Insulin Resistance and Hyperinsulinism in the Polycystic Ovary Syndrome

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SUMMARY

Insulin resistance with compensatory hyperinsulinemia has been demonstrated to occur in 50–70% of women with polycystic ovary syndrome (PCOS), regardless of weight. Hyperinsulinemia stimulates excess ovarian androgen production, thereby contributing to the hyperandrogenism and chronic anovulation characteristic of PCOS. The exact cause of insulin resistance in PCOS is unknown, but it appears to be related to a postbinding defect in insulin receptor-mediated signal transduction. Because of insulin resistance, women with PCOS are at risk for several long-term metabolic complications, including type 2 diabetes and cardiovascular disease.

Key Words: Insulin resistance; hyperinsulinism; insulin receptor-mediated signal transduction.

1. INTRODUCTION

Although the pathogenesis of polycystic ovary syndrome (PCOS) remains unknown, the discovery that many women with PCOS have underlying insulin resistance and compensatory hyperinsulinemia has led to a much better understanding of the syndrome. This metabolic abnormality contributes to the hyperandrogenism that characterizes PCOS and leads to its clinical signs and symptoms. The recognition of insulin resistance in PCOS has also influenced our understanding of the metabolic complications associated with PCOS. This chapter will provide an overview of the current body of knowledge regarding the prevalence, causes, and consequences of insulin resistance and hyperinsulinism in PCOS.

2. BACKGROUND

2.1. Overview of Insulin Resistance in PCOS

The relationship between PCOS and insulin resistance was first described by Burghen et al. in 1980 (1), with reports of a significant positive correlation between levels of androgens (testosterone and androstenedione) and insulin in a small number of obese women with PCOS. Several studies subsequently supported these findings (2–5).

Insulin resistance is defined as decreased sensitivity of target organ tissues to the action of insulin. Another way to describe insulin resistance is a decreased glucose response to a given amount of insulin, also known as decreased insulin-mediated glucose uptake. Hyperinsulinism refers to a state of elevated insulin expression, either clinically or biochemically (hyperinsulinemia).

Despite the compensatory hyperinsulinemia that accompanies insulin resistance in nondiabetic individuals, insulin-mediated glucose uptake remains subnormal (6). Interestingly, insulin resistance in PCOS does not occur in all tissues, but rather appears to be tissue-specific (7). Skeletal muscle and
adipose tissue become insulin resistant, resulting in decreased glucose uptake and increased lipolysis, respectively, whereas the ovary, adrenal, liver, and skin remain insulin sensitive (7).

In PCOS, hyperinsulinemia occurs as a compensatory response to insulin resistance. This resulting hyperinsulinemia has a stimulatory effect on the ovaries and adrenal glands that leads to enhanced androgen production by these organs. More specifically, excess insulin enhances androgen production in ovarian theca cells in response to luteinizing hormone (LH) stimulation, resulting in follicular arrest and anovulation. In addition, hyperinsulinemia stimulates proliferation of the pilosebaceous unit and sebum production, resulting in hirsutism and acne. In contrast, hyperinsulinemia acts to suppress hepatic production of sex hormone-binding globulin, the primary binding protein for testosterone in the serum. Therefore, insulin resistance with compensatory hyperinsulinemia results in hyperandrogenemia (Fig. 1).

There is also evidence that women with PCOS may have pancreatic β-cell dysfunction, as occurs in type 2 diabetes (6, 8). It has been reported that women with PCOS secrete an inadequate amount of insulin for the degree of peripheral insulin resistance that they experience (6).

2.2. Measurement of Insulin Resistance in PCOS

The gold standard method for measuring insulin sensitivity is the hyperinsulinemic-euglycemic clamp technique, first described by De Fronzo et al. (9), which measures insulin-mediated glucose uptake primarily in skeletal muscle. With this method, insulin is administered intravenously in one arm at a steady rate, while a variable glucose infusion is administered in the other arm in order to “clamp” the serum glucose level at a normal fasting concentration. Blood samples are taken fre-