

Exercise and training in NAFLD and insulin resistance

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VALORIZATION

In this chapter we will cover *(i)* the social relevance, *(ii)* the target groups for whom this work could be interesting, *(iii)* the possible applications of our work for commercial activities, *(iv)* how innovative our results are, and *(v)* the future research possibilities.

SOCIAL RELEVANCE

The prevalence of obesity is very high and is reaching epidemic proportions worldwide. Obesity is one of the most important risk factor contributing to mortality and the overall burden of disease worldwide. The World Health Organization (WHO) describes obesity as one of the most blatantly visible, yet most neglected, public health problems that threatens to overwhelm both more and less developed countries. Since 1980, the obesity prevalence has nearly doubled, affecting 1.4 billion adults in 2008. Moreover, more than 40 million children under the age of 5 suffered from obesity.

Type 2 diabetes mellitus (T2DM) may be the most devastating disease condition associated with obesity. The International Diabetes Federation (IDF) reported that worldwide 366 million people were suffering from diabetes in 2011. Ninety percent of those people suffered from T2DM, the most common form of diabetes. The World Health Organization (WHO) predicts a 2-fold increase in the prevalence of diabetes by 2030.

The development of obesity and T2DM coincides with fat accumulation in peripheral tissues. In the liver, this is referred to as non-alcoholic fatty liver (NAFL). NAFL is nowadays one of the most abundant liver diseases worldwide and has a very high prevalence in North and South America, much of Asia-Pacific, the Middle East, and Europe. The risk to develop T2DM is significantly higher in people with NAFL than in people without NAFL.

Environmental factors like consumption of high-caloric diets and low levels of physical activity are likely to underlie the increased prevalence in obesity, T2DM and NAFL. Because lack of exercise is considered an underlying cause, exercise training is considered a fundamental, important and cost-effective strategy for

treatment and prevention. Current guidelines target 150 minutes of moderate-intensity or 60 minutes of vigorous physical activity per week to prevent and treat obesity-related diseases.

TARGET GROUPS

The worldwide prevalence of obesity is very high and still increasing. As a consequence, the prevalence of obesity related comorbidities also increases. Interestingly, however, is the observation that not all people that are obese develop these comorbidities. Therefore, it is important to gather further understanding which underlying factors - related to obesity - contribute to decreased metabolic health. To answer this question, it is important to perform well-controlled clinical trials in human subjects.

In the first place, our obtained results will serve the scientific community via publications in international, peer-reviewed scientific journals. Publication of our observations will increase overall scientific knowledge and will be taken into account for future study proposals.

Secondly, our results might serve general physicians and medical doctors. In this thesis, we found that people with NAFL develop insulin resistance to a similar extend as T2DM patients. At present, people with NAFL are not treated for metabolic complications and therefore often develop T2DM later in life. Our results show that people with NAFL should be considered an important risk group to develop T2DM. Therefore, preventive treatment for metabolic complications in this population might be necessary. This knowledge might eventually be implemented in the clinic.

Exercise physiologist and lifestyle coaches are a third group of people that might use our results. Our work shows nicely that exercise training is very effective to treat obesity-related comorbidities, like insulin resistance, NAFL and the metabolic syndrome. Our results can contribute to improvements of the currently used exercise training protocols. Furthermore, we also show that - although people do improve their physical capacity with exercise training - some people do not improve their metabolic profile after exercise training. Thus, our findings might create a novel way to approach and measure exercise training effects.

ACTIVITIES AND PRODUCTS

We found that people with NAFL develop insulin resistance to a similar extent as T2DM patients. Therefore, we suggested that it might be important to start treatment for metabolic complications already in people with NAFL. This suggested approach could serve as a potential novel healthcare strategy, that might reduce the amount of people that develop T2DM. We further found that when people with NAFL performed exercise training, the IHL content decreased and the insulin sensitivity increased, thus improving the metabolic profile. So, while today there is no treatment for people with NAFL regarding metabolic complications related to T2DM, our results show that exercise training might be an effective treatment to treat metabolic complications related to high IHL content.

Interestingly, we observed that - although people do improve their physical capacity with exercise training - some people do not improve their metabolic profile after exercise training. These findings might urge for a novel research field investigating the factors that determine exercise training effects in people.

All our results described in this thesis are documented in original scientific articles that have been published or are submitted to international scientific, well-recognized, peer-reviewed journals. These articles can be found and accessed online by research scientists all over the world. Our results also have been presented on national and international conferences and can be used for future studies.

INNOVATION

The studies described in this thesis have been conducted at the department of human biology and human movement sciences of the Maastricht University Medical Center, which is known as a state of the art facility to conduct human research. Furthermore, this department holds a well-recognized scientific expertise in the field of obesity, type 2 diabetes, insulin resistance and exercise physiology research. The combination of well-recognized expertise and state of the art

research facilities makes it possible to conduct innovative research that increases the knowledge in the scientific community.

All studies outlined in this thesis were performed in human volunteers. Although research in cells and rodents gives important insight in processes and pathways involved in certain disease conditions, it is of the uttermost importance to translate this research to humans. Not all research facilities have the opportunity and knowledge to perform this translational type of research. The department of human biology and human movement sciences of the Maastricht University Medical Center is one of the leading research facilities in the world performing translational research.

Most studies were done in collaboration with the department of radiology and endocrinology. These collaborations have been essential. The current non-invasive gold-standard to measure intrahepatic lipid (IHL) content is by using proton magnetic resonance spectroscopy ($^1\text{H-MRS}$). These techniques were only available at the department of radiology. The collaboration with the department of endocrinology was necessary to elaborate the potential clinical implications of our study results.

All results described in this thesis are novel findings which have never been reported previously. Our results arise from close collaborations within the Maastricht University Medical Center, and from close collaborations with other Universities within the Netherlands and abroad.

PLANNING AND REALIZATION

In this thesis, clinical trials have been used to investigate the effects of exercise in NAFL and insulin resistance in humans. We demonstrated that exercise training is an effective treatment to lower IHL content in people with NAFL, improves insulin resistance, and improves the cardio-metabolic profile in people with the metabolic syndrome. We also observed that - although people do improve physical capacity with exercise training - some people do not improve their metabolic profile after exercise training. Further research is warranted to unravel the interrelationship between IHL content and insulin sensitivity, and to understand what causes the difference in response to exercise training in metabolically comparable people. The long-term collaboration between the department of human biology and human

movement sciences with the department of radiology and the department of endocrinology will serve as a stable foundation to perform follow-up research in the research group of Prof. Dr. P. Schrauwen and Prof. Dr. M.K.C. Hesselink.