Genetics and environmental factors in obesity and diabetes: Complex problems, complex solutions

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Abstract

Over the centuries people have become taller, heavier, and stronger. One of the major reasons for this is the increasing supply of calories in our diets. In earlier times, weight gain was extremely beneficial for health, well-being, and lifespan, but in 2012 we are at a point where weight gain has gone too far and is now detrimental. We are facing an overeating epidemic and the adverse health effects of obesity. This article discusses some of the causes of obesity and the factors affecting it.

Keywords: Obesity, Environmental factors, Genetic factors, Obesity-related diseases, Type 2 diabetes

A global problem

Obesity is a plague of modern society. Only 50 years ago, there were no statistics on obesity, but according to the World Health Organization (WHO), worldwide, obesity has more than doubled since 1980.[1] The harsh reality today is that half a billion people, representing 12% of the world's population, are considered obese.[2] And the prevalence keeps rising, fuelled by a lifestyle of bad diet and inactivity. But are these the only players?

The WHO defines obesity as an abnormal or excessive accumulation of fat that may impair health. The measure most frequently used in epidemiological studies to classify body condition is the body mass index (BMI), which is calculated as the weight in kilograms divided by the square of the height in metres. The WHO considers a BMI $\geq$30 kg/m^2 as obese.[1] Despite the popularity of the BMI, a major limitation is that it does not distinguish fat mass from lean mass.[3]

At first, obesity was a problem of high-income countries and only seen in adults, but more recently, it has spread to middle- and low-income countries and to children and adolescents.[3] Childhood obesity leads to an increased risk of obesity later in life.[4,5] In 2010, 44.2% of men and 48.3% of women were obese in the USA. Obesity is also present in Latin America. For example, in Chile, 39.1% of women are considered obese. This is also a particular problem in the Caribbean, with, for example, 52.7% of women obese in Trinidad and Tobago. In Europe, the situation is also alarming: 26.3% of women were obese in the UK in 2010. Figures are also creeping up in Southeast Asia and the Middle East, where the population has historically been thin. In China, 1% of men were overweight in 2002 but 4.1% were obese in 2010. However, an incredible 45% of men in China are considered overweight (BMI $\geq$25 kg/m^2). Africa is dealing with the double burden of undernutrition and obesity, the latter being now a particular problem in large African towns. In South Africa, for instance, 36.8% of women are obese. The worst affected region in the world is the Pacific Islands. For example, in Nauru, 84.6% of men were overweight in 2010.[6]

Hand in hand with obesity come obesity-related disorders. In fact, we now live in a world where overweight and obesity are linked to more deaths worldwide than underweight.[1]

Is obesity self-inflicted?

How do we become obese? Obesity is a gradual process resulting from an energy imbalance in which the energy taken in (calories from food and drinks) exceeds the energy going out (calories used up by physiological activities and physical activity). The end result is that excess energy is stored as body fat deposition: too much fat is a major risk factor for many diseases. This seemingly

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simple energy imbalance is, however, driven by a complex mixture of genetic, environmental, psychosocial, and cultural factors.[7]

The prevalence of obesity started to increase drastically from the mid-1980s.[3] Since our genomes have remained mainly unchanged for generations, it seems that lifestyle changes in the past few decades have had a major role in the rise of obesity prevalence. Globally, there has been an enormous increase in the consumption of unhealthy foods that are high in sugar, fats, and salt and low in nutrients and vitamins. This includes a global increase in the intake of sugary drinks, which are considered to make up a large part of the increased calorie intake leading to obesity.[8] Portion sizes have also increased and so has the consumption of processed and convenience foods, which contain high levels of sugar and fat. Another global change is that lifestyles have become more inactive and jobs more sedentary. People more often use transport instead of walking, they spend long hours in front of computers and TVs for work and leisure, and they spend little energy because everything is nearby and on-hand.

Although obesity is considered self-inflicted, social and economic changes associated with development also influence our lifestyle choices. For example, many towns have been built without sidewalks or not providing enough space for children to play in an active way. Also, healthy foods may be inaccessible or too expensive in many cases.[9] Obesity is closely related to socio-economic status, with a higher prevalence among poorer and less-educated individuals.[3] In addition, school cafeterias may not offer healthy menus, and parents may not teach healthy lifestyles.

To make matters worse, the agricultural and food industries have often selected food options for their customers based on profit rather than health. In America, between 1985 and 2000, prices for fruits and vegetables increased 118% but only 35% for fats, 46% for sugars, and 20% for carbonated soft drinks.[10]

Chemicals in our environment may also add to the problem, as certain chemicals have been shown to cause metabolic changes.[11,12] Endocrine-disrupting chemicals from packing and food processing, such as bisphenol A (BPA), can be detected in foods and in the urine and serum of most humans. Experimental studies in animals have revealed an association between low-dose foetal exposure to BPA and obesity at puberty.[13] This was also observed in an American study in humans.[14] Early antibiotic use in infants (<6 months of age) has also recently been linked to obesity.[15] Other possible factors include lack of sleep and certain medications and illnesses.[16] For example, BMI is inversely correlated with sleep duration, and obesity is associated with some psychological problems and with smoking cessation.

Is it all in our genes?

Despite this 'obesogenic' environment, some individuals remain thin and do not go on to become overweight and obese, whereas some of the overweight can't manage to lose weight. This suggests that in a population exposed to the same environment, there is inter-individual variation in obesity susceptibility, suggesting that biological mechanisms or genes influence obesity. Obesity is known to run in families, and family and twin studies have shown that BMI is 40–60% heritable.[17] Abdominal obesity, measured by waist circumference (WC) or waist-to-hip ratio (WH ratio) and considered a more reliable predictor of risk for metabolic complications of obesity, is 45–60% heritable.[18]

In the mid-1990s, several studies examined the role of genes suspected to be involved in obesity on the basis of their expression in cases of extreme or early-onset obesity and evidence from transgenic animal models. Mutant mice accumulating five times the normal amount of body fat were found to lack the single *ob* gene. This gene is active in fat cells and produces a protein that reaches the brain via the bloodstream to signal satiety. This protein was named leptin from the Greek word *leptos*, which means thin. Studies of *db* mice, a second model of obesity, were found to lack the gene for the leptin receptor and therefore could not receive the satiety message.[19,20] Several conditions of childhood obesity have been linked to mutations in these genes.[21,22] Mutations in the melanocortin receptor gene were also found to cause severe early-onset obesity.[23] Furthermore, obesity is a common phenotype shared by several different syndromes, including Prader-Willi syndrome, Bardet-Biedl syndrome, a sub-phenotype of Fragile X syndrome, and WAGR syndrome.[24] However, these single gene defects are rare and the total of all the cases does not get close to the average 33% prevalence of obesity worldwide.[23]

Towards the end of the 1990s, genome-wide linkage studies revealed approximately 300 chromosomal loci associated with obesity, but a single causal gene or variant was not found. Genome-wide association studies (GWAS) started in 2005 have been more successful.[25,26] Two million genetic variants were tested for association in extremely large, non-related samples. GWAS screening

for obesity-related traits (BMI, WC, WH ratio, body fat percentage, and extreme-early onset obesity) led to the discovery of 52 robust loci.[24,26] For BMI, 32 loci reaching genome-wide significance have been identified for white European-type adults. Of the 32 loci identified by Speliotes *et al.*,[27] eight are strongly linked to an adjacent common missense SNP (single-nucleotide polymorphism), and 15 contain genes that may be linked biologically to obesity. Despite the enormous success of GWAS, the established loci explain only a fraction of the heritability (approximately 2–4%). At present, knowing an individual's genotype at all eight loci does not provide a clinically viable test for obesity risk.[26] In fact, two traditional predictors of obesity – childhood obesity and parental obesity – appear to be the only reliable predictors of obesity risk in adult life.[28]

However, GWAS has been extremely useful in identifying genes in the susceptibility loci, thus allowing new hypotheses about the biology of common obesity.[29] *FTO* was the first obesity-associated gene to be described and is expressed in hypothalamic feeding regions.[29,30] It may affect food intake, as carriers of the risk allele have been shown to prefer energy-dense and more palatable foods.[29] Some of the genes (e.g. *MCR4, POMC,* and *BDNF*) were previously known to be involved in monogenic obesity.[27] Another gene, *SH2B1*, causes obesity when knocked out in mice and appears to be involved in leptin signalling.[31] Interestingly, many of these genes are highly expressed in the brain, particularly in the hypothalamus, suggesting a central role for the brain in the predisposition to obesity.[24] One of the most recent variants maps within the *GIPR* gene, which encodes an incretin receptor. This receptor is thought to play a role in nutrient sensing and insulin secretion in the periphery, suggesting that variations in insulin secretion may be involved in the development of obesity.[27] Speliotes estimates that 250 common variant loci for human obesity remain to be discovered and that many more loci with smaller effects will probably be identified.[27] These loci might be found in more extensive searches and by broadening searches to include children, adolescents, and adults of non-European descent.

Both environment and genetic disposition appear to participate in the development of obesity. A classical example of such a gene-environment interaction comes from the Pima Indians. Sixty-nine per cent of the Indians who live in the 'obesogenic' environment of Arizona are obese, while only about 30% of white Americans in the same environment are obese. In the 'restrictive' environment of Mexico, however, only 13% become obese, suggesting that something in the Pima Indian's genetic makeup predisposes them to obesity.[12]

Is there evidence that lifestyle factors can interact with the robust genetic loci described above? A number of studies report that physical activity attenuates the association between the *FTO* locus and obesity traits.[32] Such gene-physical activity interactions provide an important health message to the public: the genetic susceptibility to obesity may be modifiable.[12] Recent research points towards the possibility of changing gene function without changing genomic sequences. Perinatal metabolic programming appears to influence early-life obesity via epigenetic effects.[12] Another influence on genetics is assertive mating for obesity, which is estimated to have increased the prevalence for obesity in the population by about 5%.[12]

To put the current obesity epidemic into an evolutionary context, we need to consider our ancestors. O'Dea[33] believes that humans are still adapted to the ancestral hunter-gatherer diet and lifestyle. Hunter-gatherers used different strategies to survive, including gorging in times when food was abundant, preferring energy-rich foods, and minimising energy expenditure by only performing necessary physical activity. Our 'obesogenic' society is exactly what the hunter-gatherers would need to survive: an abundance of energy-dense food, easily available, with minimal effort, and at low cost! However, without the periods of 'famine' in between, the sad consequence of our biological adaption to hunger is the global epidemic of obesity and related habits.

What are the consequences of being obese?

Health consequences

Research has shown that, as body weight increases to the level defined as obese, several pathologies appear. On a social level, the increased mass of adipose tissue leads to disabilities, including effects on the quality of life such as shame, depression, disability, physical discomfort, sexual problems, and social isolation. Excess fat may also lead to sleep apnoea, due to increased abdominal pressure on the diaphragm and reduced lung volume, as well as stress on the joints leading to osteoarthritis. The risk of a second set of diseases is increased by the metabolic changes associated with obesity, as pathogenic products are released from the larger and more numerous fat cells.[34] This includes an increased risk of type 2 diabetes,

coronary heart disease, hypertension, cancers (endometrial, breast, and colon), metabolic syndrome (a combination of high blood sugar, high blood pressure, high triglycerides, and high cholesterol), dyslipidemia (e.g. high total cholesterol or triglycerides), stroke, non-alcoholic fatty liver disease, gallbladder disease, and gynaecological problems (abnormal menses, infertility). Obesity may also accelerate cognitive decline and increase deficits in academic achievement.[35,36] Risks of all of these problems are greater not only with obesity but also with overweight.

Most of the diseases associated with obesity are deadly. On average, obesity reduces life expectancy by 6–7 years, and it has become one of the leading preventable causes of death in the world.[37] The Centers for Disease Control and Prevention estimate that, in the United States, an excess of 112–365 000 deaths per year can be attributed to obesity.[38] The majority (>80%) of these deaths occur among people with a BMI greater than 30 kg/m^2.

Financial consequences

The medical costs of obesity are shocking. In the USA in 2005, costs totalled about $190.2 billion or 20.6% of all medical expenses.[38] In the UK, the National Health Service spends about £5.1 billion per year on obesity-associated medical costs, and with people living longer, the costs are expected to keep rising.[39]

Type 2 diabetes: one of the strongest risks of obesity

In 2011, 366 million people worldwide had diabetes (90% were type 2) and 4.6 million people died from the consequences of high blood sugar. Eighty per cent of those deaths occurred in low- and middle-income countries, where the burden of diabetes has increased at a dramatic rate.[40] Today, the WHO estimates that 1 in 10 adults suffer from diabetes – a startling global prevalence of 10%.[41]

Type 2 diabetes is caused by the body's ineffective use of insulin bought on by excess body weight and not enough physical exercise. The risk of type 2 diabetes increases with the level and the duration of being overweight and with the amount of visceral fat, which is the fat deposited around the abdominal organs. A study of the association between diabetes and BMI showed that at a BMI of 35 kg/m^2, the relative risk of type 2 diabetes increased 40%. However, even thin people are at risk of diabetes if they lead a sedentary or unhealthy lifestyle, such as low physical activity, irregular eating, eating a poor diet, and emotional stress, because they increase the build-up of 'invisible' visceral fat.[34] Type 2 diabetes usually appears in people over 40 years of age, but in South Asian and African-Caribbean people, it often appears after the age of 25. Also, children, some as young as 7 years of age, are more often being diagnosed with the condition.[42]

In the USA, diabetes cost $465 billion in healthcare expenses in 2000, a staggering 11% of the total healthcare expenditure. The WHO estimates that between 2006 and 2015, China will lose $551 billion in income due to heart disease, stroke, and diabetes. The situation is grave in the poorest countries, where people with diabetes and their families bear most of the cost of the medical care.[40]

Conclusions

Obesity reduces physical fitness, increases the risk for chronic diseases and disability, and significantly shortens lifespan. This has repercussions throughout communities, including reduced performance in school and at work, poor health and well-being, and massive increases in health costs.

As discussed above, becoming obese and suffering chronic diseases is not just a matter of overeating and being lazy but results from multiple and complex interactions between our genes and environments. Obesity cannot easily be fixed with fad diets or trendy exercise programmes. Indeed, the Healthy People 2010 Program set a 10-year national objective to improve obesity and nutrition in the USA.[43] The target to reduce obesity to 15% in this period completely failed and, despite national efforts, obesity actually increased from 1988 to 2008 by 47.8%. Similarly, healthful eating patterns remained well below their 2010 targets. It seems that neither individuals nor societies alone are able to change the increasing obesity incidence. Therefore, healthcare professionals, policy makers, and politicians need to make the types of changes that will lead to a supportive environment with affordable and accessible healthy food choices and physical activity. Some options could be to subvent healthy foods, to charge higher taxes for sugary or fatty foods, to promote physical activity by supporting local sport clubs, and to reward initiatives aimed at preventing overweight and engaging in healthy lifestyles. Why don't governments use a bonus point system to give financial compensation for those active in obesity and diabetes prevention? The savings in healthcare costs would be substantial, and commercial weight management programmes have shown that this strategy works.

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Clinical pharmacology series

Obesity

A growing problem…

Obesity is now a global phenomenon. It has reached epidemic proportions; almost a billion adults are overweight and one-third of these individuals can be classified as clinically obese (BMI ≥ 30 kg/m^2). In the USA the age-adjusted prevalence of obesity is 33.8% overall. Obesity can result in pathophysiological changes in regional blood flow, lean mass and an increase in fat mass. A recent review discussed the implications of obesity for drug therapy[1]. Alterations to pharmacokinetics (PK) and pharmacodynamics (PD) and any consequent requirement for dose adjustment were investigated. The authors summarised that obesity had greatest effect on the absorption of drugs given parenterally. Drug distribution was likely to be affected by changes in the volume of distribution, tissue perfusion and plasma protein binding. Both CYP and Phase II- mediated drug metabolism were altered by obesity. For drugs that were renally excreted, increased weight led to difficulties in calculating glomerular filtration rate (GFR). Additionally, GFR plus tubular secretion and reabsorption were altered in obesity. Overall, it was concluded that the changes in drug disposition in obese populations are highly variable and dependent on several factors, including drug characteristics, degree of obesity and patient-specific organ function.

A review of drug product labels and approval packages found limited information on dosing guidance in obese patients. It was recommended that the evaluation of PK and PD in obese populations become incorporated into the general drug development process.

In children

An increase in obesity has also been recorded in the paediatric population. A US report found the prevalence of obesity to be 17% in the age group 2–19 years. The consequences of obesity in this population for the disposition of drugs is less well studied compared with adults. Nevertheless, studies are starting to appear in the literature. A recent investigation examined whether obese and healthy-weight children vary with respect to drug metabolising enzyme activity[2]. The activity of the oxidative enzymes CYP1A2 and xanthine oxidase (XO) were studied along with the conjugative enzyme activity of N-acetyltransferase 2 (NAT2). No difference was observed in CYP1A2 activity. For both XO and NAT2 enzyme activity was elevated in the obese population. These findings mirrored results found in adults. It was concluded that further studies were required in the obese paediatric population, in order to determine the clinical consequences on dosage for drugs that are metabolised by these enzymes.

Drug Development

Clinical pharmacology aims to ensure that the right dose is given to the right patient at the right time. To do this an understanding is required of the inherent variability present in any patient population and the effect that it may have on drug response. Clearly obesity is a factor that may alter the PK/PD response and the consequent therapeutic dose. Given its prevalence obesity provides a further challenge for the drug innovator!

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