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The Inseverable Link between Obesity and Glucose Intolerance and How to Break It?

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Abstract

Obesity is defined as an abnormal or excessive fat accumulation that may impair health. It contributes to the majority of type 2 diabetes cases, although not all people with obesity develop diabetes. In this review, we explore the pathophysiology of adipose tissue expansion, the development of insulin resistance and the factors that lead to beta cell dysfunction. Finally, we provide a brief overview of the therapeutic options to treat obesity and type 2 Diabetes.

Keywords: Obesity; Type 2 Diabetes; Insulin Resistance.

1. Definitions

Obesity is defined as an abnormal or excessive fat accumulation that may impair health [1]. In daily clinical practice, a person is considered obese if his or her body mass index (BMI) is more than 30 kg/m², at least in Caucasians [1]. The BMI is calculated by dividing the body mass in kilograms by the square of the body height in meters, and it is used as surrogate measure to classify body weight in relation with body habitus and body composition. A BMI between 18.5 and 25 is accepted as normal, while a BMI between 25 and 30 kg/m² is considered as overweight. From a BMI of 30 kg/m² or more patients are considered obese, and morbidly obese from on a BMI of 40 kg/m² [1].Almost 30 % of the world's population is overweight or obese and this contributes to 75 % of diabetes cases, 50 % of hypertensive disease incidence and 33 % of ischemic heart and stroke disease [1, 2]. Associated with this, the life expectancy of morbidly obese people is reduced by 10 years [3]. Of note is that a BMI of ≥ 40 kg/m² does not necessarily imply the presence of diabetes. For example, in a large multi-ethnic cohort, individuals with a BMI of 40.0–49.9 kg/m² had a relative risk of 9.8 for T2D compared with age-matched controls, but only 12 % effectively developed diabetes [4].

While a high BMI is correlated with increased morbidity and mortality, it is an indirect measure and cannot distinguish between lean and fat tissue. However, abdominal obesity is one of the characteristics of the metabolic syndrome, next to dyslipidemia, glucose intolerance and hypertension. Patients that meet the critieria for metabolic syndrome, have an increased risk to develop diabetes[5] and cardiovascular morbidity and mortality [6].

Type 2 diabetes (T2D) is a progressive disease characterized by a mismatch between insulin sensitivity and production, which leads to a relative insulin deficiency and ultimately to the inability to maintain glucose and lipid homeostasis [7]. The contribution of insulin resistance versus loss of insulin production to the pathophysiology of T2D differs between patients, indicating heterogeneity in the underlying instigators of the disease.

Chronic hyperglycemia and an unfavorable lipid profile cause macrovascular and microvascular complications in patients living with diabetes [8, 9]. Coronary artery disease, peripheral arterial disease, and stroke are the most important macrovascular complications and are responsible for over 70 % of the deaths of patients with diabetes [8, 10]. Microvascular complications, including nephropathy, retinopathy and neuropathy, lead to significant burdens for the patients such as blindness and renal insufficiency requiring dialysis [8].

Today more than 400 million people worldwide suffer from diabetes mellitus and projections indicate a further steep rise resulting by 2040 in a prevalence of around 10 % of the world's population [11]. The vast majority are patients with T2D. Surprisingly, the exact cause of T2D has not been elucidated yet, although it is clear that its prevalence is linked with changes in our eating behavior and the obesity epidemic.

2. Obesity

2.1 Causes of Obesity

Obesity has many causes, some of them related to endocrine disorders such as Cushing's disease or damage to the ventromedial hypothalamus that result in altered food intake and secondary obesity. However, in the current review, we have focused on primary obesity, which has a variable genetic component in almost all cases [11].

Studies of families, twins and adoptees suggest a strong genetic influence on adiposity [12]. Twin studies show that the heritability of obesity ranges between 60 to 90%. In adoptees the BMI correlates with that of their biologic parents rather than with the BMI of their adoptive parents. In addition to the heritability of weight itself, also metabolic rate, thermic response to food, and spontaneous physical activity are heritable [13]. At least 9 loci involved in Mendelian forms of obesity and 58 loci contributing to polygenic obesity have been identified so far, but these loci still explain only a small fraction of the heritability of obesity [14].

Obesity is a feature of many genetic disorders, of which Prader-Willi syndrome and Bardet-Biedl syndrome are the best known [15, 16]. Several single-gene defects that cause obesity have been identified, which are thought to account globally for about 5 % of obesity cases. A defect in the Agouti gene, for instance, caused inhibition of melanocyte-stimulating hormone to bind to receptors in the skin (melanocortin-1 receptor, *Mc1r*) and in the hypothalamus (*Mc4r*), inducing a yellow fur and increased food intake in the Agouti mouse model [17]. Mutations in the gene encoding the *Mc4r* are reported to be the most common monogenic cause of severe obesity in childhood [18]. Absence of the leptin gene (ob/ob mice) or the leptin receptor (db/db mice, Zucker rats) result in hyperphagia, insulin resistance, hyperinsulinemia, and infertility, stressing the importance of leptin as in the negative feedback "adipostatic" signal to brain centers to reduce energy intake [19]. *Wnt10b*, an important negative signaling factor in adipocyte differentiation (see below), was shown to be able to inhibit obesity in both Agouti and ob/ob mice, after which mutation analysis confirmed a non-functioning *WNT10B* allele in a human family affected by obesity [20]. However, this was not confirmed in a recent Belgian study [21].

Large genome wide association studies have identified a multitude of obesity risk genes, some of which overlapping monogenic and polygenic obesity, such as common variants near the *MC4R*[22] and *PCSK1* gene [23]. Another gene that may contribute to common forms of obesity is Brain-derived neurotrophic factor, which plays a role in energy balance [24]. The strongest association with obesity however, has been with the Fat mass and obesity-associated protein (*FTO)* region, and recently Claussnitzer et al. implicated the *FTO* allele in repression of mitochondrial thermogenesis with pronounced pro-obesity effects [25].

Next to genetic polymorphisms that result in individual differences in susceptibility to obesity, the modern lifestyle and environment have been put forward as the main drivers of the current obesity epidemic. Indeed, the combination of availability of cheap and energy dense foods and the lack of physical activity support the hypothesis of a cumulative positive energy balance. Some culprits have been proposed, such as increased portion size [26] increased use of high-fructose corn syrup [27], vending machines [28] and less physical education in schools [29] and a "built environment" dominated by cars and elevators [30], but the list is virtually endless. Several population-wide initiatives and prevention programs, such as television advertising restrictions [31], nutrition labeling [32] and discounting healthy foods have been instated [33], with mostly positive results [34].

In any case, research has revealed that accumulating energy excess in adipose tissue is not the only reason for obesity-related co-morbidities. In fact, several components of the above mentioned Western diet, such as glucose and saturated FFAs can directly influence beta-cell function [35].

2.2 Development of Obesity: Accumulation of Fat

2.2.1 Types and distribution of adipose tissues: There are 2 functionally different types of adipose tissue: brown adipose tissue (BAT) and white adipose tissue (WAT). Accumulating evidence suggests the existence of intermediate "brite" or "beige" fat [36]. BAT plays an important role in energy expenditure and thermogenesis in babies and small mammals. It is composed of multi-loculated adipocytes that contain large numbers of mitochondria, accounting for their brown color. In adult humans, BAT is still present in supraclavicular, paraspinal and adrenal pockets and can be activated by cold exposure [37]. BAT levels and activity are inversely correlated with BMI and conversely loss of BAT activity may be associated with the accumulation of WAT [38].

The excess of WAT is the most obvious characteristic of obesity and the cause of most obesity-related co-morbidities. It consists of adipocytes with unilocolar lipid droplets and is the main site of excess energy storage, in the form of TGs. Furthermore, WAT is also important as an endocrine tissue, secreting adipokines, such as leptin and adiponectin [39].

In recent years, beige adipocytes were found in subcutaneous and visceral WAT depots [36]. These WAT cells can be induced to express Uncoupling protein 1 (UCP1) by prolonged exposure to cold, beta-adrenergic agonists, or the PPARγ agonist rosiglitazone [40]. Secreted protein named fibronectin type III domain-containing 5 (FNDC5) was found to be expressed in skeletal muscle and can be induced by exercise or Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α) overexpression. A cleaved form of FNDC5 called irisin is secreted into the bloodstream after exercise in both mice and humans and can stimulate beige cell function [41].

WAT is characterized by flexibility and plasticity to adapt to changes in positive energy balance in times of nutrient excess or negative energy balance when the expenditure is higher than the supply of energy. Having a large percentage of fat is not necessarily detrimental to an animal's health, as it can be an asset to survive in harsh environments, e.g. for polar bear and seals [42]. The modern rise in human obesity however, results from an almost unlimited supply in energy, while our sedentary lifestyle decreases the energy expenditure, thus creating a long-term positive energy (dys)-balance. Although in humans the threshold for tolerable fat differs among individuals, due to environmental and genetic variables, a massive increase in adipose tissue that is generally harmful to health [42]. Normal adipogenesis in WAT starts with commitment of multipotentmesenchymal stem cells to preadipocytes, mediated by stiffness of the extracellular matrix and a pro-adipogenicWnt profile, with low WNT10b, WNT5A and lipoprotein receptor-related protein 6 (LRP6) levels [43, 44]. A sequence of transcription factors, including CCAAT/enhancer binding protein (C/EBP) β, C/EBP-δ, CEBP-α, PPARγ, the non-canonical WNT5B but also glucocorticoids and insulin, can than result in terminal differentiation to mature white adipocytes [45]. Upon prolonged cold exposure or β-adrenergic signaling, these white adipocytes can obtain characteristics of BAT, such as expression of UCP1 [46]. Development of BAT on the other hand, resembles more closely skeletal muscle, as the progenitor cells express the early muscle marker myogenic factor 5 [47, 48].

In 1956, Vague reported the relation between fat distribution and the risk of cardiovascular pathology [49]. In android obesity, as seen typically in males, the fat will accumulate the abdominal region, infiltrating the viscera. This form is strongly associated with metabolic dysregulation, diabetes, gout and nefrolithiasis. In contrast to gynoid obesity, with primary fat accumulation in the subcutaneous gluteal and femoral areas, as is typical in females. The latter form results mostly in mechanical problems, including osteoarthritis, reduced venous and lymphatic circulation and congestive heart failure. The macroscopic difference between the 2 forms, can be explained largely by the fact that visceral fat is characterized by larger cell size and more secretion of pathogenic adipocytokines [50].

In addition to storage of energy, adipose tissue functions as a large endocrine organ, by secreting a variety of adipokines or adipocytokines that act in autocrine, paracrine and systemic ways. Here, we discuss the 3 that are most relevant because of their adipocyte specificity or implication in the metabolic syndrome.

Leptin is synthesized in and secreted from adipocytes and functions as a vital signal of existing energy deposits to its receptors in the ventromedial nucleus of the hypothalamus. Leptin levels directly reflect the adipose mass, leading to reduced food intake and increased energy expenditure. Most obese individuals however, are leptin resistant [51]. Furthermore, leptin has been shown to exert peripheral actions in blood pressure regulation [52], bone development [53] and immune function [54], including activation of hepatic stellate cells and stimulation of pro-fibrogenic cytokines in the development of non-alcoholic steatohepatitis [55].

Adiponectin is a protein produced exclusively by adipocytes, which enhances the insulin signals in muscle and liver tissue by enhancing beta-oxidation through its receptors AdipoR1 and AdipoR2, respectively [56]. Moreover, adiponectin activates glucose uptake by skeletal muscle and has anti-inflammatory actions by decreasing tumor necrosis factor alpha (TNF-α) synthesis and macrophage migration [56]. As suspected, adiponectin is negatively related to adipocyte size and risk of T2D [57].

Plasminogen activator inhibitor-1 (PAI-1) is a protein that inhibits tissue-type plasminogen activator in plasma and thus promotes thrombus formation, which explains its involvement in cardiovascular disease [58]. It is primarily produced in the liver, but also in adipose tissue, which is its main source in obesity. PAI-1 production is stimulated by insulin and corticoids and its expression is regulated by PPAR [58].

2.2.2 Adipose tissue expansion and resulting inflammation: When storing excess energy, the WAT expands by hypertrophy and hyperplasia [59, 60]. Accumulation of TAG results in increased adipocyte volume and when cell size approaches a critical boundary of about 80-100 µm diameter, insulin-dependent glucose and fatty acid transport is lost [61]. This is unlikely to be a direct cause of systemic insulin resistance since WAT takes up only a minimal portion of ingested glucose [62, 63]. However, a reduced postprandial lipid storage capacity of a terminally enlarged adipocyte, together with an increased rate of lipolysis in the fasting period [64], results in increased presentation of FFA to pancreas, liver and muscle, which contributes to the development of insulin resistance in those tissues (see below).

Ferrannini et al. [65] reported that an acute increase of FFA concentration reduced glucose uptake in hyperinsulinemic individuals, irrespective of glycemia [65]. However, when hyperglycaemia exists in the context of hypoinsulinaemia and hyperglucagonaemia, as in T2D, FFA infusion did not affect glucose uptake, but stimulated its production, suggesting that excess of lipids in the bloodstream can contribute to hyperglycaemia due to glucose synthesis [65]. Furthermore, FFA may contribute to beta-cell dysfunction, as evidenced by increased TAG uptake and decreased insulin secretion rate in islets after palmitate exposure [66].

A further increase in adipocyte size above 100 µm diameter can even interfere with the adequacy of the oxygen supply to adipocytes, as evidenced by increased hypoxia induced factor 1α, increased levels of ER stress and decreased adiponectin levels in obese mice [67, 68].

The hypertrophy itself, whether or not reinforced by hypoxia, leads to the release of secretions of inflammatory cytokines, including TNF-α, interleukin (IL)-6,- and IL-1β by the adipocytes [69]. This will trigger a chronic inflammatory reaction, executed and maintained by typical immune cells [69, 70]. Proliferation of pro-inflammatory CD8+ T-cells was seen as early as 2 weeks after the start of high fat diet in mice, while protective CD4+ T-cells and mitigating regulatory T-cells (Treg) decreased [71]. In fact, insulin resistances seems to be inversely correlated to abdominal adipose tissue's Tregs[72]. Further evidence of the pivotal role of T-cell in insulin resistance was given by the observation that insulin resistance could be reversed in diet-induced and ob/ob obese mice by treatment with anti-CD3, a T-cell co-receptor that helps to activate the cytotoxic T-cells [73]. In addition, macrophages are attracted to the adipose tissue by the pro-inflammatory cytokine environment, the immune cell profile and an upregulation of macrophage adaptor molecules, which is promoted by high leptin and low adiponectin levels [74]. Moreover those macrophages exert a M1-phenotype with high TNF-α, high inducible nitric oxide synthase andlow IL-10, which is in contrast to the M2 IL-10 secreting anti-inflammatory macrophages that reside in the adipose tissue of lean mice [75] (Figure 1).

Interestingly, different FFA have differential inflammatory effects. Saturated fatty acids are pro-inflammatory compounds, activating inflammatory signaling in adipocytes, macrophages and hepatocytes [76] through the nuclear factor kappa-light-chain-enhancer of activated B-cells (NFκB) and c-Jun N-terminal kinase (JNK) pathways, but also Toll-like receptor (TLR) 4 and 2 [76]. Omega 3 fatty acids such as docosahexaenoicand eicosapentaenoic acid have beneficial, anti-inflammatory signals, at least in part via the GPR120-signaling pathway [77].

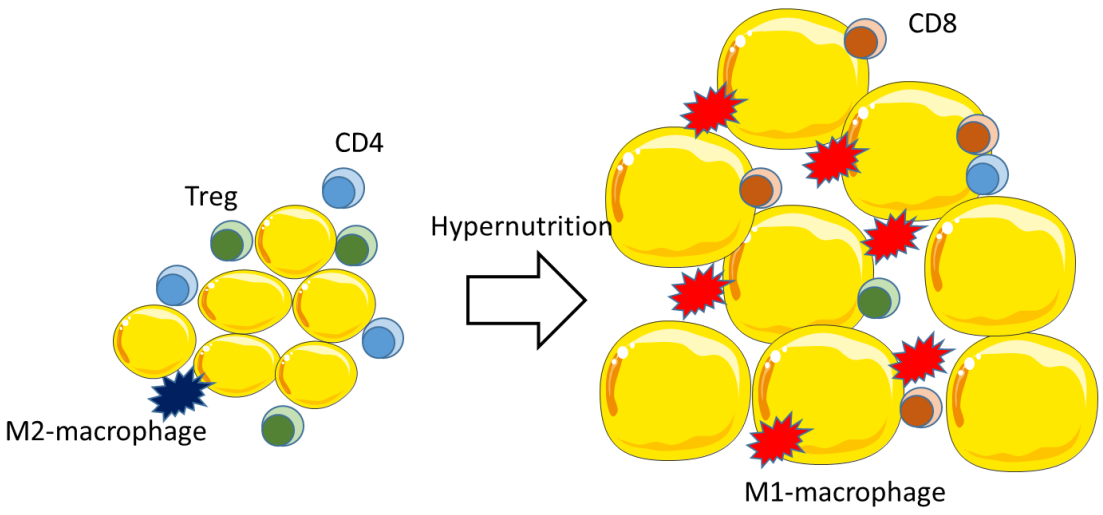

Figure 1: Schematic overview of inflammation that accompanies adipose tissue expansion as a result of chronic hypernutrition. Adapted from (McArdle 2013) [70].

A second way of adipose tissue expansion is hyperplasia. Indeed, high-fat diet feeding increases adipocyte cell size initially, followed by an increase in fat cell number upon prolonged over-nutrition [78, 60]. This is in contrast to the stable white adipocyte numbers in adult humans or animals [59, 79], that are thought to undergo approximately a 10% annual turnover [79]. Preclinical and human studies have shown that weight loss is associated with decreased adipocyte-cell size but has no effect on adipocyte-cell numbers [60, 79].

It has also been shown that treatment with thiazolidinedione (TZD), a PPARy agonist, was associated with an increase in the number of small adipocytes and a decrease in the number of large adipocytes [80]. TZD therapy is associated with increased insulin sensitivity and decreased hepatic and intramyocellular lipid, which supports the hypothesis that decreased adipocyte differentiation is a mechanism through which insulin resistance develops [81].

Interestingly, about 25% of the obese adults remain metabolically healthy [82], with conserved insulin sensitivity and absence of complications such as hypertension, dyslipidemia, or chronic inflammation [83]. In such individuals, the omental adipocytes remain significantly smaller, which is correlated with less hepatic steatosis and insulin resistance [84].

Insulin resistance through excess fat

When first the subcutaneous and later also the omental fat stores struggle to incorporate a relentless stream of excess energy, fat oxidation is decreased, lipolysis is increased, and the FFAs spill over into the circulation. Such increased FFA levels in turn, can cause direct effects on insulin sensitivity or accumulate as ectopic fat deposits in hepatic, muscular and pancreatic tissues [85]. Such an ectopic fat deposition results in insulin resistance in these peripheral tissues, much like in the setting of lipodystrophy syndromes [63].

Insulin resistance in liver

The liver is a major metabolic organ because of its important role in gluconeogenesis and glycogen storage, but also in lipogenesis and cholesterol metabolism. Hepatic insulin resistance is mainly manifested by the reduced ability of insulin to suppress endogenous glucose production [86].

FFAs from the uncontrolled lipolysis in omental fat, together with the inflammatory cytokines, are secreted into the portal vein and directly transported to the liver [63]. Through activation of JNK, FFAs can interfere directly with normal insulin signaling, thus impairing normal suppression of glycogenolysis and gluconeogenesis [87, 88]. Also inflammatory signals from other organs, especially WAT, have been shown to provoke hepatic insulin resistance via JNK and Suppressor Of Cytokine Signaling 3 (SOCS3) interactions [89, 90] (Figure 5).

Moreover, systemic inflammatory cytokines such as TNF-α and IL-6 have also been shown to induce hepatic lipogenesis and increase hepatic triglyceride production, which leads to an increase in very-low-density lipoprotein (VLDL) secretion from the liver and an overall increase in serum triglyceride levels [91, 92].

In turn, such inflammation in the obese liver has been shown to trigger hepatic secretion of inflammatory mediators and acute-phase reactants, including C-reactive protein, PAI-1, serum amyloid A and IL-6 that can induce or amplify adverse metabolic effects, such as reduced insulin sensitivity in peripheral organs [93].

Hepatic TG accumulation itself is termed hepatic steatosis, and its rising prevalence parallels that of T2D and obesity [94]. This form of Nonalcoholic fatty liver disease (NAFLD) is considered benign, but when inflammation manifests it develops to Nonalcoholic steatohepatitis (NASH) and eventually to fibrosis and cirrhosis [95].

Insulin resistance in muscle

Skeletal muscle is the major site of glucose uptake and energy consumption in the body and thus of great importance in glucose homeostasis [96]. Indeed, oxidative disposal of glucose and FFA in muscle are decreased by acute and chronic elevations in plasma FFA [97]. This results in increased oxidative stress that will contribute to muscular insulin resistance through JNK-signaling [98]. In addition, plasma FFAs interact with TLR4 on myocyte membranes [99] and elevated FFAs directly inhibit insulin receptor phosphorylation of IRS1 and subsequent phosphoinositide 3-kinase (PI3K) activity [100]. Combined these changes can result in 50 % decreased insulin-stimulated glucose transport activity, and subsequent glucogen synthesis [101].

However, in skeletal muscle insulin resistance seems to be less caused by macrophage infiltration, which is usually not observed in muscle fibers of obese animals, in contrast to the adjacent adipose tissues that do display increased infiltration compared with lean tissues [102]. Moreover, muscle does not express or release significant amounts of TNF-α or IL-6 in patients with obesity compared to healthy controls [103, 104]. Therefore is not likely to be a source for the rise in inflammatory mediators, although some studies do report an association between TNF-α expression in muscle tissue and impaired insulin sensitivity in humans with obesity [105].

On the other hand, the influence of peripheral inflammation on muscle tissue is well established. Inflammatory cytokines can induce insulin resistance in muscle cells [106, 107], which results in a decreased glucose uptake and glycogen synthesis [108]. It has been proposed that inflammatory cytokines from adipose and liver tissue can act on muscle tissue [93, 106]. Indeed, the TNF-receptor knockout mouse is resistant to the decrease in muscle glucose uptake and insulin resistance in response to TNF-α administration [109], and neutralizing antibodies to TNF-α can increase muscle insulin sensitivity [110]. As in liver, increased levels of IL-6 will activate SOCS3 with subsequent IR signaling impairment [111, 112] (Figure 2).

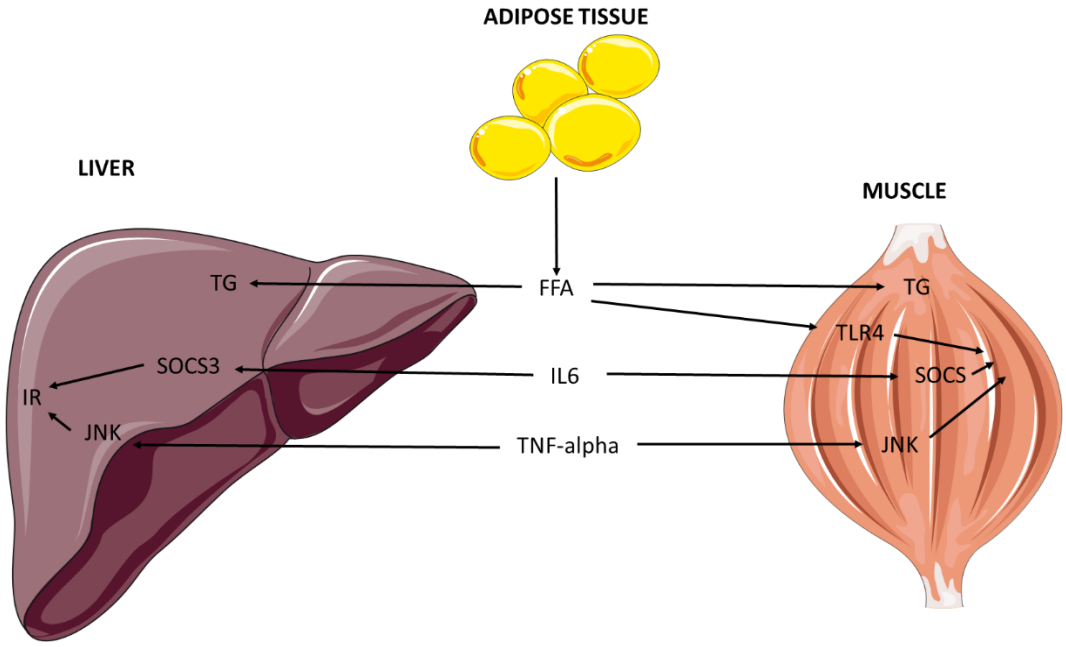

Figure 2: Schematic overview of the activation of inflammatory pathways in liver and skeletal muscle by FFA and cytokines by adipose tissue. FFA free fatty acid IL6 interleukin-6, IR insulin resistance, JNK c-Jun N-terminal kinase, SOCS3 Suppressor of cytokine signaling 3, TG triglycerides TLR4 Toll-like receptor 4, TNF-alpha Tumor necrosis factor alpha. Adapted from Dubois 2015 [112].

Insulin resistance in pancreas

Inflammatory activity in the pancreas results in increased inflammatory cytokine expression and macrophage infiltration, in parallel with the onset of glucose intolerance [113]. The main mediators appear to be IL-1β and IFN-γ, that activate the NFκB pathway [114], but JNK-signaling has also been implicated in protection from apoptosis. Indeed, JNK1-knockout mice are resistant to streptozotocin (STZ)-induced diabetes [115] and expression of a dominant-negative JNK protein in transplanted islets resulted in elevated insulin levels and decreased blood glucose in STZ-treated mice [116]. Actually, a low level inflammation in the pancreas has been hypothesized to promote beta-cell proliferation, and only fulminant inflammation causes apoptosis [117]. The low grade inflammation in obesity could drive islet proliferation and may be essential for adaptation to peripheral insulin resistance.

Insulin resistance in brain

Although not usually classified as a metabolic organ per se, the brain is the site of central regulation of appetite control and energy expenditure. Hypothalamic insulin signaling has been shown to be reduced in a rat model of diabetes [118]. Indeed, a selective decrease of hypothalamic insulin receptor caused increased adiposity and hepatic insulin resistance in rats [119]. Intriguingly, brain insulin action is able to influence hepatic glucose fluxes, as was shown by the inhibition of net hepatic glucose output by arterial cerebral insulin infusion [120]. Conversely, hepatic gluconeogenese was not fully suppressed by restoration of hepatic insulin signaling in insulin receptor knockout mice, further supporting the importance of central insulin signaling in peripheral insulin sensitivity [121].

Again, inflammatory pathways seem to be activated: Rats on a HFD have an increased expression of hypothalamic TNF-α, IL-1β, and IL-6 [122], and brain-specific activation of the inflammatory kinase IKK-β resulted in an increased food intake and body weight along with significant hypothalamic insulin and leptin resistance [123].

Pathogenesis of Type 2 Diabetes

Normal pancreas composition and glucose homeostasis

The pancreas is composed of an exocrine part, which secretes digestive enzymes and fluids, and anendocrine part, the islets of Langerhans, which consist of several cell types that function together tomaintain glucose homeostasis. The hormone-secreting cell types include insulin producing beta-cells, glucagon producing alpha-cells, somatostatin producing delta-cells, ghrelin producing epsilon-cells and pancreatic-polypeptide producing PP-cells [124].

When plasma glucose levels rise, insulin is secreted from beta-cells to promote the uptake of glucose in the liver, skeletal muscle and adipose tissue. In the liver and muscles, insulin stimulates the storage of glucose as glycogen, a multibranched polysaccharide, inhibits the release of free fatty acids (FFA) and stimulates the synthesis of triglycerides (TG) from FFA in adipose tissue [125]. Next to the anabolic effects of insulin, insulin also acts in hypothalamic areas in the brain to promote negative energy balance by reducing food intake,as well as to reduce circulating blood glucose by inhibiting hepatic gluconeogenesis[118, 125]. In the fasting state or during exercise, when blood glucose levels start to fall, the catabolic hormone glucagon is secreted by alpha-cells to increase circulating glucose levels, by promoting glycogenolysis in the liver[126].Postprandial insulin release and glucagon inhibition can be potentiated by gastrointestinal hormones called incretins [127]. Indeed, it has been known for more than 100 years that oral nutrient (glucose) intake leads to a much higher degree of insulin secretion compared with anintravenousisoglycemic glucose infusion [128, 129]. GLP-1 and gastric inhibitory peptide (GIP) are the most important incretins [130, 131]. They also delay gastric emptying [132] and reduce food intake [133], which explains the positive effect of incretinmimetics on weight loss [134, 135]. The incretins have also been shown to have a trophic effect on beta-cell mass in rodents[136]. In addition, a wide range of cardiovascular benefits have been claimed, such as lowering of blood pressure and postprandial lipids [137]. Finally, a reduction in markers of inflammation and oxidative stress have been reported[138]. The incretin effect is blunted in patients with T2D[139].

Causes of type 2 diabetes

The concordance of T2D in monozygotic twins is 70% compared with 20–30% in dizygotic twins [140], indicating that T2D has a strong genetic basis. Furthermore, the lifetime risk for developing T2D is about 40 % in offspring of one parent with T2D and almost 70 % if both parents have diabetes [141]. However, T2D does not follow a simple Mendelian inheritance pattern, but is known to be a polygenic disease, were combinations of simultaneous common DNA sequence variations lead to individual risk profiles. Genome-wide association studies have identified more than 65 genetic variants that increase the risk of type 2 diabetes by 10–30 %[142]. The most studied polymorphisms associated with T2D include *CAPN10*, *TCF7L2*, *PPARG* and *KCNJ11*.

The *CAPN10* gene that encodes calpain 10, a cysteine protease with unknown functions in glucose metabolism, was the first T2D susceptibility gene to be identified through linkage studies, but it has been difficult to replicate the findings afterwards[143]. *TCF7L2* on the other hand, has been confirmed in African, Asian and European populations, although only with a relative risk attribution of 1.4 [144]. *TCF7L2* encodes the transcription factor 7 like 2 protein, a member of the wingless-type MMTV integration site family (Wnt) signaling pathway, that is involved in beta-cell proliferation, survival and insulin secretion [145]. Another T2D risk variant was discovered in the *PPARG* gene, encoding the nuclear receptor peroxisome proliferator-activated receptor (PPAR) γ. An increased risk variant is present in 15 % of the European population, and is associated with increased transcriptional activity, increased insulin sensitivity and protection against T2D [146]. T2D risk variants in *KCJN11*, render the ATP-sensitive potassium (K-ATP) channel less sensitive in the insulin secretion mechanism [147, 148].

Environmental pollutants

Environmental pollutants, including Persistent Organic Pollutants, such as dioxins, polychlorinated biphenyls and tributyltin, as well as other ingested toxins are recognized as harmful for human health, but may also specifically contribute to the failure of the beta-cell [149]. The role of specific toxins remains elusive, and it is unlikely that toxins themselves are responsible for the T2D epidemic. However, toxins could play a role in the progression of the T2D epidemic.

Beta-cell dysfunction in type 2 diabetes

When peripheral insulin resistance is high, beta-cells have to increase insulin secretion to maintain normoglycemia. However, excessive translation of (pre-pro)insulin by ribosomes on the cytosolic surface of the ER results in unfolding or misfolding of protein, which can accumulate in the lumen of the ER, causing “ER stress” [150]. As a defense mechanism, the unfolded protein response (UPR) is initiated by sensors such as protein kinase-like ER kinase (PERK), inositol-requiring enzyme 1 (IRE1) and activating transcription factor (ATF) 6. The UPR aims to restore ER homeostasis by decreasing the translation of proteins through phosphorylation of Eukaryotic Initiation Factor 2 (EIF2) and increasing the amount of chaperones, in particular glucose-regulated protein (GRP) 78, in order to increase the ER folding capacity [151]. Upon severe or prolonged ER stress, however, the UPR will induce apoptosis to eliminate the unhealthy cell.

The pro-apoptotic C/EBP homologous protein (CHOP) is described to play a key role in this UPR-induced beta-cell death [152]. In beta-cells from pancreatic sections obtained from T2D patients, markers for both ER stress and apoptosis were increased as compared to healthy control subjects [153], suggesting that chronic hyperglycemia may deteriorate beta-cell function, at least in part, by generating ER stress.

Another mechanism of chronic hyperglycemic toxicity is by generation of reactive oxygen species (ROS), as the normal route of glycolysis saturates and a fraction is shifted towards alternative pathways [154]. Since the pancreatic islets have very low levels of antioxidant enzymes [155], they are particularly vulnerable to oxidative stress. ROS mostly exert their detrimental effects on beta-cells by impairing mitochondrial function, which is essential in glucose-stimulated insulin secretion [156]. In isolated islets from T2D patients, markers of oxidative stress were significantly higher as compared to healthy controls [157].

Chronically elevated FFA can also hamper beta-cell function, particularly in the presence of elevated glucose levels, which is referred to as glucolipotoxicity[158]. When only either of these substrates is elevated, it is oxidized preferentially, and thus less detrimental to the beta-cell [159]. In normoglycemic conditions, FFA will be coupled to coenzyme A (CoA) to be transported into the mitochondrial matrix by carnitinepalmitoyltransferase (CPT)-1, where FFA oxidation takes place [160]. When glucose levels are elevated, glycolysis will increase, leading to elevated levels of acetyl-CoA which can be converted to malonyl-CoA by acetyl-CoA carboxylase. In turn, malonyl-CoA will inhibit CPT-1, causing a cytoplasmic accumulation of long chain-fatty acid-CoA, which will result in ceramide synthesis [159]. Ceramide is a sphingolipid known to impair insulin signaling and beta-cell survival [161](Figure 3).

Another striking observation in the pancreases of patients with T2D, was the association between beta-cell loss and the occurrence of islet amyloidosis in both humans and similar animal models [162]. It is known that proislet amyloid polypeptide/amylin is co-packaged and co-secreted with insulin as a normal product of the beta-cell, and that only a state of pathological protein synthesis, trafficking and degradation as in T2D results in aggregation and polymerization into fibrils [162].

In addition to pro-inflammatory cytokines secreted from the adipocytes, there is evidence that locally produced IL-1 also plays a role in beta-cell inflammation. Islet exposure to high levels of glucose or FFA results in increased production and release of IL-1[163, 164]. This will bind to the IL-1 receptor which in turn activates the NFκB pathway, amplifying the L-1 production resulting in local inflammation. In addition, IL-1 also increases the local expression of chemokines and adhesion molecules that will allow macrophage infiltration and diminish insulin secretion [165](Figure 6).

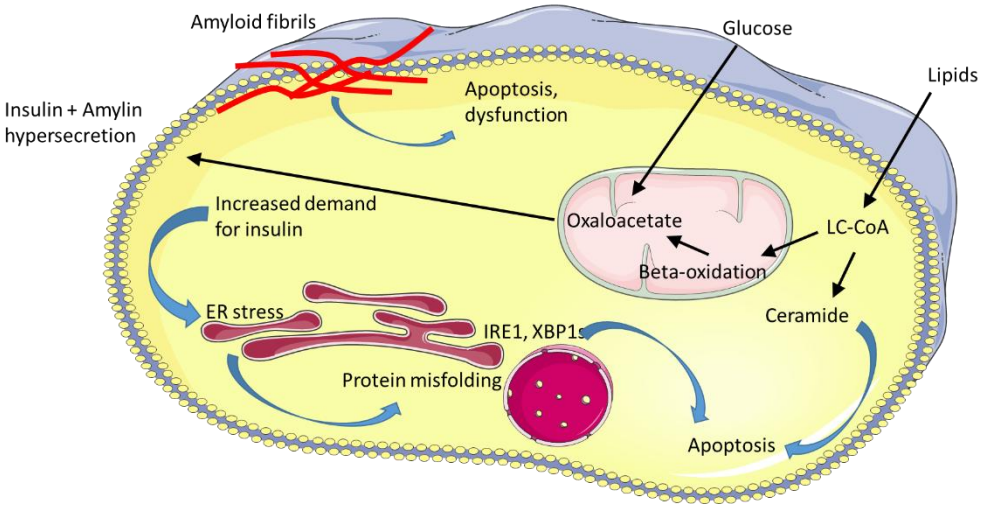

Figure 3: Schematic overview of mechanisms that lead to beta-cell dysfunction. Hypernutrition and increased lipid supply induce enzymes of β-oxidation, upregulation of pyruvate cycling, and finally basal insulin hypersecretion. The high demand for insulin increases the workload in the endoplasmic reticulum (ER), leading to ER stress and increased protein misfolding. ER stress is initially relieved by the unfolded protein response (UPR), mediated by the transcription factor XBP1, but over time, the UPR becomes less effective and leads to cell death, mediated by inositol-requiring enzyme (IRE1). Finally, insulin hypersecretion is accompanied by amylin secretion, which in humans can form amyloid fibrils that accumulate at the surface of beta-cells to induce dysfunction and apoptotic death. LC-CoA, long-chain acyl CoA.Adapted from Muoio&Newgard 2008 [166].

Loss of beta-cell mass

All these mechanisms ultimately result in beta-cell death, mostly by apoptosis or organized cell death [7, 166, 167]. Indeed, isolated islets from T2D patients showed increased caspase 3 and 8 activity [168] and several proteins that are associated with ER stress mediated apoptosis could be observed in human pancreas sections from subjects with T2D [150]. However, also necrosis and dysbalanced autophagy, the non-specific degradation-recycling process for aggregated proteins and damaged components have been reported to contribute to beta-cell loss, and thus contribute to development of T2D [169, 170]. Finally, some evidence suggests that loss of beta-cell mass, does not necessarily result from cell death, but can also be the consequence of dedifferentiation of the beta-cells into alpha-cells or aspecific dormant cells [171].

Reduced beta-cell mass and impaired beta-cell function are main drivers of T2D development, next to reduced insulin sensitivity [172]. In autopsied pancreases from patients with T2D, a 63% decrease in relative beta-cell volume was noted compared to people without diabetes, independent of eventual obesity [173]. Moreover, this study included measurements of 15 obese subjects with impaired fasting glucose in whom the relative beta-cell volume was decreased by 40% when compared to obese subjects without diabetes [173]. Indeed, most studies have shown a 40–60% decrease in beta-cell mass in patients with T2D, particularly compared with pancreata from individuals with normal glucose tolerance of similar body weight or BMI [174 - 176]. These findings correlate well with the United Kingdom Prospective Diabetes Study, which revealed that at the time of diagnosis 40-50% of beta-cell function is already lost, and a further decrease in beta-cell function occurs as the disease progresses [177]. Below we discuss the main pathophysiological mechanisms involved in the development of T2D.

Therapeutic Approaches for Obesity and Type 2 Diabetes

Weight Loss

Even a modest amount of weight loss is associated with improvement of intermediate risk factors for T2D [178, 179]. However, most observational epidemiological studies have indicated that all-cause mortality and cardiovascular mortality are increased after weight loss [180 - 183], even in subjects who were overweight or obese at baseline [182, 184]. This discrepancy is likely due to the inability of such studies to distinguish intentional from unintentional weight loss. Some, but not all epidemiological studies have suggested that intentional weight loss is indeed associated with decreased mortality [185 - 188].

Lifestyle interventions to prevent diabetes have not prevented cardiovascular disease events after more than 10 years of follow-up [189, 190]. Similarly, lifestyle interventions combined with anti-obesity medications, such as rimonabantor sibutramine,have either shown no effect on primary cardiovascular disease endpoints [146] or even an increased incidence in the drug-treated group[191]. Recently, GLP-1-receptor agonists have been approved for weight loss in obese patients with and without T2D, and effects on cardiovascular events look promising, though further confirmation is currently awaited [135, 192].

Caloric restriction remains the cornerstone of most obesity treatments, and while it does produce weight loss, compensatory decreases in energy expenditure and increased hunger signals make it very challenging. As such, the adaptive thermogenesis response refers to the decrease in basal metabolic rate after weight loss [193].Furthermore, a recent study found that weight loss reduced not only leptin and insulin levels, but also decreased peptide YY (PYY) and increased ghrelin levels [194]. These hormonal changes persisted one year after the initial weight loss, and were accompanied by significant increases in appetite [194]. Indeed, the body will unavoidably try to defend body weight [195], as was observed in the classical Minnesota starvation study [196], were the subjects regained more fat mass than their starting point after a loss of 66 % of their initial fat mass. Not surprisingly, weight loss maintenance through caloric restriction is usually not successful[197].

Increasing physical activity increases total energy expenditure, allowing a higher energy intake and requiring less food restriction. In fact, it seems that individuals who succeed in long-term weight loss maintenance actually engage in high amounts of physical activity[198].On the other hand, the lack of success in long-term weight loss maintenance suggests that most people do not succeed in sustaining the degree of behavioral changesnecessaryto keep weight off [197]. From an energy balance point of view, it should be easier to prevent obesity than to reverse it once it is present.

DRUGS

Several anti-obesity medications, such as rimonabant or sibutramine, have either shown no effect on primary cardiovascular disease endpoints [146] or even an increased incidence in the drug-treated group [191]. Currently, some drug options for weight loss are still available, one example is orlistat, which is inhibiting absorption of ingested dietary fat. New approved drugs include lorcaserin, which is a selective 5-HT2C agonist, and phentermine/topiramate combination, which is an appetite suppressor and a anticonvulsant [199]. Their efficacy and longterm effects are to be determined.

Recently, glucagon-like peptide 1 (GLP1) receptor agonists, such as liraglutide and exantide, have been approved for weight loss in obese patients with and without T2D, and effects on cardiovascular events look promising, and further confirmation is expected [135, 192]. Metformin is also frequently used in the treatment of diabetes in combination with obesity, as has been known to reduce insulin resistance and suppress hepatic glucose production. Despite the positive results in weight loss in diabetic patients, metformin is not indicated for the treatment of obesity alone currently [200].

Bariatric surgery

The Swedish Obesity Study (SOS) has shown that bariatric surgery is a powerful tool in the treatment of obesity and its co-morbidities [201]. The SOS was a prospective, non-randomized, intervention trial involving 4047 obese subjects. The outcomes in surgically treated patients (banding (*n*=376), vertical banded gastroplasty (*n*=1369) or gastric bypass (*n*=265)) were compared with those in a matched, conventionally treated control group [202].

Meanwhile, the study has been ongoing for more than 20 years, and it showed that surgery resulted in a maintained weight loss of 30%, while the control group had a slight weight gain (±3%) over the entire observation period [203]. Although the weight loss profile is the same after 20 years as after 10 years, some caution is warranted for interpretation of the 20-year follow-up data, since only a small number of patients remained in the study. Most importantly however, was the risk reduction of bariatric surgery on overall mortality of almost 30 % after 10 years [204], related to a reduced number of fatal and total cardiovascular events and cancer death [203]. Indeed, classical cardiovascular risk factors such as diabetes, hyperlipidemia and hypertension improved or even resolved in the majority of patients after bariatric surgery, with very small operative risk [205].

Historically several bariatric procedures have been developed. The initial Scopinaro procedure was based on malabsorption, which resulted in drastic weight loss, but also important nutritional deficiencies [206]. Later, restrictive procedures such as gastric banding were introduced, but they aregenerally less powerful and achieve less durable weight loss than Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), which are currently the most popular procedures (Figure 4). The success of RYGB and SG procedures is basedon their ability to induce weight loss and improve glycemic control in obese patients with T2D, while the effects of medical therapy, in particular on weight, remain disappointing [207, 208].

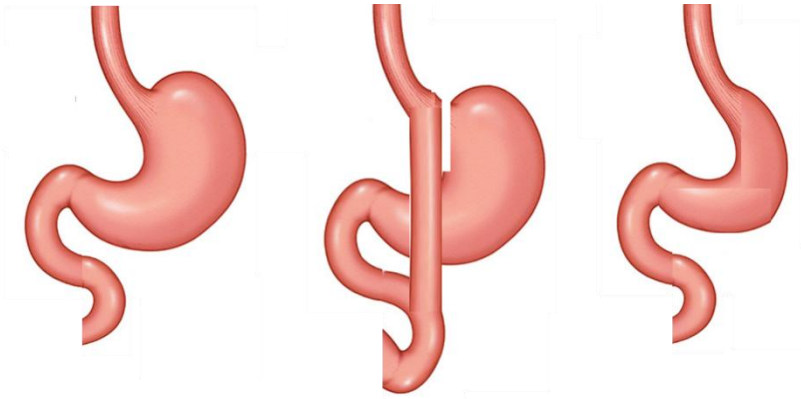

Figure 4: Schematic illustration of normal gastric anatomy (A) Roux-en-Y gastric bypass (B) and Sleeve gastrectomy procedure (C).

Although SG surgery is less complex, we focused on RYGB in this review, since it remains the gold standard andeffects are usually more pronouncedafter RYGB, probably due to additional interference with the gastrointestinal physiology. Next to restriction of food intake through reduced stomach size and altered absorption due to bypass of duodenum, several hormonal changes have been observed after RYGB, though recent research also showed similar changes after SG.

Firstly, a decrease in ghrelin was seen early and 2 years after RYGB [209, 210]. It sounds plausible in view of the reduced hunger and food intake after RYGB, and could be related to reduced central adipose tissue deposition and insulin resistance [211]. However, other researchers have contested changesin ghrelin secretion profile post-RYGB, especially when looking at the active (acylated) form of ghrelin [212, 213]. Second, leptin levels can dropafter RYGB, even before any actual weight loss [214] and RYGB in leptin-deficient mice did not result in sustained weight loss, suggesting that changes in leptin might contribute to sustained weight loss post-RYGB [215]. Similarly, plasma adiponectin is increased post-RYGB, while obese patients with diabetes have low levels [216].

Next to this, secretion of several intestinal compounds is altered after RYGB, of which PYY and GLP-1 are the most interesting. PYY is a 36-amino acid compound released from L-type endocrine cells in the distal ileum and colon, which inhibits appetite centrally and decreases gastric emptying,oro-caecal transit time and small bowel secretions. RYGB appears to restore PYY-response to nutrient intake, while it is blunted in obese patients [217 - 220]. GLP-1 is also secreted from thedistal intestinal L-cells, and mainly functions to potentiate glucosestimulated insulin secretion, inhibit glucagon release and decrease gastric emptying and food intake[221]. Given these physiological actions of GLP-1, the efficacy of GLP-1-mimetics in diabetes treatment and the observation of augmented post-prandial GLP-1 levels immediately after surgery as well as years thereafter [218, 220], a role for GLP-1 in the beneficial effects of RYGB surgery seems reasonable. Some have proposed 'the hindgut hypothesis', which refers to a faster presentation of nutrients to the distal bowel due to the anatomic shortcut [222], while others have presented the 'foregut hypothesis', where exclusion of the duodenum and proximal jejunum may prevent secretion of a putative signal that promotes insulin resistance and T2D [223]. However, a mechanistic role for GLP-1 in the beneficial effects of RYGB are controversial as postprandial GLP-1 levels also rise after SG (without altering the intestinal sequence), and recent studies in rodents showed that glucose metabolism after RYGB is not affected by reduced GLP-1 secretion or GLP-1-receptor deficiency [224, 225].

The afferent neural fibers in the celiac branches appear to develop an increased sensitivity for gut hormones post-RYGB [226]. Combined with stretch-sensitive vagal endings in the new pouch and Roux limb, may modify the feeling of satiety, decrease portion size and result in a preference for less calorie dense foods [227, 228].

The altered secretion of gut hormones might also be influenced by the undiluted bile acids (BA) to the distal bowel. Indeed, increased serum bile acid concentrations are seen after RYGB[229, 230]which could be the trigger for increased postprandial GLP-1 secretion by L-cells through activation of the G protein-coupled receptor 5[231]. In addition, BAs also influence glucose metabolism, possibly via the nuclearfarsenoid-X receptor (FXR)[232] and clearance of TG[233].

Changing the intestinal anatomy in RYGB, also affects the intestinal microbiome, which has been shown to contribute to carbohydrate metabolism and energy homeostasis by fermenting polysaccharides into short-chain fatty acids in the gastrointenstinaltract for example [234]. RYGB reverts the increased Firmicutes to Bacteroidetes ratio that is seen in stool of obese patients [234]. Moreover, transfer of fecal material of RYGB operated mice or patients to non-operated germ-free mice led to a decrease in weight and body fat mass, indicating that alterations in gut flora could contribute to the mechanisms of weight loss after the RYGB procedure[235], probably through decreased utilization of carbohydrates as fuel [236].

While the total resting energy expenditure decreases after RYGB surgery, in line with weight [237], both human and rodent studies have noted an increased postprandial energy expenditure [238, 239], which may further contribute to the long-term maintenance of weight loss. The increased energy expenditure does not seem to be caused by increased browning of adipose tissue [240], although conflicting reports exist [241].

Alterations in eating behaviour and food preferences on the other hand are consistently seen after gastric bypass, and they are likely to cause reduced intake by reduced craving [242] and decreased brain hedonic responses [243 - 246].Apparently, the taste perception is also changed[247], maybe related to decreased in lingual α-gustducin gene expression seen on tongue biopsies[246]. In any case it results in a decreased preference for high-fat diet [248], and increased consumption of proteins and vegetables [249].

The above mentioned mechanisms contribute to weight loss, and thus to reversal of obesity associated metabolic disturbances, including peripheral insulin resistance. Yet, RYGB has been reported to improve glucose homeostasis rapidly after surgery, even before significant weight loss occurs [250]. This claim has to be put in perspective in view of the postoperative caloric restriction diet, which can improve hepatic insulin sensitivity acutely [251]. Several studies have reported similar improvement ininsulin sensitivity and beta-cell function early after RYGB compared to very low-calorie diets [252]. Others observed differences in insulin resistance [253], which has been attributed at least in part to increased incretin levels after bypass [254, 255].

A RYGB-specific improvement in beta-cell function would however fit the postprandial hypoglycemia that is seen in some patients after RYGB [256]. Some small studies reported islet hyperplasia and nesidioblastosis in such subjects [257, 258], but Meier et al.found no increased beta-cell mass in pancreases from 6 patients obtained at partial pancreatectomy for post-RYGB hypoglycemia compared to lean or obese controls [259]. Theoretically, gut hormones could be responsible for altered islet morphology after RYGB, but this requires further study [260, 261].

Assessment of true beta-cell function is difficult,as measurement of insulin secretion and beta-cell function in vivo is complex and not able distinguish between physiological and non-physiological stimuli [262]. For instance, the hyperglycemic clamp typically utilizes sustained supraphysiological and intravenous delivery of glucose, which does not assess the incretin systems, and may not even reflect normal physiology [263].

A particular limitation is caused by "dumping", which is the feeling of nausea after rapid delivery of osmotically and calorically dense carbohydratesto the jejunum/proximal ileum [264]. This automatically limits the ability to use the oral glucose tolerance test, which is usually the standard oral challenge to test beta-cell function in response to a physiological challenge.

Moreover, rapid gastrointestinal transit and consequent rapid absorption of nutrients after RYGB produces large excursions of glucose, which elicit an insulin response that is more dependent on the dynamic component of beta-cell responsivity to glucose that reflects release of preformed insulin secretory granules rather than the static component that reflects synthesis and secretion of insulin in response to a sustained glucose challenge [265].

Moreover, Dutia et al. [266] showed that measures of beta-cell function normalized after RYGB during an oral glucose tolerance test, but not during an isoglycemic intravenous glucose tolerance test, suggesting that it is not the beta-cell function per se, but the orchestrated gastrointestinal effect that is responsible for improved insulin secretion [266].

Whether islet morphology and volume of islets changes, remains unknown, although a few studies report exciting observations of pancreatic hyperplasia, increased Pancreatic and duodenal homeobox 1 (PDX1) and beta-cell mass in Goto-Kakizakirats [267, 268] and pigs [269], others did not see differences in RYGB operated rats and weight matched controls [264]. The inverse relation of diabetes remission post-surgery and the duration of diabetes before surgery further suggests that (functional) beta-cell mass is not restored after RYGB [270].

Conclusion

Sedentary lifestyle and Western diet are the main drivers of the increasing prevalence of obesity. Adipose tissue expansion and subsequent chronic inflammation contribute directly to defective insulin signaling and glucose uptake, resulting in systemic insulin resistance. Type 2 diabetes develops when additional beta-cell dysfunction and loss is induced. Medical treatment options to reverse obesity and related diabetes are currently limited, but bariatric surgery has shown that sustained weight loss and restoration of glucose homeostasis is possible. Further research is warranted to study underlying mechanisms and less invasive treatment options.

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