

Pathogenesis of OBESITY

Obesity is becoming more prevalent in the UK. Professor Syed Haq and Dr Masud Haq examine its pathogenesis, the effectiveness of weight loss programmes and discuss why outcome is so poor with caloric restriction

Obesity is a chronic disease, where there is an excess accumulation of body fat storage. We tend to use the body mass index (BMI) as an index of how severe the degree of fat accumulation is. The BMI is based on a ratio between an individual's weight expressed in kg versus height in m². If we apply this equation to the adult population of the Western world, obesity is defined as a BMI ratio between 30 to 40. The term "overweight" is attributed to individuals with a BMI between 25 to 30, while morbid obesity has a BMI ratio over 40.

But there are limitations to the BMI. Even though the BMI correlates to percentage body fat in a curvilinear fashion, there are exceptions—particularly when comparing genders. In men, 15-20% of their body composition is made up of fat, while in women it is higher at 25-30%.

Other variables should be considered, such as the body frame of the patient and lean muscle mass. Mesomorphism describes a patient who is particularly muscular when compared to the average age-sex matched individual. By contrast, sarcopenia may give a false impression, as these patients have low percentage muscle mass relative to body fat—giving the idea that the individual has a normal BMI when they actually have excess fat accumulation.

Understanding the BMI limitations has given rise to the Deurenberg equation, which closely correlates to percentage body fat. The equation considers the BMI, age and sex of the individual. Other measures can help minimise errors by measuring impedance (estimating water content) and skin thickness and anthropomorphic measurements (waist circumference and waist-to-hip ratios).

The prevalence of obesity in England is epidemic in its proportions. Data from the Health Survey for England carried out between 1993 and 2005 showed that in 1993, 13.2% of all men and 16.4% of all women were obese. Over the last decade and a half, we've seen a steady rise in the level of obesity within England. In 2005, 23.1% of all men and 24.8% of all women are obese (see Fig 1).

When comparing UK obesity rates with Europe, the UK is second only to Malta in prevalence. A 2010 forecast of the preva-

lence of obesity predicts that 33% of men and 28% of women will be obese (see Fig 2, p34). Obesity rates are increasing in the younger members of the population so there are major future health implications for the UK population and for the NHS.

An array of issues can be seen concomitant with obesity including: cardiovascular disease; coronary artery disease; pulmonary hypertension; systemic hypertension; central nervous system disorders, such as stroke; cholecystitis; reflux oesophagitis; lung disease; and an increased risk of malignancy from prostate, breast, colon and lung cancer.

There are social and psychological issues such as social stigmatisation and depression, as well as metabolic syndrome with dyslipidaemia, increased insulin resistance and a greater risk of developing type II diabetes mellitus. Analysis of reproductive issues in females show an increased risk of polycystic ovarian syndrome and infertility, and hyperandrogenism.

Treatment

Treatment modalities can be categorised into two sub-groups—medical and surgical. Bariatric surgery involves a surgeon employing a variety of strategies—including gastroplasty, Roux en-Y bypass, bilio-pancreatic bypass with a duodenal switch, gastric banding, gastric sleeves and balloons—to augment the patients' need to eat and promote weight loss.

Weight loss programmes are often discussed in the media, and may or may not include an exercise programme in conjunction. Behavioural therapy and medicines such as Xenical, Acomplia and Reductil have been all used, but Acomplia and Reductil have now been taken off the clinicians list because of problematic adverse events.

To devise an effective weight loss programme, a multi-tiered approach should be considered. There are three phases: a pre-inclusion screening phase; an effective weight loss programme; and finally a maintenance phase. The first should involve a comprehensive assessment of the patient, looking at co-morbidities, body mass index, percentage body fat and family history. The ethnic origin of the patient is also important, as are cultural and

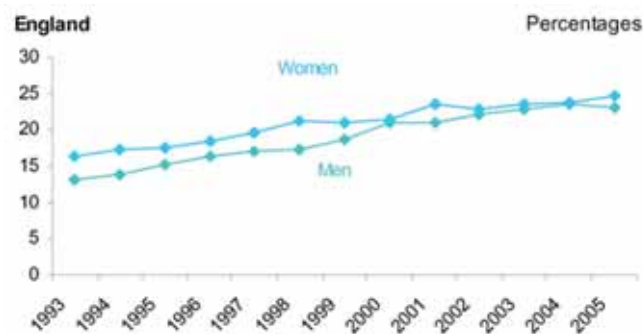


Figure 1: Prevalence of obesity among adults in England, by gender, 1993-2005 (Source: Health Survey for England)

racial differences. Following the pre-inclusion screening phase, a weight loss programme should be defined. This should involve the expertise of a multi-disciplinary team with a physician trained in internal medicine, possibly a psychiatrist or psychologist, an exercise therapist, a nutritionist or dietician and relevant sub-specialists to treat and monitor any comorbidities.

Once completed, the weight loss programme must be individualised. The need for individuality and cultural sensitivity was highlighted by data from the Obesity Reduction Black Intervention Trial (ORBIT) carried out in the US on over 1000 black women. In the trial, women were divided into two groups and over a year, they found the greatest and most sustained weight loss occurred amongst the group that had consideration of their cultural diversity. These patients were more willing and more compliant to stay on the programme.

Finally, an effective maintenance phase is essential, which should be measured over a two-year period before drawing any conclusions about sustainability and efficacy.

Caloric deficit

Caloric deficit within dietary programmes can be wide-ranging. The most extreme is starvation. A caloric intake of less than 200 calories per day, as seen in anorectic patients, is not medically indicated—it is dangerous and can lead to ketosis, electrolyte derangement, vitamin, mineral and micronutrient deficiencies, and marked potential for later morbidity or mortality.

Although caloric deficit is an essential component of any weight loss programme, essential nutrients must be introduced to allow any patient to achieve sustained weight loss without putting them into a compromised position.

There are also considerable variations in individual energy expenditures. Energy expenditure is related to the patient's body weight—22 calories per kg of energy is required for maintenance of a 1kg weight in a typical adult.

Working on that premise, a basic caloric restriction rate can be devised. This should take into account that obese subjects tend to reduce their energy expenditure with weight loss, dampening the effect of caloric deficit as their weight loss progresses. Men tend to lose more weight than women, and older subjects have increased difficulty in achieving sustained weight loss because they need less calories per decade—statistics have shown 100 calories less every 10 years.

A very low calorie diet (VLCD) is defined as a caloric intake of around 800 calories. Patients on a VLCD see weight loss of between 1.5–2.5kg per week, with optimum total loss of 20kg over 12 weeks. Weight loss velocity is initially rapid and then plateaus—no additional weight loss is achieved, even with a lower caloric intake.

A VLCD shouldn't be considered for children, adolescents, the elderly, pregnant women or patients with other clinically significant issues. It is not a sustainable form of eating and patients are generally non-compliant after six months. VLCDs are also associated with a higher rate of relapse with the classic "yo-yo" phenomenon where patients rebound, gaining more weight than their pre-diet starting weight. Additional issues include the need for specialist intervention and monitoring.

The benefits of VLCDs include glycaemic and hypertensive control. VLCDs have gained popularity as a dietary intervention that precedes bariatric surgery. But long-term complications include hair loss, skin atrophy, hypothermia, depression, cholelithiasis and electrolyte imbalance.

The US Drug and Food Administration (USDA) has a recommended daily allowance (RDA) that should be used as a definitive guide in any balanced diet, including a basic amount of water obtained from drinking water or through food—about 3.7 litres per day in men, compared to 2.7 litres per day in females.

The basic carbohydrate intake of 130g/day is comparable between the sexes, though a higher protein intake of 56g/day, and higher fibre content of 38g/day in males is needed. The percentage intake of fat should not exceed 20–35%. It should combine both omega-6 and omega-3 fatty acids, which have anti-inflammatory indications. The amount of cholesterol, trans-fats and saturated fats should always be as low as possible, and added sugar should never be more than about 25%.

Conventional-type diets can be sub-classified into: low calorie diets or reduced portion size; low fat diets; low carbohydrate diets; or mid-level diets such as the Zone diet, in which three major macronutrients, like fat, carbohydrates and protein, are eaten in similar proportions. We should not forget fad diets either which are, by their very nature, unsuccessful.

Analysis of the balanced low-calorie diet (BLCD), which focus on caloric restriction, are often described in the media—ex-

England		Numbers/Percentages								
		Total ¹	16 to 34	35 to 54	55 to 74	75 and over				
Men										
Obesity										
2003 ²	22	4,302,588	14	851,769	27	1,848,110	28	1,305,710	22	4,302,588
2010	33	6,658,953	16	1,000,442	38	2,739,197	35	1,800,426	33	6,658,953
Overweight										
2003 ²	43	8,403,365	33	2,066,211	47	3,281,310	50	2,349,520	43	8,403,365
2010	42	8,556,189	32	2,066,758	46	3,311,964	47	2,410,355	42	8,556,189
Women										
Obesity										
2003 ²	23	4,754,080	16	980,440	24	1,695,650	29	1,455,904	26	622,087
2010	28	5,984,653	22	1,340,247	29	2,120,025	28	1,552,815	23	559,090
Overweight										
2003 ²	33	6,772,757	24	1,470,007	33	2,329,645	40	2,021,398	40	951,706
2010	30	6,478,212	22	1,388,170	32	2,312,614	36	1,951,753	33	794,704
Bases (unweighted)⁴										
Men										
2003	5,966	19,391.4	1,648	6,285.1	2,179	6,944.1	1,733	4,739.1	406	1,423.1
2010	-	20,455.9	-	6,382.0	-	7,529.1	-	5,174.9	-	1,639.9
Women										
2003	7,090	20,660.9	1,876	6,205.7	2,594	7,040.1	2,004	5,049.9	616	2,365.2
2010	-	21,472.6	-	6,225.6	-	7,336.2	-	5,476.8	-	2,434.0
Bases (weighted)										
Men										
2003	6,519	-	2,154	-	2,389	-	1,607	-	369	-
Women										
2003	6,570	-	1,996	-	2,362	-	1,675	-	536	-

1. Numbers represent the estimated number of people within each age group who are either overweight or obese
2. For 2010 data, the total number of people either overweight or obese may differ from the cumulative total of the age groups presented. This is due to imprecision within the forecast modelling
3. 2003 prevalence estimates presented are based on data weighted for non-response. The weighted bases for these estimates are also presented
4. Population bases (numbers) are presented in thousands. For 2003, data from the 2003 mid population estimates have been used. For 2010, forecasted mid-year population estimates for 2010 have been applied

Figure 2: Prevalence and number of adults overweight and obese by age and gender, 2003 and 2010 (Source: Health Survey for England)

amples include Jenny Craig, Weight Watchers, Take Off Pounds Sensibly, and Overweight Anonymous dietary programmes. These types of BLCDs use a detailed dietary inventory, followed by the creation of a reasonable goal for total daily calories using divided meal plans. The central theme is reduced portion size and avoidance of calorie-dense foods. Some programmes use meal replacement shakes, bars, pre-packed meals and frozen entrées as additional aids.

Whatever their composition, diets should have adequate levels of macro- and micronutrients, as depicted by the USDA RDA. Low calorie diets involve a caloric intake of only 800–1200 calories, with a mean weight loss of around half a kilo per week. The total weight loss in an ideal setting amounts to 6–8kg. Maintaining protein intake with high biological values of over 1g/kg is important in conserving lean body mass during a weight loss programme. Many patients who start to lose weight very quickly do so because they are losing not fat, but muscle. These diets are useful for short-term weight loss only—none provide sustainable weight loss, according to the statistics.

The normal calorie diet has a caloric intake of about 1200 calories per day, subtracting 500–1000 calories from their average daily intake. Here we see the best validated dietary programmes, with a protein intake of between 0.8–1.5g/kg of body weight, not exceeding 100g per day, a fat intake of about 10–30%, a carbohydrate intake of about 50g, and a water intake of around 1.5 litres. This provides patients with adequate macro- and micronutrient supplementation, and provides better overall results than VLCDs and BLCDs.

What of the fad diets like the Atkins diet or South Beach diet? Both are high protein diets, but importantly, a low glycaemic index is advocated in the South Beach diet with higher fibre content, and moderate fat intake. There is more rapid weight loss with the Atkins diet in the first four weeks, but the South Beach diet sees steady weight loss. Patient compliance is far better with the South Beach diet and there are no long term complications. The Atkins diet comes with an increased risk of cancer, premature ageing and dyslipidaemia.

Portion control and maintaining adequate daily levels of macro- and micronutrients are essential. Excess caloric restriction should be avoided and ideally should range between 500–1000 fewer calories than the individuals' normal daily requirements. This will ensure long-term results and better patient compliance.

Food substitutes

Dieters have increasingly relied on food substitutes to aid their weight loss. Olean, or Olestra, is a sucrose polyester backbone with fatty acids that has been used as a dietary supplement and fat substitute. Olestra is too large for human digestive enzymes to break down and hydrolyse so it is impossible to absorb fat presented in association with the product.

Manufacturers have explored this principle and used it in a variety of fast foods. But it caused flatulence, bloating, diarrhoea and malabsorption of essential key fat associated or fat soluble vitamins. Most food substitutes are not to be encouraged as part of a weight loss programme, as one is effectively encouraging patients to eat from the top of the food pyramid, which creates bad dietary habits from the outset.

One of the few good fat substitutes is the plant stanol Benecol, which is a sitostanol. It is a hydrogenated plant sterol which has been esterified with fatty acids. Sitostanols are present in fruits, vegetables, nuts, legumes and rapeseed oil. It displaces cholesterol from micelles in the jejunum, so that cholesterol absorption is abrogated—it lowers total cholesterol by 10% in one

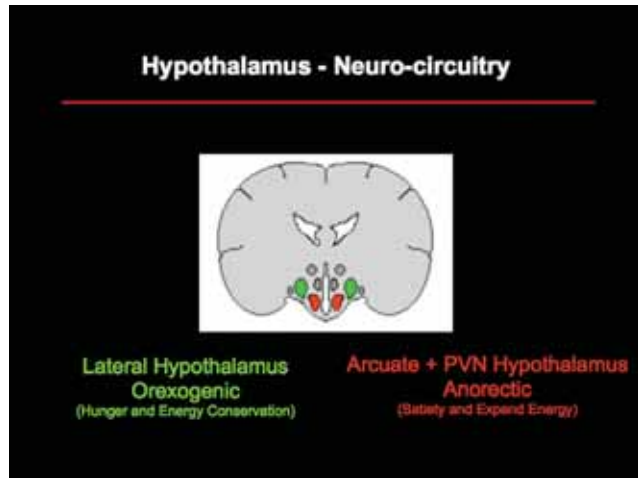


Figure 3: Hypothalamic neuro-circuitry. The lateral hypothalamus controls hunger and fat mass accumulation. Stimulation of the lateral hypothalamus leads to increased hunger and obesity (orexogenic response). The medial ventro-medial nucleus, arcuate and paraventricular nuclei when stimulated lead to a state of satiety and energy expenditure (anorectic response)

year of daily use. Benecol promotes the excretion of cholesterol but does not have an effect on triglycerides or high density lipoproteins (HDL). Sitostanols may provide a safe and effective adjunct to statins by reducing cardiovascular risk, and have been shown to lower cancer risk.

What about carbohydrate substitutes? D-tagatose is a hexose sugar found in milk. It has 92% of the sweetness of sucrose, and a third of the calorific content of sugar. It is used by diabetics and has the advantage of raising a patient's HDL. D-tagatose may also act as an anti-biofilm, a pre-biotic and a cancer protective agent. But as a weight loss substitute, D-tagatose has failed to produce significant results.

Database

The US national weight loss database follows patients for over five years with sustained weight loss of 15%. When comparing the Ornish, Zone, Atkins, South Beach and Weight Watchers diets, all exhibited minimal weight loss with no significant long-term results. Further analysis indicated that compliance and caloric deficit were the two key components of whether or not a diet would be successful. The only viable diet that has evidence to back the claims is the heart-healthy diet, which improves cardiovascular surrogate markers.

The pathogenesis of obesity is complex, with several changes taking place. A number of genetic models of obesity exist including the agouti gene product which, when elevated, can lead to hyperphagia and obesity. Leptin, an adipose released protein hormone, has been commonly advocated in obesity but it is only a fat storage regulator. Studies with injections of recombinant leptin have been shown to cause weight loss, but results are minimal.

When trying to understand the physiologic basis for obesity, we have to understand that adipose tissue changes as we get older. When we are young, we have more brown adipose tissue with greater thermogenic potential, but this is later replaced by white adipose tissue. Activity is also important in maintaining increased energy expenditure.

Patients on a diet-induced weight loss programme tend to produce more of the hunger hormone ghrelin. This is produced from cells found in the lining of the stomach and pancreas that stimulate the lateral hypothalamus, causing orexogenic changes such as increased hunger and energy conservation (see Fig 3).

This may explain why patients post-diet tend to relapse as their circulating levels of ghrelin are higher than the average

population. Obestatin, by contrast, is a putative peptide hormone that has been shown to inhibit ghrelin. Obestatin may be a crucial factor in weight loss maintenance following a dietary programme.

The balance between the lateral and arcuate/paraventricular nuclei of the hypothalamus is central to controlling obesity. There are functional elements and mediators that increase hunger pangs and others which reduce them. Patients depleted of central serotonin tend to eat more, and this may be related to depression and anxiety. There are multiple peripheral agonists including insulin, glucagon, ghrelin, low glucose and reduced hepatic glucose, which stimulate hunger. Conversely, inhibition of hunger may be caused by the ingestion of protein, fats and carbohydrates, or from the release of gut hormones such as enterostatin and cholecystokinin.

Poor outcome

While ghrelin may have a role to play by modulating hypothalamic function, it is more likely that central and peripheral adaptive changes during a prolonged dietary phase may be responsible for a poor post-diet outcome. When someone diets, central and peripheral messages are sent to produce more mature adipocytes, promoting adipogenesis.

Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptor proteins that function as transcription factors regulating the expression of genes. PPARs play essential roles in the regulation of cellular differentiation and metabolism. PPAR- γ stimulates adipogenesis and the Wnt signalling pathway—via one of its terminal components, β -catenin—tries to inhibit adipocyte differentiation.

Clinically, thiazolidinediones (TZDs) or glitazones, which are used as an adjunctive treatment in type II diabetes mellitus, have been shown to upregulate PPAR- γ . They not only treat the patient's insulin sensitivity, but also increase adipogenesis. This may constitute a mechanism and explain why patients on TZDs gain weight. One therapeutic strategy would be to inhibit PPAR- γ which could, in turn, prevent or reverse weight gain.

An alternative approach would be to focus on β -catenin, a co-transcriptional regulator and downstream target of the enzyme glycogen synthase kinase-3 (GSK-3). β -Catenin acts as a pivotal point between two signalling cascades: one for pro-adipogenesis, and another that inhibits adipogenesis.

When we look at the Wnt-signalling pathway, Wnt10b has been shown as a secreted glycoprotein ligand that stimulates the aggregation of the β -catenin degradation complex. This complex of four proteins regulates the levels of β -catenin in a cell. Stabilisation of β -catenin (Wnt10b-mediated) inhibits adipogenesis through the stimulation of a series of key genes, which are important in cell cycle arrest (see Fig 4).

When an individual diets, is under stress, or is experiencing excessive exposure to reactive oxygen species, the Wnt/ β -catenin pathway is bypassed. This results in key genes being switched off and preferentially promoting pro-adipogenesis. Once the diet ends, we may become vehicles that are ready and primed to store fat.

This has been shown in human models—receptor mutations within the Wnt pathway have been shown to cause changes including increased risk of obesity and metabolic syndrome. Gain-of-function mutations show a similar phenotype.

In summary, dieting does not provide a long-term solution unless it is done properly. Compliance and caloric restriction in tandem are the key essential components of any diet.

Central adaptive changes and peripheral reprogramming of adipocytes may cause a poor diet outcome. The

switching “off” and “on” of the PPAR- γ and Wnt β -catenin pathways may provide a mechanism as to why we are more susceptible to relapse following a prolonged period of caloric restriction. Tissue-specific targeting as a therapeutic entity in modifying obesity and obesity issues may provide a solution in the future.

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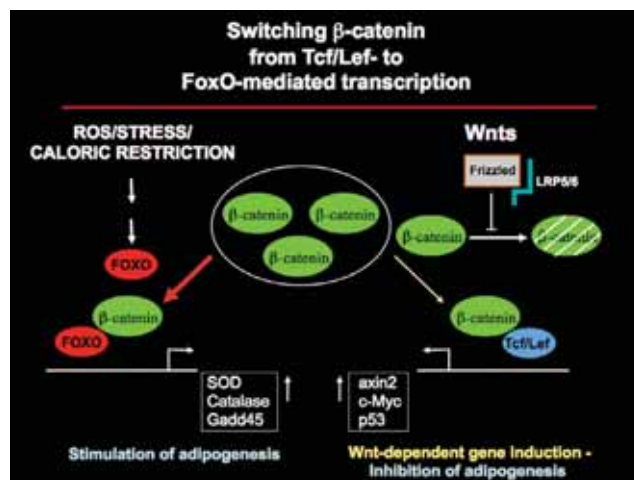


Figure 4: Adipocyte differentiation and inhibition of adipogenesis. The transcriptional co-activator β -catenin constitutes one of the key terminal components of the canonical Wnt signalling cascade and functions as a barometer between adipogenesis and inhibition of adipocyte differentiation through switching between two parallel signalling pathways

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