosis[41].

In this regard, the work of Accili et al. is of extreme interest, showing that FOXO integrates insulin-dependent pathways with glucose (nutrient)-dependent pathways, shifting the focus from debating whether insulin or glucose is responsible for abnormal beta cell functions. These researchers found that FOXO is not active in healthy beta cells, but is triggered in response to hyperglycemia. In healthy islets, FOXO1 co-localizes with insulin in the cell cytoplasm, indicating its inactivity. In the initial phases of diabetes, FOXO1 relocates to the nucleus, signifying its activation. Over time, this response diminishes, and FOXO1 diminishes accordingly. Consequently, there is a gradual decline in insulin levels. In advanced diabetes, FOXO1 diminishes in beta cells as cellular insulin levels decrease. These occurrences are interconnected: the nuclear migration of FOXO1 is an initial indication of beta cell stress, and the absence of FOXO1 results in insulin depletion, providing a new significance to the concept of "beta cell failure". FoxO1 is essential for maintaining beta cell identity in insulin-resistant diabetes as a significant portion of the endocrine mass is preserved despite severe hy-

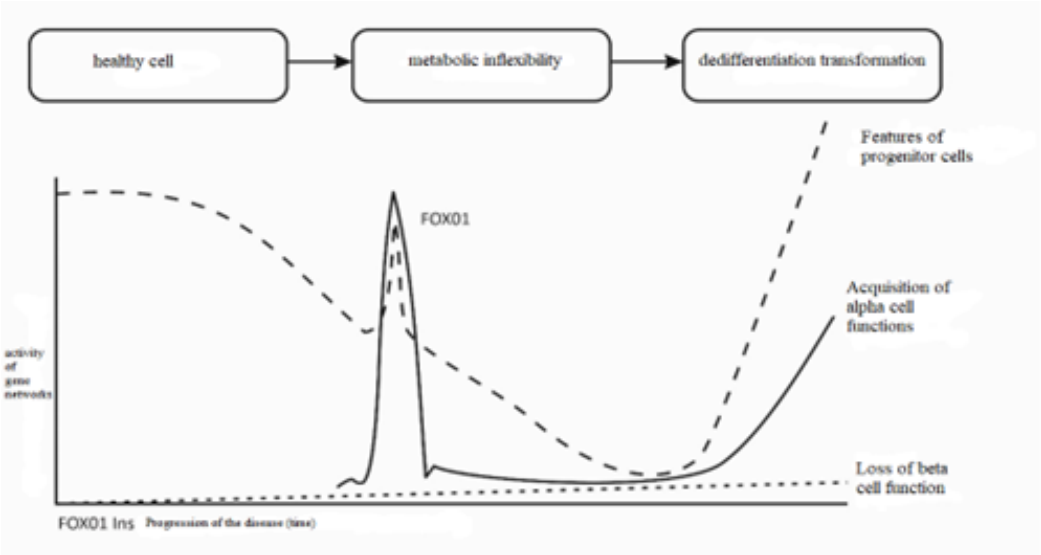

Figure 4. Stages of development of pancreatic beta cell dysfunction
Source: developed by the author according to Accili et al.9

perglycemia (500 mg/dL). Moreover, FoxO1 is essential for preserving the identity of beta cells and preventing their transformation into non-β pancreatic endocrine cells when subjected to prolonged pathophysiological stress[9].

The equilibrium between glucose and lipid oxidation is crucial. The primary function of nuclear translocation in the initial phases is to uphold the equilibrium of glucose and lipids in the generation of acetyl-CoA for mitochondrial oxidation. The presence of FOXO in the nucleus triggers the activation of certain pathways while inhibiting others. However, the activation of FOXO is temporally restricted. When FOXO levels decrease, a stage of dedifferentiation is established due to the disruption of gene expression networks required to maintain beta cell characteristics (**Figure 4**)[42].

When FOXO becomes functionally depleted, beta cells become responsive to the transcriptional effects of glucose, leading to an increase in lipid and amino acid flux. What are the enduring outcomes of metabolic inflexibility? Gradually, beta cells lose their terminally differentiated features along with insulin secretion. Dedifferentiation is reversible under the influence of insulin therapy and other types of treatment[43-45]. FOXO is extremely beta cell selective and is not a general stress reliever. Even more noteworthy, the genes specifically influenced by FOXO1 can be categorized into two subgroups:

- first involves beta cell identity regulators like pdx1, Maf A, Pax6, Hnf12, Glut2, Gpr (88), orphan receptor associated with G protein-, as well as two insulin genes.

- another set of genes governed by FOXO1 manages the balance between mitochondrial glucose metabolism and lipid utilization[11].

Clinical experience supports the theory of beta cell identity loss as a cause of functional failure. Based on numerous conducted studies, it can be inferred that metabolic disorders contribute to dedifferentiation. The key new discoveries in this field are that as beta cells lose their identity, they become similar to endocrine progenitor cells11. The idea that beta cells may dedifferentiate as diabetes progresses is supported by the daily clinical reality of treating patients with diabetes. Experienced clinicians knew that insulin secretion deteriorated every year and early clinical studies showed the benefits of "resting" beta cells[46]. Beginning with the UKDS study, these results became generally accepted law, ushering in the quest for treatments that would "preserve" beta cells and "alter" the course of the disease. Thus, the concept of dedifferentiation (hibernation) forms the foundation for the potential reversibility of beta cell failure in the initial stages of diabetes, while also elucidating the gradual decline in beta cell function.

Autopsy studies of the human pancreas allowed us to test the role of FOXO1 in the pathogenesis of type 2 diabetes in humans. Research data indicate that human expression patterns parallel those observed in rodents. FOXO1 is confined to beta cells in the healthy pancreas, and its levels diminish in diabetes, where FOXO1 also appears in a minority of alpha cells. These are cells undergoing transdifferentiation. FOXO1 serves as a potential nexus for integrating the impacts of insulin sensitivity or its absence, as well as glucose and lipid levels, in the pathogenesis of beta cell dysfunction46. Hence, a comprehensive FOXO1-dependent mechanism governing beta cell function can elucidate the interplay between insulin resistance and hyperglycemia as contributors to beta cell failure. Additionally, it provides a potential rationale for the positive effects of glucose-lowering agents and insulin sensitizers on the function of beta cells.

Therefore, a comprehensive FOXO1-dependent mechanism that regulates beta cell function could elucidate how insulin resistance interacts with hyperglycemia to cause beta cell insufficiency. This mechanism also provides a potential rationale for the beneficial effects of hypoglycemic agents and insulin sensitizers on beta cells and their function[47].

Conclusion

The past decade has witnessed significant progress in both the scientific comprehension and the management of type 2 diabetes. The onset of type 2 diabetes is characterized by a rapid decline in beta cell function, while insulin resistance remains relatively constant. Addressing insulin resistance yields superior outcomes compared to enhancing insulin secretion.

Clinical experience with individuals diagnosed with type 2 diabetes confirms the longstanding concept that beta cells in a resting state help preserve beta cell function.

If the beta cells have not undergone apoptosis or are not experiencing significant distress, like autophagy, endoplasmic reticulum stress, or the unfolded protein response, but are instead in a resting state as dedifferentiated cells and can be reprogrammed to produce insulin, it is possible to restore beta cell function and improve insulin secretion even following the onset of hyperglycemia. An analogy can be draw to what would happens when a person breaks their arm and puts it in a cast, the muscles are not used and therefore atrophy. Insulin is not produced in the hibernating beta cell, so apoptosis and even dedifferentiation are not unexpected.

Thus, the elimination of hyperglycemia does not immediately imply a return of beta cell function; instead, it requires time for differentiation and full restoration of the insulin-producing apparatus. The transition to a cellular quiescent or dedifferentiated state in a subset of pancreatic beta cells may be a natural occurrence that temporarily disrupts normal cell function, acting as a protective mechanism to prevent damage or death.

Stanning and hibernation can occur simultaneously to varying degrees in patients with beta cell

dysfunction, exacerbating (impairing) insulin-producing function. Stanning and hibernation, influenced by the elimination of glucolipotoxicity, can affect the restoration of the insulin-producing function of beta cells over specific time periods.

Authorship Declarations

G. Gendeleka conceived the study and supervised all aspects of its conduct, obtained the data, performed the analyses, interpreted the findings, and contributed to the writing of the first draft of the manuscript. The author reviewed drafts of the manuscript and approved the final version. The author is responsible for the article.

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Conflicts of Interest

The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article. No conflicts of interest.

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