Insulin resistance syndrome (syndrome X).

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Abstract:

The resistance to insulin-mediate glucose disposal is characteristic of patients with type 2 diabetes mellitus. This review article studies different aspects of this syndrome including risk factors, associated conditions such as yperinsulinemia, impaired glucose tolerance, hypertension, hypertriglyceridemia, decrease of HDL-cholesterol and truncal obesity and their management.

Key Words: Syndrome X, Insulin Resistance, Type 2 Diabetes Mellitus.

Introduction:

 The resistance to insulin-mediate glucose disposal is characteristic of patients with type 2 diabetes mellitus. Less well appreciated, however, was the fact that insulin resistant subjects able to sustain the degree of compensatory hyperinsulinemia necessary to maintain near normal glucose hemostasis were at risk to develop a cluster of additional abnormalities. In 1988, Reaven coined the term

syndrome X to describe a constellation often seen together: hyperinsulinemia, impaired glucose tolerance, hypertension, hypertriglyceridemia, decrease of HDL-cholesterol and truncal obesity.

One of 3 of the American adults has insulin resistance (about 70-80 millions of American population). Also this syndrome has been recognized as a secondary target of CHD risk reduction after LDL cholesterol.

Insulin resistance is a state of a cell, tissue or organism in which a greater than normal amount of insulin is required to elicit a quantitatively normal response. True insulin resistance is when the resistance is against both the endogenous and exogenous insulin and also the structure and biologic activity of the insulin must be intact.

Insulin resistance is influenced by both lifestyle and genetic background. However, data indicate that obesity and pysical inactivity, the two most important lifestyle variables that change insulin action, each explain ~25% of the difference in insulin action from person to person and difference in genetic background account for the remaining 50% of the variability in insulin resistance. The crucial point is that variations in body weight and level of physical activity are modulators of insulin action, they are not the primary causes of insulin resistance. Insulin is responsible for many other functions in addition to carbohydrate hemostasis such as: cellular growth and differentiation, protein synthesis, mRNA synthesis and etc. It must be noted that insulin resistance can be selective and involve only certain aspects of its action.

Mechanisms:

Obesity: Obesity is one of the most common causes of insulin resistance. Elevated levels of circulating factors, such as TNF-a or free fatty acids (FFA), have been suggested as possible causes of the insulin resistance of obesity. TNF-a and IL-6 both are expressed in adipose tissue in normal individuals. Among the known effects of these cytokines are inhibition of insulin signaling and induction of both hyperglycemia and endothelial activation.

Increased delivery and utilization of FFAs leads to increased intracellular oxidation of FFA which in turn causes inhibition of glycolysis and glucose uptake, with antagonism of insulin action.

Resistin: Claire steppan and colleagues at the university of Pennsylvania recently discovered a novel protein secreted by adipocytes

that causes insulin resistance in animals and impairs insulin induced glucose transport in vitro. This new protein has been named resistin and its levels are elevated in both genetic and diet induced obesity. Treatment of animals with the drugs called thiazolidinediones (TZD) causes a decline in expression of resistin mRNA. It is hoped that further research on the physiology of this novel protein will result in a better understanding of the molecular basis for insulin resistance.

Endothelial activation: Endothelial nitric oxide is an important molecule in both insulin and exercise-stimulated glucose uptake. Mutations in the gene that encodes the enzyme that synthesize this molecule, may limit the compensatory effects of physical activity on glucose uptake and it is related directly and indirectly to features of the metabolic syndrome.

Manifestations of insulin resistance:

Since the introduction of the syndrome the list of abnormalities associated with it has grown considerably.

Biochemical basis for the observed clinical heterogeneity in insulin resistant states can be explained by two major mechanisms.

1- Generation of multiple distinct effects on post-receptor signaling pathways within target cells.

2- Specificity spillover phenomenon: high serum hormone concentrations in states of resistance to a hormone action can affect certain hormone actions through a receptor-effector pathway different from but homologous to the natural hormone receptor-effecteor via specificity spillover phenomenon. In the insulin resistance model, the resultant hyperinsulinemia may induce some of its manifestations such as hyperandrogenism, PCOD, the skin changes of acanthosis nigricans and hypertrophice cardiomyopathy, through a functioning homologous IGF-I receptor-effecter mechanism.

Abnormalities related to insulin resistance and compensatory hyperinsulinemia

1- Glucose metabolism: Syndrome X is used to describe insulin resistant individuals who, though they may have impaired glucose tolerance, are not diabetic. Individuals with syndrome X and type 2 diabetes

share insulin resistance, but the designation of syndrome X should be limited to persons who have maintained sufficient insulin secretory function to remain nondiabetic.

2- Uric acid metabolism: Hyperuricemia: It has been shown that significant correlations exist between serum uric acid concentration and insulin resistance. It now appears that the increase in plasma uric acid concentrations in insulin resistant nondiabetic individuals is due to a reduction in renal uric acid clearance secondary to the effect of compensatory hyperinsulinemia on the renal handling of uric acid.

3- Dyslipidemia:

a- There are a series of changes in lipid metabolism in patients with syndrome X. An increased blood, T.G level appears to be the earliest clinical sign of the syndrome. Due to the effect of the chronic hyperinsulinemia in syndrome X, hepatic VLDL-TG secretion is increased. The compensatory hyperinsulinemia also enhances the hepatic conversion of FFA to TG. Also the failure of insulin to appropriately stimulate LPL activity in insulin resistant individuals accentuates the magnitude of hypertriglyceridemia.

b- Postprandial lipemia: The higher the fasting T.G concentration, the greater the postprandial accumulation of TG-rich lipoproteins.

c- HDL-cholesterol: Insulin resistance and hyperinsulinemia contribute to a low HDL-C indirectly by increasing the VLDL pool size and directly by increasing the fractional catabolic rate of APO-AI (the major apoprotein of HDL).

d- LDL particle diameter: Individuals with smaller LDL particle have higher plasma T.G and lower HDL-C concentrations, thus this change in LDL composition should be added to the cluster of abnormalities constituting syndrome X.

4- Hemodynamic: Approximately 50% of patients with hypertension are insulin resistant. This phenomenon is probably related to the changes in:

a- Sympathetic nervous system (SNS) activity and,

b- The Na+ retaining effects of insulin.

Resting heart rate is higher in patients with high B.P which could be secondary to enhanced SNS activity in insulin resistant subjects and there

is evidence that injection of insulin acutely stimulates SNS discharge. Also the acute infusion of insulin increases renal Na+ retention in both normal individuals and patients with high B.P.

Hypertension: Insulin resistant individuals are at increased risk of developing hypertension. The evidence in support of this view can be summarized as follows: 1- studies have shown that patients with high B.P are insulin resistant in comparison with normotensive persons.

2-Patients with secondary forms of hypertension are not insulin resistant. 3- Normotensive first degree relatives of patients with high B.P are insulin resistant and hyperinsuinemic in comparison with normotensive subjects without a family history of hypertension and 4- hyperinsulinmia predicts the development of high B.P in prospective studies. Although only about 50% of patients with hypertension are insulin resistant, these individuals appear to be most at risk of developing CHD.

5- Hemostatic: There is evidence that both hypercoagubility and impaired fibrinolysis are associated with insulin resistance. PAI-I: PAI-I concentrations are higher in patients with hypertriglyceridemia, hypertension and CHD suggesting that PAI-I levels are related to insulin resistance.

6- Reproductive system: PCOS is the most common endocrine abnormality in premenopausal women, and one of ten women is USA have PCO. There is new abundant evidence that insulin resistance play a fundamental role in the etiology of PCOS. Also it is worthnoting that women with PCOS are at increased risk to develop type 2 diabetes. There are two major hypothesis for the association of ovarian hyperandrogenism and insulin resistance. The first views insulin as exerting its actions through IGF-1 receptors in the ovary. The second, the action of insulin to promotes ovarian effects through insulin receptors may be maintained despite the loss of its action on pathways related to glucose hemostasis. Also an autophosphorylation defect in insulin receptor has been implicated as a potential mechanism for insulin resistance in a subset of PCO patients.

7-Acanthosis nigricans: The lesion is found in all clinical conditions that are characterized by markedly reduced insulin action at the cellular

level. Perhaps the skin lesions are caused by high levels of circulating insulin acting through receptors for IGF in the skin.

8- Truncal obesity: Cushing syndrome phenotype: the cognition of syndrome X which includes many of the findings in Cushing's syndrome (central obesity, hypertension, dyslipidemia, insulin resistance and atherosclerosis), has been termed cushing syndrome phenotype. Many syndrome X patients have shown mild abnormalities in cortisol metabolism. A recent study in rats has been shown that a single enzyme in fat cells increased cortisol level and triggers fat accumulation around the belly and its associated ill effects. Also investigators from Tennesi university have shown that levels of intracellular calcium are related to the production of cortisol in human fat cells. They showed that increased intracellular calcium levels results to a direct and rapid increment (about 3-6 folds) of cortisol production in human fat cells. In normal individuals insulin has a stimulatory effect on intracellular calcium-pump and promotes calcium loss from cells. According to these findings insulin resistance could be linked to cortisol metabolism and consequences of increased cortisol production.

9- Pseudoacromegaly: Accelerated linear growth along with acral enlargement, muscle hypertrophy, muscle cramps, widely spaced teeth and other features of acromegaly in the presence of normal or low GH levels have been observed in cases of insulin resistance, for which defects of signaling intermediates beyond the insulin receptor, involving the metabolic but not the mitogenic actions of insulin have been described.

10- Other associated features: Since the introduction of metabolic syndrome, many other symptoms and sings have been associated with it, including: increased fibrinogen, endothelin-1 and CRP concentrations and low levels of DHEA-S and antioxidant vitamins, nonalcoholic fatty liver disease and hypertrophic cardiomyopathy.

Diagnosis:

Although hyperinsulinemia is the basic abnormality leading to the manifestations of syndrome X, direct estimates of insulin resistance are not practical, and there is no gold standard for classifying an individual as being hyperinsulinemic, so it is simpler to directly assess whether or not the manifestations of syndrome X are present. Table 1 summarizes the factors associated with increased likelihood of insulin resistance.

Table 1: Risk factors for syndrome X

1- overweight: BMI³ 25kg/m2 or waist circumference: >102cm in men and >88cm in women.
2- Sedentary lifestyle.
3- Age >40 years old
4- Non-Caucasian ethnicity
5- A family history of NIDDM, hypertension or CVD.
6- A history of glucose intolerance or gestational diabetes.
7- A diagnosis of hypertension, T.G/ ⁻HDL-C or CHD.
8- Acanthosis nigricans
9- PCOS

As mentioned before, insulin resistance syndrome has been recognized as a secondary target of CHD risk reduction after LDL-C. Insulin resistance may be related to atherosclerotic heart disease, both directly and through its associated conditions. Accordingly ATP-III has suggested criteria for the identification of the metabolic syndrome in practice which has been shown in Table2.

Table 2: ATP-III criteria for the identification of the metabolic syndrome

1- Abdominal obesity: waist circumference >102 cm in men and >88cm in women.
2- Triglyceride level: ³150mg/dl
3- HDL-C level : <40 mg/dl in men, <50mg/dl in women.
4- Blood pressure: ³130/85 mmHg.
5- Fasting glucose level: ³110mg/dl, <126mg/dl.

Recently the American college of endocrinology has been emphasized the use of 2hours post glucose challenge test as the most sensitive clinically available test for the insulin resistance syndrome. For purposes of ATP-III, the diagnosis of the metabolic syndrome is made when 3 or more of the criteria shown in table 2 are present.

Management:

Management of the metabolic syndrome has a 2-fold objective 1-to reduce underlying causes (ie, obesity and physical inactivity) and 2-to treat associated nonlipid and lipid risk factors.

Non pharmacologic approach to insulin resistance syndrome:

1- Weight reduction: weight loss of 10-15 pounds inoverweight individuals will enhance insulin sensitivity and patients must be assisted in dietary modifications to attain a healthy body weight.

2- Exercise: Aerobic exercise for at least 30minutes 3 or 4 times or perfectly all days of the week is recommended.

3- Diet: The usual advice regarding replacement of saturated fat with carbohydrate may be helpful in those with elevated levels of LDL-C, but will make the manifestations of syndrome X worse. The greater the CHO content in an isocaloric diet, the more insulin must be secreted. Given this information, weight maintenance diets containing (as a percentage of total calories) 15% protein, 40% fat (<10% SF, ~20% MUF and the rest as PUF) and 45% CHO will decreases LDL-C, without any untward effects on the manifestations of syndrome X.

4- Medications: Currently, the FDA has not approved any drugs for the pharmacologic management of syndrome X. Metformin has been successfully used for some time to treat diabetes mellitus. It increases insulin sensitivity as does the new thiazolidinediones class of drugs. Pending more evidence the American diabetes association does not recommend drug therapy for the treatment of insulin resistance in the absence of diabetes.

Medical Management: In the absence of specific pharmacologic management of insulin resistance, drug treatment should focus on the manifestations of syndrome X. For example the use of fibric acid derivatives conreduce risk of CHD in individuals with high T.G and low HDL-C concentrations. In the presence of high LDL-C concentrations in insulin resistant patients the need to lower cholesterol levels should not be ignored and the use of HMG-CoA reductase inhibitors must be considered if diet alone does not control LDL-C.

Hypertension: Approximately 50% of patients with high B.P have one or more of the components of syndrome X and attention should be given to avoid the use of antihypertensive agents that will accentuate insulin resistance.

What should be the priorities for the future?

1- Development of, more accurate and better tests for detection of insulin resistance.

2- Targeted testing for individuals and families at risk .

3- Research into pharmacologic therapies to improve insulin resistance.

At this time clinicians should make it a priority to aggressively identify patients with possible insulin resistance and assist them in making appropriate lifestyle modifications.

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