Unravelling the triangular relationship between polycystic ovary syndrome, cardiometabolic disease and de novo lipogenesis

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CHAPTER ELEVEN

Impact paragraph

Polycystic ovary syndrome (PCOS) is a condition that is characterized by an irregular menstrual cycle, hyperandrogenism and a polycystic ovarian morphology. In addition, women with PCOS are often affected by subfertility, obesity, type 2 diabetes, dyslipidaemia and coronary artery disease[1]. PCOS is a very common hormonal disorder, as approximately one in every ten premenopausal women is affected[2]. Despite extensive research thus far, the pathophysiology of PCOS remains poorly understood. Particularly in light of the long-term cardiometabolic complications, it is of importance to better unravel the pathophysiology of PCOS and identify potential therapeutic targets.

In this thesis we found that PCOS by itself does not seem to be causal in increasing the risk of coronary artery disease. Rather, a dysregulation of de novo lipogenesis – the process of converting glucose or fructose into lipids which occurs primarily in the liver and is a downstream consequence of obesity[3,4] – seems to be the common factor predisposing to an increased risk of PCOS and coronary artery disease. Moreover, we identified that de novo lipogenesis links to PCOS and other cardiometabolic disorders by decreasing serum sex hormone-binding globulin (SHBG) levels.

This chapter describes how the findings of this thesis may impact scientific research and clinical practice.

PCOS and hyperandrogenism: a more personalised approach?

The results described in this thesis suggest that not all women with PCOS are at risk for developing cardiometabolic disease. Previously, it has been observed that cardiometabolic features in women with PCOS cluster primarily in those women with hyperandrogenism[5]. According to the 2018 EHSRE guidelines for the diagnosis and management of women with PCOS, the definition of biochemical hyperandrogenism is based on the levels of free testosterone or the free androgen index[6]. Our studies suggest that a more extensive phenotyping of hyperandrogenism in women with PCOS, by additionally considering the determinants of free testosterone (i.e. serum SHBG and total testosterone), may guide clinicians in better understanding the primary pathway that contributes to the development of hyperandrogenism.

In light of the findings presented in this thesis, it is hypothesized that in particular women with PCOS and low serum SHBG levels are at risk of developing cardiometabolic complications. However, it will require further study to assess whether serum SHBG is a good indicator of individual cardiometabolic risk. Although we observe that de novo lipogenesis is one of the pathways that regulates serum SHBG levels, and as such serum SHBG may be an indicator of metabolic dysfunction, there are also many other

factors that contribute to the regulation of serum SHBG levels within an individual[7]. It would, therefore, be of interest to study the predictive value of serum SHBG as a biomarker of metabolic dysfunction and, by extension, as a prognostic marker for cardiometabolic risk in women with PCOS.

The current guidelines regarding the management of cardiometabolic dysfunction in women with PCOS advise screening for obesity, dyslipidaemia, hypertension, impaired glucose tolerance and lifestyle factors (i.e. lack of physical activity and smoking)[6]. Compared to these guidelines, serum SHBG levels may be an early biomarker of metabolic dysfunction, well before signs of dyslipidaemia, hypertension or impaired glucose tolerance are present. Although obesity will likely remain the most prognostic, non-invasive marker for cardiometabolic risk, recent genetic studies have identified that there are distinct adiposity clusters that associate with favourable and unfavourable metabolic effects[8]. The latter cluster was found to associate with higher non-alcoholic fatty liver disease (NAFLD) risk, lower serum SHBG levels, and higher PCOS risk[8]. Although it is likely that unfavourable adiposity represents the majority of obese patients seen in clinical practice, it would be of interest to study whether serum SHBG may aid in further delineating the individual cardiometabolic risk of women with PCOS.

Not only clinical practice, but also scientific research may benefit from a better phenotyping of women with hyperandrogenic-PCOS. Different (hyperandrogenic) phenotypes within PCOS may be characterized by vastly different underlying pathophysiological mechanisms[9]. A better characterization of PCOS patients in scientific research would likely allow researchers to gain a better understanding the pathophysiology in PCOS as a whole and within subgroups of PCOS patients.

De novo lipogenesis as a potential therapeutic target

In this thesis, dysregulation of DNL seems to predispose to cardiometabolic disorders including type 2 diabetes and coronary artery disease in both women and men. Nevertheless, we were unable to study the extent to which de novo lipogenesis contributes to the risk of cardiometabolic disease. Therefore, the findings in this thesis justify further research assessing whether de novo lipogenesis may be a therapeutic target through which to reduce the risk of cardiometabolic disease.

Several avenues through which de novo lipogenesis could be reduced, and consequently serum SHBG could be increased, are under investigation. First, as de novo lipogenesis is highly associated with obesity, lifestyle interventions that achieve weight-loss are likely to be a successful approach[3]. Indeed, intervention trials have

shown that a weight reduction of ~10 kg has been shown to reduce intrahepatic lipid (IHL) content (~1.69%) and increase serum SHBG levels (~26%)[10]. Second, thyroid receptor hormone beta agonists, such as resmetirom which has a liver-specific profile, mimic the beneficial effects of thyroid hormones on de novo lipogenesis[11,12]. In phase II clinical trials it has been observed that resmetirom treatment resulted in a relative reduction in IHL content by ~50% and an increase in serum SHBG levels by ~116%[13]. Third, acetyl-coenzyme A carboxylase (ACC) inhibitors, which prevent the conversion of acetyl-CoA to malonyl-CoA, i.e. the first step in de novo lipogenesis, are currently undergoing clinical trials. In these trials 16 weeks of treatment with a high-dose ACC inhibitor resulted in a relative reduction in IHL content by ~65%[14]. As of yet, the effects of ACC inhibitors on serum SHBG have not been reported.

Although the initial effects of the hitherto presented interventions on IHL content and serum SHBG are beneficial[13,14], the exact clinical relevance of reducing de novo lipogenesis on hard clinical end points is yet to be investigated. The clinical trials report promising results regarding the effect of these interventions on glucose metabolism and lipid profile[13,14]. However, specifically with regard to PCOS, the effect of reducing de novo lipogenesis remains uncertain. In chapter four, de novo lipogenesis in women ranged from 1.3% to 24.5%. Based on the data in this thesis, we can extrapolate that a 10 percent point decrease in de novo lipogenesis is expected to result in ~11 nmol/l increase in serum SHBG (chapter four). Relative to the average serum SHBG levels in women with PCOS this would be a 36% increase in serum SHBG (chapter three). Consequently, this would result in ~4 pmol/l or 19% decrease in serum free testosterone levels in women with PCOS. The effect of such interventions on the phenotype of women with PCOS deserves further investigation.

Future investigation into the role of SHBG in cardiometabolic disease

It is increasingly recognized that serum SHBG has a greater role in metabolic disorders than it has been given credit for. As indicated previously, serum SHBG may be a biomarker of metabolic dysfunction, in particular de novo lipogenesis. However, serum SHBG may also be involved in the pathophysiological processes of metabolic disease including PCOS and type 2 diabetes, and initial studies indicate it may also contribute to the risk of NAFLD and coronary artery disease[15,16]. It deserves further study to assess the extent to which serum SHBG acts as a causal factor in these disorders, and whether SHBG may be a potential future target for intervening in the cardiometabolic risk profile of patients.

Conclusion

In conclusion, this chapter illustrates ways in which the findings presented in this thesis may guide future research and, ultimately, clinical practice. In particular, the current findings further our understanding on the pathophysiology that underlies PCOS and cardiometabolic disease, and highlights the role of de novo lipogenesis and serum SHBG herein. This implicates serum SHBG as a potential screening tool and de novo lipogenesis as a potential therapeutic target that may, in the long term, help to improve the long-term cardiometabolic well-being in women with PCOS. This thesis also highlights the need for a more personalised approach in the study of PCOS, as this may help to further unravel the relationship between PCOS, cardiometabolic disease and de novo lipogenesis.

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