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THEMATIC REVIEW

An adipocentric perspective of pancreatic lipotoxicity in diabetes pathogenesis

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Abstract

Obesity and diabetes represent two increasing and invalidating public health issues that often coexist. It is acknowledged that fat mass excess predisposes to insulin resistance and type 2 diabetes mellitus (T2D), with the increasing incidence of the two diseases significantly associated. Moreover, emerging evidence suggests that obesity might also accelerate the appearance of type 1 diabetes (T1D), which is now a relatively frequent comorbidity in patients with obesity. It is a common clinical finding that not all patients with obesity will develop diabetes at the same level of adiposity, with gender, genetic, and ethnic factors playing an important role in defining the timing of diabetes appearance. The adipose tissue (AT) expandability hypothesis explains this paradigm, indicating that the individual capacity to appropriately store energy surplus in the form of fat within the AT determines and prevents the toxic deposition of lipids in other organs, such as the pancreas. Thus, we posit that when the maximal storing capacity of AT is exceeded, individuals will develop T2D. In this review, we provide insight into mechanisms by which the AT controls pancreas lipid content and homeostasis in case of obesity to offer an adipocentric perspective of pancreatic lipotoxicity in the pathogenesis of diabetes. Moreover, we suggest that improving AT function is a valid therapeutic approach to fighting obesity-associated complications including diabetes.

Keywords: adipokines; adipose tissue; diabetes; lipotoxicity; pancreas

Introduction

Obesity results from an imbalance between dietary intake and energy expenditure, leading to the storage of excess energy in the form of lipids within adipose tissue (AT). The increasing prevalence of obesity worldwide is closely associated with a subsequent rise in the incidence of diabetes (GBD 2021 Diabetes Collaborators 2023), making obesity a widely recognised risk factor for the development of type 2 diabetes mellitus (T2D) (Klein *et al.* 2022). Additionally, emerging evidence also indicates that obesity accelerates the development of type 1 diabetes mellitus (T1D) (March *et al.* 2021), representing a risk factor for health in these patients (Cantley *et al.* 2021). In this review, we summarise recent advances linking obesity to the development and control of diabetes, focussing on the interplay between the AT and the pancreas.

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The close link between obesity and diabetes is supported by the evidence that increased body mass index (BMI) is associated with a higher risk for T2D (Colditz *et al.* 1995). Body fat accumulation, especially the android type of obesity where fat accumulates in visceral and abdominal sites, has been associated with systemic metabolic disturbances since 1947 when a link with insulin resistance (IR) was proposed (Vague 1947). Prospective studies with subjects at risk for T2D demonstrate that the development of abdominal obesity is correlated with the loss of β-cell function (Cnop *et al.* 2005, Menzaghi *et al.* 2006, De Boer *et al.* 2007). The first compensatory mechanism to IR is the expansion of β-cell mass and increased insulin secretion (Christensen & Gannon 2019). In addition, it has been proposed that excess adiposity could be the primary cause of initially increasing insulin secretion and IR (McGarry 2002, Fryk *et al.* 2021). Moreover, when this compensatory mechanism fails, β-cell loss and dysfunction occur, leading to hyperglycaemia and diabetes.

It is worth noting that the relationship between T2D and obesity is not linear, as not all obese people develop T2D at the same level of adiposity (Sims 2001). Evidence indicates that the individual capacity to appropriately store energy surplus in the form of fat within the AT determines and prevents toxic lipid deposition in other organs, such as the pancreas and liver (Virtue & Vidal-Puig 2010). Thus, the threshold when the maximal energy storage capacity within the AT is reached could be the individualised critical point triggering T2D onset. Therefore, we posit that understanding the factors regulating AT dysfunction and failure is essential in identifying new therapeutic targets to prevent and delay insulin secretion disruption. Here, we review the mechanisms connecting the AT expansion, dysfunction and failure linked to increased lipid influx towards the pancreas, the effects of lipid regulation on insulin secretion and the mechanism of lipotoxicity in β cells.

Disconnecting BMI from diabetes: the adipose tissue expansion failure?

From an epidemiological perspective, BMI, IR and T2D are undeniably connected. However, BMI is a crude measure that does not fully grasp the complexity of the link between excessive fat accumulation and IR, compensatory increased insulin secretion, and ultimately, β-cell failure. The complexity of this relationship is evidenced by the fact that obesity and T2D do not associate similarly in some subpopulations (Sims 2001). For example, men develop T2D at a lower BMI than women (Logue *et al.* 2011), and metabolic impairments occur in the Asian population at a lower average BMI than in the Caucasian population (Barnes 2011).

One mechanism that could explain these controversies is the AT expandability hypothesis. According to this hypothesis, every individual possesses an intrinsic capacity to expand their AT in positive energy balance. When the AT storage capacity is exceeded, the physiological function of AT to buffer lipid flux is blunted (Virtue & Vidal-Puig 2010), with a reduction of anti-lipolytic response to insulin in the postprandial states and a failure to take up lipids from the circulation (Morigny *et al.* 2021). In states of AT dysfunction, excess energy in the form of lipids is redirected towards non-adipose organs such as the liver, the skeletal muscle, the heart or the pancreas. Ectopic lipid accumulation in non-adipose organs causes organ dysfunction, often called lipotoxicity (Virtue & Vidal-Puig 2010). Moreover, overwhelmed adipocytes also express and secrete higher levels of proinflammatory adipokines and chemoattractants, promoting an inflamed state of the AT and systemic inflammation that further impedes insulin sensitivity (Hotamisligil 2017).

Individuals with congenital or acquired defects in AT, known as lipodystrophic syndromes, demonstrate the most severe manifestation of limited AT expansion (Garg 2011). In lipodystrophic syndromes, the loss or dysfunction of AT leads to lipid storage in ectopic sites, and thus to IR, diabetes, dyslipidaemia and liver complications (Vatier *et al.* 2013). The metabolic characterisation of three patients with one rare lipodystrophic syndrome, namely neutral lipid storage disease with myopathy, due to homozygosity for loss-of-function mutations in the *ATGL* gene, highlighted the consistent significant increase in pancreatic fat and visceral fat in these conditions, with subsequent impaired insulin response to glucose (Natali *et al.* 2013).The relationship between lipodystrophy and diabetes underscores the crucial role of AT homeostasis in maintaining metabolic health. A proof of concept for this concept has been demonstrated through fat depot transplantation into the lipoatrophic mouse model A-Zip, effectively reversing the metabolic defects induced by lipoatrophy (Gavrilova *et al.* 2000). Notably, the transplantation of leptin-deficient fat pads into the A-Zip mouse does not rescue the metabolic defects (Gavrilova *et al.* 2000), implying that leptin deficiency plays a crucial role in mediating lipoatrophy-induced metabolic dysfunction. Following this study, administering leptin to patients with genetic or acquired, partial or generalised lipodystrophy with decreased serum leptin levels can reverse excessive hyperphagia and improve metabolic irregularities, notably restoring insulin secretion and sensitivity (Vatier *et al.* 2016). While complex, the link between AT dysfunction and the development of the cardiometabolic complications of obesity, such as diabetes, is established, and the fluxes of lipids towards non-adipose organs could explain the aetiology of metabolic dysfunctions.

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Lipids in the pancreas: the double-edged sword

Diabetes and dyslipidaemia are interconnected conditions that often coexist and contribute to each other's progression. Increased serum free fatty acid (FFA) levels, notably in their saturated form, are positively associated with the incidence of T2D (Wang *et al.* 2003, Qureshi *et al.* 2019). Abnormal intracellular lipid accumulation and adipocyte infiltration in the pancreas, generally defined as 'pancreatic steatosis', is a pathological event associated with obesity and metabolic syndrome that predisposes to β-cell dysfunction and death (Smits & Van Geenen 2011). On the other hand, fatty acids (FAs) also promote insulin secretion, which suggests they might be initial signals communicating the need for increased insulin secretion to blunt lipolysis. These observations highlight the dual role of FAs in regulating β-cell function and the necessity to maintain appropriate lipid homeostasis to ensure appropriate glucose control.

Lipid regulation of insulin secretion

Lipids have critical physiological actions in pancreatic β cells, acting as a cofactor to boost glucose-stimulated insulin secretion (GSIS). Accordingly, a minimal level of FAs is essential for normal GSIS. Islets deprived of FAs lose their GSIS ability, which can be rescued by supplementing exogenous FAs (Stein *et al.* 1996, Roduit *et al.* 2004). Homeostatically, the increased serum FAs observed in insulin-resistant individuals might be an adaptation to potentiate insulin secretion and compensate for increased insulin needed to compensate for IR (McGarry 2002, Prentki *et al.* 2002, Nolan *et al.* 2006). Interestingly, the insulinotropic action of FAs may be linked to their chain length and degree of saturation. It has been shown that saturated FAs (SFAs), such as palmitic (C16:0) and stearate (C18:0), are better enhancers of GSIS than mono- and polyunsaturated FAs in the perfused rat pancreas (Stein *et al.* 1997). The converse has been observed in human islets where palmitoleate and oleate induced insulin secretion more potently than their saturated counterparts, palmitate and stearate (Cen *et al.* 2016). Others showed that increasing FFAs failed to potentiate insulin secretion in response to mixed meals and to intravenous glucose in non-diabetic subjects without a family history of diabetes, suggesting that genetic predisposition also plays an essential role in lipid regulation of GSIS (Kashyap *et al.* 2003). On the other hand, it should be highlighted that the relation between FFAs levels and insulin secretion is not linear. In fact, sustained lowering FAs levels achieved with long-term therapy Acipimox was shown to increase insulin secretion rates in a subset of patients with diabetes (Davoren *et al.* 1998) or at risk of diabetes (Paolisso *et al.* 1998), suggesting that FFAs homeostasis is important for insulin secretion regulation, especially in people at risk.

The precise mechanisms by which FAs enhance GSIS are partially unknown but seem to act at the extra- and intracellular levels (Prentki *et al.* 2013). We summarised them in Fig. 2A. Pancreatic β cells can sense extracellular FA through the free fatty acid receptor 1 (FFAR1) (Itoh *et al.* 2003). FFAR is a G-protein receptor highly expressed in β cells and responsible for mediating approximately 50% of the FA-induced insulin secretion (Prentki *et al.* 2013). Accordingly, high-fat diet (HFD)-fed mice lacking FFAR1 (GPR40) show a reduction of insulin secretion during i.v. glucose tolerance test when compared to WT littermates (Kebede *et al.* 2008). Significantly, FFAR1 activation does not trigger insulin secretion in the absence of glucose. Therefore, it has been hypothesised that FFAR1 agonists could improve insulin secretion without increasing the risk of hypoglycaemia in patients with T2D (Kebede *et al.* 2008). To note, FFAR1 recently gained attention as a potential pharmacological target in T2D (Li *et al.* 2018). However, research on FFAR1 agonists did not result in any available drugs because of hepatotoxicity due to the lipophilic nature of the agonists rather than their direct receptor-mediated action (Kaku *et al.* 2016). β cells also express FFAR2 and FFAR3 receptors, which are activated by short-chain FAs (under six carbons), mainly produced in the colon by gut microbiota when abundant undigested carbohydrates exist (Mishra *et al.* 2020). However, the role of these receptors regulating insulin release from β cells appears to be non-significant (Ichimura *et al.* 2014).

The metabolism of intracellular lipids is closely connected to glucose metabolism. Additionally, the esterification and lipolysis of neutral lipids, also known as glycerolipids/fatty acid cycling, play a supportive role in GSIS in β cells. Fatty acid uptake is a crucial initial step in regulating GSIS through intracellular targets. Unlike glucose, FAs easily cross the phospholipid bilayer due to their low energy barrier (Hamilton & Kamp 1999), facilitated by proteins like CD36 and fatty acid transport protein (FATP) on the plasma membrane (Noushmehr *et al.* 2005). Importantly, β cells release FAs from the plasma membrane, a process dependent on glucose concentration, to activate the FFAR1 receptor and promote GSIS (Mugabo *et al.* 2017). Interference with FA release leads to reduced calcium oscillation and impaired insulin release in β cells (Mugabo *et al.* 2017).

Lipolysis of intracellular TAGs generates FAs, which are activated to LC-CoA (long-chain FA-CoA) by long-chain acyl-CoA synthase (ACSL), before undergoing β-oxidation. The increase of intracellular glucose concentration increases the generation of malonyl CoA, suppresses the carnitine palmitoyl transferase 1

(CPT1) activity and reduces β-oxidation (Cantley *et al.* 2019). Inhibition of β-oxidation resulted in increased availability of LC-CoA that promotes GSIS by targeting ATP-sensitive potassium channels and protein kinase C (Larsson *et al.* 1996, Yaney *et al.* 2000) and by entering the glycolipid (GL)/FFA cycle (Prentki & Madiraju 2012). The GL/FFA cycle is a process of FA esterification with glycerol to form diacylglycerol (DAG) and triacylglycerols (TAGs) (lipogenic phase), followed by the hydrolysis of TAGs to regenerate monoacylglycerol (MAG), glycerol and FAs (lipolytic phase), which can re-enter the cycle. FFAs generated can exit the cell and activate FFAR1, while MAGs directly bind and activate Munc13-1, an insulin granule exocytosis-facilitating protein (Prentki & Madiraju 2012).

In addition, lipid droplets (LDs) are recognised to play an integral part in the GL/FFA cycle. LDs are intracellular organelles consisting of a monolayer phospholipid membrane and a lipid core composed of TAGs, cholesterol ester and retinol ester (Welte & Gould 2017) that are detected in adult islet β cells (Vernier *et al.* 2012, Trevino *et al.* 2015, Dai *et al.* 2016). LD formation starts as TAG accumulation within the endoplasmic reticulum (ER) membrane bilayer, and newly synthesised TAGs are primarily transferred to LDs (Nettebrock & Bohnert 2020). After emerging from the ER, LDs can grow by directly incorporating FAs into TGs via DGAT2 (Gluchowski *et al.* 2017). LD degradation releases MAG and FFAs, which support GSIS as previously described. Lipolysis of LDs is initiated by adipose triglyceride lipase (ATGL) and is regulated by multiple factors, including phosphorylation of PLIN1/5, recruitment and activation of lipases to LDs (Sztalryd & Brasaemle 2017, Yang *et al.* 2023). Two models of β-cell-specific ATGL knockout mice proposed that ATGL deficiency blunts insulin secretion (Tang *et al.* 2013, Attané *et al.* 2016). Moreover, LDs in pancreatic islets accumulate in cases of nutritional stress, diabetes and dysfunction of β cells (Tong *et al.* 2020), suggesting that impaired LD production and degradation might be involved in impaired insulin secretion.

To sum up, lipids and their metabolism are critical regulators of insulin secretion but act as potentiators more than inducers. Accordingly, FAs cannot trigger insulin secretion in the absence of glucose. However, excess lipids in the pancreas can alter β-cell functions, as discussed in more detail in the section 'Lipotoxicity in pancreas'.

Lipid regulation of glucagon secretion

Glucagon is a peptidic hormone secreted by the α cells of the pancreas when glucose availability is low, promoting gluconeogenesis and lipolysis in the liver and preventing hypoglycaemia and fuel availability. While glucagon has been demonstrated to induce lipolysis in isolated adipocytes, the expression of the glucagon receptor within adipocytes is significantly lower compared to that in hepatocytes (Duncan *et al.* 2007). Furthermore, glucagon concentration in the peripheral circulation is notably lower than in the portal vein (Duncan *et al.* 2007). Together with insulin, it regulates whole-body glucose homeostasis. In advanced stages of T2D and autoimmune diabetes, pancreatic α cells undergo deregulation, losing the ability to respond to hypoglycaemia appropriately. Clinically, this results in life-threatening hypoglycaemia, which is a limiting factor in diabetes management in clinical setting (Panzer and Caicedo 2021).

Plasmatic low glucose levels are the main signal triggering glucagon secretion in rodent and human islets (Ohneda *et al.* 1969). Interestingly, a recent study highlighted that fatty acid oxidation is required for the inhibitory effect of glucose on glucagon secretion by reducing ATP levels (Armour *et al.* 2023). On the other hand, FAs are known to promote glucagon secretion. Most studies show that short-term exposure to FAs stimulates glucagon release in isolated islets and clonal α-cell lines (Bollheimer *et al.* 2004, Olofsson *et al.* 2004). Short-term treatment with the saturated FA palmitate increases glucagon secretion by enhancing α-cell intracellular calcium entry and by relieving the inhibitory paracrine action of somatostatin, which is secreted from pancreatic δ cells (Olofsson *et al.* 2004). Similarly, the polyunsaturated FA linoleic acid increases glucagon secretion in isolated mouse and rat islets and in In-R1-G9 glucagonoma cells (Wang *et al.* 2011). Accordingly, the long-term culture of α cells with palmitate augmented glucagon release and enhanced glucagon expression and protein content, probably by activating the mitogenic mitogen-activated protein kinase (MAPK) pathway (Piro *et al.* 2010). Similarly to FA-induced insulin secretion, FA-induced glucagon secretion could also be mediated by FFAR1, constitutively expressed on the surface of α cells (Flodgren *et al.* 2007, Wang *et al.* 2011).

Similarly to β cells, FAs can also impair glucagon secretion. The inhibitory action of insulin on glucagon release was impaired when α cells were incubated with FA for a prolonged period of time. This effect was attributed to palmitate-induced insulin resistance on the insulin receptor substrate 1 (IRS-1)/phosphatidylinositol kinase (PI3K)/serine-threonine protein kinase (Akt) pathway (Piro *et al.* 2010). Of note, the survival of α cells, like β cells, is affected by glucolipotoxic conditions, as high palmitate combined with high glucose levels are able to induce apoptosis in rodent α cells (Piro *et al.* 2010).

In general, all these data support the hypothesis that α-cell secretory capacity is regulated by lipid signaling. In addition, α cells are susceptible to lipotoxicity, which contributes to the loss of the counterregulatory effect of glucagon in glycaemic control in patients with diabetes.

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Lipotoxicity in pancreas

While a minimal level of FAs is essential for normal glucose-dependent insulin secretion, prolonged exposure of islets to increased levels of FAs is associated with impaired β-cell function, leading to reduced capacity to secrete sufficient insulin to counteract IR. The detrimental effects of chronic lipid overload in pancreatic islets are well-established. It was discovered decades ago that exposure of islets isolated from Zucker rats to lipotoxic doses of FA (oleate and palmitate) results in ceramide-induced cell death (Shimabukuro *et al.* 1998*a*,*b*). One of the first *in vivo* evidence linking dyslipidaemia with impaired β-cell function was observed in hyperglycaemic Goto-Kakizaki rats, where the hyperlipidaemia induced by high-fat feeding markedly impaired glucose-induced insulin secretion in this model (Briaud *et al.* 2002).

Exposure to chronically high levels of lipids leads to cell injury through lipotoxic mechanisms (Fig. 2B). The mechanisms driving lipotoxicity in β cells are still to be fully explored but encompass signaling through FA receptors, ceramide production, and cell stress responses such as ER stress and mitochondrial dysfunction, as recently reviewed here (Oh *et al.* 2018).

Ceramide accumulation represents one of the primary mechanisms underlying lipotoxicity in β cells. Long-chain saturated FAs, such as palmitate, stearate and arachidate, stimulate *de novo* ceramide synthesis and formation (Chavez & Summers 2003). Ceramides induce apoptosis in β cells by induction of ER stress, alterations of mitochondrial membrane integrity and inhibition of the pro-survival kinase Akt (García-Ruiz *et al.* 2002, Chavez *et al.* 2003, Véret *et al.* 2011, Boslem *et al.* 2013). Accordingly, overexpression of CerS4 potentiates palmitate-induced accumulation of ceramides and enhances lipotoxicity in β cells (Véret *et al.* 2011). Similarly, exposure of β cells to the ceramide analogue C_2-ceramide enhances the pro-apoptotic and anti-proliferative effect of palmitate (Maedler *et al.* 2003). Conversely, inhibition of *de novo* ceramide synthesis using serine palmitoyl transferase (L-cycloserine) or ceramide synthase (fumonisin-B1) inhibitors attenuates FA-induced β-cell apoptosis and lowers hyperglycaemia in obese Zucker diabetic fatty rats *in vivo* (Shimabukuro *et al.* 1998*a*,*b*). Interestingly, β cells defend themselves from ceramide-induced dysfunction by secreting an active neutral ceramidase to lower FA-induced apoptosis (Tang *et al.* 2017).

ER stress is also an essential mediator of the lipotoxic insults. *In vitro* and *in vivo* studies have shown that β cells activate the unfolded protein response (UPR) following glucolipotoxic insults to maintain ER function and survival (Eizirik *et al.* 2008, Shrestha *et al.* 2020). However, excessive and prolonged UPR activation leads to the initiation of apoptosis. Both high levels of glucose (Elouil *et al.* 2007) and FAs, mainly when saturated (Cunha *et al.* 2008, Marselli *et al.* 2020), are associated with increased ER stress in human islets. In particular, SFAs induce sustained activation of the three arms of the UPR response IRE1, PERK and ATF6 (Cnop *et al.* 2007, Cunha *et al.* 2008), resulting in β-cell apoptosis. Multiple mechanisms by which SFAs directly or indirectly impair cell function through ER stress have been proposed, including protein palmitoylation (Baldwin *et al.* 2012) and impairment of sphingolipid metabolism (Boslem *et al.* 2011, Véret *et al.* 2013). These defects most likely act synergically, leading to β-cell dysfunction and apoptosis.

Altogether, there is compelling evidence that high levels of FAs, particularly their saturated counterparts, can induce a lipotoxic response evidenced by increased ceramide production and ER stress leading to β-cell dysfunction and apoptosis. These data indicate a direct role for lipotoxicity in decreasing β-cell mass in obesity-induced dyslipidaemia. Efforts to limit the lipid fluxes towards the pancreas appear promising in preventing β-cell mass reduction in obesity, thus preventing T2D onset, in addition to appropriate management of peripheral IR.

Adipose tissue control of pancreatic lipid content and function

Ogilvie *et al.* were the first to observe that obesity is associated with hypertrophy of the islets of Langerhans in the pancreas (Ogilvie 1933). Later on, Olsen *et al.* associated pancreatic steatosis with a decreased ability to secrete insulin and the development of T2D (Olsen 1978). Since then, fat accumulation in the pancreas has been referred to with various synonyms, such as pancreatic lipomatosis, fatty replacement, fatty pancreas, non-alcoholic fatty pancreatic disease or pancreatic steatosis (Smits & Van Geenen 2011). This nomenclature has the limitation of not distinguishing between the accumulation of triglycerides in acinar cells, β cells or intrapancreatic adipocytes. Histological observations of HFD-induced pancreatic steatosis showed that pancreatic ectopic fat is characterised by adipocyte infiltration rather than intracellular fat accumulation (Pinnick *et al.* 2008). Nonetheless, electron microscopy has also visualised intracellular fat accumulation even earlier than ectopic fat deposition in the pancreas itself (Moffitt *et al.* 2005, Yan *et al.* 2006).

The metabolic consequences of pancreatic ectopic adipocyte infiltration have been recently reviewed by Wagner *et al.* (2022). While preclinical evidence showed that physiologically pancreatic adipocytes stimulate insulin secretion in β cells by releasing FAs (Quiclet *et al.* 2019), clinical studies found that the pathological development of fatty pancreas is linked to β-cell dysfunction and reduced insulin secretion (Tushuizen *et al.* 2007, Van Der Zijl *et al.* 2011, Chin *et al.*

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2021, Yamazaki *et al.* 2022), although to what extent this association is preserved when diabetes is overt is uncertain (Tushuizen *et al.* 2007, Lu *et al.* 2019, Chin *et al.* 2021).

Regulation of lipid accumulation in the pancreas

The development of pancreatic lipid accumulation results from an imbalance between lipid synthesis, uptake and disposal. While *de novo* lipogenesis does not substantially contribute to pancreatic islets' fatty acid content, at least in non-stimulated states, circulating FFAs represent the primary source of pancreatic lipids. Physiologically, FFA serum levels increase during the fasted state due to AT lipolysis (Kersten 2023). Pathologically, obesity is associated with an increased FFA availability that pancreatic cells can take up (Fryk *et al.* 2021). FA uptake is mediated by specific transport membrane proteins, FA translocase (CD36), FA binding proteins and FATPs (Pownall & Moore 2014). It has been shown that CD36 is responsible for FA uptake and lipid accumulation in β cells (Khan 2018). CD36 expression is upregulated in the obese diabetic population, and inhibition of its activity *in vitro* enhances insulin secretion (Nagao *et al.* 2020). Following uptake through CD36, the FA is then activated by FATPs, which are acyl-coenzyme A (CoA) synthases that add a CoA residue to increase their water solubility (Pownall & Moore 2014). However, despite being partly regulated by transporters, the uptake of FFA by cells is primarily determined by the concentration gradient of FAs across the plasma membrane (Hamilton & Kamp 1999). The increase in the extracellular concentration of FFAs and 'metabolic trapping' of FA within cells through the formation of acyl-CoA (FATP) all promote cellular fatty acid uptake (Pownall & Moore 2014).

Beside circulating FFA, β cells can uptake lipids from lipoproteins through the action of lipoprotein lipase (LPL), and this process increases with aging (Cnop *et al.* 2000). However, to our knowledge, there has been no concrete evidence so far supporting the notion that the export of very low-density lipoprotein (VLDL)-TAG is the primary source of fat accumulation in the pancreas. However, it has been demonstrated that diabetes remission is linked to decreased hepatic VLDL-TG export, while a return to a diabetic state is associated with increased plasma VLDL-TAG levels (Al-Mrabeh *et al.* 2020). Surprisingly, murine-specific deletion of LPL in β cells does not reduce pancreatic fat and LPL overexpression in β cells only results in a mild increase in islet TAG content. However, deletion or overexpression of LPL in β cells profoundly reduces insulin secretion (Pappan *et al.* 2005), which seems independent of pancreatic lipid content.

Altogether, it can be assumed that the bioavailability of serum lipids appears to be the main driver regulating FA uptake in the pancreas.

Regulation of lipid availability by the AT

One critical organ regulating the availability of lipids is the AT. The lipid fluxes to the pancreas in fasting and fed states heavily rely on AT, which is the major contributor to plasma FFA concentrations. Various dysregulated processes in obese AT can potentially impact the transport and bioavailability of FFAs in the pancreas. The primary function of AT is energy storage and release in the form of fat, acting as a 'buffer' to the influx of dietary fat (Frayn 2002). White adipocytes are characterised by their large unilocular central lipid droplet, where fat is stored as neutral TAGs and released in the form of FFAs, depending on the energy status.

In particular, in conditions of increased energy demand such as fasting and exercise, FA mobilisation and release in the bloodstream are promoted by reduced plasma insulin and increased release of adrenaline and noradrenaline via the activity of lipases (Gjedsted *et al.* 2007). Conversely, following meal ingestion, the postprandial increase in plasma insulin efficiently blocks lipid export by suppressing lipolysis and promotes the storage of dietary lipids within the AT (Sadur & Eckel 1982, Roust & Jensen 1993). In particular, in the fed state, adipocytes take up and store lipids from the circulation in the form of FAs released from circulating triglyceride-containing lipoproteins such as chylomicrons and VLDLs bound to the capillary endothelium through the activity of LPL (Sniderman 2000). In 1996, Binnert *et al.* showed a rapid appearance in the plasma of labelled FAs after ingestion of labelled fat in humans, suggesting that there is an entry of FAs deriving from exogenous TAGs in serum FFAs pool (Binnert *et al.* 1996). Similarly, Fielding *et al.* showed that dietary fat contributes to specific post-prandial FAs profile (Fielding *et al.* 1996). This evidence together suggests that the AT does not take up a quote of FFAs arising from the hydrolysis of TAGs by LPL and joins the plasma pool in a process often referred to as 'spillover' (Karpe *et al.* 2011). It is believed that the spillover of FFAs rate is higher for chylomicrons, at approximately 30%, (Pichè *et al.* 2018), compared to VLDL, whose contribution to the FFAs pool is negligible (Bush *et al.* 2014). Intriguingly, the spillover of chylomicrons into the bloodstream appears to be more significant in lean individuals and in women but does not seem to be a pathway providing excess FFAs to non-adipose organs in obesity (Piché *et al.* 2018). This observation casts doubt on the contribution of FFAs spillover from the AT to the bloodstream FFAs pool in metabolic disease. It is worth considering that lipoprotein hydrolysis of both chylomicrons and VLDL may not be complete under specific conditions, leading to the formation of lipoprotein remnants. Interestingly, higher levels of total, very large, large, and very small (therefore reflecting remnant lipoprotein) TAG-rich lipoproteins are typically present at high concentrations in patients with T2D and are associated

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with cardiovascular diseases (Ginsberg *et al.* 2021, Matsushima-Nagata *et al.* 2023).

The release of FAs from upper-body subcutaneous AT significantly determines systemic FFAs levels (Nielsen *et al.* 2004). However, the association between obesity, FFAs serum levels and IR is not as linear as expected. It has been described that plasma FFAs levels are associated with obesity (Arner & Rydén 2015), increased fat mass (Boden 2008) and T2DM (Fraze *et al.* 1985). Nonetheless, greater postprandial FFA excursions in blood have also been associated with T2D and obesity compared to non-diabetic controls (Miles *et al.* 2003). Hence, raised postprandial FFA levels have been proposed as a pathogenetic hallmark leading to the development of β-cell dysfunction (Carpentier 2008). However, as reviewed by Karpe *et al.* in 2011, the association between obesity and increased FFA levels observed by most of the studies is relatively marginal and not consistent (Karpe *et al.* 2011). Moreover, as the fat mass increases, FFA release per kilogram of fat mass is downregulated, rather than increased, which might explain why several patients with obesity display normal FFAs serum concentration despite the excessive fat (Karpe *et al.* 2011). In line with this, McQuaid *et al.* found that men with obesity had normal systemic fasting FFAs concentration compared to lean control, but downregulation of FFAs delivery to the AT and decreased AT storage capacity after meal (McQuaid *et al.* 2011).

All these observations highlight that AT regulation and dysregulation in the case of obesity and IR are complex and still to be fully understood. However, AT is a crucial regulator of lipid bioavailability and metabolism, making AT an essential regulator of lipid deposition in the pancreas. AT dysfunction in obesity results in insufficient suppression of lipolysis and impaired lipid storage capacity, altogether contributing to the increased pancreatic FA influx of obese individuals.

Not all fat is bad

Body fat distribution, more than total body fat, is associated with the risk for glucose metabolism disruption. Classically, AT is divided into subcutaneous white AT (scWAT), which physiologically constitutes about 80% of all body fat, and visceral white AT (vWAT), which accounts for up to 10–20% of total fat in men and 5–8% in women. It increases with age (Ibrahim 2010). scWAT is located predominantly in the femorogluteal regions, while vWAT is in the abdominal cavity around internal organs. These two main body fat depots show significant endocrinological and metabolic differences.

Examination of WAT depots uncovered distinctive features between visceral and subcutaneous ATs. Notably, vWAT displays greater vascularity compared to scWAT, as observed by Villaret *et al.* (2010). Despite this enhanced vascularisation, vWAT exhibits a lower capacity for new vascular sprouting (Gealekman *et al.* 2011). Additionally, vWAT is characterised by increased innervation, a higher presence of inflammatory and immune cells, and a larger proportion of large adipocytes. Furthermore, vWAT pre-adipocytes demonstrate diminished differentiation potential, leading to an elevated percentage of large adipocytes (Skurk *et al.* 2007). vWAT cells exhibit heightened sensitivity to adrenergic stimulation and increased lipolysis (Arner *et al.* 1990, Hellmér *et al.* 1992, Lafontan & Langin 2009). Additionally, vWAT adipocytes are more prone to developing IR (Frayn 2000). Conversely, subcutaneous adipocytes in healthy individuals exhibit a greater propensity for the uptake of triglycerides and FFAs from the circulation, notably postprandially (Mårin *et al.* 1992, Misra & Vikram 2003) It therefore appears that scWAT has a higher storage capacity than vWAT. Besides their capacity to store lipids, the quality of fat stored differs between subcutaneous and visceral depots. Within obese subjects, vWAT is characterised by increased levels of non-essential MUFAs, likely *de novo* lipogenesis end products, and lower levels of the w6 arachidonic acid and w3 FAs such as DPA and DHA when compared to subcutaneous depots (Yew Tan *et al.* 2016, Petrus *et al.* 2017). However, no differences in FA composition were observed between metabolically healthy and unhealthy obese individuals, suggesting that the relative proportion of the depot sizes rather than a change in their intrinsic FA composition is associated with the development of IR (Yew Tan *et al.* 2016).

The secretion of adipokines and cytokines also differs between white adipose tissue depots. scWAT is characterised by a higher release of adiponectin (Drolet *et al.* 2009) and leptin (Van Harmelen *et al.* 1998). On the other hand, vWAT tends to release larger amounts of pro-inflammatory cytokines, such as IL-6 (Fontana *et al.* 2007). Concerning obesity, an increase of one standard deviation in subcutaneous fat mass leads to a 48% reduction in the likelihood of IR, while a one standard deviation increase in vWAT mass results in an 80% increase in the likelihood of IR (McLaughlin *et al.* 2011). In the Jackson Heart Study, while both abdominal vWAT and scWAT volumes were positively correlated with fasting plasma glucose and triglyceride levels, vWAT deposition in the abdomen was most strongly associated with hypertension, T2D, and metabolic syndrome risk (Liu *et al.* 2010). In line with this, Yamazaki *et al.* found that specific body fat distribution phenotype, particularly with the accumulation of AT in the liver, pancreas and the trunk, was associated with an increased incidence of T2D over 6 years of follow-up (Yamazaki *et al.* 2022)

All these data indicate that body fat distribution plays a significant role in diabetes pathogenesis, with upper body fat being closely associated with T2D development.

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Revisiting the non-lipid-mediated crosstalk between the AT and the pancreas

Besides regulating energy storage and release, AT also serves as an endocrine organ releasing pro- and anti-inflammatory adipokines, growth factors, cytokines, chemokines, and miRNAs, also called RNAkines (Ahima & Lazar 2008, Li *et al.* 2024). The secretion pattern of adipokines is dependent on body fat distribution and mass, with obesity being associated with increased production of proinflammatory mediators, such as TNF-alfa, leptin, IL-6, IL-12, IL-18 and the chemokines IL-8 and CCL2/MCP-1, rather than anti-inflammatory adipokines like adiponectin or omentin (Mancuso 2016). Adipokines and inflammation contribute to the crosstalk between AT and pancreatic β cells.

Amongst the adipokines mainly secreted by the adipocytes, leptin and resistin have been associated with impaired β-cell function and T2D, while adiponectin and omentin show beneficial effects. After the clinical evidence suggesting a relationship between circulating leptin levels and islet function (Ahima & Lazar 2008), leptin was the first adipokine associated with direct pancreatic effects. Leptin is a 16-kDa hormone secreted mainly by the adipocytes in the AT (Zhang *et al.* 1994) that regulates food intake at the level of the hypothalamus to maintain body fat stores (Klok *et al.* 2006). In obesity, leptin levels rise substantially as fat mass increases and in the context of leptin resistance, which limits its anorexigenic effects (Klok *et al.* 2006). Some peripheral organs express the leptin receptor, including β cells (Kieffer *et al.* 1996), and its activation triggers the MAPK/ERK pathway (Tanabe *et al.* 1997). High leptin levels have detrimental effects on β cells, inhibiting insulin secretion *in vitro* and *in vivo* and suppressing pre-proinsulin gene expression, further limiting insulin availability (Ahrèn & Larsson 1997, Seufert *et al.* 1999).

Resistin, also known as FIZZ3 or adipose tissue-specific secretory factor (ADSF), is a cysteine-rich polypeptide encoded by the RETN gene and mainly secreted by the adipocytes and to a lower level by leucocytes (Jamaluddin *et al.* 2012). It is believed to have a significant role in developing IR (Heilbronn *et al.* 2004, Menzaghi *et al.* 2006). A recent meta-analysis found that resistin levels were positively correlated with IR in T2D and obese individuals, suggesting its contribution in driving diabetes development (Su *et al.* 2019). Resistin reduces GSIS in pancreatic islets and INS-1E cell lines, but not in BTC-6 or BRIN-BD11 cells (Brown *et al.* 2007, Nakata *et al.* 2007, Sassek *et al.* 2016). It has been proposed that resistin renders β cells insulin resistant, likely through increased SOCS-3 expression and decreased Akt phosphorylation (Nakata *et al.* 2007, Sassek *et al.* 2016). However, resistin is also secreted by pancreatic islet cells, and its expression increases in diabetic patients (Al-Salam *et al.* 2011). Therefore, the contribution of AT-derived resistin in mediating β-cells dysfunction in obesity remains to be validated.

In contrast to leptin or resistin, adiponectin is a unique adipokine whose expression and circulating levels are inversely proportional to adiposity levels (Cnop *et al.* 2003, Ryan & Li 2022). The insulin sensitivity-promoting properties of adiponectin are well-established. Accordingly, adiponectin-deficient mice develop IR (Maeda *et al.* 2002), while adiponectin-overexpressing mice are protected against IR despite being more obese than their littermate controls (Kim *et al.* 2007). Adiponectin's beneficial actions are partially mediated by its capacity to promote healthy recruitment of new adipocytes (i.e. hyperplasia), increasing lipid buffering capacity in the context of obesity (Kim *et al.* 2007). Adiponectin also has direct beneficial effects on pancreas. Adiponectin receptors are expressed in the pancreas, and adiponectin mitigates β-cell loss by neutralising inflammatory and lipotoxic ceramides and diacylglycerols (Ye *et al.* 2015). Regarding omentin, a meta-analysis showed that lowered omentin-1 levels could serve as a biomarker for gestational diabetes mellitus and type 2 diabetes mellitus. However, additional investigations are needed to validate the role of omentin in preventing T2D (Pan *et al.* 2019).

Chronic inflammation of the AT of people with obesity is a well-known hallmark of metabolic disease. Immune dysregulation in AT is characterised by increased infiltration and activation of innate and adaptive immune cells, particularly AT macrophages, constituting up to 40% of all AT cells in obesity. Metabolically-activated AT macrophages are polarised into a pseudo-proinflammatory phenotype, secreting proinflammatory cytokines, such as TNF-α, IL-5, IL-1 and NO, capable of impairing insulin signaling in the AT and indirectly predisposing to diabetes (Kratz *et al.* 2014, Russo & Lumeng 2018). Interestingly, *in vitro* evidence also highlighted the direct detrimental effects of TNF-α on pancreatic-mediated insulin release (Zhang & Kim 1995, Sato *et al.* 2018).

Some obesity-related AT-derived miRNAs are also reported as emerging regulators of pancreatic β-cell function. For example, miR-132, whose levels are decreased in both AT and circulation of people with obesity (Heneghan *et al.* 2011), is beneficial for β-cell proliferation (Mziaut *et al.* 2020). In addition, serum levels of miR-15b and miR-146b were increased in children with obesity and adults with T2D, and overexpression of miR-15b and miR-146b in pancreatic β-cell line MIN6 cells decreased insulin secretion (Cui *et al.* 2018).

AT also secretes extracellular vesicles (EVs). These membrane-bound particles act as vehicles communicating organs and tissues, delivering proteins, mRNAs or miRNAs (Huang-Doran *et al.* 2017) It has been shown that EVs isolated from inflamed rodent and human adipocytes exert detrimental effects on

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pancreatic islets, survival and function, suggesting that EVs represent essential mediators in the AT-pancreas crosstalk (Gesmundo *et al.* 2021).

Finally, recent evidence suggests that basal insulin secretion may not depend solely on glucose levels but also on specific AT signals. In fact, stimulation of β3-adrenergic receptor in the AT induces insulin secretion while reducing blood glucose levels (Grujic *et al.* 1997). Similarly, a preprint recently demonstrated that acute AT-specific inhibition of PI3K activity leads to an increased insulin secretion without increasing glycaemia (Becattini *et al.* 2023). Both models are associated with increased FFA levels. Considering that FFAs alone does not trigger insulin secretion, this data suggests that the AT releases an incretin signal, yet to be discovered, to enhance insulin secretion in the fasted state.

To sum up, AT and the pancreas communicate through an intricated complex of mediators, involving FFAs, lipid mediators, cytokines, EVs, adipokines and miRNAs (Figs. 1 and 2). In the case of AT dysfunction and abnormal distribution, all these signals together directly and indirectly contribute to pancreatic dysregulation and diabetes pathogenesis.

Liver control of pancreatic function

In the attempt to connect AT dysfunction to diabetes pathogenesis and severity, the central role of liver control of lipid and glucose metabolism is worth mentioning. Under physiological conditions, the liver processes large quantities of FAs, but stores only small amounts in the form of TG, with steady-state TG contents of less than 5% (Browning *et al.* 2004, Targher *et al.* 2021). This is because the rates of acquisition of FA by uptake from the plasma and *de novo* synthesis within the liver are balanced by rates of FA oxidation and secretion into plasma as TG-enriched very low-density lipoprotein (VLDL-TAG). The relatively small quantities of TAG stored within the liver are localised in cytoplasmic LDs.

In the case of obesity, when AT expandability is reached, ectopic lipid flux is also increased towards the liver. The increased amount of FA directed to the liver exceeds its capacity to dispose of it, leading to hepatic fat accumulation. Metabolic-associated fatty liver disease (MAFLD) is the pathological hallmark of hepatic lipid deposition. MAFLD spectrum includes histologic features ranging from simple steatosis (MAFL) to steatohepatitis (metabolic-associated steatohepatitis (MASH)) and fibrosis, ultimately leading to cirrhosis (Azzu *et al.* 2020) (Fig. 1). The complex pathogenetic link from AT dysfunction to MAFLD has been extensively reviewed elsewhere (Azzu *et al.* 2020, Lee *et al.* 2023). In this paragraph, we will offer an overview of how the development of MAFLD is connected to diabetes pathogenesis. In fact, MAFLD and T2DM frequently coexist. A large meta-analysis of observational studies from 20 countries has estimated that the global prevalence of MAFLD in people with T2DM is ~56% (Morrison *et al.* 2019). Physiologically, in the fed state, insulin significantly suppresses hepatic glucose production by increasing net hepatic glycogen synthesis and suppressing hepatic gluconeogenesis (Prager *et al.* 1987, Cherrington *et al.* 1998); moreover, insulin is also a potent activator of DNL by activating SREBP-1c (Cherrington *et al.* 1998). When IR develops in the liver, there is a loss of suppression of hepatic glucose production, with subsequent hyperglycaemia and predisposition to diabetes. Despite the lipogenic activity of insulin, in the case of IR, DNL does not decrease but increases because of multiple inputs related to overnutrition able to drive the DNL programme (ChREBP, Mtorc1), leading to further hepatic fat accumulation and MAFLD. Several pathogenetic mechanisms are involved in this vicious circle, such as the increase in hepatic lipotoxic mediators, and in particular DAGs and ceramides, which directly and indirectly drive β-cell dysfunction and diabetes pathogenesis (Chavez & Summers 2012, Gadgil *et al.* 2022, Denimal *et al.* 2023).

Improving AT function to restore pancreas function

Given the relationship between the AT and the pancreas, it is plausible that improving AT function is a valuable option to protect β cells, prevent diabetes development and maintain glucose homeostasis. Moreover, international guidelines for the treatment of diabetes promote obesity management in patients with diabetes and obesity (American Diabetes Association 2018), with lifestyle dietary interventions and metabolic bariatric surgery being able to prevent, control and even reverse diabetes (Diabetes Prevention Program Research Group 2002, Lindström *et al.* 2006, Diabetes Prevention Program Research Group 2009, Hopper *et al.* 2011). In particular, data from the Diabetes Remission Clinical Trial (DIRECT) highlighted that diet-induced weight loss of over 10 kg in people with obesity and T2D was able to decrease liver and pancreatic fat content, as well as plasma TGs. However, subjects who returned to non-diabetic glucose control (responders) had shorter diabetes duration, suggesting that diabetes can be reverted as long as β-cell function is preserved (Taylor *et al.* 2018).

The growing market for oral antidiabetic medications has brought new pharmaceutical strategies targeting obesity and hyperglycaemia based on glucagon-like polypeptide 1 (GLP1) agonists. These molecules, such as liraglutide and semaglutide, are effective for diabetes management and cardiovascular complications. Their effectiveness is reflected by their capacity to reduce body weight, AT inflammation and improve body fat distribution (Wang *et al.* 2023). Moreover, GLP1 agonists have been proven

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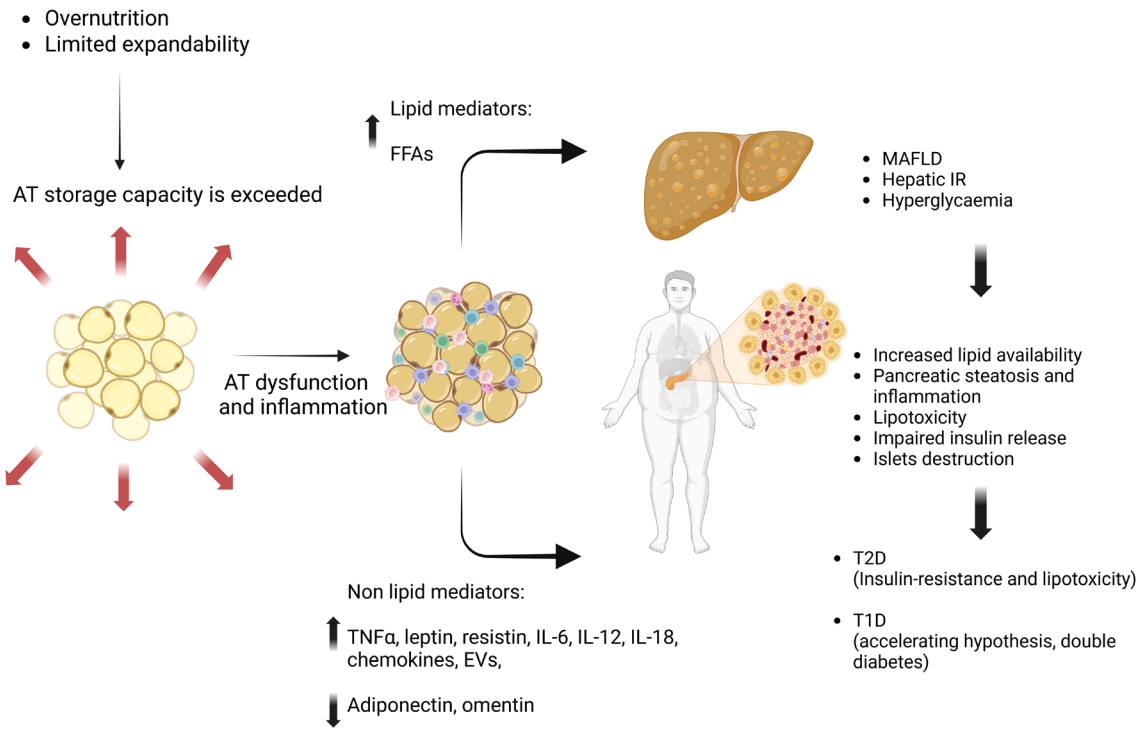

Figure 1

Diagram showing the adipocentric view of diabetes pathogenesis. In excessive energy supply, the expandability of adipose tissue (AT) is exceeded, and AT dysfunction and inflammation occur. The impaired AT sends lipid (free fatty acids) and non-lipid (adipokines, chemokines and EVs) detrimental mediators to the pancreas, leading to increased lipid availability, pancreatic lipid accumulation and inflammation, lipotoxicity, impaired insulin secretion and islet destruction. Moreover, it also leads to liver fat accumulation (MAFLD) and dysfunction, with subsequent hepatic IR and hyperglycaemia. Ultimately, this process evolves into systemic IR and type 2 diabetes pathogenesis. Moreover, it can also accelerate the appearance of T1D and aggravate its disease severity. AT, adipose tissue; EVs, extracellular vesicles; FFAs, free fatty acids; MAFLD, metabolic-associated fatty liver disease; T2D, type 2 diabetes mellitus; T1D, type 1 diabetes mellitus. Created with BioRender.com

to reduce postprandial lipaemia (Hermansen *et al.* 2013, Voukali *et al.* 2014). Pointing in this direction, the newly available antidiabetic medication, Tirzepatide, a glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 dual agonist, shows even more valuable effects on glycaemic control and body weight management (Jastreboff *et al.* 2022). Interestingly, GIP receptors are highly expressed in the AT, where they stimulate fatty acid oxidation and enhance insulin sensitivity (Yip & Wolfe 1999), suggesting that the AT might mediate – at least partially – the effectiveness of this molecule. The SURMOUNT-2 study showed that 72 weeks of treatment with once-weekly Tirzepatide 10 mg or 15 mg resulted in a significant mean weight loss versus placebo of 9.6% and 11.6%, respectively, and a mean reduction of HbA1c from 8% to 5.9%, in 1514 adults with obesity and T2D (Garvey *et al.* 2016). Moreover, a recent phase 1 study on 117 participants showed that tirzepatide treatment compared to semaglutide was able to improve more significantly β cell function, evaluated as amelioration of clamp-derived total insulin secretion rate and insulin sensitivity (Heise *et al.* 2022). These data highlight the significant efficacy of therapies targeting obesity and diabetes and the need to develop new targets and alternative drugs for both conditions.

Improving AT function using thiazolidinediones

Among the antidiabetic medications, synthetic peroxisome proliferator-activated receptor γ (PPARγ) agonists (e.g. thiazolidinediones, TZDs or glitazones) represent the most considerable example of how improving AT function is beneficial for diabetes management. PPARγ, particularly the PPARγ2 isoform, is a nuclear hormone receptor superfamily member highly expressed in the AT, where it is considered the master regulator of adipogenesis and promotes insulin sensitivity, lipogenesis, lipid storage and glucose metabolism (Semple *et al.* 2006). Preclinical studies showed that PPARγ2 is needed to promote healthy AT expansion, promoting redistribution of fat mass towards the scWAT, in mice but is also required for the β-cell expansion adaptive response to IR (Medina-Gomez *et al.* 2007) In line with the critical role of PPARγ in preventing metabolic disorders, epidemiological studies showed that specific polymorphism of the PPARγ gene affect metabolic traits and susceptibility to diabetes (Heikkinen *et al.* 2007). Moreover, a set of mutations in the PPARγ gene is associated with familial

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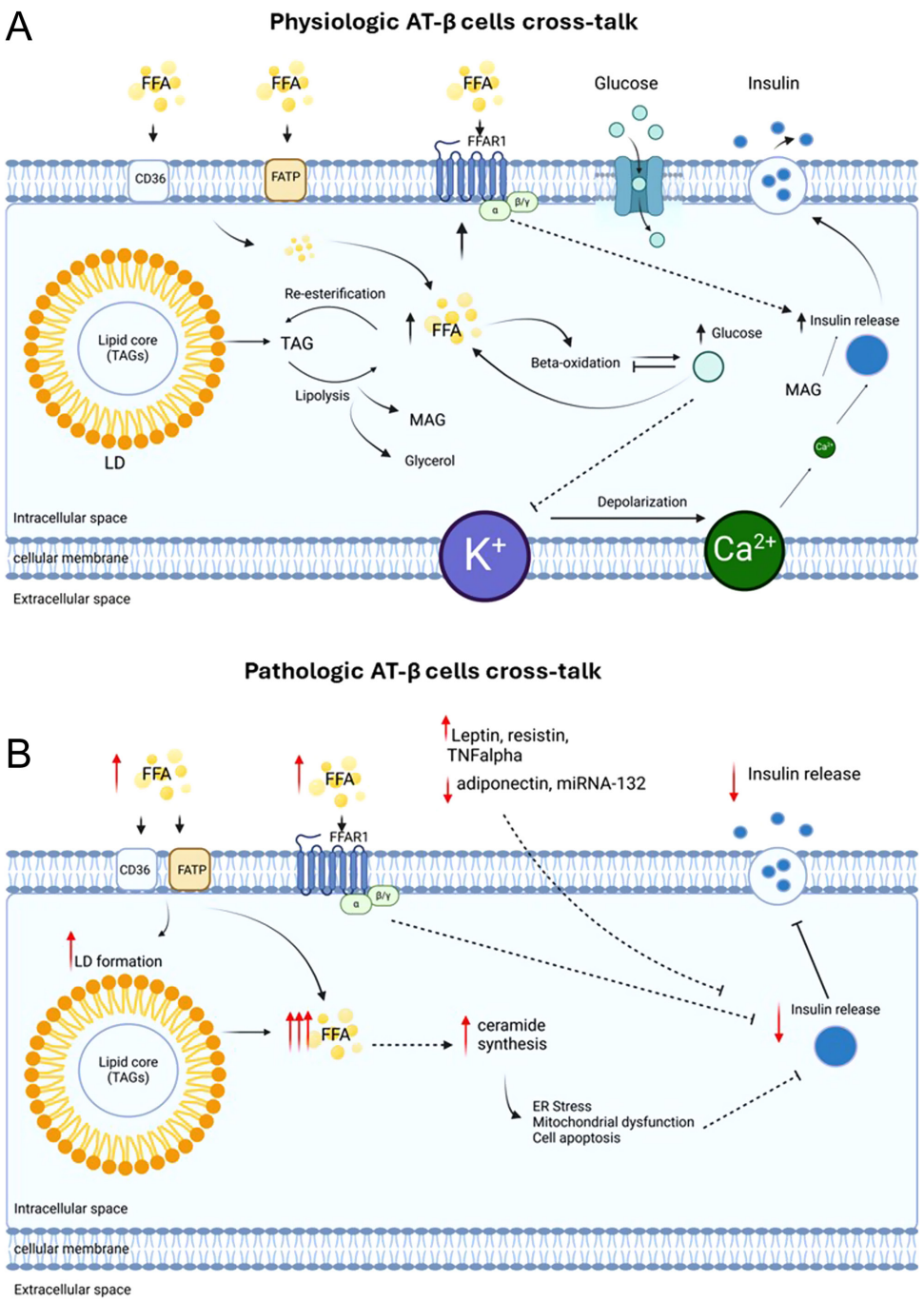

Figure 2

Physiologic (A) and pathologic (B) AT and β-cell crosstalk. (A) In physiologic conditions, a minimal level of FFAs is essential for normal GSIS. The increased intracellular glucose stimulates insulin secretion via closure of K+ channel, determining wave membrane depolarisation and intracellular Ca++ release which ultimately stimulate insulin granules release. At the extracellular level, FFAs stimulate GSIS by activating FFRA1, which increased insulin release. FFAs translocate in the cells facilitated by CD36 and FATP on the plasma membrane. The metabolism of intracellular lipid stimulates GSIS. The increased availability of FFAs contributes to activate FFAR1, β-oxidation and increase intracellular glucose levels, which stimulate insulin release. Moreover, FFAs accumulate in LDs in the form of TAGs. LDs degradation releases MAG and FFAs, which support GSIS as previously described. (B) In pathological conditions, AT dysfunction leads to increased availability of FFAs and non-lipid-mediators, such as leptin, resistin, TNF-α and to decreased levels of adiponectin and miRNA-132. The increased availability of FFAs determines lipotoxicity (ER stress, mitochondrial dysfunction and apoptosis) mainly by increasing *de novo* ceramides synthesis. All these signals together ultimately lead to β-cell dysfunction and insufficient insulin release. AT, adipose tissue; CD36, cluster of differentiation 36; FFAs, free fatty acids; FATP, fatty acid transport protein; FFRA1, free fatty acid receptor 1; GSIS, glucose-stimulated insulin secretion; LDs, lipid droplets; MAG, monoacylglycerol; TAGs, triacylglycerol. Created with BioRender.com

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partial lipodystrophies, characterised by a deficiency of limb and gluteal fat in favour of abdominal and visceral fat supporting its role in the regulation of AT distribution (Garg 2004). Pointing in the same direction, TZDs are currently prescribed worldwide to treat hyperglycaemia and diabetes. The antidiabetic effect of TZDs is traditionally explained by the PPARγ-mediated expansion of subcutaneous AT, resulting in a reduction in systemic lipid concentrations and the subsequent reversal of 'lipotoxicity' in non-adipose tissues, such as pancreatic β cells (Bays *et al.* 2004). Recent estimates of adipogenesis in obese individuals treated with pioglitazone (White *et al.* 2021) confirm earlier morphological observations (McLaughlin *et al.* 2010) that TZDs drive AT expansion by stimulating the adipocyte hyperplasia. As a result of this mode of action, TZDs promote healthy fat mass gain, improving dyslipidaemia, insulin sensitivity and glycaemic control (Kelly *et al.* 1999, Mori *et al.* 1999, Miyazaki *et al.* 2001, Shadid & Jensen 2003), confirming the role of AT expandability in metabolic impairment pathogenesis. Therefore, at least partially, the beneficial action of TZDs can be explained by their increased AT mass and insulin sensitivity, leading to a reduction in AT lipolysis and subsequent lowering of circulating FFA and triglycerides. As a result, the lipid bioavailability for the pancreas is limited, which should reduce pancreatic steatosis.

However, the use of TZDs in clinics has drastically reduced since 2009. Accordingly, rosiglitazone has been removed from the market in several countries (Cohen 2010) following the results of the RECORD trial 2019, showing an increased risk of heart failure and fractures in women (Home *et al.* 2009). A meta-analysis in 2017 confirmed the suspicion that rosiglitazone use was associated with an increased risk of myocardial infarction and cardiovascular death (Nissen & Wolski 2007). The Food and Drug Administration restricted rosiglitazone sales between 2011 and 2013 with a risk evaluation and medications strategy and then allowed its sale again afterwards (U.S. Food and Drug Administration 2015). No such restriction has ever been placed on pioglitazone, leading to glycaemic control amelioration and improvements in HbA1c, insulin sensitivity and lipid profile (Herz *et al.* 2003). As a proof of its particular effectiveness in IR management, evidence supports that pioglitazone was associated with a more significant improvement of insulin sensitivity than DPP4 inhibitors (Bae *et al.* 2019), and a significant improvement of β-cell function assessed by euglycaemic insulin clamp (Gastaldelli *et al.* 2007). However, in the clinical setting, pioglitazone is limited by its adverse effects on heart failure, peripheral oedema and bone fracture risk (Liao *et al.* 2017). In contrast, it is associated with a reduced risk of non-fatal myocardial infarction, stroke, and cardiovascular death (MACE) (Liao *et al.* 2017). Therefore, there is a need to develop new treatments to improve AT function without the cardiovascular side effects associated with TZDs.

Altogether, these data suggest that the AT represents a significant target for diabetes prevention and treatment, mediating, at least in part, the effects of novel and effective antidiabetic medications. This further proves the importance of AT health and expandability in lipotoxicity and β-cell impairment.

Adipose tissue dysfunction is also significant in autoimmune diabetes

Although T1D is traditionally considered a disease of lean people, overweight and obesity are becoming increasingly more common in individuals with T1D, defining a new phenotype of patients with T1D, often referred to as 'double diabetes' which is characterised by a mixture of T1D and T2D (Khawandanah 2019). The prevalence of obesity among patients with T1D has been reported to be between 2.8% and 37.1% (Merger *et al.* 2016, Mishra *et al.* 2018), representing an emerging clinical issue about which our knowledge is still poor.

Whereas T1D is caused by autoimmune β-cell destruction, which leads to absolute insulin deficiency, with insulin treatment classically needed from the onset of the disease, AT dysfunction might influence and amplify the pathogenesis and severity of T1D. It has been suggested that there is a likely association between higher birthweight, childhood obesity and higher BMI with an increased risk of childhood-onset T1D (Betts *et al.* 2005, Verbeeten *et al.* 2011, Wilkin 2009). A retrospective study on 168 people presenting with T1D showed that both pre-onset and post-diagnosis BMI were inversely correlated with age at onset (Betts *et al.* 2005), and a meta-analysis of four studies confirmed the association between obesity and development of T1D (Verbeeten *et al.* 2011). One hypothesis to explain this paradoxical finding is the 'accelerator hypothesis', according to which obesity and lipotoxicity impose more stress on β-cells, making them more vulnerable to earlier and stronger autoimmune destruction (Wilkin 2009).

Beyond being implicated in the earlier appearance of the disease, AT dysfunction is a risk factor for T1D severity. Patients with double diabetes are characterised by the presence of higher IR and requirements, greater cardiometabolic risk and an enhanced risk of developing chronic complications, such as dyslipidaemia, hypertension, atherosclerosis and heart failure (Kietsiriroje *et al.* 2019, Van der Schueren *et al.* 2021). Moreover, obesity represents a risk factor for worse glycaemic control in T1D (Wing & Cleary 1988).

Even though it is reasonable that targeting AT might benefit T1D, no specific guidelines are available for treating obesity and T1D. Lifestyle modifications classically recommended in patients with obesity represent a significant challenge in the clinical routine

management of patients with T1D, given the difficulties in managing hypocaloric diets and physical activity in insulin-dependent patients. Moreover, data evaluating drugs targeting AT in patients with T1D are still limited but suggest that these patients may benefit from pharmaceutical interventions targeting AT. For example, the REMOVAL study showed that the use of metformin as an adjunct therapy in T1D led to modest weight loss (Petrie *et al.* 2017); the ADJUNT studies reported that liraglutide could lead to a dose-dependent weight loss in people with T1D, however, accompanied by a slight increase in severe hypoglycaemia (Ghanim *et al.* 2020, Mathieu *et al.* 2016); noteworthy, a recent small case series showed that semaglutide treatment in early T1D was able to eliminate prandial insulin administration need and basal insulin in most patients, suggesting its potential role in delaying pancreatic β cells destruction (Dandona *et al.* 2023). Finally, pramlintide, a synthetic analogue of human amylin, is the only FDA-approved therapy for T1D (Childs 2006), and it has been shown to reduce HbA1c, daily insulin doses, and postprandial glucose concentrations, with a concomitant modest effect on body weight (Ratner *et al.* 2004).

Given the increasing overlap between obesity and T1D, scientific attention should be devoted to understanding the relationship between AT dysfunction and T1D pathogenesis and severity to offer a more personalised and targeted approach to this particular category of frail patients.

Conclusion

Obesity and diabetes represent two increasing and invalidating chronic diseases that often coexist. The increasing prevalence of obesity worldwide is closely associated with a similar dramatic trend in the incidence of diabetes (GBD 2021 Diabetes Collaborators 2023), and obesity is widely recognised as a predisposing factor for T2D (Klein *et al.* 2022).

In this review, we approach the development of β-cell dysfunction and diabetes from an adipocentric point of view, as summarised in Fig. 1. Considering the well-described deleterious effect of chronic exposure to high levels of FA on β-cell dysfunction, we believe that limiting lipid supply to the pancreas by improving AT function offers a valuable and effective target to prevent, control and reverse diabetes itself, being relevant not only in type 2 but also in type 1 diabetes mellitus.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

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