Effect of muscle mass, androgens, and glucocorticoids on health outcomes

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DOI: 10.33612/diss.625561235

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2023

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 10

Summary
Solid organ transplantation is the treatment of choice for patients suffering from end-stage organ disease. Importantly, life-expectancy for these patients remains limited compared to people of the general population. Additionally, comorbidities such as hypertension and diabetes have a high prevalence in transplanted patients. This not only results in a direct negative effect on patient health, but also indirectly contributes to premature mortality. To date, these comorbidities are usually treated with medication and lifestyle management. Unfortunately, these interventions have not yet obliterated the presence of hypertension and diabetes, and subsequently these classical risk factors still affect outcomes in transplant recipients. Other potentially modifiable factors need to be identified to allow for further improvement of patient outcomes. For example, skeletal muscles play an important role in glucose homeostasis and may therefore be an important factor in the development of diabetes. In more depth, other factors such as androgen and synthetic glucocorticoids have an anabolic and catabolic effect on muscles and may therefore also be of importance. In this thesis we aimed to determine whether non-classical risk factors such as muscle mass, androgens, and exogenous glucocorticoids may play a role in the survival of transplant recipients and whether these risk factors can potentially influence the incidence of comorbidities such as diabetes and hypertension. To gain these insights, we have performed studies in different transplant populations and in the general population.

Low muscle mass, as measured by 24h urinary creatinine excretion (CER) is an important predictor for mortality in patients with heart failure, type 2 diabetes, and people in the general population. It was, however, unknown whether low muscle mass or loss of muscle mass may be related to the prevalence or incidence of diabetes in the general population and whether this association differs between people within different BMI groups. Therefore, in chapter 2, we investigated this association and observed that low muscle mass was associated with the prevalence and incidence of type 2 diabetes and that this association is not only present in people with a high BMI, but even more strongly so in patients with a normal BMI. It has furthermore been shown that low muscle mass is an important risk factor for premature mortality in the general population and in kidney transplant recipients. In chapter 3 we show that for the transplantation population this not only holds true for kidney transplant recipients, but that it is also true for liver transplant recipients. To improve the outcome of the affected patients, there is a need for targeted interventions. Therefore, in chapter 4 we investigated whether CER might not solely be a marker for muscle mass but also for muscle strength and found this to be the case. Subsequently, CER may serve as a potential target for intervention to improve muscle mass, and muscle mass related outcomes.

Testosterone is an anabolic hormone which can stimulate muscle growth. Subsequently, it may be hypothesized that adequate levels of testosterone and other androgens are of importance
for transplant recipients. Previous studies have suggested that although testosterone levels are lower pre-transplantation, testosterone levels quickly increase after kidney transplantation and therefore do not warrant further monitoring. Nonetheless, when reviewing the current literature, it can be observed that the studies which are the fundament of current consensus have a large heterogeneity in their designs and have small sample sizes. Therefore, in chapter 5, we investigated testosterone and dihydrotestosterone levels long-term after kidney transplantation and observed that both androgens were significantly lower in male kidney transplant recipients than in healthy male controls. Furthermore, we observed that male kidney transplant recipients with low levels of testosterone and dihydrotestosterone more often had comorbidities such as hypertension and diabetes. In chapter 6, we studied the hypothesis that low androgen levels can also prospectively attribute to the development of post-transplantation diabetes mellitus in male kidney transplant recipients and observed that male kidney transplant recipients with low testosterone or dihydrotestosterone levels respectively had a 4.2-fold and 4.7-fold increased risk to develop post-transplantation diabetes mellitus.

Exogenous glucocorticoids remain a vital part of current medical practice in treating numerous immunological and inflammatory diseases, including chronic kidney diseases and a status after kidney transplantation. In recent years there has, however, emerged a plea to lower or stop the use of exogenous glucocorticoids in these diseases, due to the wide range of side-effects including hypertension and loss of muscle mass. Yet, the use of prednisolone, which is the current standard of choice, remains necessary especially in high-risk patients. Nevertheless, new insights have led to an updated understanding of the handling of different exogenous glucocorticoids. It has, for instance, been observed that prednisolone and dexamethasone are subjected to a different handling by 11β-dehydrosteroid dehydrogenase type 1 and 11β-dehydrosteroid dehydrogenase type 2, two enzymes which respectively activate and inactivate endogenous glucocorticosteroids. Therefore, in chapter 7, we hypothesize that dexamethasone may be the preferred exogenous glucocorticoid in patients with chronic kidney disease and kidney transplant recipients, as the use of dexamethasone has the potential to result in a lower prevalence of hypertension and a more localized immunosuppressive effect in the kidney. To test this hypothesis, a randomized controlled trial evaluating bio-equivalent doses of prednisone and dexamethasone is needed. Nevertheless, before a randomized controlled trial investigating the potential harms and benefits of prednisolone compared to dexamethasone can take place, there is a need for an updated understanding of the bio-equivalence of prednisolone and dexamethasone itself, as the foundation for current bio-equivalency data is based on very old studies. In chapter 8, we subsequently present the study design of the CORE study, a randomized, cross-over, investigator-initiated, clinical trial investigating the presumed bio-equivalence of prednisolone and dexamethasone in healthy subjects.
In conclusion, low muscle mass, hypogonadism, and treatment with synthetic glucocorticoids are all non-classical risk factors which may have a negative impact on outcomes in kidney and liver transplant recipients, either directly or indirectly through their association with diabetes or hypertension. To improve the prospects of kidney and liver transplant recipients future studies may want to focus on potential mechanisms to improve CER, which could include assessment of the added benefit of testosterone supplementation as sole intervention or as an intervention which is combined with other medication or lifestyle training, and could include making a population specific comparison between different synthetic glucocorticoids, whilst taking into account the intricate nature of these risk factors.