The Good, the Bad, and the Ugly – role of the pancreas, endothelium, and adipose tissue axis in the management of pancreatic β-cell failure in obesity-related type 2 diabetes

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Received: August 14, 2018
Accepted: August 21, 2018

Key words: obesity, type 2 diabetes, β-cell, pancreatic steatosis, adipose tissue, endothelium

Abbreviations: DAG – diacylglycerol; ECs – endothelial cells; eNOS – nitric oxide synthase; FA – fatty acid; FAHFAs – branched FA esters of hydroxyl FAs; GSIS – glucose-stimulated insulin secretion; HF – high-fat diet; NO – nitric oxide; SCD1 – stearoyl-CoA desaturase 1; TG – triacylglycerol

Acknowledgements: This work was funded by National Science Centre, Poland, grant UMO 2015/19/D/NZ4/03705 (J.J.) and UMO-2013/10/E/NZ3/00670 (A.D.), and National Centre for Research and Development, Poland, grant STRATEGMED3/305813/2/NCBR/2017.

ABSTRACT

During long-standing obesity and insulin resistance, pancreatic β-cells adapt in order to meet the growing demand of the periphery for insulin. The development of type 2 diabetes requires parallel pathological processes, during which β-cells are continuously exposed to an overabundant supply of specific lipid derivatives. The metabolic events that lead to inevitable β-cell damage are not completely uncovered, and for the time being, our understanding of the dynamic endothelium-adipose tissue-β-cell interactions is limited. Here, we explore various links between continuous obesity, adipose tissue spillover, a dysfunctional endothelium, and defects in islet angioarchitecture to elucidate the crosstalk between signaling systems, cellular mediators, and cell types that contribute to β-cell failure through diverse actions of fatty acids. These molecular and biochemical mechanisms initiate critical rearrangements of the pancreatic vasculature, intraorgan lipid storage capacity, and inflammatory status that subsequently have severe repercussions on β-cell function and promote diabetes.

INTRODUCTION

The global epidemic of type 2 diabetes (T2D) is primarily a consequence of obesity and a sedentary lifestyle, causing tremendous healthcare and economic burdens worldwide. Dietary interventions and efforts to promote physical activity have been sought to produce lifestyle changes that can reduce metabolic instability and progression of the disease [1]. The development of T2D is influenced by genetic predisposition and environmental factors. It is a complex metabolic disorder that results from two major pathophysiological abnormalities: insulin resistance in peripheral tissues and progressive β-cell inactivation [2]. Pancreatic β-cells constitute approximately 70–80% of the total islet mass and are unique endocrine cells that exclusively synthesize, store, and release insulin to maintain euglycemia [3]. Strong evidence indicates a complex interrelationship between insulin resistance, high serum free fatty acid (FA) levels, ectopic lipid accumulation in the pancreas, and impairments in pancreatic microvasculature [1,4]. Consequently, prolonged obesity can stress pancreatic β-cell metabolism and is a principal determinant of the poor function of β-cells. The purpose of this review is to provide a better understanding of the mechanisms that govern pancreatic β-cell failure and the pathogenesis of T2D.

LIFE BEFORE DIABETES – ROLE OF PANCREATIC VOLUME AND FAT DEPOSITION IN β-CELL FUNCTION

In obese specimens, high adipose tissue lipolysis drives the overflow of plasma nonesterified FAs whereas peripheral insulin resistance results in a surplus of triglyceride (TG)-rich particles. In circumstances when the fat supply exceeds the organ's metabolic capacity, the ectopic accumulation of lipid metabolites occurs in non-adipose tissues, including the pancreas [5]. Because of the inaccessible anatomical position of the pancreas and the lack of validated methods to employ in longitudinal studies, the pancreas remains the least studied organ despite the substantial deterioration of β-cell competence in the context of T2D progression [6]. Accumulation of lipid species within exocrine or endocrine pancreas and in β-cells is associated with parenchymal or pancreatic steatosis [5]. This association, however, is confounded by the elevated levels of visceral adipose tissue (VAT) [7]. The accumulation of TGs in the pancreas in mice that were fed a high-fat (HF) diet and islets in obese leptin-deficient rats increased relative to control lean littermates during the transition from prediabetes to diabetes [8,9]. This was consistent with higher plasma levels of free FAs and deterioration of the secretory capacity of β-cells [8,9] and paralleled the development of β-cell dysfunction that occurred proportionally with obesity, in terms of both time course and magnitude.

Although the direct imaging of β-cells is impossible in humans, the structure and chemical composition of the pancreas can be studied by combining several noninvasive modalities, including computed tomography, ultrasound, magnetic resonance

imaging, and magnetic resonance spectroscopy [6,7,10]. Larger fat deposits were observed in the body and tail than in the head of the pancreas [11]. Intrapancreatic fat content differs significantly between prediabetic and diabetic individuals, with a continuous increase in the magnetic resonance imaging-detected proton-density fat fraction in healthy controls compared with subjects with established T2D [10,12]. In a Chinese cohort, a higher ratio of abdominal subcutaneous adipose tissue to VAT (SVR) exerted a beneficial effect on β-cell function and was related to improvements in insulin sensitivity status [13]. Moreover, pancreatic densities, assessed by unenhanced computed tomography, progressively declined with impairments in glucose homeostasis and were positively associated with a higher incidence of T2D [14,15].

Pancreatic TG content was greater in T2D individuals than in healthy controls in several cross-sectional studies [6,16-18]. Fat accumulation in the pancreas was negatively associated with insulin secretion in subjects with impairments in fasting glycemia and glucose tolerance [19]. Fat accumulation in the pancreas gradually increased concomitantly with obesity and the deterioration of glucose metabolism [18]. Individuals with fatty pancreas have higher insulin resistance [18]. Interestingly, the pancreas in T2D patients is 30–50% smaller than non-diabetic individuals. The decrease in pancreatic volume is accompanied by greater irregularity of the organ contour as the duration of diabetes increases [6,20]. Furthermore, a homeostasis model assessment of β-cell function (HOMA-β) was positively correlated with pancreatic volume [6]. On the other hand, intrapancreatic fat content was strongly associated with higher basal insulin levels, β-cell glucose sensitivity, and the insulinogenic index and rate sensitivity but exclusively in normal glucose-tolerant subjects [16,17]. These findings suggest that once diabetes is established, β-cell failure is determined by factors other than solely pancreatic fat deposition [17].

Pancreatic β-cell damage that is associated with fat accumulation in the pancreas in T2D subjects is reflected by several interconnected biological processes. First, insulin resistance elevates insulin secretion by β-cells, and lipid deposition may be induced by a paracrine effect of insulin. Therefore, the shuttling of FAs into esterification promotes an excess amount of TG accumulation and drives lipoapoptosis [18]. A similar phenomenon of focal steatosis was observed in 20-60% of recipients after the transplantation of pancreatic islets into the liver portal vein [21]. Islets that are delivered to hepatic sinusoids engraft and secrete insulin, but their function is severely impaired, probably because of the lipotoxic effect of surrounding fat [21]. Second, apart from the accumulation of lipids in parenchymal cells, the positive labeling of adipocytes was found within the exocrine of pancreatic tissue in HF diet-fed mice [8]. Histological studies of pancreatic tissue from human T2D patients reported the presence of ectopic fat as adipocyte infiltration that was visible between exocrine parenchyma [5,8]. Hence, adipose tissue infiltration was enhanced with decreasing glucose tolerance [5]. Similar to metabolically active VAT, peripancreatic, interlobular, and intralobular adipose tissue infiltrates the pancreas [5,12] and alters insulin sensitivity and β-cell function through the release of various adipocytokines, inflammatory mediators, and vasoactive factors, including tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), IL-8, leptin, adiponectin, selectins, chemokines, visfatin, and resistin [22]. Chronic inflammation-mediated damage might result in significant parenchymal atrophy and the replacement of acinar cells with fat, thus affecting the size, volume, and contour of the pancreas in T2D individuals [23].

Nonetheless, a direct relationship between pancreatic fat content and lower β-cell function has not been established, but there is an interesting tendency toward this linkage with impairments in glucose metabolism [14]. Ultimately, early T2D may be regarded as a reversible condition. Weight loss in humans allowed restoration of the first-phase insulin response and normal β-cell function, which were associated with a decrease in intrapancreatic TG content [24,25]. This observation of metabolic flexibility was also corroborated in isolated islets [26]. However, stable weight needs to be sustained. Intracellular changes appear to pass a point of "no return" in T2D with a duration of more than 10 years [25]. The aforementioned findings underscore the prognostic importance of pancreas morphology and its imaging in early stages of the development of T2D to better manage the disease in patients.

LIPOADAPTATION AND LIPOTOXICITY: TWO SIDES OF THE SAME COIN

In the initial phase of insulin resistance, pancreatic islets develop a compensatory mechanism of hyperinsulinemia by increasing both secretory function and pancreatic β-cell mass [1,2]. When the obesity-triggered lipid overload is sustained, β-cells fail to properly compensate for increases in the insulin demand of peripheral tissues, manifested by progressive β-cell loss, deteriorated function, glucose intolerance, and overt diabetes [2]. A significant 24–65% reduction of β-cell mass [27] and smaller size of islets that were isolated from the pancreas of T2D cadavers compared with Body Mass Index-matched nondiabetic donors were reported [28]. Pancreatic islets are metabolically limited in their ability to store lipids. The possible mechanisms of irreversible β-cell demise in the setting of T2D progression involve interactions among many branches of cellular metabolism, including inflammation, severe endoplasmic reticulum (ER) and oxidative stress, *de novo* ceramide synthesis, mitochondrial injury, compromised autophagy, epigenetic changes, β-cell de-differentiation, and loss of β-cell identity [29,30]. Increases in circulating plasma levels of FAs and disturbances in lipid homeostasis emphasize the importance of free FAs during β-cell adaptation and the metabolic control of diabetes [29].

FATTY ACIDS AND β-CELL FUNCTION

Fatty acids induce a pleiotropic effect on β-cell function and strongly influence changes in insulin biosynthesis, the generation of signaling molecules of a lipid nature, cellular membrane composition, posttranslational modifications of proteins, and mitochondrion metabolism [31]. Depending on the time of exposure, FAs differentially affect the insulin secretory capacity of β-cells. Under fasting conditions, FAs are the main source of endogenous energy in β-cells, and acute and short-term free FA overload amplifies insulin release and promotes compensatory β-cell proliferation [2,32]. In contrast, the prolonged *in vitro* exposure of rodent and human islets and insulin-secreting β-cell lines to elevated lipid concentrations led

to lipotoxicity and was associated with severe impairments in glucose-stimulated insulin secretion (GSIS), the suppression of proinsulin synthesis, lower insulin stores, and apoptosis [33]. In fact, the prolonged 20% Intralipid Infusion severely impaired β-cell function and responsiveness in humans who were predisposed to the development of T2D [34].

The ultimate effects of specific FAs on insulin secretion and rates of β-cell death significantly depend on the length and saturation degree of the carbonated chain, the affinity for FAs, and the interaction with other FAs [32,35]. The response of islets to saturated FAs is not uniform. Thus, β-cells tolerate the presence of higher levels of octanoate (8:0), laurate (12:0), and myristate (14:0) relatively better than higher levels of palmitate (16:0) and stearate (18:0) [36]. The prolonged exposure of islets to palmitate inhibits the secretory capacity of β-cells and impairs insulin gene expression [37]. Medium- and long-chain FAs also affect β-cell function through the activation of pancreas-specific cell-surface G-protein-coupled receptor GPR40 (FFAR1) [38]. GPR40 agonists have recently attracted research attention and are promising for pharmacological anti-diabetic interventions [39]. GPR40-deficient mice were given a HF diet and exhibited improvements in parameters of islet function [40]. Saturated FAs decrease FFAR1 expression, whereas long-term *in vitro* treatment with unsaturated FAs coincided with an increase in the abundance of GPR40, and INS-1E cells were protected from lipotoxicity [41].

Saturated FAs have been linked with more adverse effects on parameters of β-cell function and survival than unsaturated FAs [35]. Large epidemiological studies linked an increase in the ratio of unsaturated to saturated FAs in serum triacylglycerols to a lower risk of T2D [42]. Stearoyl-CoA desaturase 1 (SCD1) is the rate-limiting enzyme that determines the biosynthesis of monounsaturated FAs (MUFAs) by introducing a *cis*-double bond to fatty-acyl CoAs. Palmitic and stearic acids are preferred desaturation substrates that are subsequently converted to palmitoleate (16:1n-7) and oleate (18:1n-9), respectively [43]. Targeted SCD1 deficiency protected against many aspects of metabolic syndrome, but an opposite effect appears to occur for pancreatic β-cells. *SCD1* knockdown in MIN6 or INS-1E cells augmented palmitate-induced apoptosis compared with non-targeted controls [44,45]. An increase in *SCD1* expression and desaturation activity within a subpopulation of palmitate-resistant MIN6 cells was detected [46]. Mice on a BTBR leptin$^{ob/ob}$ background that were deficient of *SCD1* exhibited a decline in GSIS, and a subpopulation of β-cells shared hallmarks of saturated FA-induced lipotoxicity [47]. A previous study by our group found that SCD1 inhibition was associated with alterations of the lipids accumulation, composition, and saturation status in cellular membranes. Moreover, SCD1 inhibition affected autophagy at the step of fusion with lysosomes and resulted in compromised GSIS in INS-1E cells [48]. Additionally, SCD1 inhibition was shown to reduce the levels of DNA methylation in adipocytes [49] and β-cells (A. Dobosz personal communication, unpublished data). Interestingly, the most abundant FA in TG fractions from the human pancreas that contained >5% fat was 18:1n-9, and the desaturation index was significantly higher, indicating an elevation of SCD1 activity. Additionally, TGs from the pancreas of HF diet-fed mice were also enriched in 18:2n-6 [8]. The source of extracellular FAs may also be provided by the turnover of phospholipids. Phospholipids in pancreatic tissue from the same animals had lower levels of the aforementioned FAs, whereas arachidonate (AA; 20:4n-6) was significantly abundant [8].

The chronic treatment of β-cells with unsaturated FAs, such as oleate, palmitoleate, and arachidonate, increased GSIS and the proliferation and survival of β-cells, and counteracted the lipotoxic effects of palmitate in rodent BRIN-BD11, INS-1E, MIN6 cell lines and human NES2Y pancreatic β-cell lines and islets, respectively [50-53]. Endocannabinoids (arachidonate derivatives) were shown to stimulate insulin secretion in INS-1E cells through cytoskeletal reorganization [54]. However, under conditions of being overweight or obese, the cytoprotective effects of unsaturated FAs are lower. The FA mixture that corresponded to the plasma profile of obese individuals with metabolic syndrome was enriched with saturated FAs (16:0, 18:0) and ω6 polyunsaturated FAs (PUFAs), including linoleic acid (LA; 18:2n6), γ-linolenic acid (LNA; 20:3n-6), and AA and had toxic effects on MIN6 cell viability, insulin secretion, and mitochondrial function [55]. Moreover, LA and LNA adversely affected cellular membrane fluidity and integrity in rat RINm5F cells and the human EndoC-βH1 β-cell line [56,57]. PUFAs are the major constituents of membrane phospholipids [58]. Perfusing the pancreas with PUFAs during lipid overload might impair the function of the ER and the subsequent processing and release of insulin stores [55].

BIOACTIVE LIPID MOLECULES WITH ANTI-DIABETIC POTENTIAL: DARK HERITAGE WITH BRIGHT FUTURE

Although circulating FAs appear to play a causal role in glucose intolerance and insulin resistance, certain FAs have advantageous anti-diabetic and antiinflammatory metabolic effects. A lipidomic analysis of adipose tissue from AG4OX mice (adipose-specific overexpression of the insulin-stimulated glucose transporter GLUT4) revealed a novel class of endogenous lipids, referred to as branched FA esters of hydroxyl FAs (FAHFAs). FAHFAs are composed of one of four different FAs and one of four distinct hydroxyl-FAs in different combinations. At least 16 FAHFA family members have been identified in serum and different tissues from humans and rodents [59,60]. Each FAHFA family consists of multiple isomers that differ in their branched ester position. Palmitic acid esters of hydroxyl stearic acid (PAHSA) were markedly decreased in subcutaneous white adipose tissue and serum in obese insulin-resistant mice and humans [59,61]. Four PAHSA isomers were confirmed in the mouse pancreas [59,62], but their effect on β-cell metabolism remains to be determined. Furthermore, serum PAHSA levels did not correlate with levels of nonesterified FAs or TGs, but they were strongly associated with insulin sensitivity, measured by euglycemic clamps in humans [59,63]. Acute oral administration of 5- or 9-PAHSA isomers in insulin-resistant HF diet-fed mice lowered ambient glycemia and improved glucose tolerance in aged chow-fed animals. Furthermore, higher GSIS in pancreatic islets from human donors was also observed after *in vitro* treatment with 5-PAHSA [59]. Interestingly, chronic PAHSA supplementation increased serum and tissue levels of PAHSA in both chow- and HF diet-fed mice, improved insulin sensitivity, and improved glucose tolerance, without affecting body weight, food intake, or β-cell

exhaustion for at least 5 months [63]. Additionally, PAHSA significantly ameliorated adipose inflammation under conditions of obesity [60,63].

Dietary ω-3 FAs, which constitute essential components of cellular membrane phospholipids, were shown to act as potent insulin sensitizers and robust antiinflammatory agents [64,65]. High fat diet-fed obese mice exhibited improvements in fasting insulin levels, higher muscle insulin sensitivity, and lower hepatic steatosis both *in vivo* and *in vitro* in a GPR120-dependent manner after diet enrichment with ω-3 FAs [64,65]. Studies of rodent islets showed that ω-3 FA supplementation can ameliorate palmitate- and LA-induced impairments in insulin secretion, improve survival, and modulate the function and redox status of pancreatic β-cells [66,67]. Furthermore, the stable transgenic production of ω-3 FAs in murine islets or the prolonged treatment of INS-1E cells with eicosapentenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3) enhanced insulin secretion, increased insulin content, and conferred strong resistance to cytokine-induced β-cell death [68,69]. Findings from meta-analyses showed that EPA, DHA, and α-linolenic acid (ALA; 18:3n-3) supplementation was associated with a lower risk of incident T2D in several human cohorts [70,71]. Additionally, baseline proportions of serum EPA, DHA, and docosapentenoic acid (DPA; 22:5n-3) were linked with a lower incidence of T2D, higher insulin sensitivity, and higher β-cell function during a median follow-up time of 11 years in a randomized Finnish cohort who had a higher risk of T2D [72]. In contrast to PAHSAs, ω-3 FAs are not synthesized endogenously *de novo*. Improvements in glucose homeostasis occur after lengthy and continuous ω-3 FA supplementation in the diet instead of a single dosage. However, similar to PAHSAs, ω-3 FAs might act on insulin secretion through GPR120 activation [59,60].

Apart from FAHFAs and ω-3 fatty acids, endogenously produced palmitoleate acts as an adipose tissue-derived lipokine that suppresses hepatosteatosis and has favorable metabolic effects on muscle insulin sensitivity [73,74]. Cellular studies corroborate the beneficial effects of 16:1 on pancreatic β-cell function [74], the secretory capacity of β-cells, and insulin production [35,75,76]. Palmitoleic acid potentiated glucose-stimulated insulin release from rat and human islets. The greatest effects were seen in the presence of 16.7 mM glucose [77], which induced β-cell proliferation [50,78] and counteracted the DNA fragmentation and apoptosis of human islets that were caused by palmitate-induced lipotoxicity [75].

PANCREATIC ISLET MICROENVIRONMENT – SIGNALING, STRUCTURE, AND FUNCTION

The pathogenesis of obesity-mediated T2D is intertwined with insulin resistance and the dysfunction and vasculature of pancreatic islets [79]. Islets of Langerhans are endocrine mini-organs with a specialized capillary network that consumes nearly 20% of the total pancreatic blood flow. Even slight alterations of the parenchymal arterial supply markedly affect pancreatic endocrine function [80]. The dense vascularization of the pancreas is the organ's response to the high need for the supply of nutrients and oxygen. Such dense vascularization is also necessary for the removal of metabolites and distribution of hormones that are produced by the tissue itself [79]. Each islet of Langerhans is supplied by 1-3 arterioles that penetrate its core and branch into the capillary network that empties into peripheral venules. The capillary system around the islet of Langerhans is ~5-times denser than the capillary system of exocrine tissue. It is composed of one layer of highly fenestrated vascular endothelial cells (ECs). Such openings facilitate the rapid *trans*-endothelial passage of secreted insulin into the blood flow and tune glucose sensing by β-cells. Therefore, each β-cell within the islet of Langerhans is surrounded by at least one EC, and these cells are necessarily exposed to each other's secretagogues [81].

Moreover, islet ECs serve as a source of a unique basement membrane (BM) that is an integral part of the islet structure. The deposition of BM native proteins (β1-laminin and collagen IV) support β-cell adhesion and improve their function over time. Endothelial cells and pancreatic β-cells have an interdependent functional relationship whereby the islet endothelium is dedicated to the delivery of oxygen and nutrients, promotion of β-cell proliferation, and induction of insulin gene expression during development [82]. Therefore, islet ECs not only function as a cellular barrier but also produce a wide range of vasoactive substances (e.g., nitric oxide [NO] and endothelin 1 [ET-1]), effectors of microvasculature integrity (e.g., platelet and endothelial cell adhesion molecule [PECAM1]), angiogenic substances, and growth factors (hepatocyte growth factor [HGF] and vascular endothelial growth factor A receptor [VEGFR]), all of which influence the β-cells activity in a paracrine fashion. On the other hand, the β-cells signal back to adjacent ECs through VEGF-A, insulin, and angiopoietin-1 (Ang-1) to catalyze the production of NO by endothelial nitric oxide synthase (eNOS) [83] and produce a dense capillary network [84]. Nitric oxide has many important functions in the endothelium. It inhibits inflammatory processes and maintains basal tone by relaxing vascular cells [85].

DYSFUNCTION OF PANCREATIC ANGIOARCHITECTURE IN OBESITY AND TYPE 2 DIABETES

In the pre-diabetes stage, the pancreatic microvasculature needs to expand and perfuse the newly formed mass of β-cells during the adaptive compensatory response of islets [86]. The number of ECs was shown to be reduced in parallel with β-cell failure under culture conditions [83]. Multiple abnormalities of islet blood flow regulation and blood pressure were reported in several animal models of T2D and could contribute to pathogenesis of the disease [87]. Dysfunctional vasculature, characterized by higher EC-mediated vasodilation, density, and thickening, the overproduction of growth factors, adhesion impairments, and greater permeability, are features that parallel the progression of T2D [88]. Rats that were maintained on a HF diet exhibited a lower velocity and rate of pancreatic microcirculatory blood flow, with irregular intermittent perfusion in some capillaries [89]. In response to insulin resistance, islet hyperplasia was associated with a greater number of ECs. However, the vascular integrity of islets in obese ZDF rats was impaired and prone to islet failure [90]. Mice that were fed a HF diet exhibited islet hypervascularization with irregular capillaries, a thicker BM, and an increase in VEGF secretion [86]. Interestingly, changes in islet angioarchitecture in mice during insulin resistance were associated with the dilation

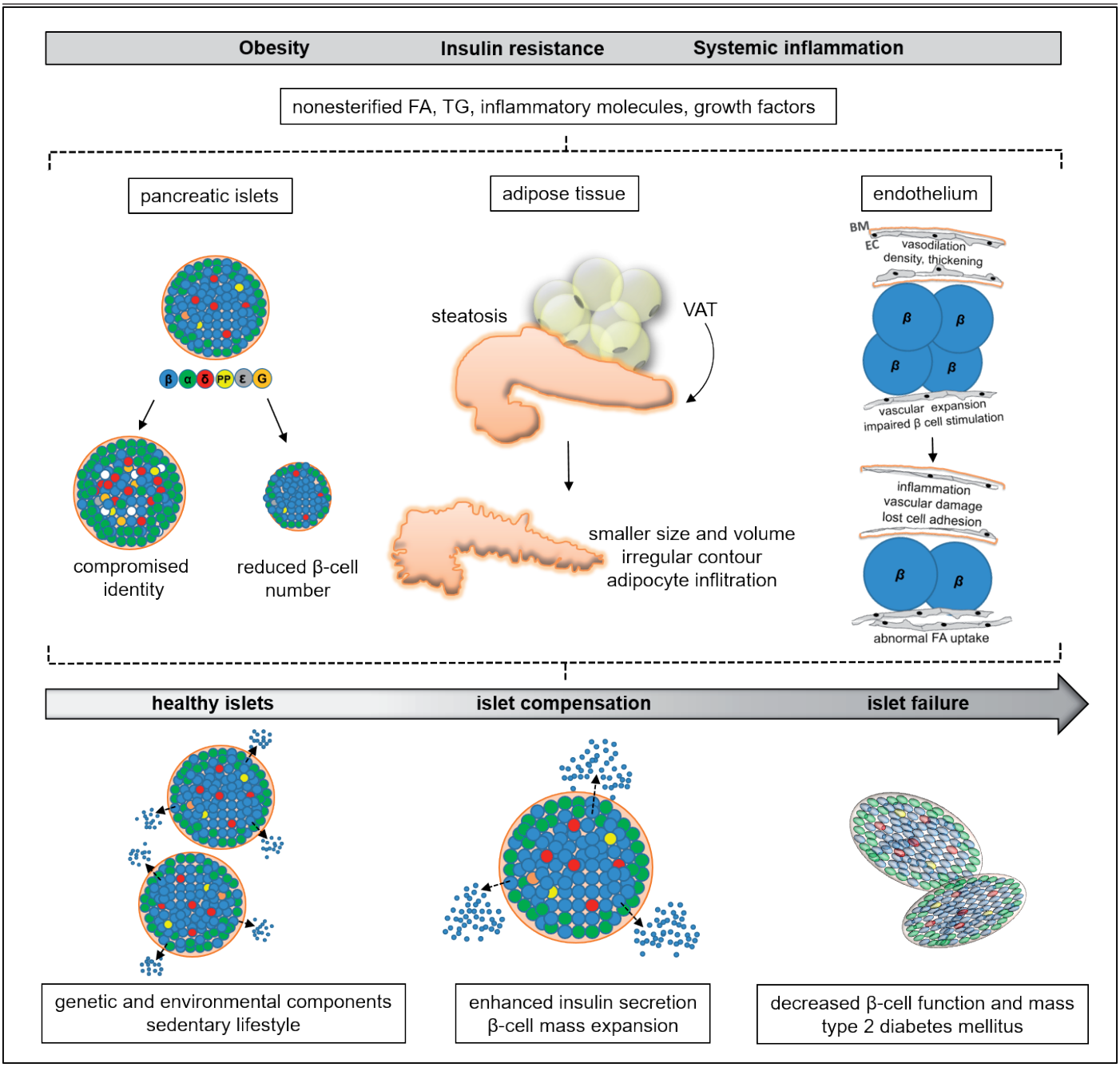

Figure 1. Natural history of the β-cell adaptation to obesity and β-cell failure in type 2 diabetes. Hyperlipidemia develops in the excessive nutritional state found in obesity, coupled with insulin resistance and systemic inflammatory response. In obese individuals, adipose tissue lipolysis elevates levels of plasma nonesterified fatty acids whereas insulin resistant periphery delivers surplus of triglyceride-rich particles and inflammation molecules. Over time, pancreatic islets adapt to increasing metabolic load by higher insulin secretion and β-cell mass. The ectopic accumulation of lipid metabolites drives pancreatic steatosis, microvascular injury in the pancreas and compromised identity of β-cells. Finally, specimens with vulnerability to genetic and environmental components experience loss of islet integrity and mass, and β-cell dysfunction occurs that mark the onset of type 2 diabetes.

and disorganization of preexisting capillaries rather than angiogenesis [91]. Similarly, increases in markers of inflammation, cell adhesion, and vasoconstriction, decreases in markers of vasodilation, and the accumulation of advanced glycation end-products were reported in primary islet ECs that were isolated from 8-week-old diabetic *db/db* mice [82]. Islets from autopsy specimens of the pancreas from patients with T2D presented capillary thickening and fragmentation and higher vessel density compared with non-diabetic controls [83]. Collectively, these studies support the notion that increases in islet vascularization and blood flow accompany an adaptive β-cell response during hyperglycemia. However, the continuation of β-cell failure coincides with the loss of islet vasculature over the course of the disease [87].

Preserving the structural integrity and full function of microvascular ECs is pivotal for protecting islets against the infiltration of adipocytes and immune cells that drive inflammation. Endothelial cells exhibit an inflammatory, pro-adhesive phenotype in T2D [81,82]. The activation of ECs potently increases the expression of surface leukocyte-homing receptors and attracts monocytes that consequently penetrate the interi-

or of the islet, causing damage and triggering architectural abnormalities through the secretion of pro-apoptotic cytokines, including IL-1β, CCL-2, and TNF-α [79,86]. On the other hand, the release of FAs from adipose tissue during periods of fasting or under conditions of obesity-related lipid overload and their subsequent endothelial-mediated uptake remain tightly controlled. Endothelial FA transport is orchestrated by VEGF-B, peroxisome proliferator-activated receptor γ, and apelin. Signaling perturbations include increases in proinflammatory cytokines (e.g., IL-6 and TNF-α) and the disruption of nitric oxide synthesis that favors deleterious reactive oxygen species (ROS) production, both of which promote the activated phenotype of ECs and abnormal FA uptake into surrounding tissues, including islets [92].

FATTY ACID METABOLITES AND ENDOTHELIAL EXHAUSTION

Fluctuations in the levels of both endogenous and exogenous FAs affect proper EC function, including endothelial-dependent vasodilation and blood pressure [93]. Endothelial cells are unable to store large amounts of lipids. Therefore, they are the first target of abnormal increases in circulating TGs, cholesterol, and serum FAs that are associated with obesity-derived insulin resistance and diabetes. Hyperlipidemia is currently considered a major risk factor for microvascular injury in the pancreas [81,88]. Free FAs impair microvascular function, thus indirectly promoting β-cell failure [94]. The exposure of pancreatic islets to media collected from MS1 cells subjected to palmitate treatment resulted in decreases in GSIS and insulin content [82]. Morbidly obese and insulin-resistant individuals exhibited an increase in pancreatic FA uptake and fat accumulation and a decrease in pancreatic blood flow. Both of these effects were inversely associated with defects in β-cell function [80].

Decreases in LA in serum lipids were positively associated with the endothelial function index in individuals with T2D. Linoleic acid has also been shown to exert vasorelaxant effects and lower blood pressure [93]. Pathological elevations of blood lipid levels are a preferential substrate for endothelial mitochondria oxidation. Impairments in nitric oxide bioavailability that were caused by the palmitate- and oleate-mediated inactivation of eNOS and prostacyclin synthase (PGI_2) and the accumulation of ROS species were shown to be hallmarks of endothelial damage. Moreover, FAs are recognized as primary stimulators of ROS production that is caused by disturbances in the synthesis of cardiolipin, mitochondrial uncoupling, and diacylglycerol-dependent protein kinase C and NADPH oxidase activation, which negatively affect both vascular tone and cell growth [88,93,95]. Endothelial dysfunction was observed in obese ZDF rats and palmitate-exposed human umbilical vein endothelial cells and the EA.hy926 cell line and associated with FA-induced NADPH oxidase subunit overexpression and ROS production [96,97]. The treatment of EA.hy926 cells with high levels of palmitic acid resulted in excessive oxidative stress and Ca^{2+}-dependent autophagy and necrotic cell death [97,98].

Epidemiological studies reported that individuals who were on a diet with high ω3 FA content had a lower risk of obesity and T2D, and were less likely to present diabetic vasculopathy. The biological functions of fish oil supplementation are partially attributable to ω3 PUFAs, such as EPA and DHA, which exert regulatory effects on the activation of extracellular signal-regulated kinase and adenosine monophosphate-activated protein kinase networks, and induce phosphorylation of the PDK1 and Akt signaling cascades and their downstream effector proteins, such as eNOS and forkhead box O3 [99].

CONCLUSIONS

Strong evidence indicates that the incidence of T2D is correlated with the higher prevalence of obesity. An imbalance in the abundance of serum free FAs promotes deterioration of peripheral insulin sensitivity. At a certain time point, the progressive loss of β-cell function becomes central to the development and progression of T2D. Impairments in microcirculatory flow of the pancreas can result in the further deterioration of β-cells (Fig. 1). The full scope of actions of different lipid species on β-cell metabolism, functional damage, and exhaustion remains to be unveiled. Crosstalk between different signaling systems, cellular responses, and pathways that promote proinflammatory responses can negatively influence islet destiny and survival. Unknown is whether alterations of islet vascularization and pancreatic lipid content are causal factors in the development of T2D. One unresolved issue is whether an increase in pancreatic microvasculature improves islet survival or promotes β-cell demise through inflammatory signaling through greater vascularization or fat accumulation in the pancreas. Ultimately, combinatorial approaches that target specific aspects of endothelial signaling and adipocyte infiltration and that utilize imaging modalities to reveal the morphology of the pancreas may result in beneficial effects on islet function. Understanding T2D as a disease that is associated with fat accumulation above an individually defined threshold may contribute to more personalized clinical treatment in both adult and pediatric populations worldwide.

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Na dobre i na złe – czyli rola oddziaływania trzustki, śródbłonka i tkanki tłuszczowej w regulacji funkcjonowania komórek β i rozwoju cukrzycy typu 2 związanej z otyłością

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Słowa kluczowe: otyłość, cukrzyca typu 2, komórki β, stłuszczenie trzustki, tkanka tłuszczowa, śródbłonek

STRESZCZENIE

Epidemia otyłości i cukrzycy typu 2 stanowi jedno z największych wyzwań współczesnych nauk biomedycznych. Etiologię cukrzycy typu 2 determinuje współistnienie dwóch stanów patofizjologicznych: insulinooporności tkanek obwodowych oraz dysfunkcji komórek β trzustki. W przypadku długotrwałej otyłości, komórki β przechodzą proces adaptacji, jednak ze względu na specyfikę działania, dysponują ograniczonymi możliwościami wewnątrzkomórkowego akumulowania związków lipidowych, które są wydzielane przez tkankę tłuszczową. Długotrwała ekspozycja trzustki na wysokie stężenia nasyconych kwasów tłuszczowych prowadzi do dysfunkcji komórek β oraz uszkodzenia śródbłonka naczyń wewnątrz wysp, które skutkują niewydolnością sekrecyjną, zmianami morfologii oraz postępującą śmiertelnością wysp trzustkowych. W niniejszej pracy przedstawiamy charakterystykę dynamicznych powiązań między hiperlipidemią, stłuszczeniem trzustki i układem mikrokrążenia wysp Langerhansa w regulacji funkcji komórek β. Omawiane w artykule mechanizmy, poprzez które kwasy tłuszczowe wpływają na unaczynienie, metabolizm oraz stan zapalny trzustki, odgrywają kluczową rolę w pogłębianiu defektu czynnościowego komórek β i prowadzą do rozwoju cukrzycy typu 2.