Obesity and Type 2 Diabetes

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Contents

This chapter separately describes the pathophysiology of type 2 diabetes and that of obesity. The relationship between these two conditions is then discussed, together with practical issues of clinical management.

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Abstract

This chapter separately describes the pathophysiology of type 2 diabetes and that of obesity, and identifies the relationship between these states. The important concept of long-term reversibility of type 2 diabetes is discussed along with the beta-cell dedifferentiation, which explains the insulin secretory defect.

Obesity brings about distinct pathophysiological changes as a consequence of individuals' pattern of food intake and levels of activity. The practical issue of clinical management is considered with particular reference to the weight management goals for type 2 diabetes.

Following therapeutic weight loss in both conditions, long-term avoidance of weight regain is vital and is optimally achieved by a combination of ongoing food energy restriction and daily physical activity.

Keywords

Type 2 Diabetes · Pathophysiology · Twin Cycle Hypothesis · De novo lipogenesis · Obesity · Whitehall II study · Hepatic insulin resistance · Long term reversibility of type 2 Diabetes · Counterpoint study · Counterbalance study · Beta-Cell Dedifferentiation · Beta-Cell reduction · Impairment of insulin secretion · Beta-Cell exhaustion · Desensitization of Beta-Cell · Endoplasmic reticulum (ER) stress · Deposition of amyloid · Muscle insulin resistance · Liver insulin resistance · Intracellular insulin action · Elevation of non-esterified-fatty-acids (NEFA) · Insulin resistance and mitochondrial function · IRS-2 phosphorylation · Physical inactivity · Visceral fat · Ectopic fat · Subcutaneous adipose tissue · Personal fat threshold (PFT) hypothesis · Management of body weight · Diabetes in Remission Clinical Trial (DiRECT) · Type 2 Diabetes dietary management · Dietary management for weight loss · United Kingdom Prospective Diabetes Study (UKPDS) · The Look AHEAD study (Action for Health in Diabetes Study) · Avoidance of weight regain approaches · Exercise · Bariatric Surgery

The Nature of Type 2 Diabetes

Pathophysiology

Over the last two decades, failure of control of liver glucose production as the primary cause of hyperglycemia in type 2 diabetes has gradually became clear (Singhal et al. 2002; Taylor et al. 1996a; Basu et al. 2005; Firth et al. 1986). This underlies both fasting and postprandial homeostasis. Insulin sensitivity of the liver is central to normal control of this process (Ravikumar et al. 2008), and in turn, this is directly regulated by the extent of liver fat accumulation. The relevance of the rising liver enzymes prior to onset of type 2 diabetes can now be fully understood (Sattar et al. 2007). The increasing alanine aminotransferase

reflected the increased liver fat levels. Insight into the potential rapid restoration of normal fasting plasma glucose levels came from the observation that weight loss secondary to gastric banding was the major factor in post-surgical remission of type 2 diabetes (Dixon et al. 2008). The major driver of this was not the method but the degree of weight loss (Dixon et al. 2008). The concept that incretins, postprandial hormones, played a role in post-bariatric surgery normalization of fasting plasma glucose (Guidone et al. 2006) was unlikely on theoretical grounds and has since been shown to be not relevant (Lingvay et al. 2013; Steven et al. 2016a). Pories originally reported that restriction of food intake identical to that enforced after bariatric surgery would normalize blood glucose control (Pories et al. 1995). The observation that this occurs within 7 days of commencing food restriction (Guidone et al. 2006; Henry et al. 1986) set in place the final piece of information for the Twin Cycle Hypothesis to be postulated (Taylor 2008). The hypothesis allows a simplified understanding of type 2 diabetes and is shown diagrammatically in Fig. 1.

The postulates of the Twin Cycle Hypothesis were tested in the Counterpoint study using a very low calorie diet (600 kcal/day for 8 weeks) (Lim et al. 2011a). Within 7 days of withdrawing metformin and initiating negative energy balance, liver fat content had decreased by 30% and liver insulin sensitivity had normalized as had normal fasting plasma glucose. Over 8 weeks, pancreas fat levels decreased and first-phase insulin response increased to within the nondiabetic control range. The degree of muscle insulin resistance did not change significantly after return to normal glucose control.

Further prospective observations supporting the Twin Cycle Hypothesis were obtained from the Whitehall II study. The 13-year trajectories of fasting and postload blood glucose, insulin sensitivity and insulin secretion leading to the diagnosis of diabetes in a large, middle-age, metabolically healthy population clearly show the relatively rapid beta cell decrease in function over the 18 months prior to diagnosis (Fig. 2). Among subjects who developed diabetes, the levels of fasting and postload glucose and insulin secretion 13 years before the diagnosis were higher and insulin sensitivity was lower than those among the group that remained normoglycemic. In the incident diabetes cases, slow linear increases in fasting and postload glucose were followed by a rapid increase prior to diabetes diagnosis (Tabak et al. 2009).

The prognostic value of detecting raised intrahepatic fat levels for development of type 2 diabetes is well established, and normal levels make diabetes unlikely over the following 7 years (Shibata et al. 2007). Reflecting this, elevated ALT was found to be a risk factor for developing type 2 diabetes, independent of obesity, body fat distribution, plasma glucose, lipid, AST, bilirubin concentrations, and family history (Ohlson et al. 1988). In a study of abnormal LFTs and their relationship to clinical findings in 175 unselected diabetic outpatients, the type 2 diabetic patients more frequently had elevated ALT (22% vs. 5.3%) and GGT (23.7% vs. 10.5%) levels than those with type 1 diabetes (Salmela et al. 1984).

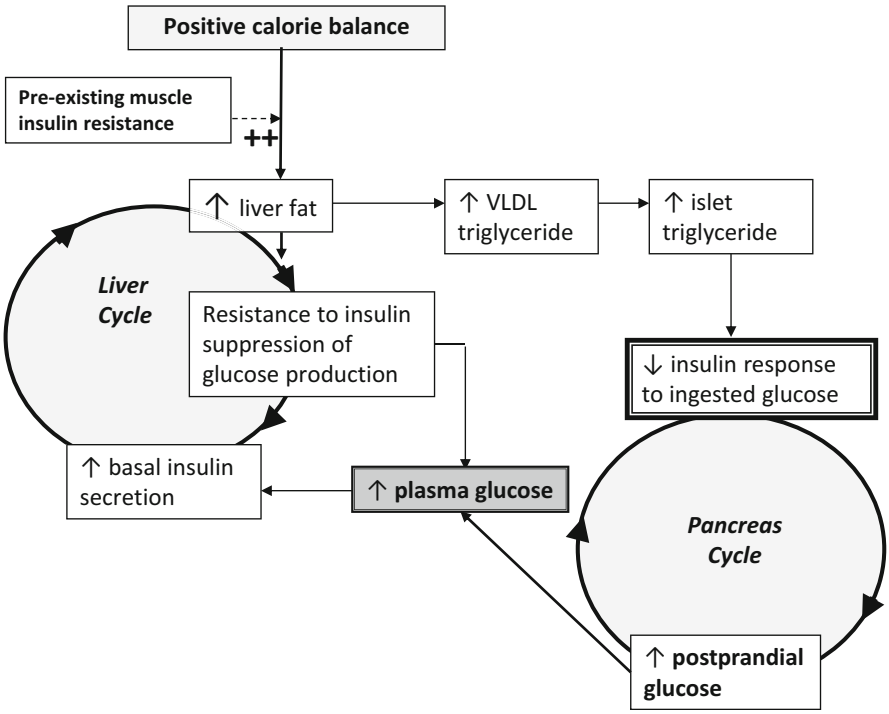

Fig. 1 The Twin Cycle Hypothesis. During long-term intake of more calories than are expended each day particularly when there is relative insulin resistance in muscle blocking glycogen synthesis, any excess carbohydrate must undergo de novo lipogenesis. This only can occur in the liver and particularly promotes local fat accumulation. Because insulin stimulates de novo lipogenesis, pre-existing insulin resistance and consequent higher plasma insulin levels (determined by family or lifestyle factors) will lead to more rapid accumulation of liver fat. In turn, the increased liver fat will cause relative resistance to insulin suppression of hepatic glucose production. Over many years, a modest increase in fasting plasma glucose level will stimulate increased basal insulin secretion rates to maintain euglycemia. The additional hyperinsulinemia will further increase the conversion of excess calories to liver fat. This process is further stimulated by elevated plasma glucose levels (Adiels et al. 2006). A cycle of hyperinsulinemia and blunted suppression of hepatic glucose production becomes established. Fatty liver leads to increased export of VLDL triacylglycerol (Adiels et al. 2006) which will increase fat delivery to all tissues, including the islets. Excess fatty acid availability in the pancreatic islet would be expected to impair the acute insulin secretion in response to ingested food (Lalloyer et al. 2006; Lee et al. 1994), and at an individual level of fatty acid exposure, postprandial hyperglycaemia will occur. The hyperglycaemia will further increase insulin secretion rates, with consequent enhancement of hepatic lipogenesis, spinning the liver cycle faster and driving the pancreas cycle. Eventually, the fatty acid and glucose inhibitory effects on the islets reach a trigger level that leads to a relatively sudden onset of clinical diabetes (Taylor 2013). Importantly, the hypothesis predicted that the cycles could be reversed, with reversal of type 2 diabetes to normal plasma glucose control (Modified from Taylor (2008) and reproduced with permission from Taylor (2013)

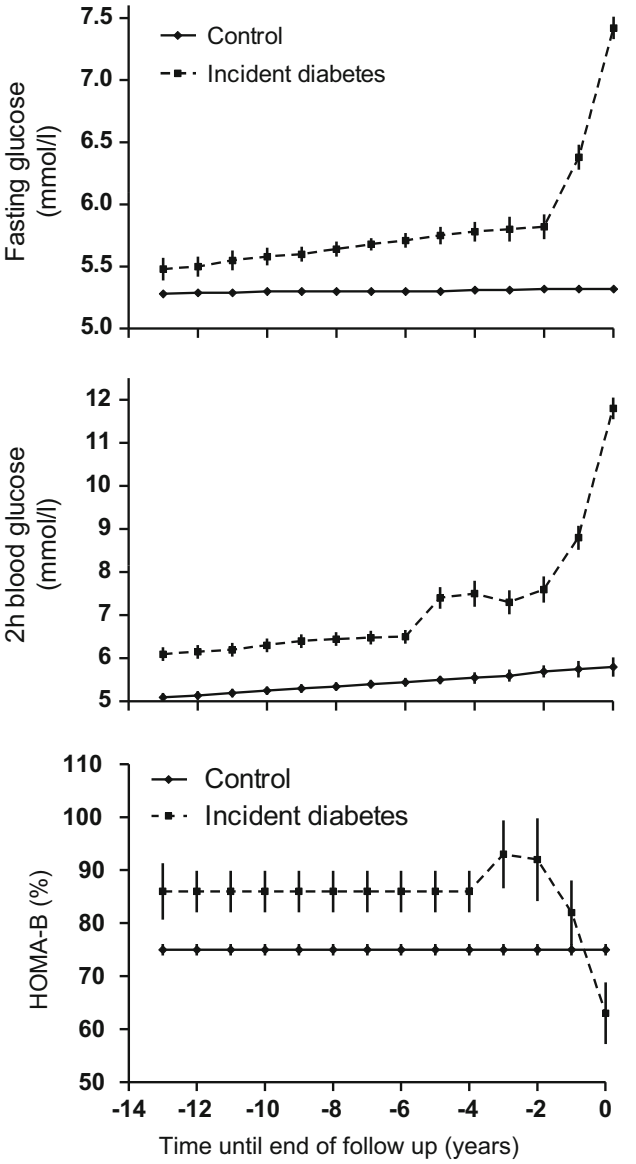

Fig. 2 Change in fasting plasma glucose (upper panel), 2 h post OGTT plasma glucose (middle panel) and HOMA-S insulin secretion during the 16 year follow-up in the Whitehall II study. Of the 6538 people, 505 developed diabetes. Time 0 was taken as diagnosis of diabetes or as end of follow-up for those remaining normoglycemia (Redrawn with permission from Tabak et al. 2009)

Long Term Reversibility of Type 2 Diabetes

After weight loss of more than 10% of initial body weight, type 2 diabetes of short duration reverses to normoglycemia in most individuals (Lim et al. 2011a; Steven et al. 2013; Steven and Taylor 2015). The underlying correction of excessive levels of fat in liver and pancreas persists providing that weight regain is avoided (Steven et al. 2016b). Several studies have reported normoglycemia over several years. The Look AHEAD study achieved an average of 8.6% weight loss at 1 year, but the range of weight loss was sufficient to achieve reversal of type 2 diabetes in 11.5% of participants (Gregg et al. 2012). After 4 years, the average weight loss from baseline had declined to 4.7%, but this average includes some with considerable weight loss and a substantial number (7.3%) had remission of diabetes (fasting glucose $<$7.0 mmol/l and HbA1c $<$6.5%). The degree of weight loss in predicting remission was notable, with those achieving weight loss of $>$6.5% having a remission rate of 16.4% at 1 year. Several smaller studies or case reports have demonstrated long-term return of blood glucose control to nondiabetic levels off all oral hypoglycemic agents (Steven et al. 2013; Paisey et al. 2002; Peters et al. 2015).

To evaluate whether longer-term return to nondiabetic blood glucose levels was accompanied by persistent normalization of liver and pancreas fat levels, a group of people who had reversed their type 2 diabetes by energy restriction were followed up for 6 months. The Counterbalance (Counteracting Beta-cell failure by Long-term Action to Normalize Calorie intake) study established that during weight stability, all abnormalities of liver and pancreas function remained reversed (Steven et al. 2016b). The major changes are summarized in Fig. 3. It was notable that the continued remission was independent of BMI, and the implications of this are discussed below.

Beta-Cell Dedifferentiation

The United Kingdom Prospective Diabetes Study (UKPDS) famously demonstrated an impairment of insulin secretion and a reduction of β-cell by 50% at the time of diagnosis of overt Type 2 Diabetes. It also showed that this progression of β-cell failure was not able to be modified by any of the current available blood glucose lowering treatment (Holman 2006). The Belfast Diet Study to evaluate the effects of intensive dietary management of newly diagnosed diabetes also showed the steady, progressive rise in FPG associated with a progressive fall in β-cell function during the first 10 years after the diagnosis during diet treatment alone (Levy et al. 1998). For both studies, beta-cell function data were modelled from fasting plasma glucose and insulin observations, permitting an overall estimate in the fasting state.

The earliest defect of insulin secretion in type 2 diabetes is a loss of first-phase insulin secretion in response to intravenous glucose (Vaag 1999). It had been accepted for many years that this was irreversible and could not be restored to a useful degree by any pharmacological treatment. However, the Counterpoint study showed in 2011 that this defect is entirely reversible in the first few years of

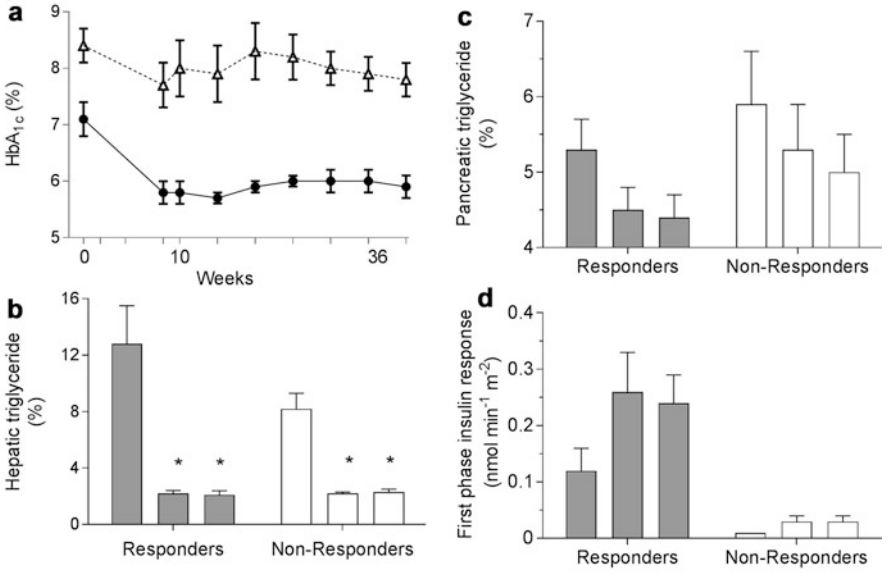

Fig. 3 The Counterbalance study. Individuals with type 2 diabetes of up to 23 years duration followed a very low calorie diet (~700 kcal/day) and lost approximately 15 kg in weight. Those with shorter duration of diabetes typically responded by achieving non-diabetic fasting plasma glucose (<7.0 mmol/l). After a stepwise transition back to normal eating they were reviewed at monthly intervals. Average weight remained steady for 6 months. Panel A: change in fasting plasma glucose in Responders (closed symbols) and Nonresponders (open symbols). Panel B: similar and sustained decrease in liver fat content in both groups despite ongoing overweight or obesity. Panel C: fall to low levels of pancreas fat in the Responders and in Nonresponders only to levels similar to baseline Responder levels. Panel D: first phase insulin response was higher in Responders at baseline and increased to normal levels, whereas the grossly deficient baseline level in Nonresponders did not change (Figure adapted with permissions from Steven et al. (2016b) and previously published as Taylor and Barnes (2017)

diagnosis of type 2 diabetes if the fat-induced stress on the beta cell was removed (Lim et al. 2011a).

Historically, several different hypotheses have been proposed in order to attempt to explain the development of beta-cell dysfunction in type 2 Diabetes. Firstly, beta-cell exhaustion due to the increased secretory demand was thought to arise from insulin resistance (DeFronzo et al. 1992). Long continued hyperinsulinemia due to obesity related insulin resistance is entirely compatible with long-term normal glucose tolerance (Kahn 2001). Also, the longitudinal data from the Pima Indians points out that beta-cell function is enhanced in apparently healthy subjects as insulin resistance progresses (Weyer et al. 1999).

Secondly, desensitization of the beta-cell due to the elevation of the glucose levels or "glucose toxicity" has also been proposed (Yki-Jarvinen 1992; Robertson et al. 1994). UKPDS data suggest that in the early stages of diabetes, glucose is unlikely to be a critical factor determining the beta-cell dysfunction progression based on

observation that the disease progressed or worsened despite the "normalization" of glucose levels and continuation of the therapy (UKPDS 1998, 1999).

Thirdly, the deposition of amyloid (Kahn et al. 1999; Opie 1901) and apoptosis as a result of the deranged metabolic state (Efanova et al. 1998; Shimabukuro et al. 1998) have been implicated in a reduction of beta-cell mass. The deposition of amyloid in the islets has been reported in a high proportion with type 2 diabetes (Westermark and Wilander 1978; Rocken et al. 1992; Johnson et al. 1989). The islet amyloid polypeptide (IAPP) is a protein component of fibrils that are forming the amyloid deposits (Westermark et al. 1987; Cooper et al. 1987). IAPP is getting produced in the islet cells and released together with insulin (Kahn et al. 1990). When islet amyloid increases in the monkey, the glucose tolerance gets worse (Howard 1986). The reduction of the beta-cell mass seems to be associated with significant islet amyloidosis (Howard and Van Bueren 1986; de Koning et al. 1993). Amyloid fibrils have been shown to be cytotoxic to the beta-cells in vitro resulting in death by apoptosis (Lorenzo et al. 1994; Janson et al. 1999). Wang et al. have studied islet amyloidosis by computerized fluorescent microscopy in transgenic mice bearing the amyloidogenic human IAPP gene and developing typical islet amyloid (Wang et al. 2001). However, type 2 diabetes occurs without accumulation of amyloid, and it appears unlikely to be the cause of decreased beta-cell function in type 2 diabetes.

Fourthly, endoplasmic reticulum (ER) stress response, an adaptive mechanism used to align ER functional capacity and demand, occurs in obesity and type 2 diabetes and in the beta-cell; prolonged ER stress has been suggested to impair the synthesis of insulin (Cnop et al. 2012). Data obtained in animal models of diabetes have suggested that the changes in lipid metabolism could contribute to the development of beta-cell dysfunction (Unger 1995). Also, a high-energy diet, associated with a high fat intake, may contribute to the decrease in beta-cell function (Tsunehara et al. 1990). These observations were nicely brought together by the studies of Anne Clark and others. When fatty acid concentrations are elevated in vitro, lipid synthesis and storage within the beta-cell is favored and chronic exposure of the beta-cell to fatty acid excess directly impairs glucose-stimulated insulin secretion (Elks 1993; Lalloyer et al. 2006; Zhou and Grill 1994). Long-term exposure to increased levels of fatty acids in vitro directly results in beta-cell stress and dysfunction (Pinnick et al. 2010). Exposure of the INS1 beta-cell line to oleic acid brings about storage in intracytoplasmic vacuoles, whereas the saturated fatty acid palmitate induces expansion of the endoplasmic reticulum producing dramatic "splits" or widening in the endoplasmic reticulum (Pinnick et al. 2010). This is associated with markers of endoplasmic reticulum stress, typically increased in human beta-cells from individuals with type 2 diabetes (Laybutt et al. 2007; Marchetti et al. 2007). The exposure to a more physiological mixture of saturated and unsaturated fatty acids decreases insulin secretion, and removal of fatty acid from the medium allows return of insulin secretion over 24 hours (Pinnick et al. 2010). This observation lays the basis for understanding the in vivo reversal of type 2 diabetes and restoration of the non-diabetic first-phase insulin response (Lim et al. 2011a; Steven et al. 2016b). Human

islets cells are known to take up fatty acids avidly, and incubation in 0.33 mmol/l palmitate brings about both a large increase in islet triglyceride content and major impairment of function (Lalloyer et al. 2006). Once hyperglycemia occurs, the additional stress of elevated glucose is likely to compound the metabolic insult (Poitout et al. 2010).

Autopsy studies of patients with type 2 diabetes have reported reduced β-cell mass, and this has long been accepted as the reason for decreased insulin secretory function (Westermark and Wilander 1978; Butler et al. 2003; Saito et al. 1979; Kloppel et al. 1985). However, in such histological studies, the apparent progressive reduction in β-cells in type 2 diabetes was judged by decreased insulin immunostaining. Such assessments were based on insulin secretory function rather than definitively identified beta-cells. Very recently, the loss of beta-cell function in type 2 diabetes was shown to be explained by beta-cell dedifferentiation rather than beta-cell death (Brereton et al. 2014; Spijker et al. 2015; Talchai et al. 2012; Wang et al. 2014; White et al. 2013). Chronic positive energy balance may result in reduced expression of beta-cell transcription factors such as Pdx1, Nkx6.1, and MafA (Brereton et al. 2014; Spijker et al. 2015; Talchai et al. 2012). This leads to the loss of end-differentiated genes including insulin and induction of dismissed genes like lactate dehydrogenase and hexokinase (Weir et al. 2013). Accili et al. proposed that enhanced FoxO1 nuclear translocation is able to maintain the activation of some of beta-cell transcription factors like MafA which preserves glucose oxidation and suppresses fatty acid oxidation resulting in limitation of mitochondrial stress. FoxO1 can initiate a compensatory response that leads to preservation of beta-cell function under metabolic stress.

Lineage tracing studies in mice with beta-cell specific deletion of FoxO1 exposed to metabolic stressors including ageing and multiple pregnancies demonstrated that loss of beta-cell mass was not due to death but rather due to dedifferentiation (Talchai et al. 2012). Loss of insulin staining was encountered together with induction of genes not normally expressed in adult beta-cells including mesenchymal marker vimentin and pancreatic progenitor marker neurogenin 3.

A further change in the stressed, dedifferentiated beta cell is highly relevant metabolically. Following loss of beta-cell specific transcription factors as a result of chronic hyperglycemia, glucagon production by beta cells becomes switched on (Brereton et al. 2014; Marroqui et al. 2015). Following reversal of type 2 diabetes in vivo, a fall to normal of fasting plasma glucagon levels occurs at the same time as return of normal beta-cell function (Steven et al. 2015).

Genetic predisposition plays a part in determining individual susceptibility to type 2 diabetes (Groop and Lyssenko 2008; Ahlqvist et al. 2011). It is likely that genetic factors underlie the susceptibility of the beta-cell to fat-related metabolic stress. Genome-wide association scans and candidate gene approaches have identified approximately 40 genes so far those have been linked with type 2 diabetes and a similar number, but mostly different, with obesity (Hayes et al. 2007; Rampersaud et al. 2007). The majority of type 2 diabetes genes have been associated with impairment of β-cell function. It is estimated that the genes identified already can predict only 15% of type 2 diabetes (Bogardus 2009).

Pathophysiological Effects of Obesity

Insulin Resistance in Muscle

Studies using the euglycemic hyperinsulinemic clamp technique have dominated opinion in this field. The term "clamp" refers to the maintenance of constant blood glucose level in by a variable infusion of glucose to balance the biological effect of constant hyperinsulinemia. The amount of glucose required is an index of the sensitivity to insulin – or conversely, resistance to insulin.

Both the euglycemic insulin clamp and limb catheterization studies have demonstrated insulin resistance in skeletal muscle as a feature of obesity (Bogardus et al. 1985; Kelley et al. 1999). At the high insulin concentrations induced, skeletal muscle may account for 70–90% of total body disposal of intravenously delivered glucose (DeFronzo et al. 1985; Yki-Jarvinen et al. 1987). Under these conditions, the liver and the gut (DeFronzo et al. 1981) and adipose tissue (Marin et al. 1987) account only for a very small proportion of glucose uptake. This information was gathered on lean subjects, and in obesity adipose tissue will account for a higher proportion of glucose uptake. Although muscle insulin resistance measured by this method has been illuminating, it does not reflect glucose disposal after a meal. In nonobese subjects, 30% of meal derived glucose is present in muscle at peak glycogen concentration 5 h after a meal (Taylor et al. 1993). This must be borne in mind when considering the clinical relevance of reported insulin resistance in muscle.

Nonetheless, whole body insulin resistance mainly reflects muscle insulin resistance is notably associated with excess fat accumulation and has been shown to be the earliest feature predicting onset of type 2 diabetes (Petersen et al. 2007).

Mechanisms: Pathway of Intracellular Insulin Action

The cause of muscle insulin resistance has been intensively researched, and as a consequence, the molecular action of insulin has been defined. In order to cause a biological effect, insulin must first to bind to specific cell surface receptors which lead to tyrosine phosphorylation of IRS-1 mediating the effect of insulin on glucose metabolism (Taniguchi et al. 2006; DeFronzo 2010; White et al. 1988). This is followed by the activation of a cascade of phosphorylation-dephosphorylation reactions. IRS-1 activates PI-3 kinase (Sun et al. 1992), which catalyses 3′ phosphorylation of PI, PI-4 phosphate, and PI-4,5 diphosphate, and augments glucose transport and glycogen synthase (Ruderman et al. 1990; Brady et al. 1997; Dent et al. 1990). Exhaustive searches for genetic links of signaling defects to obesity and type 2 diabetes have been notably unsuccessful.

Because muscle is the early pre-diabetic site of insulin resistance (Ferrannini et al. 1999; Cline et al. 1999; Kahn 1994) and is widely regarded as accounting for of the largest proportion of insulin stimulated glucose uptake, the muscle-specific insulin receptor knockout mice (MIRKO) were created with the expectation that they would be particularly susceptible to type 2 diabetes. In this mouse model, there is almost complete ablation of insulin receptor expression in all skeletal muscles (Bruning et al. 1998). It was a surprise that the MIRKO mice were able to maintaining normal

blood glucose levels up to at least 20 months of age (Bruning et al. 1998). In response to insulin, the glucose uptake into muscles was severely decreased, but it was normal in response to exercise (Wojtaszewski et al. 1999). However, the insulin stimulated glucose transport in adipose tissue was increased by approximately threefold in MIRKO mice (Kahn 2003). In man, Savage et al. have identified a PPP1R3A FS variant, which encodes a truncated protein that is mistargeted within the cell and decreases muscle glycogen synthesis activity. It increases phosphorylase activity resulting in the decrease of muscle glycogen content in humans. Even though this abolished postprandial uptake of ingested glucose and storage as muscle glycogen, no postprandial hyperglycemia necessarily occurs (Savage et al. 2008). This mutation is present in approximately 1 in 70 UK whites which increases the potential relevance of that finding (Savage et al. 2008). Again like the MIRKO mouse studies, this indicates that lack of insulin responsiveness of muscle does not necessarily cause type 2 diabetes. Other susceptibility factor(s) are clearly necessary in addition.

Mechanisms: Substrate Level Control of Measured Insulin Sensitivity

The deleterious effect of fat accumulation on glucose metabolism was described by Unger as "lipotoxicity" (Unger 2003). Studies on elevation of nonesterified-fatty-acids (NEFA) resulted in severe muscle and liver insulin resistance (Kashyap et al. 2004; Richardson et al. 2005; Dresner et al. 1999; Johnson et al. 1992). These studies also reproduced the core defects of type 2, with additional inhibition of insulin secretion in those susceptible to type 2 diabetes (Kashyap et al. 2003). It was demonstrated by the magnetic resonance spectroscopic studies that the organ specific insulin resistance was closely associated with intramyocellular and intrahepatic fat accumulation (Mayerson et al. 2002; Belfort et al. 2006; Miyazaki et al. 2002; Bajaj et al. 2003). Increased levels of intracellular intermediates of triacylglycerol and NEFA metabolism (fatty acyl CoA, diacylglycerol, ceramides) impair insulin signaling and multiple intracellular steps of glucose metabolism and cause the observed severe insulin resistance (Kashyap et al. 2004; Belfort et al. 2005; Griffin et al. 1999). As intramyocellular levels of triacylglycerol increase, insulin resistance in muscle tends to increase (Greco et al. 2002), and this gives a very direct insight into the relationship between obesity and muscle insulin resistance. However, it is relevant to note that sustained return to a nondiabetic state in humans is routinely achieved with no appreciable change in the level of muscle insulin resistance (Lim et al. 2011a).

Other Postulated Mechanisms

Insulin resistance in skeletal muscle is associated with mitochondrial function (Petersen et al. 2004). Although this was considered initially as a possible cause of type 2 diabetes, it is now clear that the changes in ATP production are secondary to the metabolic state. No defect is present in early type 2 diabetes but becomes apparent when plasma glucose is over 8 mmol/l (Schrauwen-Hinderling et al. 2007). Observed rates of mitochondrial ATP production can be modified by

increasing or decreasing plasma fatty acid concentration (Brehm et al. 2006; Lim et al. 2011b). Additionally, the onset of insulin stimulation of mitochondrial ATP synthesis is slow, gradually increasing over 2 h and distinct from the acute onset of insulin effect (Lim et al. 2010). Mitochondrial defects cannot be primary in the etiology of common type 2 diabetes (Taylor 2012).

Insulin Resistance in Liver

Hepatic insulin resistance has long been recognized to be associated with obesity (Basu et al. 2005). Fasting hepatic glucose output is raised in both obesity and further in type 2 diabetes (Singhal et al. 2002) compared with lean subjects (Taylor et al. 1996b). Post-prandial suppression of hepatic glucose output is inadequate in both conditions (Singhal et al. 2002; Taylor et al. 1996b). Unlike muscle insulin resistance, it relates closely to liver fat content and is entirely reversible (Ravikumar et al. 2008; Lim et al. 2011a). Obesity is strongly associated with fat accumulation in the liver at all ages, from early childhood to adulthood (Bedogni et al. 2005). This is a dose relationship between the degree to which children are overweight and the presence of fatty liver as demonstrated by an autopsy study (Schwimmer et al. 2006). In adolescence, 30% of obese individuals have fatty liver (Perseghin et al. 2006) and the extent of liver fat accumulation is inversely proportional to habitual daily physical activity, both in type 2 diabetes and normal glucose tolerance (Perseghin et al. 2007).

Net storage of liver fat can only occur when daily energy intake exceeds expenditure. It has to be the results of excess uptake of fatty acids, as overspill from adipose tissue, relative inhibition of lipid oxidation or de novo lipogenesis. The latter is important as individuals with muscle insulin resistance cannot store ingested glucose as muscle glycogen, and the body has only one pathway to permit safe storage of the ingested energy – synthesis of triglyceride from glucose. Overfeeding with sucrose for 3 weeks has been shown to cause a 30% increase in liver fat content (Sevastianova et al. 2012). The associated metabolic stress on hepatocytes brought about a 30% rise in serum ALT. Both liver fat and serum ALT fell to normal during a subsequent hypocaloric period. The link between fat accumulation and raised ALT is important as a general indicator of metabolic stress of the hepatocyte. Superimposed upon positive calorie balance, the extent of portal vein hyperinsulinemia will determine how rapidly conversion of excess sugars to fatty acid occurs in the liver as the pathway of de novo lipogenesis is not subject to insulin resistance. In groups of both obese and nonobese subjects, those with higher plasma insulin levels have markedly increased rates of hepatic de novo lipogenesis (Schwarz et al. 2003; Rabol et al. 2011; Petersen et al. 2012).

IRS-2 phosphorylation mediates the Insulin action in liver (Fig. 4) (DeFronzo 2010). Inside the hepatocyte, fatty acids could appear as a result of de novo lipogenesis, uptake of nonesterified fatty acid and LDL, or lipolysis of intracellular triacylglycerol (Taylor 2013). The lower ability to oxidize fat within the hepatocyte might be one of the factors for the accumulation of the liver fat (Belfort et al. 2006).

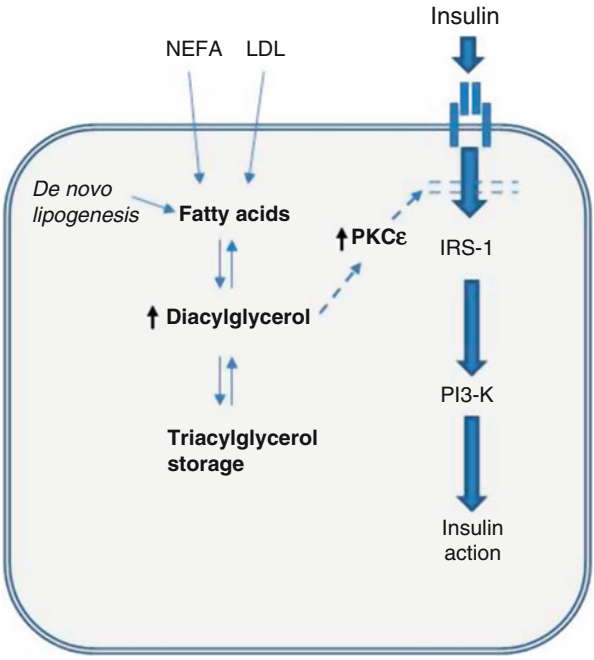

Fig. 4 Mechanisms of inhibition of insulin action within the hepatocyte. Excess fatty acids and diacylglycerol can directly inhibit critical steps in the pathway of intracellular insulin action in respect of control of hepatic glucose output (Reproduced with permission from Taylor (2013)

Diacylglycerol excess has a deleterious effect on the activation of protein kinase C epsilon type which inhibits the signaling pathway from the insulin receptor to insulin receptor substrate 1 (IRS-1) (Samuel et al. 2010) – the first post receptor step in intracellular insulin action. When there is a chronic excess of energy intake with food, a raised level of diacylglycerol inside the cell prevents the normal action of insulin, and therefore the production of glucose by the liver gets out of control (Taylor 2013). The excess fatty acids stimulate the ceramide synthesis by esterification with sphingosine and the ceramides in turn cause the sequestration of Akt2 and activation of gluconeogenic enzymes (Taylor 2013).

Insulin resistance in skeletal muscle ensures facilitation of conversion of energy from carbohydrate into the hepatic de novo lipogenesis with increased production of VLDL-triglyceride (Petersen et al. 2007). The data from this study also demonstrated that skeletal muscle insulin resistance develops before hepatic insulin resistance, and that the increased triglyceride synthesis by the liver after meals in insulin resistant people will predispose them to nonalcoholic fatty liver disease (NAFLD).

Inactivity

Relatively low levels of physical activity contribute to the positive energy balance over many years as obesity develops, and obesity itself completes the vicious circle by decreasing the ability to undertake physical activity. The increase in inactivity rates among the population is a growing problem especially in the economically rich countries.

Physical inactivity is associated with increased insulin resistance (Sigal et al. 2004). The evidence from the Finnish Diabetes Prevention Study demonstrates that weight loss and maintenance of this through the diet and physical activity reduces the incidence of type 2 diabetes by more than a half (Tuomilehto et al. 2001). Lifestyle interventions combining limitation of quantity of food with increased daily physical activity are the mainstay of programs to manage body weight (Sigal et al. 2004). Men with low physical activity levels and type 2 diabetes have much higher mortality rates compared with their fitter counterparts (Wei et al. 2000).

Increased Visceral and Ectopic Fat

Subcutaneous adipose tissue permits the safe storage of chemical energy. The evolutionary role of visceral adipose tissue is less certain, but it provides a readily mobilizable energy depot which will deliver directly to the liver. Excess visceral fat is associated with both obesity and insulin resistance (Ritchie and Connell 2007; Fox et al. 2007). It has been also linked with increased in-hospital mortality (Tsujinaka et al. 2008) and ischemic heart disease (Mathieu et al. 2008). Although visceral fat secretes leptin, adiponectin, resistin, interleukin-6, and tumor necrosis factor, each of these appears to play a modulatory role in metabolic control which is minor compared both with the primary hormones such as insulin and substrate effects on insulin sensitivity. In practice, the major significance of visceral fat is to permit ready clinical assessment of how excessive fat stores have become by the simple measurement of waist circumference. If the visceral stores are prominent, it is likely that fat will be building up in ectopic sites.

The most evident ectopic fat store is within the liver. The prevalence of NAFLD in the US adults was observed to be 46%, with progression to steatohepatitis in 12.2% (Williams et al. 2011). The extent of fat build up in the liver tends to reflect increasing adiposity. Some ethnic groups, and especially Hispanics in USA, are particularly prone to NAFLD (Williams et al. 2011). The higher prevalence in men might relate to differing sex-steroid metabolism (Browning et al. 2004) or simply greater capacity of subcutaneous fat stores in women.

Accumulation of ectopic fat in other sites has been less studied. In obesity, storage at sites such as pericardial and intramyocardial fat tends to be increased (Gaborit et al. 2012). Whether or not obesity per se is associated with increased intra-pancreatic fat content is less certain as most large studies have used methodology likely to report visceral fat contamination due to the irregular shape of the pancreas (Al-Mrabeh et al. 2017).

Relationship Between Type 2 Diabetes and Obesity

Type 2 diabetes is often regarded as a disease related to obesity. However, the majority (72%) of people with BMI over 40 kg/m^2 have no diabetes (Gregg et al. 2007). Conversely, half of all newly diagnosed people with diabetes are not

obese (Logue et al. 2013). The relationship between body weight and type 2 diabetes is nicely illustrated by data from the Nurses' Health Study. This showed that there is a fourfold increase in T2DM prevalence for women of BMI 23–25 compared with those of BMI less than 22 kg/m^2 (FB et al. 2001). The implications of this striking observation have not been widely appreciated. As would be expected, the study also confirmed the exponential relationship between type 2 diabetes and rising BMI such that the most obese category had a 37-fold increased prevalence. It is clear that obesity per se is permissive but not sufficient to cause type 2 diabetes.

The distribution of BMI for the 5102 people with newly diagnosed type 2 diabetes recruited into the United Kingdom Prospective Diabetes Study (UKPDS) is shown in Fig. 5 (UK Prospective Diabetes Study (UKPDS) 1991). The distribution is unimodal with a slight skew to the right. It demonstrates that only a minority of the newly diagnosed have a BMI greater than 35 kg/m^2 and 36% of the subjects had a BMI less than 25 kg/m^2. This distribution is right-shifted from that during the time of recruitment for UKPDS (between 1977 and 1991) when 64% of the adult UK population had a BMI less than 25 kg/m^2 (Rosenbaum et al. 1985). From today's perspective, it is remarkable that so many people with newly diagnosed type 2 diabetes had normal BMIs. Indeed, careful reviews in that era concluded that obesity did not have a major influence on type 2 diabetes (Jarrett et al. 1979; Taylor 1989; Leslie and Pyke 1985). Given that the risk of type 2 diabetes rises steeply at higher BMI's and that higher BMI's are now more prevalent, it is not surprising that the association between obesity and T2DM is much more evident today.

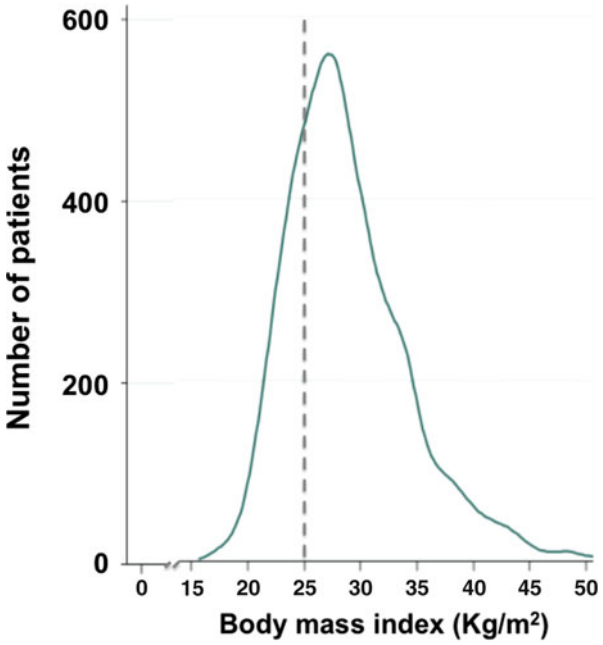

Fig. 5 BMI distribution in the entire cohort of the UK Prospective Diabetes Study. The newly diagnosed people with type 2 diabetes were recruited between 1977 and 1991. It is striking that 36% had a BMI less than 25 kg/m^2 (Reproduced with permission from Taylor and Holman (2015)

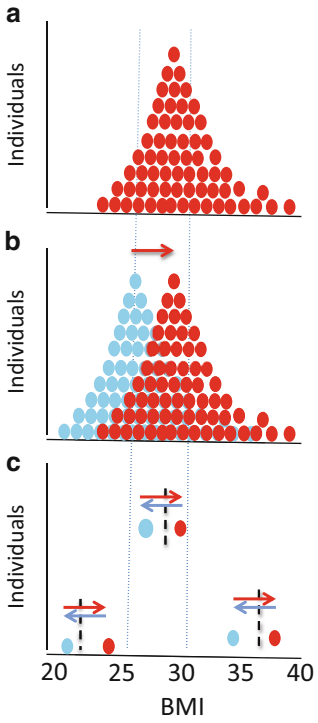

Fig. 6 The Personal Fat Threshold versus population distributions. Panel A shows a representative frequency distribution of BMI for a group of individuals with type 2 diabetes, not as a smooth curve but as individuals (T2DM). Panel B shows the frequency distribution of BMIs in blue for the individuals depicted in Fig. 2a before they gained weight. The red frequency distribution, when diabetes had developed, is right shifted (red arrow) and usually interpreted as indicating a higher prevalence of obesity in a population with type 2 diabetes. However, the arbitrary cut off points of the BMI scale do not apply to individuals. Panel C shows three illustrative individuals from Panel A, demonstrating their relative positions within the population BMI distribution. One is obese, one overweight and one normal weight. Weight loss of 15 kg in each case resulted in return to normal glucose tolerance although their classification by the population measure of BMI did not change. Each individual has a personal fat threshold (dotted line) above which excess fat is stored within liver and pancreas. This individual susceptibility has no relationship to categories of BMI, despite the higher probability of diabetes being precipitated in the obese range. For each individual, moving to the right of their personal fat threshold triggers T2DM (red arrows), and moving to the left of the line restores normal glucose tolerance (blue arrows) (Reproduced with permission from Taylor and Holman 2015)

These observations have been explained by the Personal Fat Threshold (PFT) hypothesis which focuses upon the individual rather than the populations mean (Taylor and Holman 2015). This is explained diagrammatically in Fig. 6. When an individual exceeds their personal fat threshold, they become likely to develop type 2 diabetes, and it is clear that the hypothesized PFT is independent of BMI. The majority of obese individuals are splendidly equipped to store very large quantities

of fat in a metabolically safe fashion in subcutaneous adipose tissue. But some apparently slim individuals have a low capacity in this depot, and ectopic fat builds up at low BMI's. As an extreme example, in generalized lipodystrophy and effective absence of subcutaneous fat, gross fatty liver disease occurs, and diabetes is common (Reitman et al. 2000). Depending upon the genetically determined susceptibility of the beta-cell to exhibit endoplasmic reticulum stress and consequent beta-cell de-differentiation, diabetes may or may not occur (Talchai et al. 2012; Lee et al. 1994; White et al. 2016). Prolonged Intralipid® infusion in people predisposed to develop type 2 diabetes is known to severely impair beta-cell function (Storgaard et al. 2003). If a person with recent onset type 2 diabetes loses the excess weight, going down below his or her PFT makes likely a return to normal glucose control and reversal of diabetes (Lim et al. 2011a; Steven et al. 2016b; Taylor and Holman 2015). Moderate calorie restriction achieving weight reduction by approximately 8 kg is accompanied by reversal of hepatic steatosis and hepatic insulin resistance leading to a normalization of basal rates of hepatic glucose production and improvement in fasting plasma glucose (Ravikumar et al. 2008; Petersen et al. 2005). The Counterpoint study employed a very low-calorie diet in recently diagnosed people with type 2 diabetes and demonstrated reduction of liver fat by 30% within the 7 days and normalization of fasting plasma glucose (Lim et al. 2011a). Continuation of the weight loss brings about decrease in pancreatic fat and return of glucose stimulated insulin secretion in type 2 diabetes (Lim et al. 2011a; Steven et al. 2016b; Taylor and Holman 2015).

Appreciation of the individual susceptibility to type 2 diabetes appears to be determined both by the relative inability to store fat safely in subcutaneous tissues at any given BMI and by the relative susceptibility of beta-cells to de-differentiate in the presence of excess intrapancreatic fat. This allows understanding of the phenomenon that type 2 diabetes can occur at any BMI reflecting a degree of weight gain excessive for the individual. It also allows understanding that weight loss resulting in a BMI above 30 kg/m^2 can achieve metabolic normality.

Management of Body Weight in Type 2 Diabetes

Goals

The twin goals of management of body weight in type 2 diabetes are achievement of weight loss and, very importantly, long-term avoidance of weight regain. Wing and Hill proposed criteria for successful weight loss and maintenance: Loss at least 10% of their body weight and weight stability for at least 1 year (Wing and Hill 2001). Six key strategies were proposed based on the data from the National Weight Control Registry: high level of physical activity, low energy, and low-fat diet, eating breakfast, self-monitoring weight on the regular basis, keeping the consistent eating pattern, and catching "slips" before they turn into lager weight regain (Wing and Phelan 2005). However, application of cross-sectional data introduces confounders,

and care is required in interpreting such data. In particular, different strategies are required to achieve weight loss, and to achieve long-term weight stability.

How much weight loss is sufficient to lose diabetes and put it into the long-term remission? This question had been raised in the Counterpoint study where participants have lost on average 15 kg of weight during 8 weeks of VLCD (800 kcal) and the majority reversed type 2 diabetes (Lim et al. 2011c). Reversal of diabetes was not observed with weight loss of less than 8 kg.

Currently the Diabetes in Remission Clinical Trial (DiRECT) is underway in UK Primary Care (Leslie et al. 2016). This trial uses the low-energy liquid diet to achieve substantial weight loss in subjects with early type 2 diabetes (< 6 years duration). A distinct subsequent long-term phase uses limitation of overall food intake and increased daily physical activity together with regular contact with health care professional. The co-primary endpoints are the reduction of weight at 1 year 15 kg or more and the reversal of type 2 diabetes with HBA1C <48 mmol/mol at 1 year. This study has a longitudinal follow up of subjects for total of 2 years. It will help to determine the success of a defined period of weight loss followed by a sustained support program for long-term weight maintenance (The first year results now published showed that almost 9 out of 10 people (86%) who lost 15 kg or more put their Type 2 diabetes into remission. Lean et al. Lancet. 2018;391(10120):541–51. https://doi.org/10.1016/S0140-6736(17)33102-1).

Reported Dietary Weight Loss Interventions in Type 2 Diabetes

Dietary management for the people with type 2 diabetes has been evolving over many decades. It differs from primary prevention advice to be applied to populations at risk in that there is a potent motivator for people who have been diagnosed – to escape from diabetes entirely and avoid the risk of blindness, amputation, and premature death.

In UKPDS, the response to the diet was reported in the 3044 newly diagnosed who had fasting plasma glucose of 12.1 ± 3.7 mmol/l and weight of 130 ± 26% ideal body weight (UKPDS Group 1990). Initial body weight did not determine the glycemic response to weight loss, as could be predicted from the Personal Fat Threshold hypothesis (Taylor and Holman 2015). In this study, 16% of the group reached a normal FPG less than 6 mmol/l after 3 months, reflecting variable motivation to achieve a large reduction in energy intake and meaningful weight loss (UKPDS Group 1990). The Belfast Diet Study showed that treatment with diet alone for the first 10 years after the diagnosis of type 2 diabetes is associated with progressive rise in FPG, but this study concentrated on composition of food rather than quantity (Levy et al. 1998).

The longest randomized controlled study to date of an intensive lifestyle intervention for weight management is Look AHEAD (Action for Health in Diabetes Study). This study showed that over 8 years overweight or obese people with type 2 diabetes lost 4.7% of initial body weight in the intensive lifestyle intervention group (versus 2.1% in usual care group) (LookAhead 2014). 26.9% of the intervention group lost >10% of initial body weight by the end of a trial. The degree of weight

loss in predicting remission was notable, with those achieving weight loss of >6.5% having a remission rate of 16.4% at 1 year. However, these results appeared less impressive than may have been desired in view of the intensive and expensive nature of the intervention. There was an emphasis on exercise in LookAhead, and this may have been counterproductive (see below).

Very low energy diets rapidly improve plasma glucose control. The old extremely low energy diets (330 Cal/day) brought about weight loss of 10.5 ± 0.4 kg with improvement in fasting plasma glucose (Henry et al. 1985). Using a modern 600kcal/day liquid formula diet, superior average weight loss (15.2 kg) has been reported, with complete normalization of plasma glucose within 7 days (Lim et al. 2011c). Although it has been assumed that rapid weight loss is always followed by weight regain, this concept developed in the absence of appropriate continuing support programs. Ongoing weight stability following rapid weight loss and a careful step-wise reintroduction of normal foodstuffs has been shown to be achievable (Steven et al. 2016b).

Approaches to Long-Term Avoidance of Weight Regain

The principal dietary interventions for long-term use which are supported by evidence will be considered: low-fat diet, restricted carbohydrate diet, Mediterranean diet, and intermittent energy restriction.

A low-fat diet (<30% total energy from fat) has long been widely advised. The idea became popularized by an epidemiological association between different countries of high fat intake with cardiovascular death (Keys 1953). Such associations from cross-sectional studies have repeatedly been shown not represent cause and effect (Feinman et al. 2015), but the belief in a low fat diet for health is very widespread and reflected in current guidelines for type 2 diabetes. A head-to-head comparison of low-fat diet with an energy-restricted diet showed no significant difference in weight loss (Jeffery et al. 1995), whereas combination of the low-fat plus low-energy diet versus low-fat diet alone (Schlundt et al. 1993; Pascale et al. 1995).

Moderate carbohydrate restriction is simple to implement, particularly in the context of family eating. Low-carbohydrate diets continue to arouse strong feelings, possibly as a backlash against more extreme carbohydrate avoidance diets (Feinman et al. 2015; Spiro and Stanner 2016). A restricted carbohydrate diet brings about an increase in the proportion of calories from fat, conflicting with long-held beliefs about the risks of higher-fat diets. However, the practical outcome has been shown to be beneficial for both weight management and improvement in cardiovascular risk factors (Bazzano et al. 2014). The macronutrient composition of diet, for equivalent weight loss, does not affect liver fat content or any other aspect of fat distribution (de Souza et al. 2012). These points have been incorporated into evidence-based nutrition guidelines (Dyson et al. 2011).

The Mediterranean diet consistently has been reported to be advantageous in terms of weight control and cardiovascular health (Estruch et al. 2016; Garcia-Fernandez et al. 2014; Martinez-Gonzalez and Martin-Calvo 2016), with a

decreased diabetes incidence independent of weight (Salas-Salvado et al. 2011). A combination of Mediterranean with carbohydrate restriction may be beneficial (Esposito et al. 2014).

Time-limited approaches to eating (such as alternate day or intermittent fasting) appear to be very suitable for some individuals as an alternative to daily calorie restriction. This is as effective as calorie restriction for weight loss and maintenance for up to 12 months (Davis et al. 2016). The proportion of people losing more than 5% in weight has been reported to be higher with intermittent energy reduction (60–65%) compared to daily energy restriction (37%) (Harvie et al. 2013). For ongoing avoidance of weight regain, 1 day of energy restriction per week was found to be successful. Using the 5:2 approach in type 2 diabetes achieves comparable reductions in weight and HbA1c to calorie restriction with no adverse effects on exercise levels or appetite (Carter et al. 2016; Harvie and Howell 2016). Longer-term weight maintenance outcomes are currently lacking.

Omission of breakfast runs counter to beliefs about this meal, although the latter mainly derived from cross-sectional studies, often with a potential commercial bias (Brown et al. 2013). Clearly the approach of not eating before noon suits some people and not others. Prospective study suggests a major energy advantage of this pattern of eating with no disbenefit in terms of eating more later in the day (Clayton et al. 2016; Kealey 2016).

Over recent years, guidelines have moved away from enforcing any particular macronutrient composition to acknowledging that there is no "one best diet" for every individual with diabetes (Dyson et al. 2011). In practice, long-term energy intake can be minimized by using an approach suited to the individual. Taken together, these studies illustrate important points. Clear separation of a limited duration weight-loss phase followed by a weight-maintenance phase of both calorie limitation and increased physical activity may be a more successful approach (Steven et al. 2016b). Confirmation of this in a large population is currently being sought (Leslie et al. 2016). The nature of support and advice about eating during long-term weight maintenance clearly deserves close study.

Exercise

The energy expenditure achieved by the amount of exercise feasible for overweight, older people is modest and easily cancelled out by a snack. To maximize weight loss, the initial approach must recognize the dangers of compensatory eating brought about by any sudden increase in exercise (Finlayson et al. 2009; Hopkins et al. 2014; King et al. 2012). This increase in energy intake, partly conscious and partly subconscious is counterproductive and underlies the common observation that exercise in overweight people does not result in weight loss. The impact of compensatory overeating varies between individuals (Hopkins et al. 2014) but can be entirely avoided. Studies focused on decreased energy intake with no additional exercise achieve ~15% weight loss in 8 weeks. In contrast, the intensive exercise advised in LookAhead, only achieved a maximum weight loss of 8.5% despite

dietary input (LookAhead 2014). This matter must be seen as distinct from the extremely important role of increased physical activity in achieving long-term weight control (Wing and Phelan 2005).

A sustained increase in physical activity is without doubt vital for the long-term avoidance of weight regain and is the single most solid outcome of research across the weight-maintenance field (Pronk and Wing 1994; Kayman et al. 1990). A combination of diet and exercise achieves better weight loss compared with diet alone after 20 weeks of treatment (8.3 kg vs. 5.6 kg respectively) and in 1 year (7.9 vs. 3.8 kg) (Wing 1989). It is possible that the effect of increasing daily physical activity on food limitation is greater in men (Wood et al. 1991).

Bariatric Surgery

For individuals who are not able to achieve weight loss by overall restriction of energy intake, bariatric surgery is an effective option. The overall effects of surgery – including involuntary restriction of food intake, rapid weight loss, post-prandial hypoglycemia, risk of surgical complications – must be discussed with the individual and spouse/partner. Randomized studies comparing outcomes are not informative, as individuals most suited to surgery are not the same people as those most suited to an effective dietary approach. The multicenter Swedish Obese Subjects study (SOS) is important as an observational nonrandomized study comparing different types of bariatric surgeries with medical weight loss treatment (Sjostrom et al. 2004). The remission was three times greater and the risk of type 2 diabetes development was more than three times lower for the bariatric surgery group at 10 years of follow up (Sjostrom et al. 2004).

Bariatric surgery is very successful in achieving sustained major weight loss (Dixon et al. 2008; Buchwald et al. 2009). Indeed, it is the only successful weight loss intervention which can be done by doctors to patients irrespective of the degree of motivation to lose weight. The nature of the operation is important only in the degree of energy restriction enforced, as illustrated by the lesser effect of gastric banding or the equivalent effects of gastric sleeve surgery compared with Roux-en-Y gastric bypass (Dixon et al. 2008; Schauer et al. 2012). Any procedure which results in rapid food entry into the ileum will bring about a greatly increased GLP-1 response after, and many studies have drawn attention to the association with metabolic changes (Guidone et al. 2006; Jorgensen et al. 2012; Laferrere et al. 2007). However, such studies do not indicate any causal relationship and matched feeding studies demonstrate very precisely that identical metabolic changes in type 2 diabetes are achieved by pair feeding studies (Lingvay et al. 2013). Detailed examination of the metabolic changes demonstrates no detectable effect of the GLP-1 spike itself (Steven et al. 2016c; Isbell et al. 2010a; Jimenez et al. 2013). These observations solely concern the early metabolic response to bariatric surgery and other potential effects of the enhanced postprandial GLP-1 response, such as on appetite in the long term, remain to be definitively established.

Other effects of bariatric surgery include changes in bile acid handling and in the gut microbiota, and the consequences of these await precise evaluation. The re-

routing of nutrients after bariatric surgery may affect enterohepatic recirculation of bile acids with potential effects upon glucose metabolism (Pournaras et al. 2012). Obesity alters the gut microbiota, and conversely distinct changes occur after successful treatment by bariatric surgery (Palleja et al. 2016; Zhang et al. 2009). Other hypotheses concerning the metabolic effects of bariatric surgery have been postulated, based largely upon rodent studies. The foregut hypothesis that exclusion of nutrients from the proximal small bowel is unlikely to be relevant to humans, given the striking similarity between the metabolic effects of sleeve gastrectomy and Roux-en-Y gastric bypass for any given degree of weight loss (Schauer et al. 2014). The hindgut hypotheses of incretin production effect is effectively ruled out by the observations on paired feeding studies and other direct human observations (Lingvay et al. 2013; Steven et al. 2015; Isbell et al. 2010b).

Weight loss achieved by bariatric surgery decreases mortality in diabetes by up to 92% (Adams et al. 2007). On the basis of all the evidence to date, The International Diabetes Organization have issued a treatment algorithm for bariatric surgery for type 2 diabetes, supporting use in people with BMI 35–39.9 kg/m^2 when hyperglycemia is inadequately controlled by lifestyle and optimal medical therapy and in those with BMI $\geq$ 40 kg/m^2 (Rubino et al. 2016). Nonetheless, it should be considered whether an individual has exhausted the available dietary methods of weight loss shown to be effective before referring for surgery.

Conclusions

The recent advances in understanding of type 2 diabetes have allowed clarification of the interaction between the effects of accumulating stores of excess fat. Currently in the UK, around half of people newly presenting with type 2 diabetes are obese, setting in perspective the relationship between the two conditions. As the BMI distribution of the population shifts further to the right, continued increase in prevalence of type 2 diabetes can be predicted. At the individual level, personal action to decrease body weight can return a person from the state of having type 2 diabetes to normal metabolic control. The sustained reversal of type 2 diabetes may or may not be associated with decrease of BMI below 30 kg/m^2.

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