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Obesity: Causes, Consequences and Patient-Centred Therapeutic Approaches

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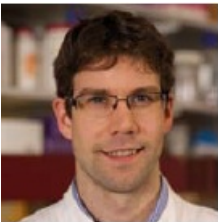
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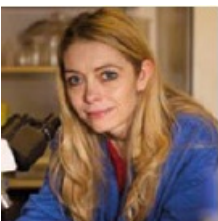
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Obesity is one of the greatest 21st century public health challenges. However, government strategies aimed at reducing the unprecedented levels of obesity have been largely unsuccessful to date (Institute of Medicine 2013). Only in 2013 the American Medical Association (AMA) identified the necessity for prevention and medical interventions in the obesity field, suggesting that clinicians are also lagging behind in the fight to halt the obesity epidemic (American Medical Association 2013). Excess weight is the fifth leading risk factor for global deaths. At least 2.8 million adults die each year as a result of being overweight or obese. In addition, approximately 44% of the type 2 diabetes (T2D) burden, 23% of the ischaemic heart disease burden and between 7% and 41% of certain cancer burdens are attributable to overweight and obesity. Obesity is also a major risk factor for numerous other health problems, including hypertension, respiratory and musculoskeletal problems. Mortality also increases above the overweight threshold in direct proportion to increasing body mass index (BMI) (Whitlock et al. 2009). In this article, we will briefly summarise the epidemiologic and economic burdens of obesity. We will also discuss the role of biological factors, with a focus on the gastrointestinal (GI) tract, the pathophysiology of obesity and how understanding the biology may hold the key to novel therapeutic approaches.

Obesity Trends

It has been estimated that obesity has nearly doubled worldwide since 1980. In Europe its prevalence has tripled in many European Union (EU) countries since the 1980s. In 2008 more than 1.4 billion adults, aged 20 and older, were overweight (defined as BMI 25.0 – 29.9 kg/m²) and over 500 million were obese (defined as BMI >30.0 kg/m²) (WHO Regional Office for Europe 2013). These trends are dramatic also in the paediatric setting, with more than 40 million overweight children in 2011. Based on the latest available data, more than half (52%) of the adult population in the EU are overweight or obese. The prevalence of overweight and obesity among adults exceeds 50% in no less than 18 of 27 EU member states. Obesity varies threefold among countries, from a low of around 8% in Romania (and Switzerland) to over 25% in Hungary and the UK. Across EU member states 17% of the adult population is obese on average. There is little difference in the average obesity rate between men and women. However, there is some variation among individual countries, with more men than women being obese in Malta, Iceland and Norway, whereas a higher proportion of women are obese in Latvia, Turkey and Hungary. The largest disparities were in Latvia, whereas there was little, if any difference in male and female obesity rates in the Czech Republic, Greece and the UK. The rate of obesity has doubled over the past 20 years in many European countries, regardless of previous levels. For example, in both France and the UK, the prevalence of obesity in 2010 is close to twice that of 1990, even though the rate in France is currently half that of the UK (WHO Regional Office for Europe 2013).

Costs of Obesity

There are innumerable costs associated with obesity and its comorbidities in the health economic setting, fitting into two broad categories: 1) direct costs, which are the result of outpatient and inpatient health services (laboratory and radiological investigations, medications and bariatric surgery) and 2) indirect costs, which are the lost resources as a result of a health condition, for example days missed from work, insurance or wages. Obesity is associated with very high, preventable costs, and it has been estimated that it is already responsible for 2-8% of health costs (Organisation for Economic Co-operation and Development 2012). Although this cost quantification is complex, the overall cost of obesity in Europe in 2010 has been estimated at about 460 billion Euros per annum. The enormity of this obesity-related economic burden is beginning to raise global political awareness that individuals, communities, states, nations and international organisations must do more to face the rising tide of obesity (Organisation for Economic Co-operation and Development 2012).

Evolutionary Context

The widely expounded, but somewhat simplistic, understanding of why individuals develop obesity is based on the premise that a chronic state of energy intake exceeding energy expenditure results in excess calories being stored as body fat. However, this simplistic view does not take into account the multitude of factors that affect what we eat, how physically active we are and how our bodies process energy and adapt to changes in energy availability or expenditure. In this regard, we must consider the evolutionary context of how procurement of food is critical for survival. Drive for food is one of the most powerful human and animal behaviours, and it is fundamental for preservation of the species. There are several systems controlling food intake and body weight (Berthoud 2011; Coll et al. 2007). These biological drivers have adapted during the evolution of the human body over the millennia. One hypothesis that has been put forward is that 'thrifty' genotypes have been positively selected because of the survival and fecundity advantages conferred by a better use of scarce energy resources (Neel 1962). In modern society, such genotypes may be counterproductive, because they promote fat deposition in preparation for a famine that never comes, and the result is widespread obesity. However, the high prevalence of normal bodyweight in the face of an obesogenic environment suggests that other hypotheses such as the 'drifty gene' hypothesis may better explain our genetic propensity to obesity (Speakman 2008). This hypothesis points to the gradual advent of a reduced risk of predation as an important event in our evolutionary history, which in turn led to progressively less negative selection for factors predisposing to excess weight. Thus, this reduced risk of predation was subsequently followed by random genetic mutations, affecting energy balance control systems, which over time became more numerous and prevalent, i.e. an upward 'drift' in the genetic susceptibility to obesity. Undoubtedly, it has been the recent dramatic changes in our environment, including the increasingly wide availability of food and sedentary lifestyle, that have rapidly unveiled this slow burning underlying genetic susceptibility to obesity (Speakman et al. 2011).

Gastrointestinal Tract

In recent years the role of the GI tract as the body's largest endocrine organ has emerged. Cells in the GI tract called enteroendocrine cells produce hormones that play an important role in regulating bodyweight. These hormones act through a complex neuroendocrine system, including the hypothalamus and brain reward centres, to regulate energy homeostasis. In obesity there is increasing evidence that this gut-brain homeostatic balance is disrupted, either through alterations in circulating hormone levels or through altered responsiveness in key brain homeostatic or hedonic centres (Hussain and Bloom 2013).

Peptide YY (PYY) is a 36-amino-acid peptide hormone that is co-secreted from enteroendocrine L-cells with the incretin hormone glucagon-like peptide-1 (GLP-1). PYY₃₋₃₆, the major circulating form, is produced upon N-terminal cleavage of PYY₁₋₃₆ by the enzyme dipeptidyl peptidase-4 (DPP-4). PYY₃₋₃₆ is the anorectic form of PYY, and its role as a regulator of energy homeostasis was first highlighted only in 2002 (Batterham

et al. 2002). This role was firmly established through multiple human and animal studies revealing that physiological levels of circulating PYY3-36, achieved by exogenous administration, reduce food intake by a central action (Batterham et al. 2003). Moreover, circulating PYY3-36 levels are reduced in obese individuals, but the anorectic effect of PYY remains intact, raising high expectations for a new therapy for obesity (Batterham et al. 2006). Studies using functional neuroimaging indicate that PYY3-36 mediates its anorectic effects predominantly by acting upon central appetite-regulating circuits, within key brain regions involved in eating control and food reward (Batterham et al. 2007).

GLP-1 is a gut hormone secreted in response to nutrient ingestion, and it is a key gut hormone responsible for enhancing the insulin response to nutrient ingestion, a phenomenon known as the 'incretin effect' (Drucker 2007). For this reason GLP-1-based pharmacotherapies are already a mainstay of treatment for T2D. Nevertheless, there is strong evidence that supraphysiological circulating GLP-1 levels also have appetite-suppressing effects through direct activation of energy homeostatic centres in the brain (De Silva et al. 2011). These observations have led to the development of a GLP-1 receptor agonist, used for treatment of T2D, as an anti-obesity agent, and its licence may soon be extended to this indication also (Manning et al. 2014).

Ghrelin is a peptide produced by cells located in the stomach, and it is the only known circulating orexigenic (appetite-stimulating) factor. The pattern of circulating ghrelin levels is opposite to that of PYY3-36, being higher after a fast and falling after food intake. Ghrelin increases hunger and the amount of food eaten, acting upon key brain regions that control eating and reward (Cummings et al. 2002; Malik et al. 2008). Due to its orexigenic and metabolic effects, it could have potential benefits in antagonising weight loss in catabolic conditions. Theoretically, antagonism of the ghrelin receptor or the more specific approach of blocking ghrelin O-acyltransferase (GOAT), the enzyme responsible for generating active ghrelin, could be employed as anti-obesity therapeutic approaches (Kirchner et al. 2012).

Treatment

Dietary modifications, such as caloric restriction, have long been the firstline obesity treatments. Lifestyle intervention programmes, which may include dietetic, exercise or psychological aspects, are effective in reducing weight in the short to medium term, as are more intensive meal replacements or very low energy diets for patients with severe obesity. However, in the long term, most will regain much of their lost weight (Manning et al. 2014). Currently, the role of anti-obesity drugs in Europe is limited, after many were withdrawn due to their association with severe psychiatric and/or cardiovascular side effects. At present, the only EU licensed drug for weight management is orlistat, which is an inhibitor of gastric and pancreatic lipases that block fat absorption from the gut, resulting in an average weight loss of about 3 kgs. In the US two novel agents have been approved; lorcaserin (Belviq, a selective serotonin type 2C receptor agonist) and a combination of low-dose phentermine/topiramate (Qsymia, non-selective stimulator of synaptic noradrenaline, dopamine and serotonin release + weight loss-inducing anticonvulsant) are centrally acting agents that can induce an average percentage of weight loss of about 3.5 and 9% respectively (Manning et al. 2014).

Surgery

Bariatric/metabolic surgery is an efficacious treatment modality for obesity, producing durable weight loss, amelioration of obesity-associated comorbidities and reduced mortality (Sjostrom et al. 2007). To date bariatric/metabolic surgery is the only effective way for patients with obesity to achieve a meaningful and sustainable weight loss in the long term (Sjostrom et al. 2007). Consequently, the number of bariatric procedures undertaken within Europe has doubled in the last five years with 112,000 procedures undertaken in 2011 (Buchwald and Oien 2013). Metabolic surgery is considered for the treatment of patients with severe obesity (BMI \geq 40.0 kg/m²) or with BMI \geq 35.0 kg/m² plus co-morbid conditions that will be improved by weight loss. The three most performed procedures worldwide are Roux-en-Y gastric bypass (RYGBP), sleeve gastrectomy (SG) and adjustable gastric band (AGB). In contrast to AGB, both RYGBP and SG alter the anatomy of the normal gastrointestinal tract resulting in an accelerated passage of food through the gut, and also produce more weight loss and comorbidity improvements than AGB (Franco et al. 2011).

Central to the increasing popularity of metabolic surgery are the marked beneficial effects of metabolic surgery on obesity-related comorbidities such as T2D, hypertension, dyslipidaemia, cardiovascular disease, obstructive sleep apnoea, subfertility, non alcoholic fatty liver disease all together with a reduced mortality rate (Sjostrom et al. 2007). Perhaps the most striking effects of RYGBP and SG are the rapid beneficial changes in glucose homeostasis and insulin secretion, which occur within days of the operation, before any significant weight change, and are sustained in the long term, proving these procedures to be the most effective therapy for T2D. In 2009 a systematic review reported that T2D was resolved or improved in 87% of patients following metabolic surgery (Buchwald et al. 2009).

According to a report from the UK Office of Health Economics in September 2010, if 5% of the 1.1 million patients eligible for metabolic surgery, according to the National Institute for Health and Care Excellence (NICE) guidelines, underwent metabolic surgery the economy would gain 382m within 3 years (reduced NHS burden, reduced benefits and income tax generated by those back in work), and if 25% underwent metabolic surgery, a saving of 1.3bn would be realised within three years, even taking into account the cost of the surgery itself (Office of Health Economics 2010).

In recent years evidence has emerged that surgically-induced alterations in circulating gut hormones mediate the weightloss and metabolic beneficial effects of bariatric surgery (Scott and Batterham 2011). In contrast, sustained counterregulatory mechanisms during dieting are thought to provide a strong physiological basis for the high failure rate of nonsurgical approaches to weight loss (Larder and O-Rahilly 2012). During a diet PYY and GLP-1 decrease (Sumithran et al. 2011), while RYGBP and SG result in weight loss independent of enhanced PYY and GLP-1 responses after a meal. While diet-mediated weight loss results in increased circulating ghrelin concentrations, in contrast, several studies report low circulating ghrelin concentrations after SG, potentially leading to a stable reduction of hunger and food intake (Cummings et al. 2002). As a consequence of these hormonal changes the final effect of a diet is increased hunger and less satiety, leading to increased food intake and ultimately diet failure. Conversely, surgery-induced hormonal changes result in reduced hunger and more satiety leading to sustained weight loss. Moreover, there is a decrease in metabolic rate/energy expenditure during a diet, and a formerly obese person requires about 15-

20% fewer calories to maintain a 'normal' weight than someone who has not been obese (Major et al. 2007). The body defends against weight loss presumably to ensure that reproductive capacity and/or survival will not be compromised. Understanding the mechanisms underlying the metabolic benefits of bariatric surgery is the basis for a burgeoning field of metabolic research. Metabolic surgery is an intriguing model to understand the roles of potential biological drivers such as alterations in gut hormones, gut microbiota, bile acids, neural activity, adipokines and other factors with the aim of elucidating novel therapeutic strategies or achieving a 'medical' or 'knifeless' metabolic surgery.

Conclusion

In summary, given the vast extent of the obesity epidemic, prevention of obesity is central to public health strategy. Ideally, preventative efforts must encourage a healthier environment, promote education, and identify people with a higher risk who could benefit from more intensive interventions. Active treatment of obesity must also be addressed at a population level. However, in the context of the complexity of energy balance, we envisage that development of novel medical approaches for treating obesity is likely to require a better understanding of the biology of genetic risk as well as gaining insights into the successes of bariatric surgery.

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