Diabesity: Pathogenesis and novel preventive and management strategies

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Article points

1. An obesity epidemic throughout the world has resulted in an increase in the number of people diagnosed with type 2 diabetes, so much so that the term "diabesity" has been coined.
2. Contributors to this epidemic include caloric over-consumption, sedentary lifestyles, sleep deprivation, thermo-neutral environments and eating-related behaviour.
3. Management strategies include lifestyle modification, bariatric surgery and, potentially, the activation of brown adipose tissue, which is a means of enhancing metabolism through converting fat into heat. Cultural and behavioural changes are also important.

Key words

- Diabesity
- Obesity
- Type 2 diabetes

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The global obesity epidemic has fuelled a global epidemic of type 2 diabetes (T2D). Diabesity, the frequent combination of obesity with T2D, represents one of the biggest health threats. Underlying this scourge for humanity is a complex array of contributors, including chronic caloric over-consumption, sedentary lifestyle, sleep deprivation, thermo-neutral environments and eating-related behaviour. Regarding the management of diabesity, lifestyle modification can be effective, although often difficult to sustain over longer durations. Bariatric surgery is an excellent treatment option for diabesity, although its cost precludes widespread application. Activation of brown adipose tissue (a means of enhancing metabolism through converting fat into heat) represents a promising novel preventive and management future strategy. Finally, cultural and behavioural changes regarding calorie consumption and physical activity are important.

Evolution, through eons of caloric-deprivation, has well-equipped us with strong biological processes and drivers that mitigate one of the biggest evolutionary threats to species survival: starvation. Unfortunately, such evolutionary genetic and physiological endowment has ill-equipped us for the current biggest threat to human survival: our calorie-dense obesogenic environments that have emerged over the last 40 years. During this time, worldwide obesity has doubled. In 2008, >1.4 billion adults were either overweight or obese, of whom >200 million men and 300 million women were obese (Yatsuya et al, 2014). More recent data show that >50% of the populations of US and Europe are either overweight or obese (Yatsuya et al, 2014). The seemingly relentless progression of global obesity, attributed to caloric over-consumption and sedentary lifestyle, has driven an explosion in obesity-related disease. This is a huge and complex challenge, but a challenge that we all must face.

One of the most burdensome manifestations of the obesity epidemic is an explosion in the global prevalence of type 2 diabetes (T2D). Globally, there were 382 million people with diabetes in 2013, expected to increase to 592 million by 2035 (Forouhi and Wareham, 2014). The close pathogenic link between obesity and T2D (including insulin resistance) is reflected by strong epidemiological overlap (Saboor Aftab et al, 2013). In this context, "diabesity" has been used to define a majority of people with T2D who also are obese. In this brief review, diabesity is explored from perspectives of underlying pathogenic mechanisms and preventive and management strategies.

Pathogenesis of diabesity

The usual suspects

Chronic over-consumption of highly calorific foods and sedentary lifestyles are important contributors to diabesity (McAllister et al, 2009). Modern technology often limits activity-related metabolism. Strategies to reduce caloric intake and enhance activity-related metabolism are cornerstones of weight management through lifestyle modification.

Sleep deprivation and quality

As a potential contributor to the obesity epidemic, sleep has received relatively little attention. We are a sleep-deprived nation. In westernised societies like the US and UK, average nightly duration of sleep has reduced by 1 hour, compared to what our parents and grandparents enjoyed in the 1960s (Spiegel et al, 2004). In the UK, over 30% of adults aged between 30 and 64 years report sleeping less than 6 hours per night (Cappuccio et al, 2008).

There is a clear association between sleep duration and risk of obesity. In a meta-analysis, it was reported that adults who sleep for <5 hours per night have a 60% increase in the risk for obesity, compared with adults who sleep for longer durations each night (Cappuccio et al, 2008). Children need more sleep than adults, but a similar association between childhood sleep deprivation and obesity pertains (Cappuccio et al, 2008). The Wisconsin Sleep Study shows evidence for a U-shaped correlation between nightly sleep duration and BMI; for adults, 7.5 hours of sleep each night appears optimal and is associated with a relatively low BMI (Taheri et al, 2004).

Mechanisms that link sleep duration with obesity and subsequent risk for T2D and other metabolic dysfunction are incompletely understood. However, it is clear that appetite and appetite-regulating hormones are influenced by sleep duration. In one study on healthy young men, it was shown that after just 2 nights of sleep curtailment, appetite for high-carbohydrate foods increased by 32%, ghrelin levels (an appetite-regulating hormone) increased by 28% and hunger increased by 24%, leading to increased caloric consumption (Spiegel et al, 2004).

Sleep quality is also important for metabolic health. There is an association between BMI and apnoea–hypopnoea index (AHI), a marker of sleep quality used to diagnose obstructive sleep apnoea (OSA). A third of morbidly obese adults (BMI >40 kg/m^2) have an AHI ≥65, which is indicative of severe OSA (Valencia-Flores et al, 2000). There are complex multi-directional mechanisms that link obesity, OSA, insulin resistance and metabolic risk, including T2D development (Saboor Aftab et al, 2013). There is also sex-specific interplay between weight gain, sleep and reproductive axes in both men (Saboor Aftab et al, 2013) and women (Barber and Franks, 2013).

Sleep deprivation and OSA are contributory to pathogenesis of diabesity. It is important that sleep duration is optimised within the population and that raised awareness, screening for and effective management of OSA are prioritised to mitigate the harmful metabolic effects of sleep deprivation and OSA.

Thermo-neutrality

Humans tend to prefer living in a thermo-neutral zone, defined as a temperature between 25–30°C. In recent years, average ambient environmental temperature has increased. Between 1970 and 2000, average temperature inside UK-based homes increased from 13°C to 18°C (McAllister et al, 2009). There is evidence for a link between ambient temperature and metabolic rate in humans. In one study, it was shown that energy expenditure in men exposed to an ambient temperature of 22°C was 167 calories per day lower than at 16°C (McAllister et al, 2009). Although the effects of ambient temperature on metabolism appear relatively subtle, over time this thermoneutral-induced reduction in metabolic rate would be expected to contribute towards weight-gain (McAllister et al, 2009). Through this mechanism, it is likely that warmer living environments have contributed towards pathogenesis of diabesity.

"Fast" food

Human metabolism is broadly divided into three major components: basal metabolic rate (BMR); activity-related metabolism (ARM); and thermic effect of food (TEF). BMR is usually constant and obligatory, and simply reflects the magnitude of metabolism required to maintain cellular function to sustain life. Conversely, the two facultative components of metabolism, ARM and TEF are variable between individuals and influenced by levels of activity and food-related behaviour respectively. ARM and TEF provide opportunities for us to enhance our metabolism to mitigate harmful effects of chronic caloric over-consumption.

Much has been surmised with regards to how our modern-day sedentary lifestyles limit ARM, providing a rationale for advocating increased exercise and activity levels as part of healthy living (Villablanca et al, 2015). The potential influence of TEF on body weight has received less attention. My own group studied the effect of meal duration on TEF in obese normoglycaemic women in a

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2. Humans tend to prefer living in a thermo-neutral zone, defined as a temperature between 25–30°C. It is likely that warmer living environments have contributed towards pathogenesis of diabesity.
3. Our lifestyle and "fast food" culture may limit the thermic effect of food and this may facilitate weight gain over time.

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whole-body calorimeter at the Human Metabolism Research Unit (University of Warwick, University Hospitals Coventry and Warwickshire NHS Trust; Reddy et al, 2015). On separate days, a standard meal was eaten by each participant over 40 minutes (D40) and 10 minutes (D10). Postprandial TEF over 4-hours was significantly greater for D40 compared with D10 (80.9 calories versus 29.9 calories, respectively). Furthermore, compared with D10, D40 was associated with significantly reduced plasma non-esterified fatty acids and elevated adiponectin levels in the postprandial period (Reddy et al, 2015). Other epidemiological studies suggest associations between self-reported speed of eating with obesity and cardiovascular risk (Ohkuma et al, 2013).

Our data suggest that meal duration influences TEF. Our busy lifestyles and "fast food" culture may limit TEF, thereby facilitating weight-gain over time. Sedentary lifestyle and fast eating behaviour seem to minimise facultative components of metabolism, ARM and TEF respectively.

Medical conditions affecting metabolism

A common misconception is that low BMR contributes to weight-gain. In reality, when BMR is adjusted for lean body mass (a major determinant of BMR), rates between individuals are similar (Goran, 2000). Occasionally, as with hypothyroidism, slower BMR may contribute to weight-gain over time. Metabolic changes may also contribute to weight gain in other conditions, such as polycystic ovary syndrome (Barber et al, 2006) and Cushing's Syndrome (Ferrau and Korbonits, 2015).

The explosion in the prevalence of diabesity is perhaps not surprising when one considers the harmful effects of modern daily life on our metabolic health. It seems that every aspect of our modern lives, including sleep duration and quality, what we eat, how we eat, what we do and our environmental temperatures have conspired to increase risk for development of diabesity (*Figure 1*). A final piece in the dysmetabolic jigsaw is perhaps mental stress, a common feature of modern daily living, which is

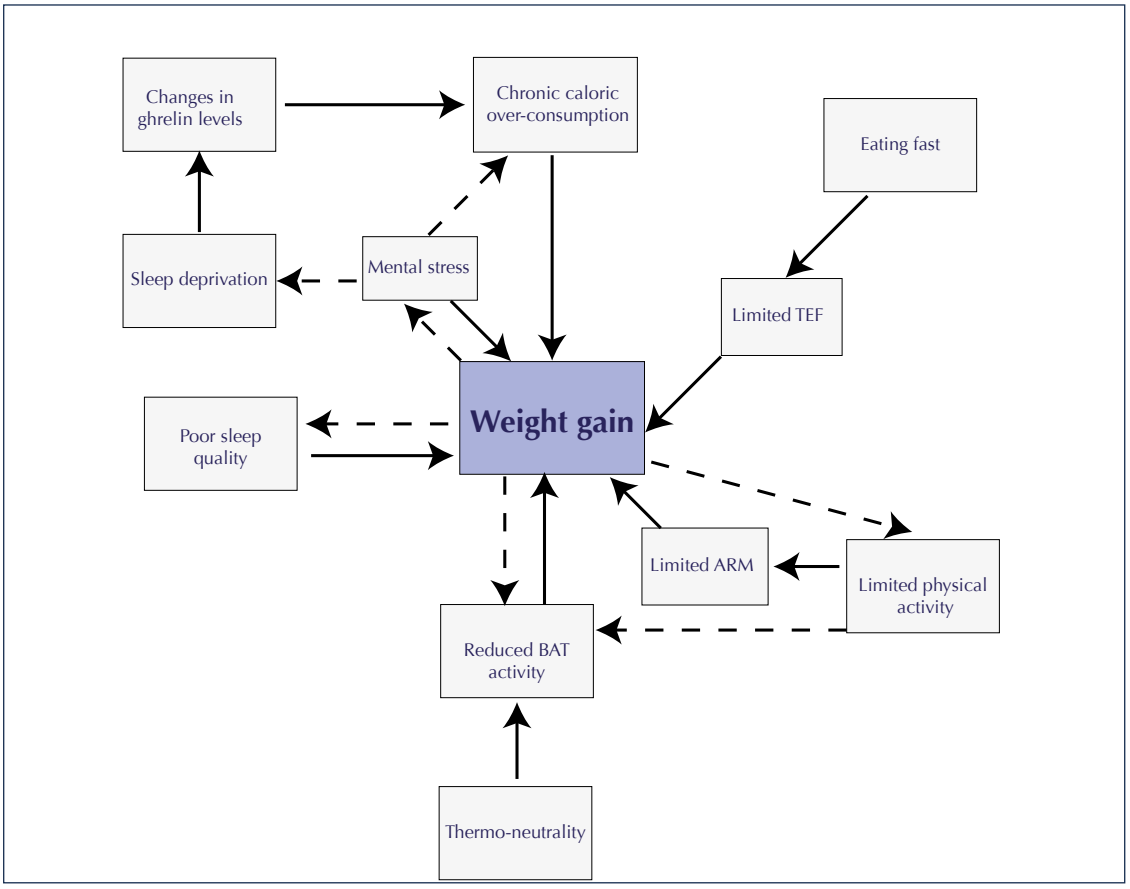

Figure 1. Pathogenesis of diabesity: factors associated with our modern-day obesogenic environment. ARM= activity-related metabolism; BAT=brown adipose tissue; TEF=thermic effect of food.

likely to contribute towards risk of diabesity, both directly and indirectly in multiple ways. In the next section, strategies to prevent and manage diabesity are explored.

Preventive and treatment strategies for diabesity

Lifestyle modification

Effective lifestyle change remains first-line management and the preferred preventive strategy for diabesity. Although dramatic effects on metabolic health are achievable in some, sustained lifestyle modification is challenging. The principles of lifestyle change include dietary modification, physical activity and behavioural change. Its effective implementation often requires multidisciplinary input from dietitians, specialist psychologists and bariatric physicians. Dietary principles include encouragement of individuals to weigh themselves regularly, eat breakfast regularly, avoid snacking between meals, avoid high-sugar fizzy drinks, limit consumption of fats and carbohydrates, and pay close attention to portion sizes. Psychological techniques include motivational interviewing, stimulus control, environmental change, problem-solving and cognitive restructuring to identify and modify negative thoughts and enhance rewarding thoughts (Dalle Grave et al, 2013).

Unfortunately, successful weight-loss (characterised by loss of fat mass) through lifestyle modification is frequently associated with concomitant decline in lean tissue. Lean body mass is a key determinant of BMR (Stiegler and Cunliffe, 2006). Therefore, metabolic rate often declines with successful weight loss. This is one reason why sustained weight-loss is often difficult and why levels of physical activity often need to be enhanced following weight-loss, to compensate for a reduction in BMR and to mitigate against the resulting tendency for weight re-gain. There is ongoing research on how to protect lean mass during weight-loss (through protein and exercise, for example), thereby maintaining BMR at a level that is more conducive to sustained weight-loss (Stiegler and Cunliffe, 2006).

In certain scenarios, such as prior to bariatric surgery, a "very low calorie diet" (VLCD; a diet of <800 calories per day) can help to facilitate more rapid weight-loss. VLCDs are associated with short-term effects on glycaemic control, insulin sensitivity and inflammatory markers, and can also help to promote liver shrinkage (Boden et al, 2005). Although some studies have demonstrated the safety of VLCD when used for durations longer than 6 months (Sumithran and Proietto, 2008), the longer-term effects of VLCD on body weight and clinical outcomes in people with diabesity are yet to be fully demonstrated, and should be an area for ongoing focused research.

The role of bariatric surgery

Bariatric surgical techniques are broadly divided into restrictive (laparoscopic adjustable gastric band and sleeve gastrectomy) and by-pass procedures (Roux-en-Y gastric bypass and bilio-pancreatic diversion). Bariatric surgery can be an excellent treatment option for diabesity. In one meta-analysis that included >600 studies and >135 000 people, it was demonstrated that following bariatric surgery, T2D resolved in 78% of cases (Buchwald et al, 2009). Current consensus is that gastric bypass procedures facilitate expedited delivery of nutrients into the distal small bowel. This in turn results in a more pronounced release of incretins, such as glucagon-like peptide-1 (GLP-1) and peptide YY, that have effects on postprandial glucose levels through modulation of insulin and glucagon release, and also have direct appetite suppressant effects (le Roux et al, 2006). This "hind-gut" hypothesis is thought to play an important role in the establishment of euglycaemia in people with diabesity following gastric bypass procedures (le Roux et al, 2006). People with diabesity who undergo sleeve gastrectomy also have a high rate of T2D resolution post-procedure. This in part relates to reduced plasma levels of the appetite-stimulating hormone ghrelin, released from the gastric fundus (Anderson et al, 2013).

Our best evidence for the beneficial effects of bariatric surgery on morbidity, mortality and sustainability of weight-loss over the longer term originates from the Swedish Obese Subjects study. In an analysis of >40 000 patient years following bariatric surgery (over 15 years), there was a 24% reduction in overall mortality and a 67% remission rate for T2D at 10 years following bariatric surgery (Sjostrom, 2013). Although the cost of bariatric surgery remains a barrier to its widespread

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1. Activation of brown adipose tissue (BAT) represents a promising future novel strategy for the prevention and effective management of diabesity.
2. Application of magnetic resonance-based imaging may provide a means of quantifying BAT that could be developed for assessing future therapies that augment BAT. Research should focus on development of novel activators of BAT, including nutritional strategies.

implementation, it is hard to over-emphasise the important role that this option, which is endorsed by NICE guidelines CG189 (2014), can play in the effective long-term management of diabesity.

Brown fat activation

Currently in the UK, there is only orlistat licensed for weight-loss (Arch, 2015). Orlistat can work well in some people, although its use is limited by unpleasant gastrointestinal side-effects. The situation for diabesity has improved in recent years with the availability of two new classes of therapies licensed in adults with T2D for improving glycaemic control, the GLP-1 receptor agonist and sodium-glucose co-transporter-2 (SGLT-2) inhibitor classes. Their weight-losing properties are welcome in the treatment paradigm of diabesity (Barber et al, 2010), especially when combined with effective lifestyle modification strategies.

In my view, activation of brown adipose tissue (BAT) represents a promising future novel strategy (and even potential metabolic panacea) for the prevention and effective management of diabesity. BAT and white adipose tissue (WAT) each evolved to mitigate two major threats to species survival: hypothermia (through generation of heat in BAT) and starvation (through storage of energy in WAT; Enerback, 2010). BAT is packed full of mitochondria that contain uncoupling protein-1, which uncouple oxidative phosphorylation. Instead of formation of adenosine triphosphate, energy from fat oxidation within BAT is released as heat (Reddy et al, 2014a). It has been estimated that just a sugar-cube size of BAT, if maximally activated for a whole year, would transform into heat the energy contained within 3.5 kg of WAT (Enerback, 2010). During BAT activation, both lipids and glucose are utilised and over time, weight-loss would be expected to ensue.

Recently, the future therapeutic potential of BAT became closer to reality through serendipitous observations of active BAT in some human adults on [18F]-fluorodeoxyglucose PET-CT scans performed for clinical reasons (Enerback, 2010). Active BAT appears to predominate within cervical, axillary, intra-mediastinal and para-vertebral locations. Although cold ambient temperature is known to activate BAT (Enerback, 2010), an important unanswered question and one that has therapeutic implications, is how many of us actually have BAT, and in how many of us is it activated. Estimates of BAT activity are variable (Izzi-Engbeaya et al, 2015) and this remains contentious. It is possible that we all have BAT, but that in most of us it remains inactive in adulthood and would not therefore reveal itself on a [18F]-fluorodeoxyglucose PET-CT scan in most scenarios.

To gain further insight into human BAT, my own group published the first demonstration of magnetic resonance (MR)-based imaging of BAT in a living human adult (Reddy et al, 2014b). Application of MR-based imaging may provide a means of quantifying BAT that could be developed for assessing future therapies that augment BAT. Research should focus on development of novel activators of BAT, including nutritional strategies. Examples include enhanced TEF through capsaicin-induced activation of BAT via the sympathetic nervous system (Yoneshiro et al, 2012), and development of irisin as a possible enhancer of metabolism through BAT activation (Piya et al, 2014). Future food-based solutions to diabesity should include assessment of enhancement of BAT-related metabolism

Conclusions and future directions

Diabesity is an ugly manifestation of our modern lifestyles and behaviour. The perfect storm for a global diabesity epidemic has become established through strong genetic and physiological drivers to mitigate harmful effects of under-nutrition and starvation, combined with exposure to our modern obesogenic, busy, mentally-stressful, "24-hour" and thermo-neutral environment: one that represents an antithesis to our evolutionary environment.

The complexity of diabesity pathogenesis, extending beyond caloric over-consumption and sedentariness, demands a multifaceted approach to prevention and effective management. Lifestyle remains a cornerstone but is often difficult to sustain. Bariatric surgery is a potential solution although unlikely to ever be available to the majority of people with diabesity. It is important that ongoing research focuses on novel strategies, such as manipulation of BAT, to tackle this complex problem.

An important group, worthy of special focus, is our children, including their diets, lifestyles, sleeping habits and behaviour. It is imperative that these are

all optimised for a healthy future. It is incumbent on all of us to effect cultural and behavioural change to slow and ultimately reverse the global diabesity epidemic. ■

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