Gene analysis for studying the process of weight regain after weight loss

Valorisation

This thesis focusses on extending the fundamental knowledge about the underlying process of the seemingly inevitable weight regain after weight loss of overweight and obese humans.

Social and economic relevance

The prevalence of obesity has reached epidemic proportions. In 2014, the World Health Organization estimated that 39% of adults aged 18 years and over were overweight (BMI≥25) and 13% were obese (BMI>30) (1). This means that more than 1.9 billion adults are affected by overweight including obesity. Worldwide, overweight tends to be more common for woman compared to men (40% women vs 38% men), which is similar for obesity (15% women vs 11% men). The global prevalence of obesity has more than doubled between 1980 and 2014. The increasing prevalence of obesity is a major health concern since it increases the risk for developing type 2 diabetes mellitus, cardiovascular diseases and several types of cancer (2-4). In 2010, around 3.4 million adults died as a result of being overweight or obese (5). In addition to the health problems, overweight and obesity have a considerable economic impact and increase healthcare costs. In the Netherlands, the total direct and indirect costs of overweight and obesity is estimated at 3 billion euros per year. Of these 3 billion euros, 1.2 billion is directly linked to healthcare costs caused by overweight and obesity and 2 billion are linked to the lost productivity which is a result from days taken off sick. These facts clearly indicate that obesity and its associated diseases have a profound impact on our society.

The remedy to obesity is losing weight which can be achieved by limiting energy/food intake and increasing daily physical activity for a longer period of time. A reduction in body weight lowers the risk for developing diseases and improves the metabolic profile in overweight and obese people (6-8). However, long-term weight loss maintenance has been proven to be difficult (9, 10). Generally, up to 80% of the people are unsuccessful in maintaining weight loss (11, 12). It is crucial to prevent or reduce weight regain on a long-term basis since it would lead to a tremendous reduction of the disease burden and the financial costs related to the diseases. This thesis provides more insight into the mechanisms involved in the biological process for weight regain which can contribute to solving the problem of the seemingly inevitable weight regain after weight loss.

Scientific gain of this thesis

During a negative energy balance, cellular stress may arise in adipocytes due to the misfit between the lowered cell volume and the surrounding ECM. This stress needs to be resolved which can be achieved by remodeling of the ECM or by the re-storing of triglycerides within the adipocytes to increase the cell volume. This thesis focused on determining the involvement of stress- and ECM-related factors in the underlying mechanisms of weight regain.

- We have found that not the weight loss period per se is crucial in the underlying mechanisms involved in weight regain, but that especially the weeks after weight loss, when returning to energy balance, are linked to the risk of weight regain. In other words, studying the period after weight loss, when people increase their food intake to meet their energy requirements, may lead to the identification of risk markers for weight regain after weight loss.
- We have shown that changes of stress- and ECM-related genes and the interaction of these changes during the weeks after weight loss, when returning to energy balance, are highly related with weight regain during follow-up. Studying these stress and ECM genes, which are linked to several biological processes, may lead to the identification of genetic risk factors

involved in the process of weight regain after weight loss and may provide targets for intervention.

- We have observed that people have a higher risk for weight regain when there is a stronger downregulation of ECM-remodelling when returning to energy balance. This may lead to the retaining of more immune cells in the adipose tissue suggesting that resident inflammation after weight loss increases the risk for weight regain. Studying inflammation after weight loss may lead to the identification of risk markers for weight regain and inflammation-related targets for intervention.
- Several of the investigated single nucleotide polymorphisms (SNPs) of ECM genes are linked with weight regain. Possibly, these SNPs can be used to create a genetic risk profile to select people that are at high risk of weight regain, who can be better guided to achieve weight maintenance after weight loss.

Innovation

The present thesis presents various novel findings and insights. The aim was to determining the involvement of stress- and ECM-related factors in the underlying mechanisms of weight regain. We were able to show that the change of multiple stress-related markers influenced the regain of weight during follow-up, which confirms the proposed role of cellular stress as a driver of weight regain. Surprisingly, the change during the weeks after weight loss seems at least as important in this process as the change during weight loss. Similar to the stress markers, we showed that changes of ECM-related genes after weight loss were associated with weight regain. Here, we specifically saw that when returning to energy balance a stronger reduction of ECM remodelling capacity leads to more retention of immune cells in the adipose tissue. This indicates that inflammation after weight loss increases the risk for weight regain and as such adds a novel dimension to the biological mechanism of weight regain. However, stress- and ECM-related factors are not only influencing the risk for weight regain separately but also have a combined effect. Several stress and ECM gene interactions were highly related to weight regain after weight loss. Together these interactions indicate that changes in the epidermal growth factor signalling, when returning to energy balance, influence the risk of weight regain, which may be mediated by alpha-actinin phosphorylation and modified by expression of integrin beta 4, cystatin C and laminin alpha-3. It connects endocrine or autocrine signals, yet to be identified, to adipocyte stress as a factor for weight regain.
Furthermore, in this thesis we have shown that several SNPs of ECM genes are linked with weight regain. In men, SNPs of the ECM genes collagen type XXIII alpha1, fibulin-5, laminin-β1 and, periostin were linked while in women fibronectin 1 was linked. These SNPs could add to a genetic risk profile for weight regain. The SNPs were different for men and woman, which is not uncommon for research on weight regulation, underscoring the importance for sex-specific research.

Target groups

The results described in this thesis are available for the scientific community through publications in international peer-reviewed journals. Also, results were presented at important international congresses. Yet, the most important target group is society itself. News articles on our research have been published on various news websites, which has enabled a broader audience to take notice of our results. The scientific gain of this thesis will help to fight obesity on the long-term by determining the risk for weight regain of overweight and obese subjects. People with a higher risk can be guided

better by providing a specific, personalized guideline during weight loss but especially also during weight maintenance. This will enhance the efficiency of the weight loss treatment and of weight maintenance, which will contribute to the reduction of the health burden for society. For example, people with an increased risk for weight regain should receive a more stringent and/or frequent guidance than those with a lower risk. To achieve this, high quality prediction models are needed, which requires collaborations between research groups and companies to explore large-scale genome data. The prediction models and treatment guidelines can be used by trained dieticians, specialists in the hospital and obesity clinics.

Planning and implementation

The prediction models and treatment guidelines need to be made, however, this requires collaborations with other research groups within and outside the university as well as collaborations with the industry. For example, bioinformatics and biostatistics with a focus on modelling are needed to use the available data and create a clear model for weight regain. These collaborations will lead to better and more accurate insight into the underlying mechanism for the risk weight regain and the risk condition of each individual. The findings presented in this thesis are the starting point in this respect and at the moment we are collaborating with the Maastricht Centre for Systems Biology (MaCSBio) to create a model for weight regain. Within the coming years this model will be finished and available for society. This model will lead to better and more accurate insight into the process of weight regain and assist the specialists to provide specific, personalized guidance to people to create optimal conditions for weight maintenance after weight loss. It should be noted that this model requires the use of genetic information of individuals and this might lead to ethical issues, especially about privacy of the individual. Privacy concerns arise because organisations and institutions might be interested in knowing a person's genetic status which may result in stigmatization, discrimination, and other adverse effects. For example, if an insurance company knows that an individual is predisposed to develop obesity by looking at his/hers genetic information, they might increase the individual's insurance bill already to prevent possible extra costs later on, while the individual might never get sick. On the other hand, it might be beneficial to know if someone is predisposed to develop a specific disease because than actions can be taken to prevent the disease from occurring. Those and other questions have still to be worked out for a complex trait as overweight and obesity which requires the active involvement of scientists from multiple disciplines and of politicians.

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