Obesity and Muscle

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CHAPTER 7

Summary, General Discussion and Future Perspectives

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SUMMARY

Obesity is a worldwide public health problem that has increased over the years, with a projected global prevalence of 30% by 2030. It can lead to numerous health complications, such as type 2 diabetes and hypertension. Weight reduction is the most effective way to treat obesity and its related diseases, with lifestyle changes being the first line of treatment. Pharmaceutical treatment shows promising results in sustained weight loss, and bariatric surgery is currently the best method to obtain sustained weight loss and reduction of obesity-related comorbidities in patients with a high BMI (>35 kg/m²). The current classification of obesity, using BMI, does not differentiate between muscle and fat mass. Body composition, especially the ability to quantify visceral fat and muscle mass, could help to identify certain risk factors and conditions, such as sarcopenic obesity (SO). SO is a condition in which obesity occurs simultaneously with sarcopenia and is characterized by high fat mass with low muscle mass and muscle function. SO increases the risks of type 2 diabetes and hypertension but also decreases psychological health and quality of life. Weight loss therapies, such as bariatric surgery, induce loss of both fat and muscle mass, which can increase the risk of sarcopenia and possibly lead to a lower response to surgery, in terms of total weight loss and remission of comorbidities. Therefore, the preservation of muscle mass during weight loss is clinically relevant and should be monitored.

Part I – Measuring body composition in obesity

In Part I, we focused on the different methods to measure body composition and especially muscle mass. This dissertation has a particular focus on methods to measure body composition in obesity since existing measurement methods have yet to be validated for this specific population.

In **Chapter 2**, we reviewed methods to measure muscle mass and their applicability in populations with obesity. Most imaging techniques (magnetic resonance imaging, computed tomography, and dual-energy X-ray absorptiometry (DXA)) had similar limitations regarding maximal weight or abdominal circumference. The only imaging technique without

these limitations is ultrasound (US), however, this technique has not been validated in populations with obesity. Other methods include bioelectrical impedance analysis (BIA), air displacement plethysmography (ADP), and anthropometric measurements. BIA and ADP underestimate total body fat and overestimate muscle mass in people with obesity. Additionally, BIA is influenced by many external factors, and ADP is quite expensive and impractical. Anthropometric methods include circumference and skinfold thickness (SFT). The circumference does not distinguish between different tissues, whereas the SFT does. However, SFT is less precise in populations with obesity, due to the larger fat mass, and is more difficult to measure and to identify the skinfolds. Both anthropometric methods can be used together to calculate muscle mass. Overall, most limitations are caused by higher weight or body composition differences, especially in patients with obesity. Moreover, these above-mentioned methods are lacking in validation, or are not suitable based on the weight limitations. Therefore, these findings suggest that there is a need for cheaper, more accessible methods to measure muscle mass in obesity.

In **Chapter 3**, we describe the results of two prospective studies to validate ultrasonography against DXA for the measurement of fat and fat-free mass in a population with obesity. The first study investigated the reliability of the subcutaneous fat measurement. The results show that the US is feasible and has excellent intra- and inter-observer reliability when measuring subcutaneous fat in people with obesity. The second study investigated the performance of US-derived body composition formulas compared to DXA. In this study, we developed and validated two formulas, to measure total fat mass with seven- and three-points, using the subcutaneous adipose tissue thickness. Firstly, the results showed that the seven-point formula has excellent validity. Subsequently, we reduced the number of US measurements to create a three-point formula. The three-point formula also showed excellent validity (intraclass correlation). Moreover, the three-point formula was used to estimate the fat-free mass (FFM) by subtracting the fat mass from the total weight. The estimated FFM also showed excellent validity compared to DXA. We concluded that the ultrasonography-based measurement of adipose tissue thickness provides a cheap and reliable tool to assess fat and fat-free mass in a population with class II/III obesity.

After validating the ultrasound, we were interested in how the ultrasound compares to other cheap and accessible methods to measure (proxies of) muscle mass in people with obesity. These methods included BIA, anthropometric methods and creatinine excretion rate (CER), and are described in **Chapter 4**. Of these, the two different BIA formulas were most comparable to the DXA results with excellent validity and high correlation but both formulas showed a proportional error. The SFT showed a moderate correlation and poor validity. The CER showed a high correlation with moderate validity. When comparing these results to the ultrasound with the estimated FFM, the ultrasound seems to be the best option, as there was only a small systematic error and no proportional bias. Alternatively, the BIA Lukaski formula also showed promising results, however, the proportional bias should be taken into account when using this method.

Part II – Consequences of low muscle mass

In Part II, we investigated the prevalence of SO and low muscle mass, together with the relationship between low muscle mass and obesity-related comorbidities. Previous studies have shown that the prevalence of SO ranged from 0 to 85%, depending on the definition, diagnostic criteria and the specific population in which it was measured.[1–3]

In **Chapter 5**, we investigated whether the known association of type 2 diabetes with muscle mass was different between weight classes in a prospective population-based cohort of 152.000 adults of the Dutch Lifelines cohort study. A low muscle mass, measured by CER, was associated with the prevalence of type 2 diabetes in the general population. Additionally, this association was strongest in people with normal weight and decreased in people with overweight and obesity. This chapter also showed that loss of muscle mass over five years was associated with an increased risk of development of type 2 diabetes, but only for women with a normal weight. We have reinforced the knowledge about type 2 diabetes and muscle mass, but also show that this association loses strength in higher BMI classes.

After investigating techniques to measure muscle mass and the effects of muscle mass on type 2 diabetes, we were also interested in defining sarcopenic obesity (SO) in our population. In 2022, a consensus statement on SO of the European Association for the Study of Obesity (EASO) and the European Society for Clinical Nutrition and Metabolism (ESPEN) was published. In this statement, a definition of SO is proposed together with diagnostic criteria, using both muscle mass and function. In **Chapter 6**, we have applied this approach to investigate the prevalence of SO in a population with a high BMI (>35 kg/m^2). Furthermore, we also investigated the association between known SO-related comorbidities and body composition. Our population had a very low prevalence of SO (0 to 1.2%) as defined by the consensus, but a relatively high prevalence of a low muscle mass (54.8%) defined by Poggiogalle et al. (2016).[4] Further investigation showed that a low muscle mass was associated with an older age, higher HbA1c and higher total body fat percentage. However, we did not find an association between low muscle mass and comorbidities. This lack of an association might be due to the small sample size. However, another explanation is that the effect of muscle mass on diabetes seems to weaken in people with a higher BMI (Chapter 5). SO-related comorbidities (hypertension and type 2 diabetes) were associated with older age, higher HbA1c, larger waist circumference and increased visceral adipose tissue. Contradictory, SO-related comorbidities were associated with a lower fat percentage but not with muscle parameters.

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DISCUSSION OF THE MAIN FINDINGS

Part I – Measuring muscle mass in obesity

The use of ultrasound to estimate lean mass is reliable and valid; it shows promising results compared to other methods to measure proxies of muscle mass in people with obesity (Chapters 3 and 4). However, as mentioned in the chapters, both studies were cross-sectional and only investigated the correlation at one time point. Due to the excellent intra- and interobserver reliability, the ultrasound can accurately be used during weight maintenance. However, it is unknown how weight loss or weight gain influences the accuracy of the ultrasound. In obesity, treatment mostly focuses on weight loss. Bariatric surgery can lead to rapid weight loss in which both fat and fat-free mass decrease.[5,6] This can increase the risk of a low muscle mass and potentially sarcopenia or sarcopenic obesity. Therefore, future studies should validate the ultrasound for use after (rapid) weight loss. Currently, a follow-up study has started in which the validity of the ultrasound will be examined after bariatric surgery.[7] If the results of this study are as valid as the first validation study (Chapter 3), the US can be used as a tool to monitor patients before and after bariatric surgery in order to identify patients who lose more muscle mass than expected and early (dietary or lifestyle) intervention should be aimed for in these patients.

In people with obesity, the bioelectrical impedance analysis (BIA) showed a small systematic error (Chapter 4). The BIA used in our study was a single-frequency BIA (SF-BIA) in which both formulas for the estimation of fat-free mass showed a significant proportional bias. The multi-frequency BIA (MF-BIA) could be a more refined option in obesity as the different frequencies can be used to calculate extracellular and total body water.[8,9] Moreover, the segmental MF-BIA could theoretically be even more accurate as it assesses different segments of the body (e.g. trunk, arms, legs). However, the segmental MF-BIA has been examined in a population with obesity and showed similar results to our study with the SF-BIA. There was a significant proportional bias, which led to an underestimation of fat-free mass at lower values and an overestimation at higher values (compared to DXA).[10] This significant proportional bias should be taken into account when using BIA in populations with obesity.

With the increasing worldwide prevalence of obesity, it is essential that new measurement methods are validated for people with overweight and obesity. Moreover, it is beneficial to measure body composition instead of only using BMI for estimating obesity. It is known that BMI is an unreliable tool to measure obesity (excess fat mass) and could lead to an underestimation of obesity prevalence.[11] Another important aspect of the measurement of body composition in obesity is the overall applicability and affordability of these methods. Practically, methods - that are valid in obesity - should also take costs, setting and patient burden into account before implementation within standard care.

Part II – Low muscle mass in obesity

Current literature describes the role of muscle mass and function in the mortality and morbidity related to sarcopenic obesity (SO).[15–17] Previous studies have found that people with SO have a higher occurrence of diabetes.[18,19] Adipose tissue, or body fat, is recognized as a contributor to insulin resistance. Excess fat accumulation, especially visceral adiposity, is associated with chronic inflammation and the release of adipokines that disrupt insulin signalling, leading to insulin resistance and elevated blood glucose levels.[20] In addition, skeletal muscle is critical in glucose metabolism, serving as a primary site for glucose uptake and clearance. Increased muscle mass is associated with improved insulin sensitivity, which helps regulate blood glucose levels and to mitigate diabetes risk.[21,22] The intricate relationship between fat and muscle mass is complex.[23,24] Therefore, comprehensive evaluation of both fat and muscle mass is essential for the assessment of diabetes risk. In this dissertation, we also found that muscle mass plays a role in the development of diabetes. However, in obesity, the accumulation of excess fat mass appears to have a greater impact on type 2 diabetes, possibly overwhelming the protective effect of muscle mass. (Chapters 5 and 6) The reduction of excessive fat, while aiming to maintain or even increase muscle mass, could be a valuable strategy for the prevention and management of type 2 diabetes. This is already part of the existing combined lifestyle intervention for type 2 diabetes (such as Keer Diabetes 2 Om), in which among others (mild) caloric restriction and exercise are pillars of the treatment. Unfortunately, results are quite variable and therefore more advanced therapeutic options are necessary.[25] More research is necessary to examine the interplay between these factors and the effect of targeted interventions for more effective prevention and management of diabetes.

Obesity has become a global epidemic, affecting individuals of all ages and populations worldwide. Moreover, the world is experiencing a demographic transition with a rapidly ageing population. It is estimated that by 2025, 22% of the global population will be aged 60 years and older.[26] There is a complex interplay between ageing and obesity, which involves various physiological mechanisms, including slowing down of metabolism and increased muscle mass loss.[27] With the wide range in the prevalence of sarcopenic obesity

(SO) due to the numerous different definitions, it is difficult to examine its specific prevalence for older adults. However, the prevalence of SO is estimated to be higher in older adults compared to younger adults.[28] In this dissertation, we focused mainly on a relatively young population of people eligible for bariatric surgery (< 65 years). However, with the recent broadening of the age limitations in bariatric surgery guidelines[29], there is a need to investigate both measuring methods and low muscle mass in this elderly group with obesity as well.

Chapter 6 showed a low prevalence of SO but a high prevalence of low muscle mass. This study included participants eligible for bariatric surgery and most of the participants will receive this intervention after approval of multi-disciplinary screening. It remains unknown how preoperative low muscle mass will affect the results of bariatric surgery, in terms of weight loss and comorbidity resolution. A previous meta-analysis showed significant muscle, lean and fat-free mass loss after bariatric surgery. More than half of this loss occurred within three months after surgery. The average proportional loss of lean or fat-free mass is approximately 20% of the total weight loss (TWL).[30,31] This underlines the need for further investigation into high-risk patients and optimization of exercise guidelines and protein supplementation.

After bariatric surgery, the benefits of weight loss may outweigh the burden of muscle mass loss initially, but this loss might be unfavourable in the long term compared to those with less postoperative muscle loss. For instance, muscle mass is involved in metabolic health and functional capacity and is likely to decrease further with age.[32] In gastrointestinal surgeries, muscle mass has already been shown to be an important factor in the development of (serious) postoperative complications.[33] In bariatric surgery, the effect of preoperative muscle mass on postoperative complications has yet to be thoroughly investigated. More is known about fat mass because high visceral fat area (VFA) and low abdominal muscle have been shown to predict postoperative complications after bariatric surgery.[34] Moreover, one study showed that a high (preoperative) VFA increases the risk of early complications after bariatric surgery.[35] More studies are needed to investigate the effect of body composition and loss of muscle and fat mass on postoperative outcomes after bariatric surgery, including the resolution of comorbidities.

A previous study has looked at the effect of muscle loss after bariatric surgery on glycaemic profile. This study found that postoperative muscle loss in bariatric surgery is related to preoperative glycaemic profile; patients with controlled glycaemic profiles experienced less muscle mass loss. Patients with less loss of muscle mass had a better improvement in the glycaemic profile after bariatric surgery, compared to those with a higher muscle loss.[36] Another study found that post-bariatric surgery fat-free mass was associated with both pre-bariatric surgery fat-free mass and preoperative insulin resistance, which indicates that preoperative conditions can have an important effect on postoperative loss of muscle.[37] Future research is necessary to investigate the effect of muscle loss on glycaemic profile and other morbidities, especially in weight loss surgery or anti-obesity medication.

FUTURE PERSPECTIVES

In the coming years, body composition continues to gain importance and should be part of evaluation in standard practice when looking at obesity and weight loss. This is already visible in current research, such as body composition measurements in clinical trials that evaluate anti-obesity medication.[38,39] Ideally, body composition would become more important than BMI in the characterization and treatment of obesity. The measurement of both lean and fat mass can also help to identify different phenotypes of obesity and can be used to make a risk profile for patients. If US-algorithms prove to be as robust in further studies, as they are in this dissertation, they can be easily applied in daily practice for risk evaluation pre-op and follow-up after surgery to identify those patients who need timely intervention.

The ultrasound has numerous uses; in this dissertation, we focused on body composition, but it could also help to identify muscle quality and morbidities such as liver fibrosis.

In obesity, the measurement of muscle quality can be used to improve the understanding of the musculoskeletal consequences of excess adipose tissue. Moreover, obesity is associated with changes in muscle composition, including intramuscular fat deposition and a decrease in muscle mass and strength.[40,41] Ultrasound provides a non-invasive and easy method to assess muscle quality by the quantification of muscle echogenicity and the degree of intramuscular fat infiltration.[42,43]

The use of ultrasound for the measurement of liver fibrosis in individuals with obesity represents a significant advancement in the non-invasive assessment of liver health. Obesity is a risk factor for the development of non-alcoholic fatty liver disease (NAFLD), a condition that often progresses to liver fibrosis and cirrhosis.[44] Ultrasound-based techniques can provide an accurate and robust measurement of liver stiffness, which is indicative of fibrotic changes in the liver tissue.[45] The ultrasound is a safe and practical choice for routine monitoring of liver fibrosis in patients with obesity, allowing for early detection and intervention in the progression of NAFLD.[46]

Additionally, adipose tissue fibrosis, as a non-invasive indicator of inflammation, may also become an integral aspect of the US assessment of adipose tissue.[47]

Overall, the implementation of ultrasonography in standard practice could provide more than just body composition and can provide valuable information on other conditions. Moreover, it can reduce the need for invasive procedures and minimize associated risks, making healthcare safer and more patient-friendly.

Ultimately, reliable body composition measurements are a starting point after which interventions to increase loss of fat mass and prevent muscle loss during (rapid) weight loss, should be investigated. Even with the loss in muscle mass, the muscle strength could be unaffected, and other parameters such as Timed Up and Go and gait speed improve after bariatric surgery due to the weight loss.[14] Overall, exercise is an important part of a healthy lifestyle and could play an integral role in preventing muscle loss after bariatric surgery.

Protein supplementation after bariatric surgery can help improve body composition by enhancing the loss of fat mass and reducing the loss of muscle mass.[48] However, a RCT showed that protein supplementation improved blood parameters such as albumin, magnesium and iron, but did not significantly improve muscle mass maintenance or prevent muscle mass loss.[49] In line, a recent systematic review showed inconclusive results in studies of post-bariatric protein intake, ranging from no effect on lean body mass to lean body mass conservation.[50] This difference can be explained by discrepancies in daily protein intake, type of bariatric surgery and measurement tools, and indicates that more research is necessary. Moreover, most studies did not combine protein supplementation with an exercise program, which reduces the effect of the protein intake by not having an anabolic stimulus.[51] In the coming years, guidelines about protein intake, supplementation and exercise after bariatric surgery should be developed, in an effort to reduce muscle loss.

Next to exercise and protein intake, another interesting development is a drug that aims to treat pathological muscle loss and weakness, bimagrumab. This human monoclonal antibody binds to the activin type II receptor on skeletal muscle. The binding of this antibody blocks the binding of ligands that can negatively impact skeletal muscle growth.[52] In people with type 2 diabetes and overweight or obesity, bimagrumab showed a decrease in body weight (6.5%), decreased fat mass (20.5%) and at the same time an increase in lean mass (3.6%).[53] This study was done as part of a phase 2 clinical trial, however, it shows potential in the maintenance and increase in lean mass while decreasing total body fat (and weight). Bimagrumab could be a last resort to maintain and increase muscle mass in patients with symptomatic sarcopenia.

Body composition can be accurately assessed by ultrasonography and may be a powerful tool to study weight loss results in patients with type II/III obesity. Thus, awareness of adequate muscle mass and its preservation may become a feasible and individual target to optimize weight loss strategies and result in improved remission of comorbidities.

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