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Review article

Treating insulin resistance in the polycystic ovary syndrome

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RESUMEN

El síndrome de ovarios poliquísticos es la principal causa de esterilidad anovulatoria, su frecuencia es cercana a 7%. El síndrome de ovarios poliquísticos no tiene un perfil hormonal constante, por eso ha sido necesario recurrir a criterios, como los de Rotterdam, para establecer su diagnóstico. La demostración del efecto de la insulina en el ovario modificó el concepto de especificidad en la acción de la insulina sobre ciertos tejidos; por lo tanto, la resistencia a la acción de la insulina induce el hiperinsulinismo compensatorio que trata de estimular todos los tejidos pero que, en forma secundaria, agrava el trastorno de la esteroidogénesis ovárica. Los fármacos "sensibilizadores de insulina" se indican en el tratamiento de ciertas formas de diabetes mellitus, como la metformina y las tiazolidinedionas (roziglitazona y pioglitazona). Hace poco comenzó a prescribirse un compuesto a base de aminoácidos y oligoelementos (diamel) que en la célula neutraliza los radicales libres y restablece las señales intracelulares de la insulina. El efecto a largo plazo quizá no corrija el síndrome de ovarios poliquísticos porque la resistencia a la insulina se asocia con mayor riesgo de incremento de la intolerancia a la glucosa, diabetes, dislipidemia, aterosclerosis y enfermedad vascular. Por lo tanto, deben implantarse las medidas preventivas que estén al alcance.

Palabras clave: síndrome de ovarios poliquísticos, resistencia a la insulina, sensibilizadores a la insulina.

ABSTRACT

The polycystic ovary syndrome (PCOS) is the main cause of anovulatory sterility. Its prevalence is almost 7%. PCOS does have not a constant hormonal profile, which it why using approaches such as the Rotterdam criteria is necessary to diagnose it. The proven effect of insulin on the ovary modified the concept of the specificity in insulin's action on certain tissues: resistance to insulin's action results in the compensatory hyperinsulinism that tries to stimulate all the tissues, but also worsens ovarian steroidogenesis. There are drugs known as "insulin sensitizers" that are used to treat certain forms of diabetes mellitus which include metformin and thiazolidinediones (rosiglitazone and pioglitazone). Recently a compound that is composed of amino acids and trace elements (Diamel) has been used to neutralize the free radicals in the cell and restore the intracellular signals of the insulin. The long term effect however, might not correct the polycystic ovary syndrome as insulin resistance is associated to a higher risk of increased glucose intolerance, diabetes, dyslipidemia, atherosclerosis and vascular disease. Therefore, preventive measures that are currently available should used.

Key words: polycystic ovary syndrome, insulin resistance, insulin sensitizers

RÉSUMÉ

Syndrome des ovaires polykystiques est la principale cause d'infertilité anovulatoire, sa fréquence est proche de 7%. Syndrome des ovaires polykystiques n'a pas un profil hormonal cohérente, il a donc été nécessaire d'utiliser des critères tels que Rotterdam, pour établir le diagnostic. La démonstration de l'effet de l'insuline dans l'ovaire changé le concept de spécificité en action de l'insuline sur certains tissus, par conséquent, la résistance à l'insuline induit une hyperinsulinémie compensatoire est encourageant tous les tissus mais , secondairement, augmente le trouble de la stéroïdogenèse ovarienne. «Sensibilisateurs à l'insuline» Les médicaments sont indiqués dans le traitement de certaines formes de diabète sucré, tels que la metformine et les thiazolidinediones (pioglitazone et roziglitazona). J'ai récemment commencé à être prescrit un composé à base d'acides aminés et oligo-éléments (Diamel) que dans la cellule neutralise les radicaux libres et restaure les signaux intracellulaires de l'insuline. L'effet à long terme ne peut pas corriger le syndrome des ovaires polykystiques, car résistance à l'insuline est associée à un risque accru d'intolérance au glucose a augmenté, le diabète, les dyslipidémies, l'athérosclérose et les maladies vasculaires. Par conséquent, des mesures préventives doivent être mises en œuvre à la portée.

Mots-clés: syndrome des ovaires polykystiques, résistance à l'insuline, sensibilisateurs à l'insuline.

RESUMO

Síndrome do ovário policístico é a principal causa de infertilidade anovulatória, sua freqüência é quase 7%. Síndrome dos ovários policísticos não tem um perfil hormonal consistente, por isso foi necessário o uso de critérios tais como Roterdão, para estabelecer o diagnóstico. A demonstração do efeito da insulina no ovário mudou o conceito de especificidade na ação da insulina em certos tecidos, portanto, a resistência à insulina induz hiperinsulinemia compensatória é incentivar todos os tecidos, mas , secundariamente, aumenta a desordem da esteroidogênese ovariana. "Sensibilizadores de insulina" A droga é indicada no tratamento de certas formas de diabetes mellitus, tais como a metformina e as tiazolidinedionas (roziglitazona e pioglitazona). Recentemente, começou a ser prescrito um composto à base de aminoácidos e oligoelementos (Diamel) do que no celular neutraliza os radicais livres e restaura os sinais intracelulares da insulina. O efeito a longo prazo não podem corrigir a síndrome dos ovários policísticos, pois a resistência à insulina está associada com maior risco de intolerância à glicose aumentado, diabetes, dislipidemia, aterosclerose e doença vascular. Portanto, medidas preventivas devem ser aplicadas dentro do alcance.

Palavras-chave: síndrome dos ovários policísticos, resistência à insulina, sensibilizadores de insulina.

The polycystic ovary syndrome is the most common endocrine disorder during a woman's reproductive cycle. Its prevalence is 4 to 7%,[1,2] with extreme reports of up to 32%, depending on the population under study;[3] it is therefore the main cause of anovulatory sterility. The way patients suffering from polycystic ovary syndrome are treated is constantly changing due to progress in therapeutic, metabolic research and that done on infertility.

The polycystic ovary syndrome does have not a constant hormonal profile. Measuring circulating hormones using the existing analytical methods gives extremely varied results, which in many cases are difficult to interpret; that is why certain approaches have been used to diagnose it.[4] The National Institutes of Health of the United States consider the polycystic ovary syndrome to be chronic anovulation that, according to clinical and biochemical evidence and after excluding other ailments, is associated with an excess of androgens. At the consensus meeting held in Rotterdam, the polycystic ovary syndrome was defined as "a concurrent set of symptoms, signs and biochemical features that can occur in various combinations". It can exist without hyperandrogenism. (Table 1)[5-8]

Endocrinal changes

The characteristic changes of the polycystic ovary syndrome affect the endocrine system, which results in hyperandrogenism and, in turn, it affects a woman's appearance. Knowledge about the effect of insulin on the ovary changed the concept of the specificity in insulin's action on certain tissues (liver, skeletal muscles and fatty tissue) and also the evidence proving that there are extragonadal factors involved in ovarian functions.[9,10] When there is resistance to the action of insulin in various tissues, compensatory hyperinsulinemia occurs to try and stimulate these tissues, but then later, it worsens the ovarian steroidogenesis disorder due to the over stimulated ovarian receptors; this is what triggers off the series of metabolic changes of the polycystic ovary syndrome. This disorder is due to the fact that the somatomedin IGF-1 (the insulin-like growth factor type I) vigorously stimulates the cytochrome enzyme P450c-17 in the ovary. That is why the circulating insulin can join the IGF-I receptor and transmit the biological message to increase the production of androgens in the ovarian follicles. Moreover, as IGF-I and FSH share common signalling pathways, not enough of the latter is produced, which then limits the production of estradiol and the follicles don't mature. Consequently, FSH is suppressed and this significantly increases the LH and diverts the metabolic pathway towards the adrogens.[11,12]

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Table 1. Diagnostic criteria of the polycystic ovary syndrome

National Institute Health (1990)	*Rotterdam 82003)*	*Androgen Excess Polycystic Ovary Syndrome (2009)*
Chonic anovulation Clinical or biochemical excess of androgens Ruling out other disorders	Oligoovulation or anovulation or both Clinical or biochemical signs of hyperandrogenism Polycystic ovaries (Positive with two criteria)	Ovarian dysfunction (oligo-anovulation or polycystic ovaries or both) Hyperandrogenism (clinical or biochemical) Ruling out related disorders Existence of the syndrome without evidence of hyperandrogenism existing

Fauser BCJM. Hum Reprod 2004;19:41-47. Azziz R. J Clin Endocrinol Metab 2006;91:781-785. Azziz R. Fertil Esteril 2009;91:456-488.

In some cases of insulin resistance, various genes associated with the steroidogenisis enzymes are altered, such as the gene of the steroid synthesis CYP 11 alpha-hydroxylase and the genetic defects that increase the serine phosphorylation activity. In turn, this increases the activity of 17, 20 lyases and, consequently, triggers off hyperandrogenism and hyperinsulinemia. This genetic defect in the post-receptor can also cause an abnormality in the insulin receptor's serine phosphorylation, with a decrease in the intracellular signalling, which could explain the resistance to the action of the insulin.[13,14]

Determining insulin resistance

Insulin resistance should only be considered as a concept, as there is no laboratory proof that could be clinically used to identify insulin resistance among the population in general. There are tests, such as the *(euglycemic clamp)* and the glucose tolerance test that are used to calculate the glycemic index. However this is only useful for research and its clinical use is limited; moreover, there isn't a standard technique for the insulin tests.[15,16] Another observation made from some of the studies is that more than half of the patients suffering from the polycystic ovary syndrome, obese or slim, suffer from insulin resistance and that's why the prevalence is found to be between 50% and 75%. Nevertheless, the ratio of this finding depends on the screening test used.[17,18] For the time being, it has been suggested that insulin resistance might be the future cause of type 2 diabetes, which has its own implications.[19]

Treatment

The treatment for patients suffering from the polycystic ovary syndrome is basically symptomatic. The reason why the patient consults the doctor must be accurately established, what the menstrual disorders could be, infertility, hyperandrogenism, obesity and metabolic alterations that give a different response to the different forms of treatment should also be determined. Existing health care focuses on treating the condition of insulin resistance, because when it is corrected a large part of the ovarian functions are restored.[14,15]

Drug treatment

Insulin resistance and hyperinsulinemia are of interest due to their involvement in pathophysiology and in the symptoms (hyperandrogenism and obesity). Consequently a lot of research has been carried out to determine how useful the "insulin sensitizers", that are recommended to treat certain types of diabetes mellitus actually, are (Table 2). The main test is that carried out with a biguanide (metformin) and thiazolidinediones (rosiglitazone and pioglitazone), which can decrease obesity and restore menstruation, even ovulation.[16,17] The dose of metformin is between 500 and 1,000 mg a day. It is taken orally, with meals, to cut down on unpleasant effects such as: dry mouth, nausea, general discomfort and a feeling of weakness.

Treatment for hyperinsulinemia and insulin resistance can partially reduce hyperandrogenism, although this would not apply the other way round. This means to say that correcting hyperandrogenism does not eliminate insulin resistance. The metformin decreases the concentrations of insulin, testosterone, estradiol and glucose but it increases the SHBG,[18] which is considered to be beneficial.

Some observations show that these drugs increase the effectiveness of the ovulation inducers (clomiphene). Studies have also been carried out to find out about the preventive effect of diabetes mellitus when insulin

Table 2. Stratified analysis of the drug response in the polycystic ovary syndrome

Variable	*Clomifene*	*Metformin*	*Thiazolidinediones*	*Diamel*
Insulin resistance	↔	↓	↓	↓
Menstrual changes	↓	↓	↔	↓
Hyperandrogenism	↓	↔	↓	↓
Obesity	↔	↓	↓	↓
Anovulation	↓	↓	↔	↔
Hyperlipidemia	↔	↓	↓	↓
Return of cysts	↓	↓	↔	↓
Pregnancy	↑	↑	↔	↔

Modified from: Legro RS et al. N Engl J Med 2007;356:551. Velazquez EM et al. Metabolism 1994;43:647-654. Cosma M et al. J Clin Endocrinol Metab 2008;93:1135-1142.

resistance is corrected in women with the polycystic ovary syndrome.[19] An oral glucose tolerance test should be carried out on obese women, as there is more risk of diabetes and the appropriate diagnosis is essential, especially when there is a family history of diabetes.[20]

Recently, a compound made up of amino acids and trace elements (Diamel) was used. During tests and in vivo it stimulated the pancreatic metabolism and reduced the insulin resistance evaluated by means of the HOMA method. The mechanism of action involves certain molecules from the compound that stimulate the production of insulin (carnitine and ornithine). It reduces the amount of glucose absorbed in the intestine (glycine, sodium methylparaben, fumaric acid, pridoxal), neutralizes the free radicals in the cell due to the antioxidant effect (Zinc, C, B, calcium, folic acid) and restores insulin's intracellular signals, so the most is made of the insulin.[21] The lipid concentration in the blood (arginine) is also seen to drop, which helps to reduce insulin resistance. These beneficial changes have been observed in a significant number of patients with insulin resistance when they are treated with a dose of 660 mg every 12 hours[22]. On the whole, clinical effectiveness has been proved in preliminary observations of patients suffering from the polycystic ovary syndrome and insulin resistance.

CONCLUSIONS

Nowadays, the polycystic ovary syndrome is considered to be a state of ovarian hyperactivity that upsets the steroidogenesis which then leads to an excess production of androgens; this might be caused by certain altered genes and environmental factors. The components and the intensity of the medical condition, just like its progress, are variable; therefore is why it is a good idea to carry out an extensive diagnosis in order to correct the disorder properly. The treatment must be personalised, in particular when it is given to correct the metabolic part. Firstly, the reason why the patient has come to see the doctor must be taken into consideration. At the moment, there are many therapeutic options available to treat ovarian cysts; nevertheless, the results aren't very consistent in the majority of cases. A pre-established standard is needed to set up which patients must be treated and if the treatment does indeed depend on the type of ovarian cyst. Patients have to be informed of the long term effects of not correcting the polycystic ovary syndrome. The fact that insulin resistance is associated with a greater risk of glucose intolerance, diabetes, dyslipidemia, atherosclerosis, vascular disease and the obstructive sleep dysnea should be emphasized.[23,24] Preventive measures including changing the patient's life style, low fat, high fibre diet, regular

exercise of at least 15 minutes a day and reduce their weight by 5% should also be recommended; this has proven to be enough to restore ovulation.

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