
OBESITY, DIABETES AND GLP 1



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OBESITY – CAUSE AND EFFECTS

Obesity is defined by the World Health Organisation as the accumulation of fat to a level that is deleterious to health. Body Mass Index (BMI) is the most common measure used to quantify obesity and overweight. It is a simple calculation of weight to height ratio and is defined as the weight in kg divided by the square of the height in metres and so has the units of kg/m². Overweight is defined as a BMI greater than 25 while obesity is a BMI greater than 30. It is important to note that the correlation between physiologically dangerous levels of fat accumulation and BMI is not absolute or precise nonetheless,

it provides a useful guide.

According to a report from January 2023¹, the proportion of adults in the UK that are overweight or obese stood at one in six of which one in four were classified as obese. The trend is perhaps even more worrying among children. Among this age group, one in ten were found to be obese by age 5, rising to more than one in five by age 11.

This has consequences in the greater prevalence of cardiovascular disease, type 2 diabetes and asthma. The prevalence of type 2 diabetes in obese individuals is over 5 times that of the non-obese. Similar enhancements in disease states are seen in a range of other

ailments². In addition to having a greater likelihood of suffering from a range of diseases, stress and infection can exacerbate the severity of illness in the obese.

Even after adjusting for a range of health conditions, the rate of death involving COVID-19 remained 1.64 and 1.62 times greater for men and women with obesity, compared to those who were not obese². This was perhaps most graphically illustrated by the severity of the illness that afflicted the then Prime Minister, Boris Johnson whose BMI was widely reported to be about 36, when he was admitted to hospital and whose recovery was impaired.

The effects may not simply be transient. It has been found that,

post COVID-19 infection, "... obesity (is a) factor associated with more severe physical and mental health impairments 1 year after hospital discharge."³

Furthermore, "obesity costs the NHS £6 billion annually and this is expected to rise to over £9.7 billion annually by 2050"⁴ with ancillary societal costs amounting to £27 billion annually⁵.

DIABETES

Diabetes can take one of two forms. Type 1 diabetes is a consequence of the pancreas not producing sufficient insulin because the insulin producing cells (beta cells) have been destroyed in an autoimmune reaction. The remedy for this is the administration of insulin since, if it is introduced then the body's reaction to it is normal. Without added insulin, people with type 1 diabetes are in a permanent state of hyperglycaemia. Only about 10% of diabetics have type 1 diabetes. The remainder have type 2 diabetes.

Type 2 diabetes occurs when the body is no longer able to use insulin effectively. Although one of the main consequences of type 2 diabetes is the same as type 1 diabetes (hyperglycaemia) the causes are different. Overweight is often cited as a trigger for type 2 diabetes there is also a genetic component. There are a number of genes associated with the risk of developing type 2 diabetes and the heritability of type 2 diabetes has been estimated to be in the range 10-70%⁶. The realisation of the potential to develop full blown type 2 diabetes is linked to weight and to BMI. Obesity is believed to account for 80-85% of the risk of developing type 2 diabetes, while recent research suggests

that obese people are up to 80 times more likely to develop type 2 diabetes than those with a BMI of less than 22. The mechanism is thought to involve the production of pro-inflammatory molecules by fat cells which can make the body less sensitive to the insulin it produces by disrupting the function of insulin responsive cells and their ability to respond to insulin⁷.

In 2023, Diabetes UK reported the impact of diabetes on the NHS budget costing the NHS in England and Wales an estimated £25,000 per minute⁸. Type 1 diabetes only accounts for 10% of this cost further demonstrating the impact of obesity and type 2 diabetes on public funds.

GLP-1 AGONISTS

GLP-1 is the abbreviation for Glucagon Like Peptide 1. It is a hormone produced in the gut in response to nutrient intake. It increases satiety and potentiates insulin release. It also decreases gastric emptying. One of the problems with therapies associated with GLP-1 directly is that it is a relatively short-lived hormone and is rapidly broken down. Agonists are molecules that produce a physiological effect at a receptor. GLP-1 agonists mimic the action of GLP-1 by binding to the same receptor as GLP-1. In people with diabetes, this has the effect of preventing hyperglycemia. Its effect on satiety (and other physiological effects) means that intake of it can result in significant levels of weight loss. The particular advantage of GLP-1 agonists is that they can be designed such that they have a much longer half life in the body and so will continue to suppress appetite and to stimulate insulin production long after the natural

hormone will have been metabolised and excreted.

In addition to its effect on nutrient absorption and as an aid to weight loss, some GLP-1 agonists have been reported to have a beneficial effect on other outcomes of diabetes and obesity including cardiovascular disease⁹. This is thought to be a consequence of the GLP-1 receptor being expressed (at low levels) in the heart and vasculature.

GLP-1 AGONISTS – SIDE EFFECTS

There are a number of side effects noted with GLP-1 agonists including, commonly, constipation; diarrhoea; fatigue; gastrointestinal discomfort; gastrointestinal disorders. It is suggested that, in the case of using one of the most common GLP-1 agonists, Wegovy for weight loss, if after 6 months use, the patient has been unable to lose at least 5% of their body weight then continued treatment should be reviewed.

GLP-1 LONG TERM EFFECTS

In the long term, a rebound effect has been noted with semaglutide (Wegovy). One year after discontinuing use, people regained two thirds of their weight loss and cardiometabolic improvements reverted to baseline¹⁰. Treatment of obesity requires, therefore, continuous treatment and pharmacological intervention should not be regarded as an option for short term weight loss. The underlying condition will remain. In addition weight loss tends to plateau after 12-18 months and ongoing chronic administration of the drug is required to maintain the loss.

ADMINISTRATION

Most GLP-1 agonists approved by the US Food and Drug Administration (FDA) for type 2 diabetes and weight management are drug-device combinations containing active ingredients sold together with delivery devices. This creates a complex patent landscape and creates barriers to the introduction of new or generic products into the market where developers may not have access to accessible and cost effective drug delivery devices.

Biophys Ltd, a Wales based consultancy, have experience of the use of microarray patches and other technologies for the administration of measured doses of bioactive compounds (<https://www.biophys.co.uk/>) that could support development of new drugs or drug device combinations.

SUMMARY

While there are relatively few long-term studies on the use of GLP-1 agonists, it has been noted that the use of the drug is not a 'magic bullet' either to cure Type II diabetes or to enable people to lose weight and to maintain that loss. Lifestyle changes are also necessary and, the evidence collected so far suggests that, even with lifestyle changes, continual use of the drug is necessary if weight loss and improvements in cardiovascular health are to be maintained.

Since the reference price from NICE for Wegovy is about £200 per month, this means that a 10-year intervention will cost almost £250k (£200x12x10). There are 12 million people in the UK who are obese, so, if all of them are treated, this will cost almost £30 billion a year. The cost:benefit assessment of the widespread use of GLP-1

agonists should be assessed carefully considering that NICE claims that obesity costs the NHS about £6 billion annually^{4,5}. Even in the US where list prices are \$12 000 to \$16 000 per year and applying maximum negotiated discounts, costs will likely exceed \$6500 per patient per year. If all eligible US adults received GLP-1 agonists at discounts, the annual cost would be \$600 billion¹¹.

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