Pathogenesis and remission of type 2 diabetes: what has the twin cycle hypothesis taught us?

Ahmad Al-Mrabeh

Type 2 diabetes has been regarded a complex multifactorial disease that lead to serious health complications including high cardiovascular risks. The twin cycle hypothesis postulated that both hepatic insulin resistance and dysfunction rather than death of beta (β) cell determine diabetes onset. Several studies were carried out to test this hypothesis, and all demonstrated that chronic excess calorie intake and ectopic fat accumulation within the liver and pancreas are fundamental to the development of this disease. However, these recent research advances cannot determine the exact cause of this disease. In this review, the major factors that contribute to the pathogenesis and remission of type 2 diabetes will be outlined. Importantly, the effect of disordered lipid metabolism, characterized by altered hepatic triglyceride export will be discussed. Additionally, the observed changes in pancreas morphology in type 2 diabetes will be highlighted and discussed in relation to β cell function. *Cardiovasc Endocrinol Metab* 9: 132–142

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Magnetic Resonance Centre, Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK

Correspondence to Ahmad Al-Mrabeh, PhD, Faculty of Medical Sciences, Newcastle Magnetic Resonance Centre, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, UK
E-mail: ahmad.al-mrabeh2@ncl.ac.uk

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Introduction

Type 2 diabetes (T2DM) has become a global concern. According to the WHO and International Diabetes Federation reports, 425 million of the world population have diabetes, and this is expected to double in the next few decades due to the large number of people at prediabetes stage [1,2]. These figures are alarming, and would place a major burden on national health systems across world. In the UK alone, there are 3.8 million people diagnosed with diabetes, and T2DM is currently costing 10% of the National Health System budget [3].

T2DM is a slow onset disease that develops over many years of insulin resistance and progressive decline of β-cell function [4]. Despite contribution of genetic and environmental factors [5], metabolic factors are critical in determining the onset of T2DM. Excess calorie intake over many years is the factor that triggers ectopic fat storage and subsequent derangement in lipid metabolism. The latter will lead to a number of cellular processes that limit hepatic responsiveness to insulin function and decreased β-cell function. In the early years of disease development, blood glucose levels remain normal due to the high compensatory ability of the β-cell to encounter insulin resistance. Hence, it is unlikely that high glucose is the initiating factor of β-cell damage. Eventually, the continued fat-driven impairment of β-cell function will lead to the development of T2DM when approximately 40–60% of β-cell functional mass is lost [6–8].

For many years, T2DM has been considered a chronic disease, which is inevitably progressive. However, a series of studies – Counterpoint, Counterbalance and the Diabetes Remission Clinical Trial (DiRECT) – have changed this view. It has been demonstrated that long-term remission of T2DM is achievable via effective diet-induced weight loss [9–12]. The underlying pathophysiologic mechanisms that determine diabetes development are now broadly understood. The twin cycle hypothesis was published in 2008 to predict the aetiology and pathophysiology of T2DM development and reversal [13]. This was tested in several studies [9,10], and all emphasized the role of excess fat within the liver and pancreas on the pathogenesis of this disease [9,10,14]. DiRECT has clearly demonstrated that remission of T2DM is feasible and durable by dietary weight loss in the routine primary care environment [11,12]. In addition, the mechanistic studies of DiRECT confirmed and extended our previous observations related to T2DM development. It has been confirmed that a decrease in both hepatic and intrapancreatic fat is a prerequisite for diabetes remission provided that β-cell ability to recover after removal of this metabolic burden is retained [15]. Recently, the central importance of hepatic lipoprotein export on intrapancreatic fat accumulation and β-cell function was shown to be associated with both remission and redevelopment of T2DM [16]. Moreover, re-emergence of diabetes was related to increased enrichment of palmitic acid within the lipoproteins exported from the liver. This is important as palmitic acid is the obligatory product of de-novo lipogenesis (DNL) and the most toxic fatty acid to the β-cell. Further work is needed to understand the disordered lipoprotein and lipid metabolism in

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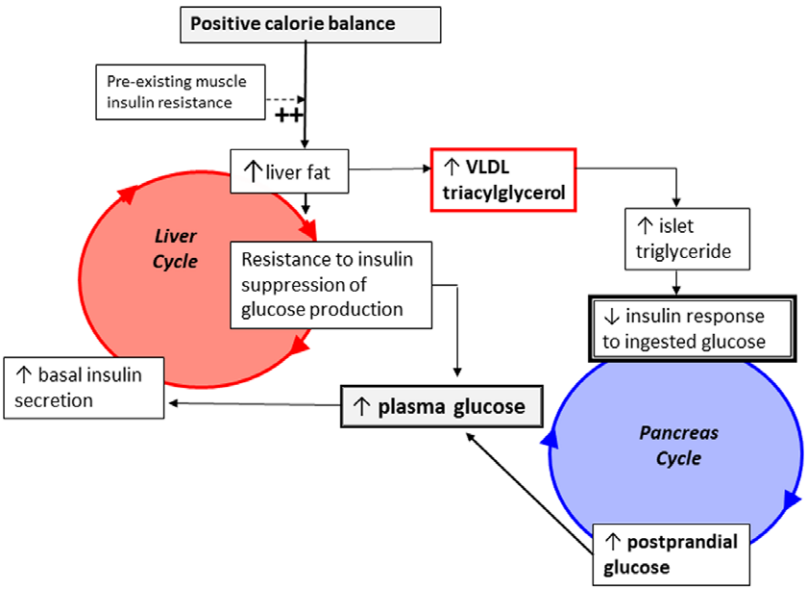
T2DM, especially in view of the increased risk of cardiovascular diseases. Many questions remain to be answered about lipid species, and fatty acid intermediates associated T2DM development and their relation to cardiovascular risks [17,18].

In this review, the pathogenesis of T2DM will be discussed from the perspective of the twin cycle hypothesis and its related studies. The disordered lipid metabolism related to the change in hepatic lipoprotein metabolism will be explained. Specifically, the effect of toxic lipid metabolites on β-cell function in respect to both diabetes development and remission will be discussed. Furthermore, our observations about abnormal pancreas morphology in T2DM and potential effects on the pathogenesis of this disease will be highlighted.

The twin cycle

It is over a decade since the twin cycle hypothesis, describing the route for reversibility of T2DM, was postulated [13]. It hypothesized that excess calorie intake over long term will divert excess energy storage towards the liver and other ectopic sites in the form of triglycerides. Excess lipid in the liver will decrease hepatocytes response to insulin leading to hepatic insulin resistance, thereby failing to switch off gluconeogenesis resulting in high plasma glucose and subsequently insulin levels. It was demonstrated that de-novo synthesis of fatty acids contributes largely to hepatic steatosis in human and animal models, and this is largely stimulated by insulin [19,20]. In T2DM, this will initiate the vicious cycle of hyperlipidaemia and hyperglycaemia due to a high basal insulin level. In the early years during T2DM development, β-cells respond to hepatic insulin resistance by increasing insulin secretion, raising the basal insulin level and reinforcing the liver cycle. Under these circumstances, hepatic export of very low-density lipoprotein triglycerides (VLDL-TG) will increase, pushing up the triglyceride level in circulation [21]. Subcutaneous adipose tissue provides a metabolically well tolerated fat storage area, but its capacity for storage is limited to a different extent in different individuals. In the face of increased hepatic VLDL-TG export, a personal fat threshold will be exceeded and ectopic fat accumulation will occur within the pancreas and other tissues [22]. This will initiate the pancreas cycle, whereby toxic fat metabolites will cause β-cell dysfunction in susceptible individuals. This is tolerated at the early stage of disease progress due to the compensatory ability of β-cell. However, when β-cell fail to compensate for increased loss of their functional mass, T2DM will emerge (Fig. 1).

Fig. 1



The twin cycle hypothesis of the aetiology of T2DM. Liver cycle: Prolonged exposure of excess calorie intake under pre-existed muscle insulin resistance will divert energy storage from glycogen storage into adipose tissues through activating de-novo lipogenesis (DNL) pathway. When the maximum subcutaneous fat storage capacity is reached or fat storage within the adipocytes is impaired, the plasma triglycerides level will rise and diverted into the liver. Toxic lipid intermediates from triglycerides and fatty acids metabolism will cause hepatic insulin resistance, which leads to elevated levels of fasting insulin to compensate for insulin resistance. High insulin levels will enhance DNL and enforce the liver cycle. Pancreas cycle: Excess fat accumulation within the liver leads to elevation in hepatic VLDL-TG export to other tissues. This will increase exposure of the pancreas to high triglyceride concentrations, which increase fatty acids uptake and storage within the pancreatic tissues initiating the pancreas cycle. A long-term exposure of fatty acids and related toxic metabolites including high glucose would lead to impairment in β-cell function. β-cell will overcome this stress in early years during diabetes onset by secreting more insulin. However, when 50–60% of β-cell became dysfunctional, β-cell fail to maintain normal blood glucose and T2DM will emerge. High glycaemia associated with high fasting insulinaemia will drive more DNL which will enforce both the liver and pancreas cycles. Adapted with permission from [13]. T2DM, type 2 diabetes; VLDL-TG, very low-density lipoprotein triglycerides.

Liver fat and insulin resistance

The liver is central to regulation of blood glucose through endogenous glucose production. The association between insulin resistance and nonalcoholic fatty liver disease (NAFLD) is well documented [23–26]. Although it is not clear whether NAFLD is a causative factor or a result of insulin resistance, it is widely accepted that both are related to the pathogenesis of T2DM [24,27,28]. Elucidation of the exact mechanism of hepatic insulin resistance has been a major focus for many research groups [27,29,30]. Recent data from animal and human studies highlighted the role of diacylglycerol (DAG) in activation of hepatic protein kinase Cε (PKCε), which impairs insulin signalling [31–33]. In addition, saturated fatty acids also activate toll-like receptor 4 (TLR-4) in the liver and generate ceramides potentially inhibiting insulin signalling [33–35]. However, there are contradicting reports about the role of ceramides in driving insulin resistance in human [36,37].

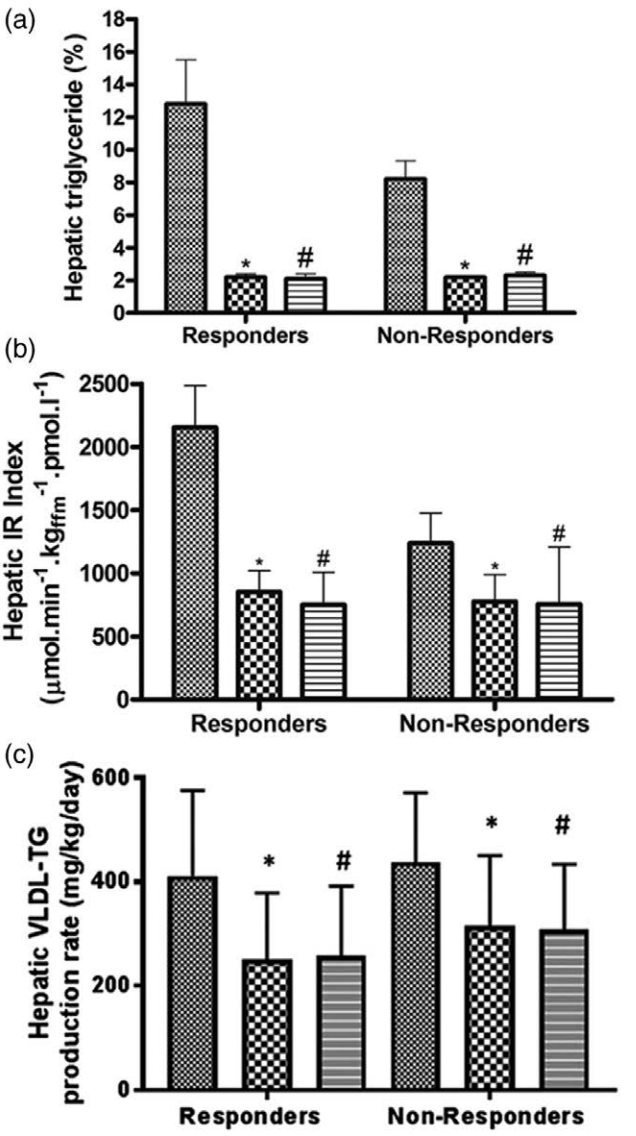
NAFLD is known to increase cardiovascular risks in patients with T2DM [28]. This is likely to be related to a high atherogenic profile associated with altered lipid metabolism. In our studies, almost all people with T2DM have NAFLD at varied degrees, and liver fat was normalized rapidly after weight loss, Fig.2 [9,10,15]. Importantly, this was associated with major decrease in hepatic VLDL-TG export and normalization of hepatic insulin resistance, Fig.2 [10,16].

Polymorphisms in several genes are related to NAFLD; the PNPLA3 gene was reported to be strongly associated with NAFLD [38]. Work is currently ongoing to analyse the effect PNPLA3 polymorphism on lipid metabolism and T2DM remission within DiRECT.

Hepatic triglycerides export and lipoprotein metabolism

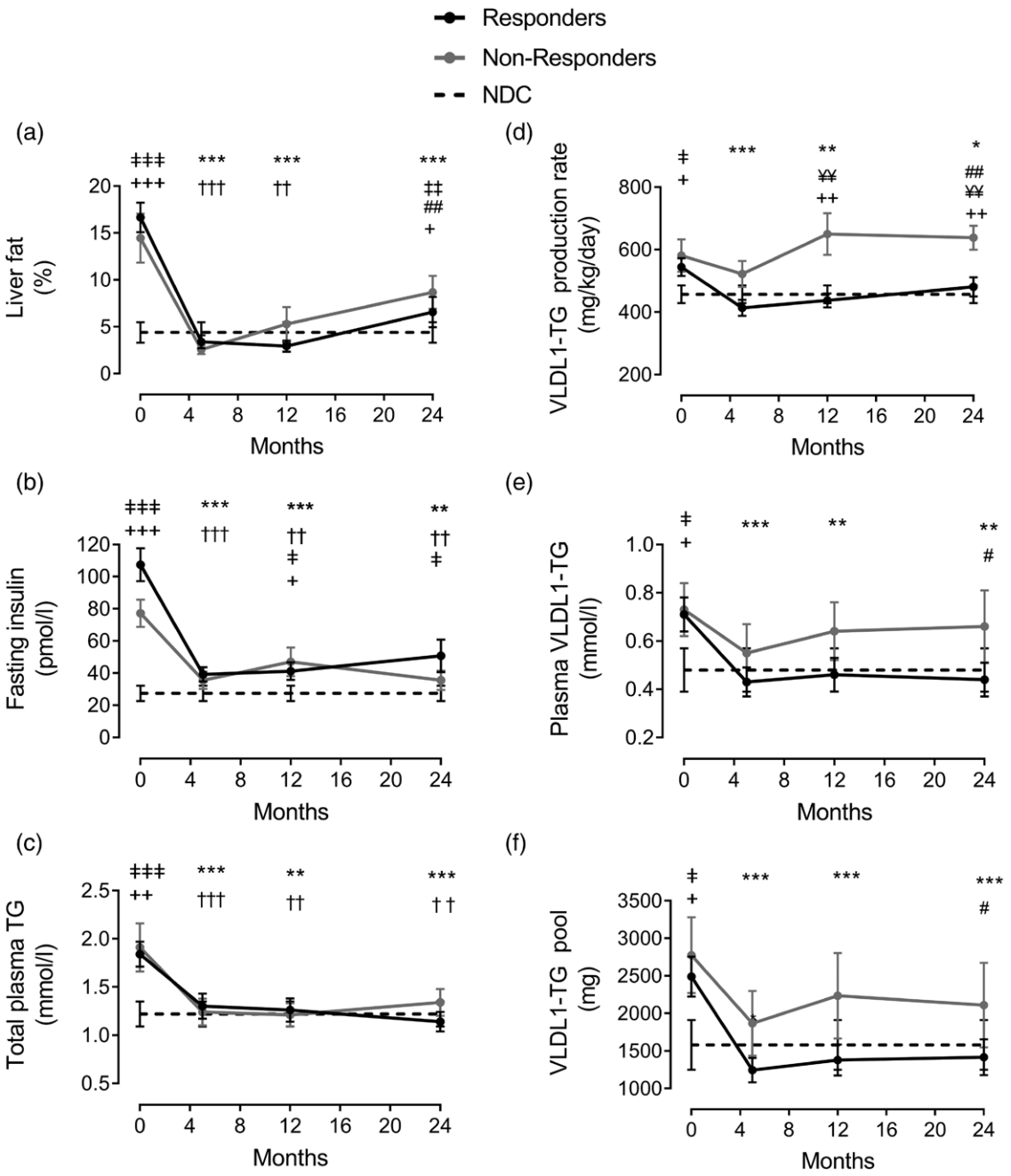
Another major function of the liver is to maintain lipid homeostasis. This is mainly regulated through VLDL-TG export and clearance of other lipoprotein remnants. In T2DM, lipid metabolism is abnormal, and this is a major risk factor for cardiovascular disease (CVD) development [17,18]. Disordered lipid metabolism in T2DM is characterized by overproduction of hepatic VLDL-TG [21]. This in turn is related to the expression of transcription factors that activate lipogenesis genes under elevated levels of glucose and insulin [39]. Free fatty acids derived from adipose tissue lipolysis are the major substrate for VLDL-TG production under fasting condition in healthy individuals. However, in T2DM, the contribution of DNL rises substantially [40,41]. We reported a major fall in hepatic VLDL-TG production after weight loss and this was significant only in those who achieved remission of diabetes, Fig. 3 [15,16]. This decrease was associated with sustained normalization of plasma concentration of plasma total and VLDL-specific triglycerides provided remission was maintained [16]. In those who did not achieve remission, the changes in both VLDL-TG production and plasma VLDL-TG concentration were modest (Fig. 3). On the other hand, loss of remission was associated with major rise in hepatic VLDL-TG production and plasma VLDL-TG concentration (Fig. 4),

Fig. 2



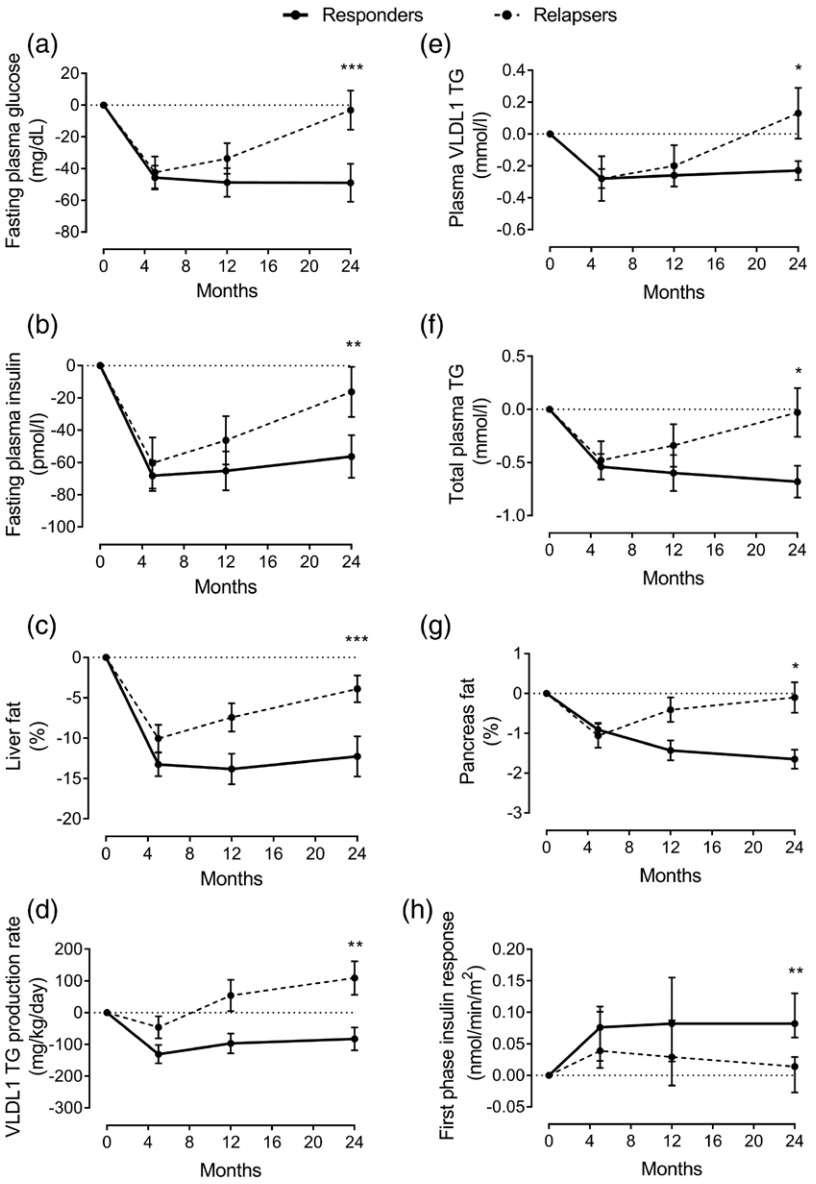
Change in liver fat, hepatic insulin resistance, and VLDL-TG production within the Counterbalance study. Hepatic triglyceride content (a), hepatic insulin resistance index (b), and hepatic VLDL1-triglyceride production (c) in those who reversed diabetes (responders: fasting blood glucose <7 mmol/L after return to isocaloric diet) and in those who failed to achieve reverse (nonresponders) at baseline (hatched bars), after VLCD (checkered bars), and after 6 months of weight maintenance (striped bars). *$P<0.05$ for baseline–to–post-VLCD difference; #$P<0.05$ for baseline–to–month 6 difference. Taken from [10], with permission from the American Diabetes Association. IR, insulin resistance; T2DM, type 2 diabetes; VLCD: very low calorie diet; VLDL-TG, very low-density lipoprotein triglycerides.

Fig. 3



Change in lipid parameters after remission of T2DM within the DiRECT study. Liver fat (a), fasting plasma insulin (b), total plasma triglyceride (c), hepatic VLDL1-TG production (d), fasting plasma VLDL1-TG (e), and VLDL1-TG pool (f) at baseline, post weight loss (5, 12, and 24 months). Responders are presented as a solid black line, nonresponders as a solid grey line, and nondiabetic controls (NDC: measured on one occasion) as a dotted line. Data are presented as means ± SEM. Weight loss itself brought about no significant differences between responders and nonresponders at any time point. Responders vs. baseline: **P*<0.05, ***P*<0.01, ****P*<0.001. Nonresponders vs. baseline: †*P*<0.05, ††*P*<0.01, †††*P*<0.001. Responders vs. 5 months: ‡*P*<0.05, ‡‡*P*<0.01. Nonresponders vs. 5 months: #*P*<0.05, ##*P*<0.01; Responders vs. NDC: ǂ*P*<0.05, ǂǂ*P*<0.01, ǂǂǂ*P*<0.001; Nonresponders vs. NDC: +*P*<0.05, ++*P*<0.01, +++*P*<0.001. Responders vs. nonresponders: ¥¥*P*<0.001. Reproduced from [16] with permission from Cell Metabolism. DiRECT, Diabetes Remission Clinical Trial; T2DM, type 2 diabetes; VLDL-TG, very low-density lipoprotein triglycerides. Responders: Those who achieved remission of diabetes: HbA1c<48 mmol/mol (6.5%) and fasting blood glucose <7.0 mmol/l off all anti-diabetes medication.

Fig. 4



β-cell failure in response to change in lipid parameters during re-emergence of T2DM within DiRECT study. Change from baseline in fasting plasma glucose (a), fasting plasma insulin (b), liver fat (c), hepatic VLDL1-TG production (d), fasting plasma VLDL1-TG (e), total plasma triglyceride (f), intrapancreatic fat (g), and β-cell function (h) at 5 months (responders $n=38$; relapsers $n=13$), 12 months ($n=28/n=13$, respectively), and 24 months ($n=20/n=13$, respectively). Responders are presented as a solid black line and relapsers as a dashed line. The dotted line is the gridline at y value=0. Paired data between baseline and each time point are presented. Data are presented as mean ± SEM except for the first phase insulin (median with IQ range) vs. 5 months in relapsers: *$P<0.05$, **$P<0.01$, ***$P<0.001$. Taken from [16], with permission from Cell Metabolism. DiRECT, Diabetes Remission Clinical Trial; T2DM, type 2 diabetes; VLDL-TG, very low-density lipoprotein triglycerides. Responders: Those who achieved remission of diabetes: HbA1c<48 mmol/mol (6.5%) and fasting blood glucose <7.0 mmol/l off all anti-diabetes medication-Relapsers: Those who returned to diabetes state after initial remission.

which suggest a causative effect of VLDL-TG on T2DM development although this work required to be tested in a suitable animal model to prove causality [16].

ApoB and ApoE are two major lipoproteins that regulate VLDL secretion and metabolism. Liver synthesis of ApoB is essential for successful assembly and secretion of VLDL particles, and this could be a regulatory process [42]. In contract, ApoE determines the hepatic uptake of lipoprotein remnants through binding to specific receptors on the hepatocyte. ApoE is therefore critical for clearance of these highly atherogenic lipoprotein species from circulation [43]. We reported that the HDL cholesterol level increased significantly after remission of T2DM [16]. It would be therefore of interest to study

the change in plasma ApoB and ApoE kinetics following remission of diabetes. Moreover, genetic polymorphisms in the ApoE gens were reported to affect lipid metabolism in Alzheimer and CVD [44,45]. The ApoE genotyping study in respect to the pathogenesis of T2DM would be of major relevance to understand lipoprotein and lipid metabolism disorders in T2DM, and this is currently underway for DiRECT study.

Adipose tissue storage

Energy from excess calorie intake has to be stored for future usage. Glycogen synthesis allows storage of glucose in the liver and muscle, and this process is regulated by insulin function [46]. When glycogen stores are filled, excess energy will be diverted as triglycerides into adipocytes, normally located in subcutaneous adipose tissues under the skin. In T2DM, hepatic and muscle insulin resistance will limit glycogen storage and will drive excess energy towards the adipose tissues [47]. Indeed, high levels of glucose and insulin can stimulate transcription factors of lipogenesis, which make this pathway dominant in T2DM [39].

The capacity of subcutaneous adipose storage is limited, and this is determined by several factors including genetics, sex, and age [48–50]. In fact, these are the major factors that determine susceptibility to develop T2DM among individuals [22]. Moreover, inflammation was reported to suppress adipose tissue capacity for expansion [51,52]. There are several alterations in metabolic processes associated with expansion of adipose tissues in T2DM. First, insulin function in suppression of lipolysis would be limited due to insulin resistance in adipose tissues [53,54]. As a result, hepatic VLDL-TG production will rise due to high fatty acids substrate coming from lipolysis of the adipose tissue. Second, excess energy in the form of VLDL-TG will be diverted into circulation to be saved into and around internal body organs [13,21]. Third, high concentrations of saturated fatty acids can elicit inflammatory response [55], which can downregulate the capacity of adipose storage and directing fat to ectopic sites [51]. Finally, metabolism of excess triglycerides within the liver and pancreas will result in toxic lipid metabolites activating cellular process that impairs both hepatocyte and β-cell function [14,15].

In addition to store energy, adipocyte produces several regulatory adipokines that can affect our metabolism [55]. Leptin and adiponectin were reported to have antidiabetic effects through regulation of glucose and fatty acids metabolism [56–58]. Moreover, the plasma-leptin-to-adiponectin ratio is considered a marker of atherogenicity in T2DM and metabolic syndrome [59,60]. In this review, white adipose tissues that compromise the majority of the total body adipose tissues were discussed. However, brown adipose tissues, which are beyond the scope of this review, have important regulatory function on body metabolism [61]. Understanding the biology of these brown adipose tissues and their role in T2DM pathogenesis may permit greater understanding.

Pancreas fat and β-cell function

The concept of fatty pancreas is becoming widely accepted, and this has been reported to be common in most pancreas-related diseases including T2DM, pancreatitis, and pancreatic cancers [15,62,63]. We reported that intrapancreatic fat is elevated in people with T2DM compared with nondiabetic controls and reversal of diabetes has always been associated with a major decrease in pancreas fat and normalization of insulin secretion [9,10,15,16,64,65]. According to the twin cycle hypothesis, excess fat is delivered to the pancreas via hepatic VLDL-TG export [13], and initial studies demonstrated that fall in VLDL-TG export was associated with a gradual decrease in intrapancreatic fat concurrent with the restoration of β-cell function [9,10]. Further studies in DiRECT confirmed those findings, and showed that changes in VLDL-TG production and intrapancreatic fat content to be related to both diabetes reversal and redevelopment, Fig. 4 [15,16]. Furthermore, we have confirmed that a specific enrichment of palmitic acid within the VLDL-TG is likely to drive these processes [16]. The deleterious effect of saturated fatty acids on β-cell function has been known for a long time [66], and several concepts to explain the lipid-induced β-cell damage were proposed including cell apoptosis and cell dedifferentiation [6,67,68]. The exact mechanism that causes β-cell dysfunction remains uncertain [6,7,69–71]. However, β-cell dedifferentiation appears to be the most likely and has become the most widely accepted to explain β-cell failure in T2DM [67,72,73]. It proposes that under metabolic conditions of excess fat and eventually glucose, β-cell is converted to an α-cell phenotype [73,74]. Conclusive data about β-cell dedifferentiation are limited, especially in human studies [73,75]. Recently, two major regulators of β-cell dedifferentiation were reported [76]. Considering the lack of β-cell–specific markers, identification of generic biomarkers for cell stress and differentiation would be useful. In this respect, growth and differentiation factor-15 (GDF-15) and fibroblast growth factor-21(FGF-21) could serve a potential candidates considering reports of their effect on lipid metabolism and nutritional stress in T2DM [77–79]. More work is needed to exclusively determine the factor (s) that cause β-cell dysfunction and recovery in T2DM.

Data from animal and human studies indicate the potential role of saturated fatty acids in inducing endoplasmic reticulum (ER) stress that lead to β-cell dysfunction [80–83]. Recent studies emphasized the role of branched-chain amino acids (BCAAs) in T2DM [84–86]. It has been reported that BCAA stimulates insulin secretion and activates the mTORC1 kinase which is related to β-cell mass and function [87]. mTORC1 is a negative

regulator of autophagy, a process that known to regulate lipid metabolism [88], is reported to be regulated by calorie restriction [89,90]. β-cell autophagy was reported to be abnormal under condition of high lipids, and removing this metabolic stress restored autophagy function [91]. Several cellular mechanisms were proposed to explain β-cell dedifferentiation [75]. Clinical and metabolic studies together with other cellular and animal studies support that the process is driven by fat-induced metabolites that cause ER stress [72,81,82] leading to β-cell dysfunction. Our data confirm that β-cell damage is reversible in the early years after diabetes onset, which supports the theory of β-cell dedifferentiation rather than apoptosis. The process underlying reversal of T2DM is likely to be redifferentiation following removal of the toxic metabolic conditions after weight loss, but this remains to be determined experimentally [14]. It is possible that normalization of autophagy function after decreasing β-cell exposure to palmitic acid might contribute to β-cell redifferentiation.

Pancreas morphology

Despite its central importance to whole body metabolism, the pancreas remains one of the least studied organs. This is largely due to the complex anatomical structural and deep position within the abdomen [92]. In the past 20 years, magnetic resonance techniques have emerged as one of the most useful tools to study this organ [93]. We have successfully developed and employed techniques to study pancreas morphology and fat content in T2DM [9,65,94,95]. We found that pancreas volume is around one-third lower than normal in T2DM and the organ has very irregular borders, present soon after diagnosis and the volume appears to decrease further with increasing duration of diabetes [94,95]. It has not been established whether T2DM develops more readily in those born with a small pancreas or loss of volume is secondary to the disease process. Insulin acts as a potent growth hormone at high concentration such as experienced by parenchymal pancreas tissues by paracrine action after a meal [47,96]. Therefore, lack of local acute insulin secretion in T2DM may explain the decline in pancreas volume. In support of this notion, it was reported that pancreas volume is decreased in people diagnosed with type 1 diabetes, where local insulin secretion is completely absent [97,98]. Restoration of insulin secretion did not bring about any improvement in pancreas volume during the first 6 months after diabetes remission [95]. However, this is expected considering the long-term of insulin deficiency experienced by pancreatic tissues during T2DM onset, which is expected to be around 10 years, and a longer-term fellow-up within DiRECT revealed a significant increase in pancreas volume only in those who achieved return of insulin secretion [99]. It is notable that insulin and insulin like growth factor-1 (IGF-1) receptors share high homology, and insulin can therefore bind to the IGF-1 receptor at low affinity, which explain the trophic effects of insulin at high concentration [100]. It is possible that lack of both IGF-1 and insulin are involved in pancreatic tissue atrophy observed to happen in T2DM. Further work on the change in IGF-1 levels following T2DM remission, and how this could be related to change in pancreas volume is required.

Synthesis of information

The twin cycle hypothesis and evolving studies have changed the perception about T2DM being a long-term progressive disease. The counterpoint study demonstrated remission from T2DM for the first time, and the counterbalance identified the effect of diabetes duration on the likelihood of return to normal blood control [9,10]. Recently, DiRECT extended our previous findings [11,12]. This had changed the clinical guidelines, which now acknowledge and apply definitive weight loss in T2DM management programmes [101]. Understanding the pathophysiological processes that lead to T2DM development and reversal is crucial to control this disease. The twin cycle hypothesis was formulated after prior study of liver metabolism. It outlined the main aetiological features of T2DM and predicted the potential route for reversal [13,102]. Until now, the exact mechanism(s) that explain how T2DM is reversed after weight loss are lacking, but hepatic insulin resistance and β-cell dysfunction have now been shown to be the major determining factors for the pathogenesis of this disease [14]. There is an accumulated body of evidence from clinical and metabolic studies over the past 10-15 years [9,10,15,16] supported by other cellular and animal studies, all emphasized the deleterious effect of lipids on hepatic insulin resistance [29,32,33,103] and β-cell function [80–83].

The lipotoxic effect of fat-derived metabolites on the hepatic insulin resistance is widely accepted. Toxic lipid intermediates were derived from fatty acids metabolism including DAG and ceramides [36,103]. In the pancreas, there are conflicting opinions whether lipotoxicity or glucotoxicty is the cause of β-cell dysfunction in T2DM [69]. It is difficult to rule out the effect of glucose from the effect of fatty acids. However, it is clear that high glucose levels cannot initiate the process. Once T2DM is established, it is likely that both glucose and fatty acids could synergistically add to the metabolic stress and lead to β-cell dysfunction [70,104], and this is more likely at advanced stages during the progress of this disease. However, there has to be an initiating factor for loss of β-cell capacity before diabetes onset. The precise mechanism of fat/glucose-induced damage to the β-cell is not finally established. Apoptosis or cell death can be observed after in-vitro β-cell exposure to saturated fatty acids [66,69,105–107]. However, it has been demonstrated recently that β-cell undergoes dedifferentiation rather than apoptosis under metabolic stress [67,73,75,108,109]. Data derived from diabetes reversal after weight loss support the dedifferentiation concept

and propose that the return of β-cell function can happen through the process of redifferentiation [72].

One of the major predictions of the twin cycle hypothesis is hepatic VLDL-TG being the upstream process to deliver the toxic lipid metabolites to peripheral tissues including the pancreas [13]. We and others have confirmed that hepatic VLDL-TG production is elevated in T2DM [10,13,15,21]. We also found that the change in hepatic VLDL-TG production was associated with both remission and redevelopment of T2DM [10,15,16]. It has been established for many years that prolonged β-cell exposure to saturated fatty acids is harmful [81,105,110]. Palmitic acid is predominately produced during DNL, and incubation of β-cells with relatively low concentration of palmitic acid induced ER stress [81,83,107]. In obesity and T2DM, palmitic acid was reported to initiate the inflammatory response that causes β-cell damage via TLR4-dependent pathway [110,111]. Furthermore, T2DM is associated with raised levels of inflammatory cytokines including interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), and nuclear factor kappa-B (NF-κB) [107,112,113]. Importantly, the palmitic acid content of the exported VLDL-TG was shown to decrease after remission and markedly increase in response to relapse into diabetes [16]. Taken together, these data suggest the important role of hepatic VLDL-TG in delivering toxic lipid metabolites that may initiate harmful cellular process. Further work is required to verify the causality factor of VLDL-TG on β-cell function.

The pancreas is composed of endocrine and exocrine systems, and both systems are required to maintain normal function. We have reported that pancreas morphology is abnormal in T2DM, and this was evident from the time of diagnosis [94,95]. Acinar cell mass reflects the total pancreas volume considering the small contribution of islet and ductal systems (~5%). Clinical and observational studies of the pancreas have naturally focussed on islet function itself, but the relevance of acinar cells to endocrine function has not been considered [114–117]. While intrapancreatic fat was found to increase with long diabetes duration, both β-cell function and pancreas volume were reported to decline [10,95,118] raising the question of possible causative relationships between these variables. In the ZDF rat model of T2DM, fat replacement of the acinar cells developed into fibrosis [119], and advanced fibrosis may lead to destruction of the islets and β-cell dysfunction [116,119–121]. Immunohistochemistry studies of postmortem tissues of pancreas from people with T2DM indicated that loss of β-cell function was associated with acinar cell fibrosis [122]. Plasticity and regeneration of acinar cells are well documented [123–125], and elucidation of the physiological and molecular associations of acinar cell mass regeneration is required. IGF-1 is anabolic and growth factor hormone produced mainly in the liver [126]. If the trophic effect of insulin affects pancreas volume, IGF-1 would be expected to have a greater effect due to its higher growth function ability. This is likely to be achieved in collaboration with insulin considering the affinity between insulin and IGF-1 binding protein [100]. IGF-1 has been reported to decrease in type 1 diabetes, ageing, and T2DM [127–130] where pancreas volume was reported to decline [94,97,118]. Additionally, studies on postmortem pancreas of people with T2DM have shown fibrosis in exocrine tissues associated with decline in β-cell and increase in α-cell mass [122]. Whether this morphometric changes in acinar cells are related or secondary to loss of β-cell function warrants more investigation.

Conclusion

In summary, T2DM can now be viewed as a state of excess liver and intrapancreatic fat content. The underlying pathophysiologic mechanisms that determine diabetes development and remission are partially understood. However, disordered hepatic VLDL-TG export and the associated abnormalities in lipid metabolism during excess calorie intake appear to be central to the pathogenesis of this disease. Further investigations to identify toxic lipid metabolites and the precise in-vivo mechanisms by which they lead to β-cell dysfunction are required. Heterogeneity of T2DM has been overstated and relates largely to individual capacities both for subcutaneous storage of fat and susceptibility to fat-induced β-cell dysfunction. There is major overlap in the basic pathogenesis of both pathogenesis of both CVD and T2DM. Additionally, the relevance of abnormal pancreas morphology to the pathogenesis of T2DM requires more definitive study to identify the factors that cause acinar cell loss and regeneration and how this may affect β-cell function.

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Conflicts of interest

There is no conflict of interest.

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