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COMMENTARY

Overweight, Obesity and Diabetes: Global Trends and a Better Future?

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ABSTRACT

The related overweight, obesity and diabetes epidemics are more than five decades old and have progressed inexorably. A billion people in the world are now obese, and nearly a billion are diabetic. The belief that diabetes is caused by overweight and obesity has led to public health advice focused on lifestyle change as the main preventive approach. This advice has shifted over time, and some parts of the public health community have started to switch from a lifestyle to an environmental perspective. There is a growing but not yet conclusive evidence base that rather than diabetes being caused by overweight and obesity, the three conditions have a common third cause, and difficulties in controlling weight and blood glucose emerge in tandem. New classes of medications, including semaglutides and tirzepatides, effectively address these processes. They are in the early stages of development but have accumulated a safety record over the last decade. They are largely currently available only to those who can afford their relatively high cost, but new generations of related medications are capable of becoming lower cost, and wider access to them could transform the overweight, obesity and diabetes pandemics. There is a marked absence of enthusiasm for their potential role in the public health community. This appears to reflect stigmatized attitudes to overweight and obesity, which contrast with attitudes to diabetes. A successful medical treatment may be the key to resolving that stigma and reversing the three pandemics.

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A Pandemic Out of Control

The trajectory of overweight, obesity and diabetes over at least the last five decades has been dispiriting from a public health perspective. Since it was first identified that overweight trends were departing from historic norms in the 1970s, the spread of this condition has been inexorable. Figure 1 shows the global trends in "obesity" and "overweight" (defined as BMI > 30 and BMI > 25, respectively[1]) and the number of people with diabetes of either type. The data suggest an uninterrupted and unslowed procession that has doubled obesity rates from under 6% in 1980 to over 13% in 2014, implying that over one billion people now live with the condition while the prevalence of diabetes has increased nearly as much (by 80%) over the same period. The situation continues to deteriorate in high, middle and low income countries alike.[1]

The situations of the different parts of the globe making up these totals are highly diverse. A minority of people in 126 countries—more than half—are currently defined as "normal" weight or below, challenging the designation of "normal;" in eight countries, all small Pacific Island nations, more than half the population is obese. At the other end of the scale, overweight affects less than 10% of people in Ethiopia, and less than 15% in Timor Leste.[2] Among high-income countries, Japan has the lowest obesity rate at 4.5%, and at the other end of the scale, Kuwait, the Bahamas, Antigua and Barbuda, and the United States have the highest rates, all around 43%.[3]

In the five decades since recognition of this growing and eventually pandemic issue, science, theories and ideas about its underlying processes have evolved in tandem but until very recently, neither clinical medicine nor public health approaches have had much success, as Figure 1 attests.

The Connection Between Overweight, Obesity and Diabetes: A Common Cause?

The correlation between overweight, obesity and the development of type 2 diabetes (T2DM), which accounts for about 90% of all diabetes cases,[3] has been long ascribed to a causation of type 2 diabetes by the individual behaviors of excessive food consumption and

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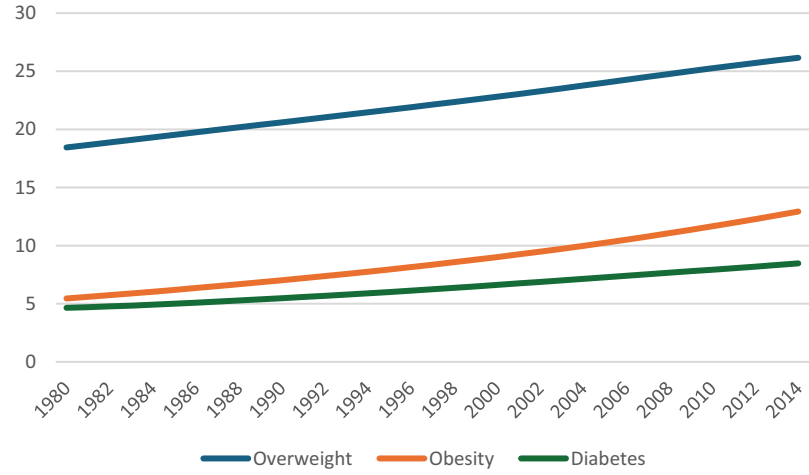

Figure 1. Overweight, obesity and diabetes: % of global population, 1980–2014. Source: https://ncdrisc.org/ (Data provided separately for men and women combined using simple average).

insufficient exercise. Hence, public health approaches to diabetes have focused on diet and exercise prescriptions within individual lifestyles to prevent and resolve both sets of conditions.

However, for over a decade now, it has been suspected that this etiological logic is fallacious and the lack of evidence of causal mechanisms from overweight and obesity to diabetes has been highlighted. In a series of articles published in 2012, Pories and Dohm[4] and Corkey[5] consider the implications of the identified curative impact of bariatric surgery on T2DM, implying that the origins of diabetes are in the gut rather than in adipose tissue and that hyperinsulinism and insulin resistance emerge together as a result of damage to β cells (the cells that make insulin; the damage might originate in environmental toxins), are mutually reinforcing, and explain the inability to maintain a lean body and to regulate blood glucose in tandem. Nevertheless, a recent review[6] suggests that the evidence to support this understanding in humans as opposed to rats is still inconclusive.

The Failure of Public Health Approaches to Overweight, Obesity and Diabetes

Whether the β cell hypothesis is ultimately accepted as the explanation of the relationship between overweight, obesity and diabetes, what is unarguable is that the public health approach to controlling the two interrelated pandemics has failed over the nearly five decades for which Figure 1 shows data. Official dietary advice has shifted dramatically from the recommendations of low-fat diets in the 1970s, a period in which evidence that sugar played a larger role in the etiology of metabolic system dysfunction was actively suppressed.[7] There is now robust evidence recognizing the role played by excessive carbohydrates and sugar in metabolic disorders, and that carbohydrate restriction achieves more favorable outcomes than fat restriction in dietary intervention studies (for example, Li et al.[8] and Nicholas et al.[9]), although much official advice fails to recognize this evidence.

Public health approaches have pivoted, at least in some domains, from the "victim blaming" focus on lifestyle, implying an active choice to engage in less healthy dietary and exercise practices, to a focus on the shaping of the opportunities for healthy choices in contemporary environments. An obesogenic food and physical activity environment is characterized by abundance of cheap, ultra-processed, high-sugar and calorie-dense food, heavily marketed especially to children whose eating habits are in formation. The world of work has increasingly trapped employees in long hours of sedentariness, often operating through computer screens.[10] Many urban settings provide little opportunity for exercise, with "active transport" modes such as walking, cycling and using public transport in decline.[11]

While recognition of the constrained choices of populations confronted by obesogenic environments is essential to understanding the factors that underpin global trends, the extent to which it offers solutions is more limited. Improving the affordability of healthy alternatives to ultra-processed foods, restricting the aggressive marketing of those foods, and transforming the nature of work and transport systems all require political action that is complex and which political systems have to date been largely unable or unwilling to take. In the cases of the few exceptions to those political failures, such as taxes on sugar-sweetened beverages and restrictions on

advertising of unhealthy food to children, evidence of effectiveness is not yet convincing. Hence, public health approaches continue to fail to offer realistic and implementable solutions to the relentless pandemic of overweight and obesity.

Underlying Biological Complexity

The lifestyle change advice favored by the popular discourse above all other approaches to addressing overweight and obesity has studiously ignored understandings of barriers to long-term weight loss arising from the neuro-hormonal system (neural and hormonal signals between the pancreas, gastrointestinal system and adipose tissue, and the brain). Of those who intentionally lose weight, nearly all will return to at least their baseline weight within five years,[12] a reality identified at least as early as 1959.[13] Greenway summarizes the complex processes involved within the neuro-hormonal system.[14] These operate through the hypothalamus and stimulate hunger, convey information about short-term energy intake and long-term energy balance and govern "hedonic" reward pathways. Greenway indicates that evidence continues to accumulate that compensatory responses to dieting and weight loss favor weight regain, by both increasing hunger and appetite and promoting energy storage. Rosenbaum et al. for example showed that in a controlled experiment, those who had lost weight, even up to six years earlier, burned fewer calories while undertaking the same exercises compared to those who had not lost weight.[15] Those who have lost weight in the past are hungrier have a higher tendency to store calories as fat and have greater difficulty burning energy stores than those who have not.

While it is clear that both exercise and healthy diet are helpful for maintaining healthy weight, and that sugar and carbohydrates are important components of unhealthy diets, it remains unclear that any currently recommended approach is sufficient for most of those who are not a healthy weight to permanently recover from that position. Moreover, lifestyle change prescriptions, in as many new guises as clinical ones over the last decades, seem to have had the serious side effects of entrenching biological processes involved in overweight, obesity and T2DM that remain poorly understood. This could be a counsel of despair for the billion people now living with obesity, the near billion currently suffering from diabetes, and the further billions classified as overweight and pre-diabetic.

New Medicines: The Breakthrough the Pandemic Has Been Waiting For?

It is therefore more than timely that a new generation of pharmaceuticals is proving capable of acting on the neuro-hormonal pathways now clearly identified as at the center of the resistance of human biology to permanent weight loss and simultaneously in the processes of metabolic disorder leading to diabetes. GLP1 (glucagon-like peptide) is among the chemical receptors involved in the short-term signaling of energy availability in the hypothalamus[10] and is targeted by a set of medicines including semaglutides (for example, the brands Ozempic and Wegovy); while the tirzepatides (for example, Mounjaro) additionally target the glucose-dependent insulinotropic polypeptide (GIP) which plays a similar role. The evidence that these medicines are effective in helping people lose weight and manage their metabolisms is robust.[16] Trial data suggest semaglutide to be associated with a mean 10.2% weight reduction[17] and tirzepatides with a mean 15.0% weight reduction[18] in patients without diabetes after one year, while both medications are well established as glucose lowering agents with increasing capacity to treat T2DM.[19,20] Continuing use appears to be necessary to maintain and further enhance weight loss[21] and to sustain impacts on diabetes. While the medicines are relatively new for use in weight loss for patients without diabetes, their more established long-term use by diabetic patients suggests that safety issues are unlikely to prompt the withdrawal of the medicines as with previous weight loss medicines. Ozempic, for example, was first approved for diabetic use in 2017 in the US. Other semaglutides were approved even earlier.

While it is important to recognize that this class of drugs is in its infancy and there is still much to learn about the medicines, the larger issues at this stage may be the limited access to them given the scale of the problem and its concentration in lower income populations at least in high-income countries. At present the vast majority of people accessing them are paying for them privately.[22] In the USA the price is approximately $1,000 USD per month depending on the brand in question, and while cheaper in other high-income countries, the cost is still prohibitive for a large share of those who could benefit. In middle income countries, even higher proportions will be excluded by current pricing even if worldwide shortages allow for consistent access in those countries at all. In India, for example, the country with the largest number of obese people after China and the USA, and the second largest number of people with diabetes after China, a small

wealthy cohort is achieving probably irregular access through the "grey market" in the absence of other opportunities.[23]

This implies not only egregious inequities but also that the population level effect of the medicines is far short of potential. Pandey et al.[24] suggest that improved distribution of the medicines could be associated with 42,000 fewer deaths annually, including over 11,000 deaths among people with type 2 diabetes in the USA alone. Nevertheless, dramatic impacts on the systems that shape the pandemic of excess weight and diabetes are already being noticed with both the food industries and alcohol industries recognizing and responding to changing customer behavior.[25,26]

While this situation of limited and unfairly distributed access is clearly unacceptable, there is room for optimism about the future should these medicines continue to demonstrate safety over larger populations and longer, potentially lifelong exposure to their use. The peptides that both semaglutides and tirzepatides rely on are labor-intensive and expensive to produce,[27] but the expiry of their patents will enable somewhat cheaper versions to be marketed and in a number of these countries the patent for Ozempic has already expired or will shortly expire. Generic versions of semaglutides are already in development.[27,28] More promising still are new drugs based on cheaper-to-produce non-peptide molecules that appear even more effective. One of these, Retatrutide has achieved average 24.2% reductions in body weight over 11 months of treatment surpassing the efficacy of both semaglutides and tirzepatides.[19] As these roll out, there is a plausible prospect of the first reversal of the pandemic since at least the 1970s.

Why are We Not More Excited?

Given the potential revolutionary impacts on the associated pandemics of overweight, obesity and diabetes (and on the basis of emerging evidence, a host of other conditions[29]), the lack of excitement about these medicines in the public health community is curious. A level of caution is appropriate given the infant stage of development and gaps in data for long-term use, although the tendency to emphasize those over the potential breakthrough is part of the curiosity. Is it conceivable that a breakthrough with this amount of promise for any other condition would be met by so much disinterest, even disdain?

Several factors may help to explain a low level of enthusiasm. Dowd and Mehta[30] suggest that there is reluctance to divert attention from the structural causes of the pandemics. These have political as well as public health salience, and while these structural factors are certainly critical to the long-term resolution of health problems of all kinds, they are not for other conditions considered rationales for not providing treatment. Moral judgments are often barely hidden in the discourse over overweight, obesity and diabetes,[31–33] and medical professionals are not immune.[34] Some seem to see the need for the overweight and obese to atone through starvation and self-denial. A pill (or for most, an injection) is equated to an unearned "easy way out."

In contrast, those suffering from diabetes have been recognized as having a medical diagnosis and as worthy recipients of medical treatment especially when the medicines were first in use for weight loss and supply shortages threatened their availability to diabetics.[35] Nevertheless, diabetics are also condemned to moral judgments based on the understanding that their condition is caused by overweight and obesity. This dichotomy seems also to underlie the perspective that a pharmaceutical solution at least for overweight and obesity is "magical thinking"—that medical technology is somehow uniquely ill-equipped to respond to the particular health problems associated with excess weight. These are stigmatized beliefs that will not lift until there is an effective long-term resolution to weight, diabetes and other related health problems that demonstrate that overweight and obesity problems are as much medical conditions as cancer, heart disease and diabetes itself.

Note

[1] Despite recent reconsideration of the identification of these measurements with underlying health problems, I use them throughout this commentary, recognizing their limitations but with no other data available to describe population-level patterns.

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