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Obesity and Type 2 Diabetes Mellitus

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Abstract

The global obesity epidemic is showing no signs of abating, and is fuelling an explosion in numbers of Type 2 Diabetes Mellitus (T2D) worldwide. Despite clear epidemiological and pathophysiological links between obesity and T2D, the actual mechanisms are complex given that some people with obesity appear to be protected in some way from developing T2D, and T2D can develop in a minority of lean people. Obesity and T2D form part of the metabolic syndrome, which combined with hypertension and dyslipidaemia result in premature mortality from cardiovascular disease in millions of people globally each year. Long-term microvascular sequelae from T2D and multiple co-morbidities associated with obesity (including psychological, musculoskeletal, respiratory and reproductive) also have a major adverse impact on quality of life and pose an enormous fiscal burden on global health authorities. Major factors contributing towards 'diabesity' include chronic overconsumption of energy-dense foods and lack of physical activity.

Recently, it was recognized that T2D is characterized by impaired fat metabolism in addition to glucotoxicity. Overconsumption of energy-dense foods results in excessive fat deposition and enhanced insulin resistance. Free fatty acids (FFAs) delivered to the liver via the portal vein result in fatty liver. FFAs spill into the systemic circulation resulting in lipotoxicity of organs such as pancreas, heart and muscles initiating a viscous cycle of fat damage, inflammation, worsening insulin resistance and beta cell insulin secretion, and ultimately manifestation of T2D. Visceral fat content is an independent predictor of insulin resistance, whilst adipokines such as adiponectin protect against obesity-induced T2D. Further study of the precise mechanisms of lipotoxicity in the development of T2D will enable development of novel strategies to manage and eventually prevent onset of T2D in the context of obesity. In this brief review article, we discuss the currently-understood intricate associations between obesity and T2D and options for management.

Keywords: Diabetes mellitus; Obesity management

Introduction

Epidemiology of obesity and type 2 diabetes mellitus

Obesity and Type 2 Diabetes Mellitus (T2D) are serious health concerns. The global epidemic of obesity and T2D is worsening. According to updated World Health Organization (WHO) reports, worldwide obesity has almost doubled since 1980. In 2008, >1.4 billion adults aged >20 years were either overweight or obese. Of these, >200 million men and about 300 million women were obese [1]. The new International Association for the Study of Obesity/International Obesity Taskforce analysis (2010) estimates that approximately 1 billion adults are currently overweight (Body Mass Index [BMI] 25-29.9 Kg/m²), and a further 475 million adults are obese. With an Asian-specific definition of obesity (BMI >28 kg/m²), global obesity prevalence in adults is estimated at >600 million [2].

Updated WHO reports mention that 347 million people worldwide have Diabetes Mellitus (DM) [3,4], of which T2D comprises the vast majority (90%). T2D is closely associated with excessive body fat and physical inactivity [5]. In 2012, figures from the International Diabetes Federation (IDF) showed that there are >371 million people with DM, with the number of people with DM increasing in every country [6]. Studies using HbA1C on adults ≥ 20 years from the US between 2003 and 2006 (incorporating both diagnosed and undiagnosed DM and those at high-risk for developing DM [pre-Diabetes]) showed the prevalence of DM to be 20.4 million [7]. It is predicted that there will be a growing burden of DM, and that the world prevalence of DM amongst adults aged 20-79 years will increase to 439 million by 2030 [8]. It has been reported that 86% of adults with T2D are overweight or obese; 52% have obesity and 8.1% have morbid obesity [9]. In the next section, we discuss the association between obesity and T2D in more detail.

Association between obesity and T2D

There is a close association between BMI and risk of developing T2D, the relative risk of T2D increasing with BMI. For each kilogram of weight gained annually over a period of 10 years, there is an associated 49% increase in the risk of developing T2D in the subsequent 10 years. Conversely, for each kilogram of weight lost annually over 10 years, there is an associated 33% reduction in the risk of developing T2D in the subsequent 10 years [10]. Health Technology Assessment systematic reviews showed that weight loss was beneficial for long-term T2D-related outcomes and risk of developing T2D in overweight, obese and morbidly-obese participants [11].

Factors other than fat mass *per se* also influence risk of development of T2D. It is clear that fat distribution is relevant to the risk of developing T2D, with central (visceral) adiposity conferring the greatest risk. Waist circumference, a useful clinical surrogate measure of visceral fat, is a useful predictor for subsequent development of T2D. An increase in waist circumference is associated with an increase in the risk of developing T2D. There are also racial/ethnic factors that modify risk of T2D development, with people of Asian origin being at a greater risk that those of Caucasian origin for example, possibly contributed to by differences in fat distribution and associated levels of insulin resistance [12].

The association of obesity with T2D is demonstrated well when comparing Odds Ratios (ORs) for development of T2D according to BMI range. In one study, age-adjusted ORs for development of T2D in overweight and obese men were reported as 2.73 and 7.26 respectively, and concluded that overweight and obesity accounts for a major

proportion of T2D and that prevention of obesity would reduce the incidence of T2D [13]. More recently, Nguyen and colleagues explored the relationship between obesity and T2D in a US adult population based on findings from the National Health and Nutrition Examination Survey, 1999–2006 [14]: Amongst the 21,205 surveyed adults, 2,894 (13.6%) had T2D. Amongst those with T2D, 80.3% were overweight and 49.1% were obese, the prevalence of T2D increasing according to severity of obesity [14].

It is clear from the data presented above that BMI and (particularly visceral) adiposity are associated with the development of T2D. There is also clear evidence that effective weight loss improves glycaemic control in adults with established T2D, and in certain cases (for example following weight loss with bariatric surgery) euglycaemia can be achieved. 'Look AHEAD', a large multicenter trial demonstrated that intentional weight loss in obese and overweight adults with T2D randomized to intensive lifestyle intervention (decreased calorie intake and increased physical activity) had an average of 8.6% weight loss compared to 0.7% weight loss in the control group (that were offered Diabetes support and education). Clinically significant weight-loss at 1-year in T2D was associated with improved diabetes control [15].

The close epidemiological and pathogenic associations between obesity and T2D have led to use of the term, 'diabesity': a term that not only describes the co-existence of obesity and T2D across a spectrum of pre-clinical and clinical presentations, but also highlights pathogenic mechanisms that are common to both obesity and T2D. Throughout this review, our reference to 'diabesity' indicates the concurrence of obesity with T2D. Physiologically, glucose homeostasis is maintained by an intricate balance between insulin secretion from pancreatic beta-cells and insulin sensitivity of peripheral tissues, both of which are influenced by (particularly visceral) fat mass through effects of adipokines and lipotoxicity (Figure 1). Our current understanding of Diabesity however does not explain the whole picture given that T2D can develop in lean adults, and not all obese adults develop T2D. Further research is required to gain a clearer understanding of the pathogenesis of T2D and the complex mechanisms involved that fully explain how obesity and T2D are linked. In the following sub-sections, we outline some of the current main hypotheses regarding obesity-related pathogenesis of T2D.

FFAs and ectopic fat in the development of obesity-related T2D

Development of T2D is closely associated with both overall and abdominal adiposity, highlighting the importance of waist circumference measurement in clinical assessment [16]. Sagittal abdominal diameter and BMI measurement may also predict

Figure 1: A simplified depiction of the interrelationships between Type 2 diabetes mellitus and obesity.

development of T2D [17]. Duration of abdominal obesity is also associated with risk for development of T2D independent of severity of abdominal adiposity [18]. These observations implicate central (visceral) adiposity as an important fat depot for T2D development. One hypothesis is that increased visceral fat results in greater amounts of FFAs reaching the liver via the portal vein resulting in fatty liver. This is associated with elevated non-esterified fatty acid (NEFA) levels in the plasma that in turn result in insulin resistance via Randle's effect in the peripheral insulin target tissues such as muscle [19,20]. In addition to the 'excessive FFA' hypothesis, other hypotheses implicate impaired adipose tissue fat storage, ectopic fat storage, dysfunctional regulation of adipokines and release of adipose-related inflammatory cytokines [20,21]. This latter hypothesis views T2D as a state of chronic inflammation, and the beta-cell dysfunction and insulin resistance as manifestations of a broader systemic chronic inflammatory condition.

In the so-called 'ectopic fat-storage syndrome', there appears to be a critical visceral adipose tissue depot threshold, beyond which this expanding adipose tissue depot is no longer able to store excess fat adequately [22,23]. At this point, fat deposition is diverted to extra-adipose tissue sites such as liver, skeletal muscle and the pancreatic insulin-secreting beta cell, resulting in worsening insulin resistance, impaired beta-cell function and ultimately T2D [21-24]. Ectopic fat deposition is believed to be the result of synergistic effects of increased dietary intake, decreased fat oxidation, and impaired adipogenesis beyond the critical visceral adipose tissue depot threshold [25]. Oxidative stress has been proposed to be a pathogenic mechanism underlying development of insulin resistance, T2D, obesity and cardiovascular disease [26,27]. Excessive intracellular Reactive Oxygen Species activate multiple signalling cascades and kinases that ultimately result in inhibition of insulin action [26], mitochondrial damage and enhanced beta-cell apoptosis, all of which play important roles in the development of obesity-related T2D [26-28].

Adipocytokines in the development of obesity-related T2D

The characteristic enlarged adipocytes in the expanding fat mass observed in obese adults are believed to be in a 'distressed' state. When this occurs, adipocytes release fatty acids, mediators of inflammation and various adipocytokines [29,30]. In response to diverse nutrient and neuro-hormonal signals, adipose tissue secretes adipocytokines that control feeding, thermogenesis, immunity, and neuroendocrine function [29,30]. These adipocytokines serve to alter insulin sensitivity of various insulin-target organs, thereby contributing to pathogenesis of obesity-related T2D. Important adipocytokines in this regard include leptin, adiponectin, resistin, and visfatin [29-32]. The mechanisms whereby each of these adipocytokines may mediate the development of T2D in obesity are outlined below.

Leptin: Elevated leptin levels signal satiety to the brain through receptors in hypothalamic and brainstem neurons. Leptin increases levels of anorexigenic peptides, and inhibits orexigenic peptides. Leptin also has peripheral effects with leptin receptors having been observed in myocytes, liver and pancreas. Peripherally, leptin has been demonstrated to have beneficial effects on glucose metabolism and prevention of hyperglycaemia, and some of these effects are thought to be additive to those of insulin action [29,30]. Furthermore, leptin stimulates fatty acid oxidation and insulin release, and enhances peripheral insulin action via regulation of the enzymes, Phophatidyl-inositol 3 (PI-3) kinase, suppressor of cytokine signaling-3 (SOCS-3), and AMP-activated protein kinase in the brain and peripheral tissues [31]. However, despite these beneficial effects of leptin, obesity is
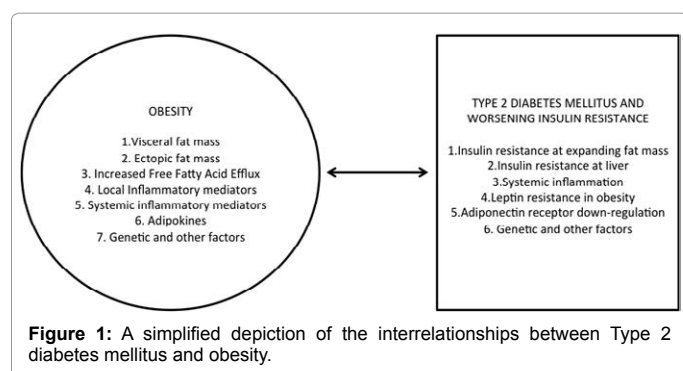
associated with hypothalamic leptin resistance through saturation of leptin's central transport system and inhibition of its intracellular pathway of action [30]. This leptin resistance in obesity is perhaps one mechanism whereby the normal physiological effects of leptin including suppression of appetite and promotion of insulin's effects, appear to be overcome and result in a downward spiral where weight gain begets further weight gain and insulin resistance.

Adiponectin: Adiponectin has been linked to glucose, lipid, and cardiometabolic regulation with potent insulin-mimetic, insulin-sensitizing and anti-inflammatory properties [29-32]. Obesity, T2D and atherosclerosis are associated with reduced serum adiponectin levels. Administration of adiponectin reverses insulin resistance (possibly via an Activated Protein Kinase [AMPK]-mediated process). In obese and insulin-resistant states, receptors for adiponectin are also down-regulated, further reducing its beneficial effects. In obesity and insulin resistant states, reduced serum adiponectin levels are influenced by effects on adiponectin gene transcription, and repression of adiponectin production by tumour necrosis factor-alpha (TNF-alpha) and Interleukin-6 (IL-6) [29,33,34].

Resistin: Elevated serum levels of resistin in obesity results in an increase in the production of adipocyte-derived chemotactic agents and pro-inflammatory cytokines. These cytokines suppress hepatocyte Insulin Receptor Substrate-2 (IRS-2) and uncouple the insulin-signalling pathway in hepatocytes [29,35-38], thereby contributing towards hepatic insulin resistance. In skeletal myocytes, resistin also impairs glucose-uptake and blocks the insulin transduction pathway [38]. Through its effects on hepatocytes and myocytes, resistin is believed to play an important role in the development of T2D in obesity.

Visfatin: Recent studies suggest that visfatin may represent a pro-inflammatory cytokine that is influenced by serum levels of insulin and degree of insulin resistance. In this way, visfatin may also play a role in the development of T2D in obesity [29,39].

It is clear from the above discussion that there are many known adipocytokines that correlate with severity of obesity and degree of insulin resistance, and that probably play important roles in the development of T2D in obesity. It is likely that further adipocytokines will be identified in future years that may add to the complexity of diabesity. It is also clear, however, that some of the mechanisms identified for various adipocytokines (such as visfatin) implicate inflammatory pathways. Our view of diabesity in recent years has migrated towards that of a chronic inflammatory condition. Recent evidence implicates inflammatory pathways in the development of T2D in obesity. This is discussed further in the next section.

Inflammation in the development of obesity-related T2D

Low-grade inflammation at the level of the adipocyte and systemically are characteristic of diabesity states. It is likely that inflammatory signals interfere with metabolic pathways at the cellular level, such effects including impairment of the insulin-signalling pathway in peripheral tissues. In this way, it is thought that chronic inflammation may promote insulin resistance in obesity thereby contributing towards the development of T2D. Various molecules have been implicated in the chronic inflammation that characterises diabesity. These include pro-inflammatory cytokines derived from both the adipocyte and macrophages within adipose tissue [29,40,41]. Other molecules that are likely to be implicated in the chronic inflammation of diabesity include Interleukin-1 (IL-1), IL-6, TNF-alpha, c-Jun N-terminal kinase-1 (JNK-1) and also I kappa-B kinase-beta (IKK-β).

It is likely that these molecules play important roles in the development of T2D in obesity [40-45]. The intricate role of chronic inflammation in diabesity, how this interacts with the metabolome and metabolic pathways, and the mechanisms whereby chronic inflammation develops in obesity and insulin resistant states (and the upstream triggers for this process) are all areas of current and future research. Through developing a clearer and more complete understanding of these pathways and triggers, we will establish novel targets for therapies that are targeted towards key pathways in the development of diabesity, thereby potentially for use in the prevention and treatment of T2D in obese and insulin-resistant states. In the next section, we outline the currently available management strategies for diabesity.

Management of diabesity

In the previous sections, we have outlined the epidemiological and pathophysiological overlaps between obesity and T2D, and highlighted the important role that obesity often plays in the development of T2D. This important role that obesity plays forms a rationale for obesity management in adults with diabesity. In addition to reducing the likelihood of developing T2D in those with obesity, weight loss also has a beneficial impact on glycaemic control and other metabolic features in diabesity. As a result of improved glycaemic control through weight-loss, pharmacotherapy for glycaemia may need to be modified accordingly, and this should be reviewed regularly. There are several approaches to the management of diabesity that include lifestyle-, medical- and surgical-based approaches, each of which is outlined below.

Lifestyle modification in management of diabesity

Sustainable weight-loss in diabesity is often a challenge. Lifestyle modification, through changes in diet, physical activity and behaviour, is generally the first-line strategy. In such cases, realistic short and longer-term targets for weight loss should be set. Patients should be encouraged to eat breakfast regularly, to weigh themselves regularly, to avoid snacking between meals, and to pay close attention to portion sizes. Avoidance of high-sugar fizzy drinks is also important. Regular physical activity should be encouraged (although there are often barriers to this in morbid obesity that include musculoskeletal and psycho-social problems), and patients should be encouraged to monitor closely changes in glycaemic control that may result from weight loss and/or improved metabolic status [29,46]. The effects of excess dietary fat and carbohydrate are particularly pertinent in this context. The deleterious effects of excessive dietary fat intake include increased adipose tissue depot mass, reduced diet-induced thermogenesis, effects on satiety and increased insulin resistance and associated dysmetabolism. Dietary intake of fats and carbohydrates (including starchy foods such as bread and pasta) should be reduced.

It should be made clear that to maintain weight loss, and if further weight loss is desired, additional dietary energy restriction would usually be required. The role of modern very low calorie diets (VLCD), a diet of < 800 Kcal/day, has been noted to result in short-term benefits with regards to glycaemic control, insulin sensitivity and inflammatory markers. VLCDs are especially useful for selected patients with diabesity under close medical supervision, particularly those who await a bariatric surgical procedure (in whom benefits include hepatic shrinkage) [47-50]. The long-term effects of VLCDs are however yet to be demonstrated [49,50].

In addition to dietary changes, behaviour modification and motivation form an important component of weight management in

diabesity. Approaches include setting realistic targets for weight-loss, improving self-monitoring of weight, stimulus control, environmental changes and problem-solving. Another technique includes cognitive restructuring to identify and modify negative thoughts, and enhance rewarding thoughts [51]. Enhanced physical activity is also important in the prevention and management of diabesity through improvements to energy balance and metabolic control. Encouragement of physical activity should be tailored and targeted for the individual, and if applied successfully should improve the success of weight management, though long-term maintenance of enhanced physical activity remains an important concern [52-55].

Medical approaches to management of diabesity

It is often a challenge for patients with diabesity to achieve and sustain substantial weight-loss through lifestyle approaches, and often alternative strategies are required [56]. Unfortunately, as healthcare professionals we are very limited in what we can offer with regards to medical therapies for obesity, and development of safe and effective weight-loss therapies, particularly in those patients with diabesity should be a priority for the future. To make the problem worse, some of the traditional therapies for T2D including sulphonylureas and insulin therapies are associated with weight gain thereby worsening insulin resistance. (One sulphonylurea drug, Glibenclamide was shown to result in weight gain of around 3-4kg within the first year of therapy [57]). Other therapies such as metformin (used as a first line therapy in drug-treated patients with T2D following lifestyle implementation [57]) and the Dipeptidyl Peptidase-4 (DPP-4) inhibitors are weight-neutral. However, recent developments have been exciting with the injectable incretin (Glucagon-Like Peptide-1 [GLP-1]) based therapies being associated with (sustained) weight-loss, in addition to being safe and generally well-tolerable [58]. Likewise, the new Gliflozin class of therapies for T2D based on inhibition of the Sodium-dependent Glucose co-transporter-2 (SGLT2-inhibitors) also promote weight-loss in an entirely different (and complementary) way from the injectable incretin-based therapies.

Currently, Orlistat is the only weight-loss therapy licensed for management of obesity. Orlistat can be useful as an adjunct to other therapies (lifestyle and medical) for promotion of weight-loss in diabesity. Orlistat can result in improvements to glycaemic control and inflammatory and metabolic parameters in diabesity that are likely related to the associated weight-loss with this therapy [59,60]. Whilst Orlistat can be a useful agent, its unpleasant side-effect profile (that includes oily faeces and excessive flatulence) can pose a problem for compliance with this therapy.

Unfortunately, obesity often begets further weight gain and worsening of obesity and there are a number of complex mechanisms that are likely to be implicated that include effects on appetite, stomach capacity (and feelings of fullness), leptin resistance, brown fat activity, changes in energy expenditure related to expansion of fat depots, and changes in physical activity. Despite the efforts of a multi-disciplinary team, instigation of lifestyle (including dietary) changes and optimal use of medical therapies in diabesity, lack of weight loss and even further weight gain may continue to be a problem. In such cases, careful consideration should be given to a surgical management approach which forms the topic of the next section.

Surgical approaches to management of diabesity

Metabolic surgical techniques are broadly divided into restrictive (including insertion of a gastric band and sleeve gastrectomy) and by-pass procedures (including Roux-en-Y Gastric Bypass and Bilio-Pancreatic Diversion). Metabolic surgery can be an attractive option for patients with diabesity, especially if performed before the stage at which irreversible beta-cell insulin secretory failure ensues. One advantage of metabolic surgery is that maintenance of weight-loss (which is particularly difficult to achieve through lifestyle modification in patients with diabesity) is often achievable with this treatment modality [61]. In addition to being an effective means of promoting weight loss, metabolic surgery also often results in improvements to glycaemic control in patients with diabesity. Various mechanisms have been proposed for the improved glycaemic control following metabolic surgery in diabesity, including modification of dietary intake and calorie restriction, changes in gut hormone release that in turn affect appetite and pancreatic function, reversal of abnormal intra-myocellular fat deposition in skeletal muscles and improved effectiveness in hepatic glucose-handling [62-66]. Metabolic surgery can result in euglycaemia in some patients with diabesity, and associated reduction in cardiometabolic risk [67-70]. The actual mechanisms by which metabolic surgery improves weight and glycaemic control in diabesity should be a focus for future research, and should inform future development of novel strategies to manage diabesity (perhaps based on therapies that replicate the gut hormone changes that occur following by-pass procedures for example).

Facing the challenges of the 'emerging and converging' epidemic of T2D and obesity

Diabesity is common, and its global prevalence is increasing at an alarming rate. Diabesity is being fuelled by the obesity epidemic that in turn is a result of our modern obesogenic environment with ready access to highly calorific foods, technology that seems to limit our energy expenditure and our '24-hour' society with associated sleep deprivation (and effects on appetite control and metabolism). Unfortunately, we as a species are maladapted genetically to our modern-day environment, having evolved (as with all other species) in the context of food scarcity, frequent famine and a biology that is well-adapted to protect us from the potentially life-threatening effects of famine. This same biology which is very useful in the context of famine is unfortunately extremely harmful in the context of chronic over-nutrition.

There is a close epidemiological and pathophysiological association between obesity and T2D. Obesity (particularly visceral adiposity) is an important risk factor in the development of T2D, and some of the currently understood mechanisms implicated have been outlined here. In addition to these mechanisms, other factors contributing to diabesity, such as the role of genetic traits, quantitative genetic analysis of obesity, behavioral changes, neonatal factors and childhood obesity have been reviewed recently [71,72]. However, there are likely to be other mechanisms at play in, for example the minority of lean adults who develop T2D. Furthermore, we do not fully understand why some adults with obesity (and sometimes morbid obesity) appear to be protected in some way from developing T2D and other adverse metabolic features that characterise the metabolic syndrome. The establishment of a clear understanding of these mechanisms should be a focus for future research in this field.

Traditionally, the therapies used to treat patients with T2D have resulted in weight gain that worsens insulin resistance and further contributes to metabolic problems. Some of the newer therapies for T2D (injectable GLP-1 based therapies and SGLT2 inhibitors) are associated with weight-loss and this is an exciting development. Metabolic surgery remains the most effective strategy to promote

weight loss and improve glycaemic control in many patients with diabesity, although its cost is a little prohibitive, and will currently prevent wide-scale application of this approach. It is important that further research is focused on exploring the mechanisms implicated in weight-loss following metabolic surgery. This would inform future novel therapeutic strategies for diabesity that potentially avoid the need for a surgical procedure, but are rather based on medical therapies (a 'medical-bypass').

Conclusion

Obesity and T2D, whether individually or whether co-existing as Diabesity, are of major importance with regards to premature mortality, quality of life, associated chronic microvascular complications (in the case of T2D), obesity-associated co-morbidities, and the global healthcare economy. A better understanding of the causative and therapeutic interrelationships between these two conditions is essential. Tackling the worsening global epidemic of diabesity effectively will require a multifaceted approach focused on both adults and children that includes governments, changes to environments, changes to cultures (particularly around food) and development of novel, safe and effective therapies that promote weight-loss and improve the dysmetabolic state. These efforts should be a major priority. Now is the time to act.

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