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Concomitant dysregulation of androgen secretion and dysfunction of adipose tissue induced insulin resistance

Al-Nimer MS. Interactions between hyperinsulinemia and androgen excess

Abstract

Hyperandrogenism and hyperinsulinemia have resulted from dysfunction of the theca cell of the ovary and adipose tissue, and each one potentiates the other in patients with androgen excess disorders *e.g.,* polycystic ovary disease and idiopathic hirsutism. Possible external and/or internal triggers can produce such cellular dysfunction. There is evidence that sodium valproate acts as a trigger of cellular dysfunction and produces both hyperinsulinemia and hyperandrogenism. Therefore, the elimination of these triggers can help the patients to recover from hyperinsulinemia, insulin resistance, and hyperandrogenism.

Key Words: Hyperandrogenism; Hyperinsulinism; Central triggers; Polycystic ovary disease

Al-Nimer MS. Concomitant dysregulation of androgen secretion and dysfunction of adipose tissue induced insulin resistance. *World J Diabetes* 2022; In press

Core Tip: There is a close relationship between hyperinsulinemia and androgen excess in patients with androgen excess disorders. These disorders resulted from the dysfunction of gonad and adipose cells under the influence of a specific trigger. Sodium valproate is an example of an external trigger that produces concomitant hyperinsulinemia and androgenism leading to polycystic ovary syndrome. Therefore, elimination of the triggers can lead to recovery from antiepileptic drugs, while using insulin sensitizers and/or anti-androgens are partly solved the pathological problem.

TO THE EDITOR

I read with great interest an elegant review by Unluhizarci *et al*[1] who presented the role of insulin in the androgen excess disorders (AEDs) taking polycystic ovary syndrome (PCOS) and idiopathic hirsutism as examples of AEDs. The authors filled the gap about the relation between hyperandrogenism and hyperinsulinism, and they

highlighted the following important points: (1) The severity of insulin resistance is related to the phenotype of PCOS; (2) Hyperinsulinemia promotes the ovarian androgen synthesis in a mechanism not related to the gonadotropins; and (3) Using sodium valproate can cause androgen excess and hirsutism. Therefore, according to these important points, it is possible to consider that PCOS is a functional disease of concomitant dysregulation of androgen excess and dysfunction of the adipose tissue which is triggered by exogenous and/or endogenous insult at the hypothalamus-pituitary-target organs (gonads and adrenals)[2,3]. Some authors believe dysregulation of the androgen secretion in the theca cell of the ovary and adrenal gland can produce functional ovarian and adrenal hyperandrogenism, which not necessarily lead to hyperinsulinism and insulin resistance, while dysfunction of the adipose tissue can cause hyperinsulinism and insulin resistance[4]. Therefore a question has arisen that which factor or, trigger substance or, event that can cause the dysfunction of the theca cells and adipose tissue is still unknown.

So any therapeutic intervention at the ovarian cell or adipose tissue will ultimately affect the other factor, because each factor potentiates the effect of another factor as Unluhizarci *et al*[1] mentioned in their review (Figure 1). Therefore, using insulin sensitizers and/or anti-androgens are of value in ameliorating the biochemical and clinical features of PCOS[5,6], but these medicines, when used as monotherapy, cannot correct hyperandrogenism and hyperinsulinemia at the same time.

Sodium valproate is a modifiable risk factor for the development of PCOS in epileptic women and bipolar disorder by increasing body weight and androgen production[7,8]. In addition, sodium valproate induced hyperinsulinism by a direct effect on the beta-cell of the pancreas and indirectly by suppressing peripheral insulin-glucose uptake[9]. According to the valproate example, PCOS is the result of the vicious cycle (hyperinsulinism-hyperandrogenism) triggered by external, or internal modifiable factors which are producing ovarian cell dysfunction. According to pieces of literature, the triggers that cause dysfunction of the ovaries and adrenal glands act on the hypothalamic-pituitary-gonadal axis, and this explained why valproate can produce

manifestations of PCOS in epileptic and bipolar depression women. This effect seems to be gender-based because the relationship between insulin resistance and circulating androgens in obese young men is significantly inversed, while in PCOS women is significantly positive, indicating that there is a trigger factor that causes specific dysfunction of ovarian cells[10].

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