Causes of obesity left with substantial open questions – are imposed interventions justified?

The metabolism between energy intake and expenditure and the combined effect of environment and genetics needs more investigation and consideration.

Nutrition is an important field of interest for public health. Fortunately, worldwide food security can be ensured except for manmade and, more seldomly, natural disasters. Vitamin and micronutrient undernutrition remains a hidden problem. Obvious and expanding overnutrition and obesity turned out to be significant health problems. Since the 'Journal Club' started in January 2020 (2563), various topics in nutrition have been reviewed. Worth mentioning is the increased risk of dying by infection through overnutrition and obesity during COVID-19 (1). Contradictory trends in nutritional opinions, such as condemning carbohydrates (the devilish carbs) and the presently advocated 'climate-saving' vegetarian diet, and different kinds and motivations for fasting were discussed (2-4). Assessing different coping strategies for overnutrition since the second half of the last century and new research results in biochemistry tried to provide a balanced view on the 'weight paradigm,' 'health at every size,' and 'metabolic healthy obesity' (5).

Nutrition – the target of regulatory forces

Nutrition is in danger of being drawn into the maelstrom of the climate ideology and efforts to regulate the population's nutritional intake. For instance, in Germany, kindergartens were reported to provide only vegetarian meals to youngsters. The growing organism needs a balanced diet, including animal protein. It is suggested to control the nutritional intake of 'unhealthy' products through price increases and taxes (6), and salt intake is labeled as a target to reduce non-communicable diseases (7, 8). The intake of sugar in nutritional products and drinks should also be limited (9). Despite all good reasons to control risk factors for NCDs, it is frightful to think that with rigorous force, the two most essential ingredients for the taste of meals and drinks are restricted. However, governmental regulations and publicity evoke counter actions, such as 'health at every size' against the 'weight paradigm.' Further on, there are important unanswered questions about the causes of obesity, as pointed out recently by Speakman et al. (2023) (10). Lacking fundamental background knowledge, it might be unwise to campaign forcefully against overweight and obesity, evoking discrediting and even harming affected population groups.

The nutritional status – an interaction of genes and environment

A preceding tour d'horizon of this blog about a balanced view on overnutrition cited the remark that 'human obesity is a heritable neurobehavioral disorder that is highly sensitive to environmental conditions' (5, 11). The statement incorporated genetics, the brain's involvement in food intake and energy expenditure, and the environment involved in the very complex condition of obesity. Yet, the expression 'highly sensitive to the environment' should be challenged. It is not genes against the environment but a combined effect of genes and the

environment, bearing in mind that the variance in obesity among individuals heavily depends on the genetics (10).

Protein against carbohydrate and food density

As far as the environment is concerned, the alimentary intake is heavily discussed. The disapproval of carbohydrate intake instead of preferring a high protein diet was reviewed some time ago in this blog (2). It is concluded that the effects of too high or too low protein intake are unclear and need further evaluation (10).

High food density, i.e., high fat intake, is blamed for the increasing prevalence of obesity within the population. With water and fruits, food density could be reduced (12). However, high fructose intake could result in 'ectopic fat' (13). Insulin resistance and metabolic disorders result in ectopic fat buildup in the liver and muscle, including the heart (14). Recommendations to increase the intake of fibers are counteracted by the high availability of ultra-processed food, which is linked to a high energy intake (14). The conflicting and partly controversial line of different dietary recommendations forbids interfering with individual choices of food intake by authoritative influence, mainly when based on ideology.

Energy intake and expenditure

While shifting from debating the value of different food items to the metabolism, little is known about the balance between nutrient and energy needs and how the resting metabolic rate and free fat mass regulate expenditure to intake (15). The different ways of energy expenditure by physical activity, rest, and thermoregulation might not be controlled independently and additively, and what happens when starting to change the proportion of lean body mass to adipose tissue is unclear. Take the example of young men heavily involved in time-consuming sportive activities. Wishing not to be at odds with a newly married wife who complains he spends too much time with his buddies. Giving in to her wishes, physical activities are reduced, his intake remains the same, and his weight increases. The wife, going through pregnancy, has difficulty reducing her weight to the former range. Both spouse and husband, with increasing age, the risk for overnutrition and obesity rises. With obesity, lean body mass increases, including the danger of 'increased deposition' of fat related to metabolic diseases (10).

How the nutritional status is regulated – the setpoint model

Mechanisms are discussed, which should explain that energy intake and expenditure are more or less static. The Chancellor of German unification, Mr. Kohl, was an excellent example of the meaning of the 'setpoint model' in nutritional science. The long-time conservative politician was obese, and every year went to Austria to lose weight. After a four-week holiday, a more or less slim Chancellor appeared in the news for a short time, and then the nation could observe how he soon turned back into his former frame. This phenomenon is well known and suggested to be an active feedback mechanism based on physiology, genetics, and molecular biology with a link to the brain (16). A more sophisticated, two-point model reflected the body's energy stores and different aspects of energy expenditure by considering genes and different environments (17). Animal investigations with rodents hinted that leptin independently regulates fat mass as a

homeostat named ‘gravitostat’ (18). Obviously, the models generally work ineffectually. Otherwise, the overall rapid increase of overnutrition and obesity could not be observed, and an even better insight into the development of obesity is needed (10).

Obesity, overnutrition, and the genes

When treating obese patients and giving advice to reduce weight, the doctor often gets the frustrated remark from the patient that her or his condition is out of control and depends on the genes. What the patient has in his mind is monogenic obesity, and the doctor probably also doesn’t realize that the patient’s nutritional status is due to polygenic obesity with an epigenetic background. The difference between the forms of genetic manifestation was explained previously (19). Yet, an elderly patient hardly has a rare, monogenic obese disease, which is a domain for pediatrics.

In populations with consanguinity, often homozygosity with severe mutations occurs. In several Pakistani children, the genes encoding the leptin receptor (LEPR) and the melanocortin 4 receptor (MC4R) were detected for 30% and single gene defects for about 50% (20). The role of LEPR in body-weight regulation links leptin to neuroendocrine function and MC4R to appetite behavior. In an overview of severe and early-onset obesity, fourteen genes involved are listed (21). Syndromic obesity, one form of the Mendelian pattern, is often accompanied by mental retardation, microcephaly and macrocephaly, and abnormalities in various organs. Of seventy-nine obesity syndromes, only a minority of the underlying genes or chromosomes has been wholly or partly defined (22, 23). Twenty-three obesity syndromes show a wide heterogenicity in phenotypes (22). Besides syndromic obesity, there are some rare monogenetic (non-syndromic) obesity illnesses known (23). These rare genetic diseases are of interest to specialists and precision medicine. The polygenic form of obesity is of major interest to clinicians and the general health of populations (19).

Nucleotide polymorphism and obesity

In obesity and overnutrition, like other common traits, single-nucleotide polymorphisms (SBPs) are the predominant genetic connection to overnutrition. ‘Defining obesity by BMI, quite a number of studies from families, twins, and adopted individuals suggest that obesity could be inherited’ (23). The variation of fat distribution depends on 30 to 50% of genetic components, but BMI is an inadequate indicator of how fat is disseminated through the body (24). From anthropometric measurements, the Waist-Hip-Ratio (WHR) ‘has a significant genetic component’ (25, 26). There are even better ways to assess body fat, such as magnetic resonance imaging (MRT) and dual-energy X-ray absorptiometry (DXA) (23). As long as BMI indicates obesity, only 6% of variants are linked to this marker of the nutritional status (27, 28). Those with a genetic risk for obesity are also vulnerable to the ‘gene-by-environmental interaction,’ in other words, the nutritional status also depends on epigenetic systems (23).

Obesity and epigenetics

Epigenetics expands our understanding of how the physical and social environment shapes the profile in our genome to increase the risk of acquiring diseases (29). DNA methylation, histone

modification, and non-coding microRNA (miRNA) are well-known epigenetic mechanisms. From nine environmental factors, such as physical activity, alcohol intake, weight loss intervention, drugs, and pregnancy, at least two DNA methylation, three histone modifications, and one miRNA event have been found related to obesity (23). Examples of environment-affected genes are related to sleep disorders, energy metabolism, adrenocortical response to stress, mental and behavior changes during the day, regulator of lipid metabolism, the leptin receptor, preference intake on carbohydrates, fatty acid storage, and glucose metabolism (see Table 3) (23).

The genetic and gene-environment connection in obesity and overnutrition has to be considered while working on an overall strategy to influence diet and nutritional behavior.

The GLP-1 receptor agonist

The pharmaceutical industry is especially interested in what happens in the scenario of genes connected to obesity. Since obesity is labeled a disease, medical treatment appears justified. So far, a number of pharmaceutical developments proved to be too unsafe for side effects.

In a recent editorial publication, the Science magazine advertised what is known as the 'glucagon-like peptide 1 receptor (GLP-1) agonist' as an… 'effective obesity treatment'…which… 'exists for the first time' (30). The glucagon-like peptide 1 (GLP-1) links to neurons related to hunger and satiety, which can promote or inhibit eating. The GLP-1 receptor agonist was meant to be a medicine for treating type 2 diabetes but was found to help in weight loss and proved quite effective in obesity. The pharmacological action normalizes blood glucose through insulin stimulation, slowing the gastric mechanism and giving the feeling of satiety. Carving for food, in the obesity-related terms called 'food noise, is reported by the patients to decline.

From five different GLP-1 medications, the focus presently is laid on Semaglutide named Ozempic. The Food and Drug Administration (FDA) approved Semaglutide for weight loss in overweight and obese people with dangerous conditions, such as high blood pressure. The drug is applied through a weekly injection.

The therapy is costly and has several unpleasant side effects. Once treatment is ceased, weight gain follows again. In June 2023, the drug found its way into the general media because of the suspicion of causing mental depression and suicidal thoughts (31). Considering the brain connection of the leptin-melanocortin pathway and the satiety signal, mental disturbances are not surprising (see Fig.1) (23).

Further improvement of the drug to avoid injection and lifelong medication is one of the necessities before the medication becomes so effective that the 'fat decades' will be a closed chapter in the history of public health (30).

Conclusion

Solving the problem of obesity through injection or even more suitable drug applications might be a dream within the pharmaceutical industry. Many more investigations are necessary to achieve a comprehensive picture of the causes of this ailment. The interplay of the environment and genetics is, at large, unexplored. Different ethnicities might have different genetic variations of obesity (32). Within the population, different types of obesity need further investigation when considering the gynoid versus android fat distribution (5). For now, recommendations for food free from infective germs and toxic harm, a balanced diet in protein, fat, and carbohydrates, as well as in micronutrients and vitamins, remain advisable. In addition, the balance of energy intake over energy expenditure should be observed. Well-founded recommendations and a generally better understanding of complex circumstances based on improved education and overall knowledge within the population might be helpful. While in high-income countries, the BMI starts to remain high but seems steady, the general global rise in obesity remains (32). However, imposing drastic measures to cope with the problem of overnutrition and obesity is not advisable.

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