How humans economize: energy restriction and end energy expenditure

Valorization

Overweight and obesity are defined as an excessive accumulation of body fat to the extent that it may impair health. Worldwide, obesity prevalence has doubled since 1980 and in 2008 more than 1.4 billion adults aged 20 years or older were overweight. More than 200 million men and nearly 300 million women of these overweight people were obese. Overweight and obesity are related to health problems such as type 2 diabetes, cardiovascular diseases and certain forms of cancer, which makes it one of the leading risks for global deaths. Each year, around 3.4 million adults die as a result of being overweight or obese. Currently, almost 50 million children under the age of 5 are overweight or obese and the rate of increase of childhood overweight and obesity has been more than 30% higher in developing countries with emerging economies compared to that of developed countries. Childhood obesity is associated with a higher chance of obesity as well as an increased risk of related non-communicable diseases later in life. The larger increase in developing countries has made overweight and obesity a clear worldwide problem that can no longer be considered as a typical Western disease. In addition to the health problems, overweight and obesity also have a considerable economic impact and increase healthcare costs. In the Netherlands where almost 50% of the adult population is overweight, it was responsible for an extra 2 billion euro on medical and social costs in 2010.

Weight gain and obesity occur when energy intake exceeds energy expenditure and the positive energy balance will result in the storage of excess energy as body fat. The prevalence of overweight and obesity coincided with technological developments like computers, cars, washing machines and television, contributing to a sedentary lifestyle, suggesting a causal link. However, doubly labeled water measurements showed that physical activity induced energy expenditure did not decrease between 1983 and 2005 while obesity rates doubled over the same period. The latter implies that an increased intake is responsible for the energy imbalance resulting in the gain of weight and subsequently obesity. It is supported by the fact that during the same period dietary habits changed, with increased portion sizes, changed meal composition and eating out, plus the fact that palatable, energy-dense foods became readily available. The change of our environment to an obesogenic risk factor cannot fully explain the development of obesity at an individual level, since there are still many individuals who manage to remain lean. In fact, the susceptibility to become obese also depends on behavioral, social, cultural, economic, metabolic, physiological and genetic factors.

There is a simple remedy to obesity, i.e. losing weight by creating a negative energy balance for a longer period of time. This can be realized by dietary intervention, increased physical activity, or pharmacological and/or surgical treatment. Although weight loss strategies target both sides of the energy balance, the success of long-term weight loss maintenance is low. Thus, measures to improve the success of weight loss maintenance are warranted. Understanding how the body responds to energy restriction can lead to important knowledge on, and improve the success of, weight loss strategies and can improve the long-term results.

Therefore, energy expenditure components and physical activity were measured before and after weight loss and were followed up to one year of weight maintenance. The changes in energy expenditure and physical activity as a result of energy restriction were linked to: 1) changes in glucose and fatty acid metabolism in fat cells, 2) plasma leptin levels and 3) single nucleotide polymorphisms previously associated with obesity, in order to unravel part of the underlying pathways of these adaptations. In the next paragraphs, it is described how the key findings can be translated to society to have an impact that goes beyond science.

Adaptive thermogenesis, a disproportional reduction in resting energy expenditure, was observed and quantified during energy restriction and it was positively correlated to the amount of lost weight. Historically, it was important to preserve energy when energy supply was low; nowadays it is seen as undesirable during intentional weight loss since adaptive thermogenesis can reduce the negative energy gap. Quantification of adaptive thermogenesis can lead to more successful weight loss as it can be used for a better calculation of energy requirements during energy restriction. It is plausible that a smaller negative energy balance causes less pronounced adaptive thermogenesis. Therefore, a smaller negative energy gap should be preferred over faster weight loss. Especially, since it was shown that adaptive thermogenesis was sustained up to 44 weeks after the diet; after severe weight loss, adaptive thermogenesis has even been observed up to 6 years. After energy restriction, adaptive thermogenesis promotes a positive energy balance that can lead to weight regain. Since, the success of long-term weight loss maintenance is low, increased knowledge about impairing factors are important. The quantification of adaptive thermogenesis during weight maintenance can lead to more successful weight maintenance as it provides improved tools to calculate energy requirements after weight loss. As previously stated, a smaller negative energy balance during weight loss could be a method to minimize or avoid adaptive thermogenesis and consequently sustained adaptive thermogenesis. Additionally, adaptive thermogenesis long after weight loss raises concern about weight loss and weight regain cycles. It is not uncommon for people to regain weight after weight loss and then start energy restriction again before reaching the initial body weight. Under these conditions, adaptive thermogenesis could add up and may lead to permanently reduced resting energy expenditure.

Energy restriction reduces body movement and activity induced energy expenditure. The decrease in physical activity during weight loss decreases the negative energy balance and can slow down weight loss. Therefore, it should be encouraged to maintain the level of physical activity despite being in a negative energy balance. Additionally, the results showed that avoiding or minimizing the decrease in physical activity during weight loss has an extra beneficial effect on the improvement of insulin sensitivity. Improved insulin sensitivity will require smaller amounts of insulin to keep blood glucose levels stable. Low insulin sensitivity is associated with type 2 diabetes and the bodies' response to produce more insulin is

associated with a variety of health problems like damage to blood vessels, high blood pressure, heart disease and heart failure. Monitoring physical activity during weight loss could be a way to avoid the unintentional decrease of physical activity. Therefore, accelerometry devices could be used; they are minimally obtrusive and just have to be carried along to have a measurement of physical activity. Consequently, it can affect the success of weight loss and improve insulin sensitivity.

Hormones and proteins involved in adipose tissue metabolism, revealed a link between changes on a physiological level and changes of the molecular metabolism in fat cells and these could be considered as a target for future research. In turn, this could lead to the development of drugs that could help avoid the adaptations in energy expenditure and improve the success of weight loss and weight loss maintenance. It was shown that the decrease in leptin was related to adaptive thermogenesis and increased movement economy. Together with previous results, it leads to the suggestion of a central role for leptin in the underlying mechanism of metabolic adaptations. In physique sports, periodic refeeding has become common during longer periods of energy restriction. The goal of periodic refeeding is to temporarily increase circulating leptin and stimulate energy expenditure. This strategy could be translated from sports to weight loss in general. Moreover, administration of leptin during energy restriction could be a future method to minimize or reverse metabolic adaptations. Additionally, results showed that metabolic adaptations were correlated to obesity-related polymorphisms. Genetic profiling could lead to individualized intervention and drug treatment programs with higher success rates of weight loss maintenance.

In general, the results can be translated to generate more successful weight loss and weight loss maintenance. However, with regard to overweight and obesity, prevention cannot go unmentioned. The results showed that there was a decrease in physical activity during energy restriction; previously, it has been shown that there seems to be no increase in physical activity induced by overeating. Similarly, an exercise-induced increase in energy expenditure will lead to increased energy intake to compensate the additional requirement, while a change from a physically active to a more sedentary lifestyle does not induce an equivalent reduction in energy intake. These interactions implicate that eating less instead of moving more is the way to reduce body weight, and that the best method for weight maintenance is to prevent overeating.

The results described in this thesis are written in original articles that have been published or submitted to scientific journals in the field of obesity, diabetes and nutrition. Moreover, the articles can be found online and are accessible to scientists who are interested in this topic. In addition, results have been presented on international conferences to colleagues inside and outside the specific field and have been discussed for possible explanations or innovative ways to look at certain associations or results. The present studies help to

understand metabolic adaptations as a result of energy restriction and explore adipose tissue for possible pathways.