Introduction

The first descriptions of women with polycystic ovary syndrome (PCOS)-like phenotypes were in the early 1900s, where Stein and Leventhal reported the occurrence of seven patients with enhanced ovaries, menstrual disturbances and hyperandrogenism (Azziz & Adashi 2016). Since this time, the syndrome has been investigated from several angles but debates regarding the diagnosis, aetiology and pathogenesis of PCOS are ongoing. PCOS is now considered the most common endocrine abnormality in reproductive-aged women, with a prevalence of 6-25% depending on the diagnostic criteria (Azziz et al. 2009; 2004; Zawadzki & Dunaif 1992).

PCOS is associated with reproductive disturbances and is characterised by the presence of polycystic ovaries, menstrual dysfunction, reduced fertility or infertility and hyperandrogenism (Azziz et al. 2009; Azziz et al. 2006). Although the reproductive consequences of PCOS have been known for around 80 years, the metabolic side effects of PCOS have only been investigated for the last four decades. In 1980, Burghen et al. were the first to report hyperinsulinemia in women with PCOS (Burghen et al. 1980), thereby introducing an increased risk of insulin resistance in PCOS. Several other studies have subsequently confirmed this finding (Chang et al. 1983; Shoupe et al. 1983; Dunaif et al. 1985; Flier et al. 1985; Pasquali et al. 1990; Mather et al. 2000). The consequences of reduced insulin sensitivity in women with PCOS are an increased long-term risk of developing the metabolic syndrome (Glueck et al. 2003; Huang & Coviello 2012; Hillman et al. 2014) and type 2 diabetes (Glintborg et al. 2015; Gambineri et al. 2012; Yildir et al. 2013). Hence, PCOS-related healthcare is considered a huge economic burden for society. Estimates have not been performed in Denmark, but, in the United States, the estimated cost in 2010 was $1.16 billion, with treatment of diabetes by far the greatest contributor (Jason 2011).

Interestingly, in 1989, Dunaif et al. reported the presence of peripheral insulin resistance independent of obesity (Dunaif et al. 1989a) and subsequent research has confirmed this finding (Stepto et al. 2013; Svendsen et al. 2008). Although the exact prevalence of obesity is uncertain, it is in the estimated range of 35-50% of all women with PCOS (Kiddy et al. 1990; Kyrkou et al. 2016) which means that a large proportion of women with PCOS are lean. However, insulin resistance is not a consistent finding in PCOS (Moran et al. 2010; Azziz et al. 2009; Cussons et al. 2006; Legro et al. 1999; Carmina et al. 1992; Ehrmann et al. 1999) and the underlying factors contributing to this diversity is not clear. Thus, greater knowledge is required in order to understand the underlying mechanism contributing to insulin resistance in lean women with PCOS.
Skeletal muscle is the main organ responsible for glucose uptake during insulin stimulation (DeFronzo et al. 1981; Baron et al. 1988) and molecular abnormalities in skeletal muscle glucose and lipid metabolism have previously been linked to insulin resistance in obese women with PCOS (Hojlund et al. 2008; Glintborg et al. 2008; Scott et al. 2016). When comparing studies of type 2 diabetes, obesity and PCOS directly, the degree of insulin resistance observed in women with PCOS is strikingly similar or even worse than in middle-aged, obese patients with type 2 diabetes. These findings indicate that, in women with PCOS, factors other than those in type 2 diabetes and obesity contribute to insulin resistance, which resulted in the hypothesis of a unique pathogenesis for insulin resistance in PCOS (Dunaif et al. 1989b). However, the characteristic of skeletal muscle in lean women with PCOS together with underlying mechanisms responsible for peripheral insulin resistance have not been clarified, which is why a better understanding of the pathophysiology of PCOS independent of obesity is needed.

The treatment of PCOS is primarily of a medical nature, but, during the last 15 years, improvement of the syndrome by lifestyle changes has been of increasing interest and research has intensified. Exercise training has been shown to improve insulin sensitivity in healthy and diabetic patients by enhancing insulin-stimulated glucose uptake in skeletal muscle (reviewed in (Richter & Hargreaves 2013; Borghouts & Keizer 2000)) and to reduce the risk of diabetes (Laaksonen et al. 2005), cardiovascular events (Manson et al. 2002) and mortality (Lee et al. 2004). Thus, exercise training has now been characterised as a beneficial therapy to improve health in women with PCOS (Haqq et al. 2015; Moran et al. 2011). To date, training studies have primarily included overweight and obese women with PCOS and often with a concomitant loss of bodyweight. However, lean women do not have a similar opportunity for weight loss as obese women. Importantly, aerobic exercise training without loss of bodyweight or dietary modifications has been shown to increase whole body insulin sensitivity in healthy, lean (Poehlman et al. 2000; Mandrup et al. 2017) and obese women (Ross et al. 2004). Only a few studies have investigated the effect of exercise training without loss of bodyweight on insulin sensitivity in lean women with PCOS and only with the use of surrogate measures to determine insulin sensitivity (Almenning et al. 2015; Turan et al. 2015; Nidhi et al. 2012). Furthermore, training-induced adaptations in glucose uptake and molecular alterations in insulin-sensitive tissues such as skeletal muscle have not previously been investigated in women with PCOS. Consequently, there is need for greater knowledge in this regard.
Therefore, the overall aim of my PhD thesis was to focus on lean women with PCOS and compare them to healthy, matched control (CON) subjects in order to:

1) Characterise skeletal muscles from lean, hyperandrogenic women with PCOS to investigate possible molecular mechanisms contributing to insulin resistance. The hypothesis was that insulin sensitivity is impaired in lean, hyperandrogenic women with PCOS and this could be associated with molecular abnormalities in skeletal muscle glucose and lipid metabolism.

2) Evaluate the effect of exercise training with bodyweight maintenance on whole body insulin sensitivity in lean, hyperandrogenic women with PCOS and investigate training adaptations in glucose uptake and underlying molecular events in skeletal muscle. The hypothesis for Study 2 was that exercise training with weight maintenance without dietary modifications would improve whole body insulin sensitivity in lean, hyperandrogenic women with PCOS; this was underlined in skeletal muscle glucose uptake and skeletal muscle molecular adaptations.

Chapter 1 is devoted to discussing insulin resistance in lean women with PCOS and furthermore evaluating potential underlying mechanisms both in the circulation and in skeletal muscle contributing to insulin resistance in lean women with PCOS. This chapter includes both Study 1 and Study 2. Chapter 2 is dedicated to evaluating the effect of exercise training on whole body insulin sensitivity in lean, hyperandrogenic women with PCOS. This includes an evaluation of the contribution of endogenous glucose production and skeletal muscle glucose uptake together with regularity mechanisms in skeletal muscle. This chapter is based on Study 2 and the current literature. Data from studies in non-PCOS and animals are included when necessary. Furthermore, methodological considerations are debated when appropriate.