University of Basra / Collage of pharmacy

INSULIN RESISTANCE : CLINICAL MANIFESTATIONS & MANAGEMENT

Graduation project

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Insulin resistance : Clinical manifestations and management

Summary

Insulin resistance is an impaired biologic response to insulin stimulation of target tissues, primarily the liver, muscle, and adipose tissue.

There are two types of insulin resistance : Type A it is primarily an inherited condition related to mutations in the Insulin Receptor (INSR) gene and Type B is an especially autoimmune disorder (acquired) .

Insulin resistance is a feature of a number of clinical disorders, including

1- Type 2 diabetes/glucose intolerance .
2- Dyslipidemia
3- Cardiac disease
4- Obesity & visceral obesity
5- Hypertension clustering in the so-called metabolic syndrome.
6- PCOS .

There is no single test that can directly diagnose insulin resistance, however the following tests are essential to reach the diagnosis of insulin resistance :

1. Fating blood sugar test
2. Glycated hemoglobin (A1c)
3. Fasting insulin test (all these will elevated)
4. Test LDL cholesterol , Triglycerides ,VLDL (all these will elevated) and HDL cholesterol (will decrease)
5. Androgen level (will increase)
6. CRP (will increase)
7. Blood pressure (high)

Treatment of insulin resistance (and improving insulin sensitivity) primarily involves pharmacological and non pharmacological treatment

Non pharmacological treatment include making changes in lifestyle and diet .

Pharmacological treatment include medications mainly metformin .

Both children and adults can develop insulin resistance and metabolic syndromes .

KEY WORDS

Insulin resistance , obesity , polycystic ovary syndrome , insulin growth factor-1 , dyslipidemia .

INSULIN

Insulin is a peptide hormone secreted by the β cells of the pancreatic islets of Langerhans and maintains normal blood glucose levels by :

1. Facilitating cellular glucose uptake
2. Regulating carbohydrate, lipid and protein metabolism
3. Promoting cell division and growth through its mitogenic effects . (1)

Insulin structure

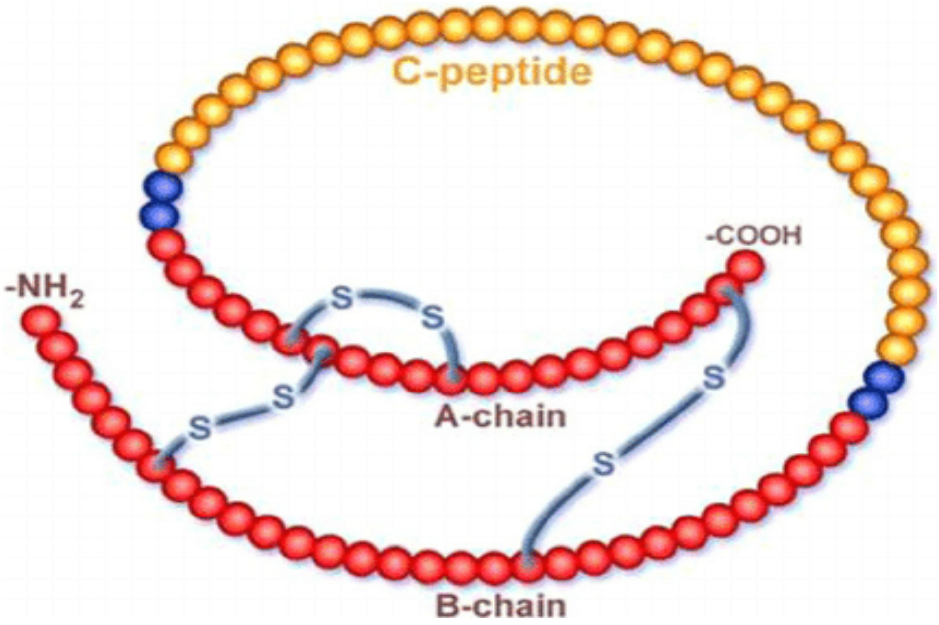
Insulin is composed of two peptide chains referred to as the A chain (consists of 21 amino acids) and B chain (consists of 30 amino acids) .

The A and B chains become linked together by two sulfur-sulfur (disulfide) bonds.

Insulin is derived from a 74-amino-acid prohormone molecule called proinsulin. Proinsulin is relatively inactive, and under normal conditions only a small amount of it is secreted .

The A chain terminal residues A1 glycine, A5 glutamine, A19 tyrosine and A21 asparagine are on the surface of the molecule. They are invariant and not involved in the aggregation of the molecule. Their deletion affects both the structure and activity of insulin.

Substitution at A1 glycine, especially of bulky groups, reduces activity substantially but seems to affect the molecular structure less.



Physiology

At the whole body level, the actions of insulin are influenced by the interplay of other hormones.

1. Insulin, though the dominant hormone driving metabolic processes in the fed state, acts in concert with growth hormone and IGF-1; growth hormone is secreted in response to insulin, among other stimuli , preventing insulin-induced hypoglycemia.
2. Other counter-regulatory hormones include glucagon, glucocorticoids and catecholamines. These hormones drive metabolic processes in the fasting state. Glucagon promotes glycogenolysis, gluconeogenesis and ketogenesis.

The ratio of insulin / glucagons determines the degree of phosphorylation or dephosphorylation of the relevant enzymes.

Catecholamines promote lipolysis and glycogenolysis & glucocorticoids promote muscle catabolism, gluconeogenesis and lipolysis.

Excess secretion of these hormones may contribute to insulin resistance in particular settings, but does not account for the vast majority of insulin resistant states.(1)

Pathology

Hypoinsulinemia : Permanently down levels of insulin causes insulin deficient diabetes (Type 1) , and the hormonal actions of insulin are necessary for the life of complex organisms .

Hyperinsulinemia : Permanently elevated levels of insulin may cause disturbance of normal cellular physiology and organ function such as insulin resistance , obesity , cardiovascular disease and diabetes type 2 .

INSULIN RESISTANCE

Insulin resistance is an impaired biologic response to insulin stimulation of target tissues, primarily the liver, muscle, and adipose tissue; it is primarily an acquired condition related to excess body fat, though genetic causes are identified as well.

Clinically, insulin resistance is recognized via the metabolic consequences associated with insulin resistance as described in metabolic syndrome and insulin resistance syndrome .

Insulin resistance may cause :

1. Impairing glucose disposal, resulting in a compensatory increase in beta-cell insulin production and hyperinsulinemia, classically this refers to impaired sensitivity to insulin mediated glucose disposal . Compensatory hyperinsulinemia occurs when pancreatic β cell secretion increases to maintain normal blood glucose levels in the setting of peripheral insulin resistance in muscle and adipose tissue.
2. The metabolic consequences of insulin resistance can result in hyperglycemia, hypertension, dyslipidemia, visceral adiposity, hyperuricemia, elevated inflammatory markers, endothelial dysfunction, and a prothrombotic state.
3. Progression of insulin resistance can lead to metabolic syndrome, nonalcoholic fatty liver disease (NAFLD), and type 2 diabetes mellitus.(2)

Insulin resistance in most cases at the cellular level appears via post-receptor defects in insulin signalling.

The Possible mechanisms that causes insulin resistance:-

1. Down-regulation
2. Deficiencies or genetic polymorphisms of tyrosine phosphorylation of the insulin receptor,
3. Insulin Receptor Substrate (IRS) or PIP-3 kinase

Inflammatory molecules and lipid metabolites inhibit insulin signalling by stimulating a number of different serine kinases which are responsible for serine phosphorylation of Insulin Receptor Substrate-1 (IRS-1). (7)

4. Abnormalities of GLUT 4 function .

Types of insulin resistance

1) Type A

Type A insulin resistance syndrome is one of a group of related conditions described as inherited severe insulin resistance syndromes , is a rare disorder in which the body's tissues and organs do not respond properly to the hormone insulin.

Patients with type A insulin resistance syndrome are non_obese and demonstrate severe hyperinsulinemia , hyperandrogenism , and acanthosis nigricans.

These disorders, which also include Donohue syndrome and Rabson-Mendenhall syndrome, are considered part of a spectrum.

Type A insulin resistance syndrome represents the mildest end of the spectrum (its features often do not become apparent until puberty or later, and it is generally not life-thratining) . (3)

Causes of type A :

Type A insulin resistance syndrome results from mutations in the Insulin Receptor (INSR) gene { This gene provides instructions for making a protein called an insulin receptor, which is found in many types of cells}. Insulin receptors are embedded in the outer membrane surrounding the cell, where they attach to insulin circulating in the bloodstream & this binding triggers signaling pathways that influence many cell functions. Most of the INSR gene mutations that cause type A insulin resistance syndrome lead to the production of a faulty insulin receptor that cannot transmit signals properly.

Although insulin is present in the bloodstream , the defective receptors make it less able to exert its effects on cells and tissues { This severe resistance to the effects of insulin impairs blood sugar regulation and leads to diabetes mellitus} . (3)

In females with type A insulin resistance syndrome , excess insulin in the bloodstream interacts with hormonal factors during adolescence and cause many abnormalities including :

1. Abnormalities in the menstrual cycle :
   Many affected females do not begin menstruation by age 16 (primary amenorrhea) or their periods may be light and irregular (oligomenorrhea)
2. Abnormalities in ovarian cysts :

They develop cysts on the ovaries and excessive body hair growth (hirsutism)

3. Most affected females also develop a skin condition called acanthosis nigricans, in which the skin in the body folds and creases becomes thick, dark, and velvety.

Unlike most people with insulin resistance, females with type A insulin resistance syndrome are usually not overweight.(3)
The clinical features are more severe in affected females than in males, and they mostly become apparent at the age of puberty. (4)
So, this condition is often more diagnosed in females than in males , may due to females having more health problems associated with this condition.

2) Type B

Type B insulin resistance syndrome (TBIRS) is an especially autoimmune disorder with unknown prevalence, caused by immunoglobulin G polyclonal antibodies that antagonize the insulin receptor (whose effects are quantitatively most noticeable in skeletal muscle, liver and adipose tissue) , this antagonism leads to abnormal cellular and metabolic responses to insulin, marked by elevated levels of circulating insulin(insulin resistance) & hyperglycemia .
It is generally described in middle-aged people and may be associated with another autoimmune conditions (coexists with autoimmune diseases) like Systemic lupus erythematosus is the most common underlying disease of the syndrome, as well as systemic lupus erythematosus who completely recovered after undergoing immunosuppressive therapy, specifically pulse therapy utilizing intravenous immunoglobulin. (6)

Insulin receptor autoantibodies have three mechanisms that lead to insulin resistance.

- Mechanism 1: Autoantibodies bind to insulin receptors and competitively inhibit insulin binding, preventing its action .
- Mechanism 2: They accelerate the receptor degradation rate .
- Mechanism 3: Paradoxically, these antibodies can act both as insulin agonists and antagonists, causing a biphasic response of hypo and hyperglycemia in the same patient . (5)

Typical features of type B :

1. A rapid progression of hyperglycemia due to compensatory insulin hypersecretion, usually at levels at which normoglycemia cannot be maintained
2. Less common presenting features include hypoglycaemia and hyperandrogenism/female virilisation.

✓ Hypoglycemia due to the receptor autoantibodies can present an insulin-like effect & leading to hypoglycemia . In hypoglycemia, the antibody acts as a partial agonist and can be found in low titers .

✓ So the TBIRS can cause both insulin resistance and significant hyperglycemia, as well as hypoglycemia which is difficult to control , depending on receptor inhibition or activation .

3. Acanthosis nigricans are often described.
4. There is a strong association with systemic lupus erythematosus (SLE).

Diagnosis of type B :

This syndrome is difficult to diagnose, as it may present as hyper- or hypoglycemia which is difficult to control.

Diagnosis is given by

1. Positive anti-insulin receptor antibody .
2. The insulin level test at fasting state .

Individuals who require insulin at doses greater than 3 U/kg/day and have concomitant autoimmune diseases should be investigated for TBIRS.

Treatment of type B :

TBIRS is associated with autoimmune disorders and poor glycemic control despite correct adherence to treatment.

Treatment includes :-

1. Glycemic control measures
2. Sometimes immunosuppression, but there is no standard immunosuppression protocol .
3. Hospitalization is often required for administration of extremely high doses of insulin, or for monitoring severe and difficult to control hypoglycemia that is related to high mortality rates. (5)

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

Insulin resistance is a feature of a number of clinical disorders, including :

1- Type 2 diabetes/glucose intolerance
2- Dyslipidaemia
3- Cardiac disease
4- Obesity & visceral obesity
5- Hypertension clustering in the so-called metabolic syndrome
6- PCOS

Type 2 diabetes / glucose intolerance

Is a condition in which cells cannot use blood sugar (glucose) efficiently for energy. This happens when the cells become insensitive to insulin and the blood sugar gradually gets too high , it's occurs when the pancreatic β cell is no longer able to maintain the degree of hyperinsulinemia needed to overcome resistance to insulin mediated glucose disposal by muscle and insulin-induced inhibition of adipose tissue lipolysis .

Insulin resistance is a fundamental defect in patients with types 2 diabetes; essentially all patients with type 2diabetes are insulin-resistant. (25)

Dyslipidemia

A disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency and it is an important risk factor for coronary heart disease (CHD) and stroke .

Elevated triglycerides , cholesterol & Free fatty acid (FFA) and decreased high-density lipoprotein (HDL) , all this often is observed in patients who are insulin resistant due to impairing the ability of insulin to suppress lipolysis .

Increased FFA concentrations, in turn, are thought to be a major mediator of insulin resistance and have been shown to cause endothelial dysfunction , impair pancreatic β-cell function , and acutely raise blood pressure.

Increased delivery of FFA to skeletal muscle can result in insulin resistance in that tissue, either directly or via accumulation of increased intramyocellular triglyceride stores .

Similarly, increased delivery of FFA to the liver may be responsible for hepatic insulin resistance , accumulation of intrahepatocellular triglyceride , and increased synthesis and secretion of VLDL . (16)
Patients with insulin resistance have an increase in VLDL cholesterol, which is more atherogenic than LDL cholesterol.
Insulin resistance also decreases lipoprotein lipase activity, the major mediator of VLDL clearance, which may make a smaller contribution to elevated triglycerides in this setting.
VLDL is metabolized to remnant lipoproteins and LDL, both strongly associated with atherosclerotic risk. (10)

Cardiac diseases

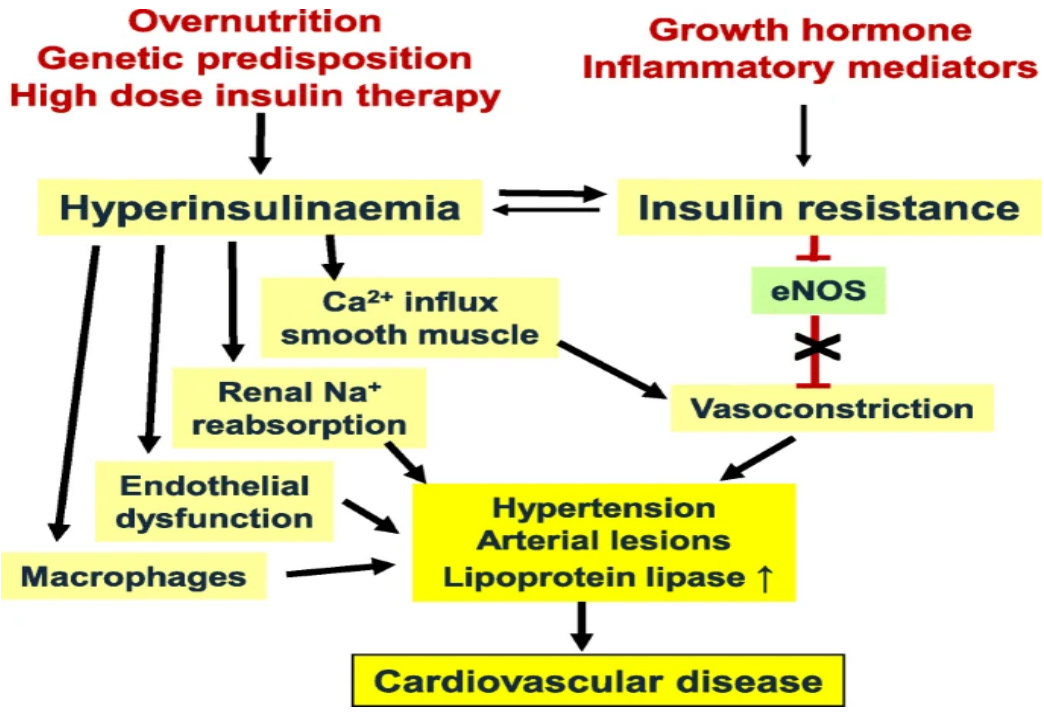
Is the name for the group of disorders of heart and blood vessels , including :
Hypertension (high blood pressure) , coronary heart disease (heart attack) , cerebrovascular disease (stroke) , peripheral vascular diseases (atherosclerosis) and myocardial infarction (MI) .
Insulin resistance has been found to play a critical role in the development of cardiovascular disease, particularly in patients with type 2 diabetes.
A major indicator of insulin resistance is considered as a risk factor for coronary disease and may cause atherosclerosis .

Mechanism of insulin resistance in cardiac disease :

Hyperinsulinemia and insulin resistance enhance the risk of cardiovascular disease by several mechanisms :

1) Inducing endothelial dysfunction
   IR has reduced effects on the phosphatidylinositol 3 kinase (PI3K) pathway, whereas mitogen activated protein kinase activity is maintained , may result is an exaggeration of the mitogenic actions of insulin leading to vascular smooth muscle proliferation and elevated plasminogen activator inhibitor (PAI)-1 .
2) Suppression of endothelial nitric oxide synthase (eNOS) , further contributing to atherogenicity.
3) Activation and promotion of calcium ion influx into smooth muscle cells, resulting in increased vascular tone .
4) Enhanced reabsorption of sodium ions in renal tubules .
5) Adhesion of macrophages to the vessel wall

6) Development of arterial lesions with increased lipoprotein lipase activity and cardiovascular disease .



Obesity

Obesity, particularly central obesity, is associated with insulin resistance and the relationship between insulin resistance and obesity, including lipid accumulation in muscle and liver and the recently discovered adipocytokines . (11)

In obese individuals, adipose tissue releases increased amounts of non-esterified fatty acids, glycerol, hormones, pro-inflammatory cytokines and other factors that are involved in the development of insulin resistance. (13)

Macrophages are components of adipose tissue and actively participate in its activities.

Adipose tissue is known to express and secrete a variety of products known as ‘adipokines’, including (leptin, adiponectin, resistin and visfatin) , as well as cytokines and chemokines such as (tumor necrosis factor-alpha, interleukin-6 and monocyte chemoattractant protein-1) , all these products will contribute in insulin resistance .

Visceral obesity

The accumulation of fat in the upper body is associated with metabolic complications of obesity and the mechanism responsible for

this association is insulin resistance, which is frequently present in individuals with upper body obesity and is associated with increased cardiovascular risk .

Impaired insulin suppression of adipose tissue lipolysis is a feature of insulin resistance and may even be the primary cause of, insulin resistance.

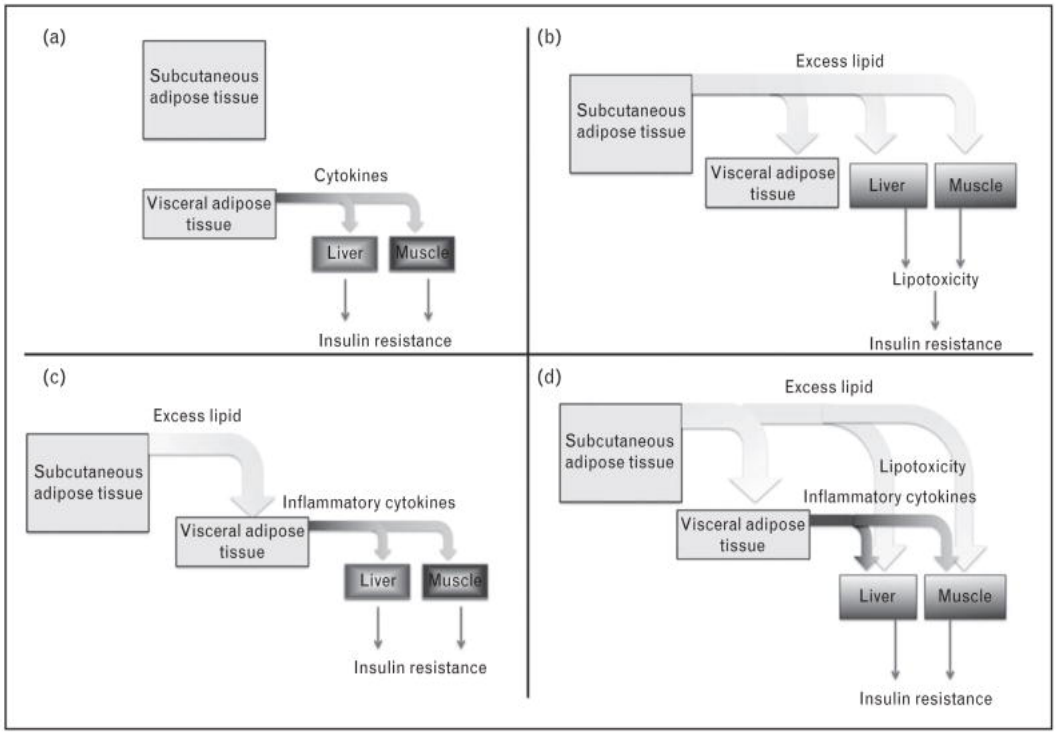
Pathogenesis of insulin resistance in visceral obesity :

1- One possibility is that visceral fat itself is inherently diabetogenic , it secretes adipokines that impair insulin sensitivity in tissues such as liver and muscle, which increase upon expansion of this depot (Fig. 1a).

2- Another possibility is that the accumulation of visceral fat is a surrogate indicator of ectopic lipid accumulation and lipotoxicity, which occur in parallel in liver and muscle, causing insulin resistance in these tissues (Fig. 1b).

3- A third possibility is that excess lipid accumulation in visceral adipose tissue actually causes its acquisition of diabetogenic properties , visceral adipose tissue indeed accumulates macrophages that release inflammatory cytokines, which can impair insulin sensitivity (Fig. 1c) .

4- A fourth possibility is one in which lipotoxicity in peripheral tissues and visceral adipose tissue cytokine production, both contribute to systemic insulin resistance (Fig. 1d). (16)



Pro_thrombotic state

Loss of platelet inhibition by insulin is a major determinant of platelet hyperactivity during obesity .

Hypertriglyceridaemia and increased concentration of free fatty acids exert an pro_aggregating effect .

Hypo_HDL anemia influences platelet aggregation, possibly because HDL opposes the activation properties of low-density lipoprotein (LDL) on platelets , so can cause increase in pro_thrombotic state. (18)

Hypertension

Insulin in normal levels have effect on blood pressure by two mechanisms :

1- By effect on arteries cause vasodilation and decrease blood pressure

2- The effect on the kidney causes sodium reabsorption and increases blood pressure.

These two mechanisms work together to control or balance blood pressure.

While in insulin resistance the effect on arteries was lost just the effect on kidney and cause increase in blood pressure also increase angiotensin II and uric acid in plasma which contribute to increase blood pressure.

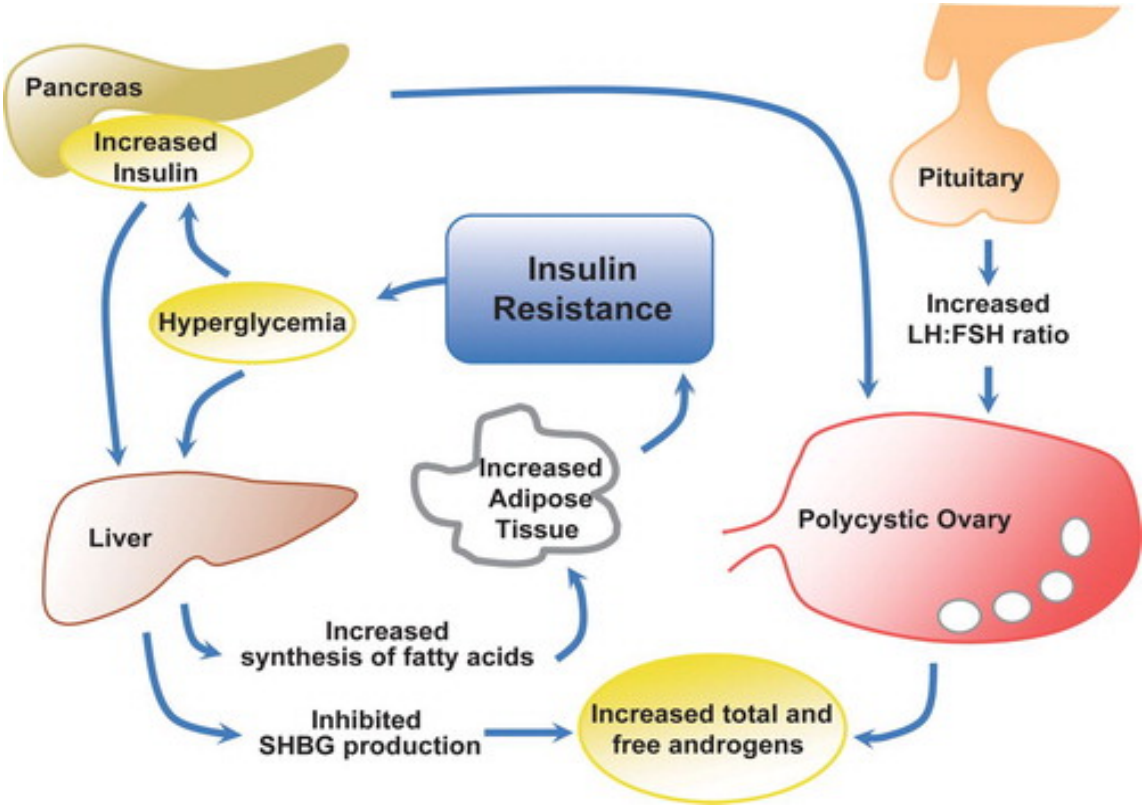
The prevalence of hypertension rises with exacerbation of stages of impaired glucose metabolism , however , only in the early stages of impaired insulin metabolism do hyperglycemia and hyperinsulinemia appear to be significant contributors to the presence of hypertension. (21)

Polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome (PCOS) has major metabolic sequelae related to insulin resistance and insulin resistance plays an important role in the pathogenesis of the reproductive abnormalities of the disorder. Women with PCOS are at significantly increased risk of developing type 2 diabetes mellitus (DM). (22)

The pathophysiology of PCOS is complex and remains elusive , however , insulin resistance and hyperandrogenism play key roles in the aetiology . The role of insulin resistance in PCOS is more complex , since insulin plays both direct and in direct roles in the pathogenesis of hyperandrogenemia .

IR and hyperinsulinemia may directly stimulate production of androgens via ovarian tissue steroidogenesis (insulin acts synergistically with LH) and independently of changes in gonadotropin concentration .
Hyperinsulinaemia also plays an indirect role in hyperandrogenism by inhibiting hepatic synthesis of sex hormone_binding globulin (SHBG) production, thus increasing the amount of unbound (free) or bioactive testosterone in the circulation and increasing the effect of circulation androgens .

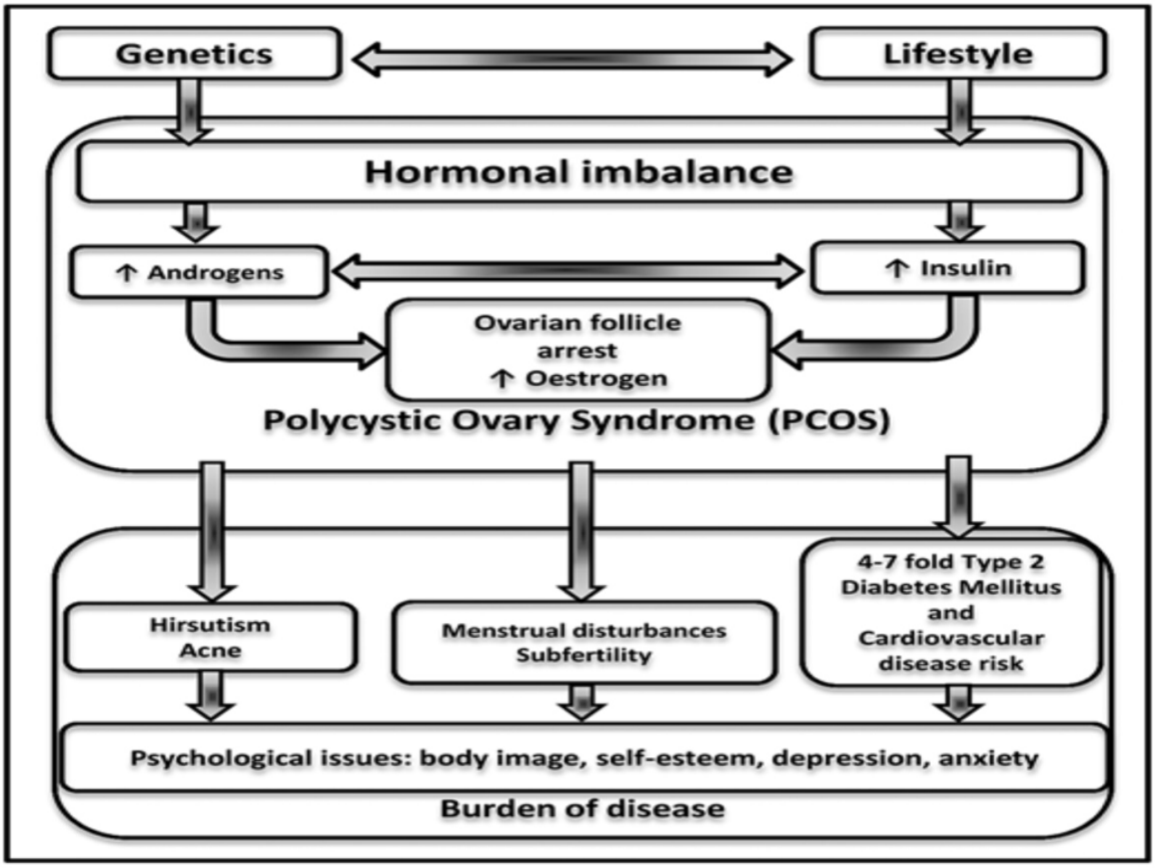


Low SHBG levels are also increased by insulin_sensitising medication. However, the strength of the relationship between IR and SHBG is unclear and the potential role of SHBG as a clinical marker of IR in PCOS is yet to be determined. (23)
Increased adiposity worsens insulin resistance and thus exacerbates the metabolic and endocrine derangements of PCOS .
It is generally accepted that obese women with PCOS are insulin resistant. Obesity is known to increase circulating androgen and insulin levels, may increase PCOS prevalence and exacerbates the clinical features of PCOS . Consensus is yet to be achieved in lean women with PCOS as insulin resistance is not consistently demonstrated . It is hypothesised that insulin resistance is intrinsic to PCOS and exacerbated

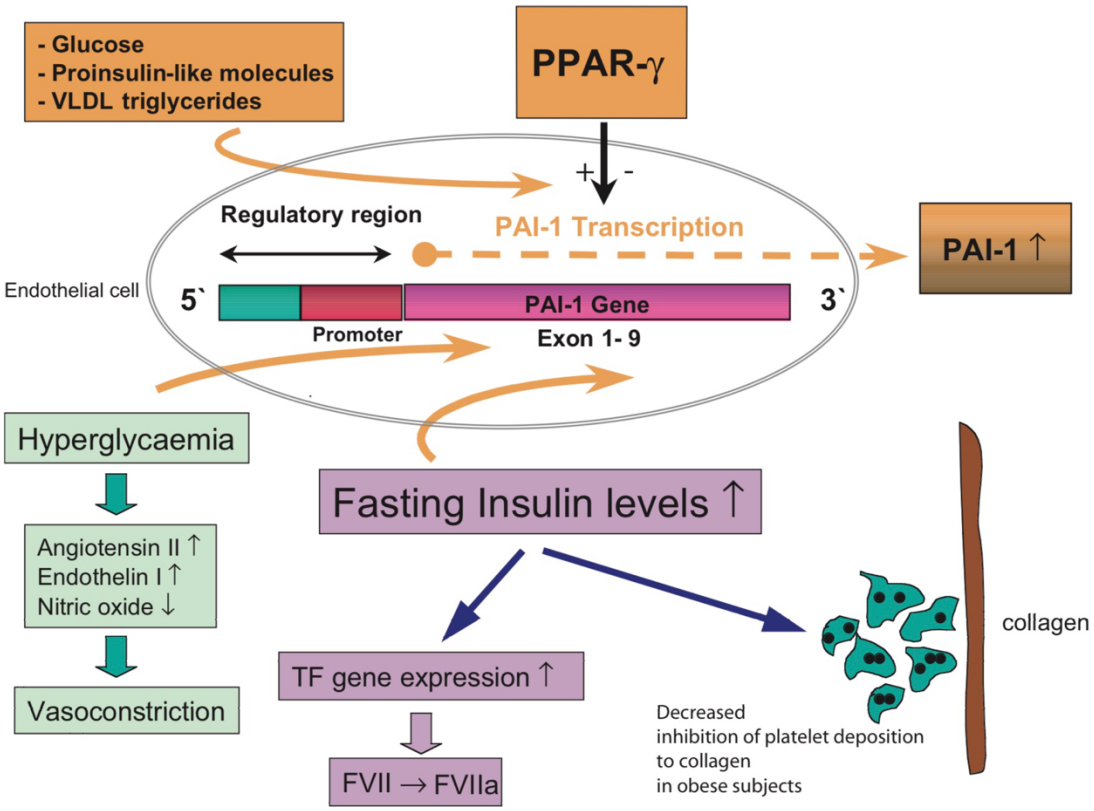
by obesity , however, research is needed to establish whether IR in PCOS is independent of obesity. (23)

Excessive serine phosphorylation of the insulin receptor or downstream signaling proteins may be involved in the pathogenesis of insulin resistance in PCOS.

The explanations for tissue_specific and signaling pathway_specific differences in insulin action in PCOS are unknown but may involve differential roles of insulin receptor substrate (IRS)-1 and IRS-2 in insulin signal transduction. (22)



Diagnostic flow chart depicting the aetiological, hormonal and clinical features of polycystic ovary syndrome (PCOS)



Explanation of the diagram :

1. Glucose, proinsulin-like molecules and VLDL triglycerides increase PAI-1 transcription in endothelial cells and therefore lead to increased PAI-1 plasma concentrations.

✓ Peroxisomal proliferator_activated receptor-gamma (PPAR-g) may also regulate PAI-1 expression in human endothelial cells.

2. Hyperglycaemia not only induces PAI-1 transcription but also leads to an increase in angiotensin II and endothelin I and a decrease in nitric oxide, therefore leading to vasoconstriction.
3. Increased fasting insulin levels induce tissue factor (TF) gene expression and a decrease in platelet inhibition, both leading to a pro_coagulant state.

✓ Tissue factor activates FVII to FVIIa. This initiates the coagulation process of the extrinsic pathway.(20)

✓ So the insulin resistance features is interaction of insulin with plasminogen activator inhibitor-1 (PAI-1) and tissue factor (TF) gene expression, platelet activation and vascular tone .

Clinical manifestations of insulin resistance

Insulin resistance can present in a wide spectrum of clinical manifestations , these include :

1- Acanthosis nigricans (It appears as dark, velvety patches often on the backs of the neck, groin, and armpits) , skin tags , hirsutism , ovarian hyperandrogenism and androgenetic alopecia .

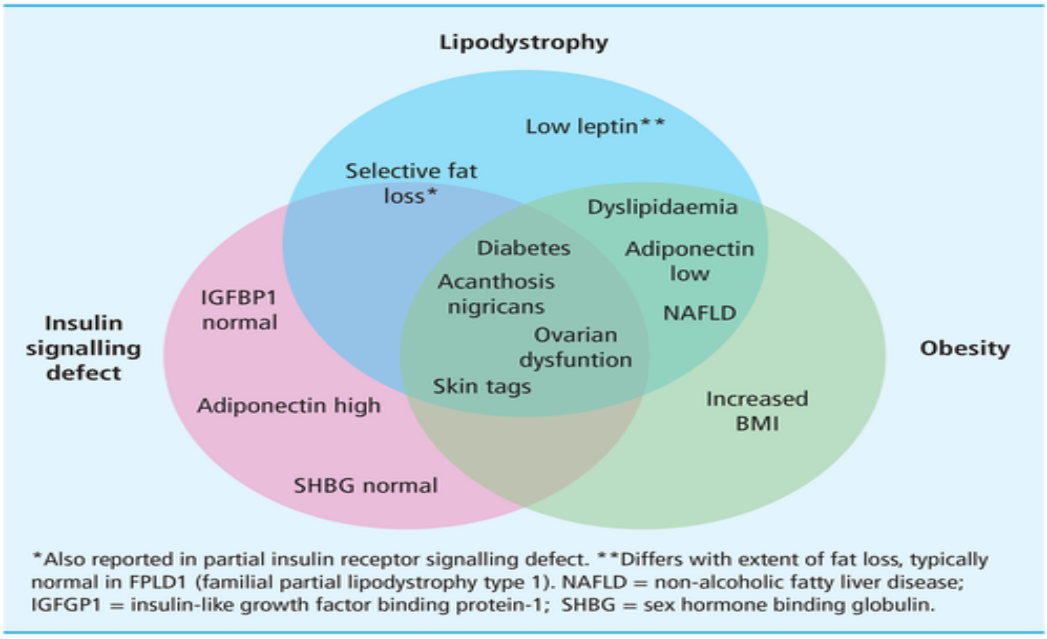
- ❖ The biologic plausibility of this association relies on the fact that hyperinsulinemia activates insulin growth factor-1 (IGF-1) receptors located in fibroblasts and keratinocytes directly and indirectly, stimulating their proliferation .

2- Hyperinsulinemia can also influence the production of sex steroids.

3- Also, insulin and IGF-1 increase ovarian androgens by stimulating the ovaries to produce androgens via the increase of 17-hydroxylase local activity and inhibiting hepatic synthesis of sex hormone-binding globulin (SHBG), which increases the availability of free testosterone .

4- It is also important to mention that skin diseases such as psoriasis, hidradenitis suppurativa, and vitiligo have been strongly associated with insulin resistance and metabolic syndrome . (24)

5- Classic diabetes symptoms include :- extreme thirsty , feeling hungry even after a meal , increased or frequent urination , tingling sensations in hands or feet , feeling more tired than usual, frequent infections , evidence in blood work .



DIAGNOSIS

There is no single test that can directly diagnose insulin resistance. Instead, a healthcare practitioner will consider several factors, including medical history, physical exam, signs and symptoms as well as test results.(26)

So the IR and it's outcome can be diagnosed by different type of laboratory tests:-

Diabetes mellitus

Glycated hemoglobin (A1c) test : Reflects your average blood glucose over the past 3 months

Normal rang Less 5.7%

Prediabetes 5.7-6.5%

Diabetes more 6.5%

Fasting blood sugar test (FBST)

Normal less than 100 mg/dL

Prediabetes 100-125 mg/dL

Diabetes 126 mg/dL or higher

Oral glucose tolerance test (OGTT)

Normal less than 140 mg/dL

Prediabetes 140-199 mg/dL

Diabetes more than 200 mg/dL (32)

- The FBST and OGTT show your blood glucose level at the time of the test.
- All these tests are used to screen for, diagnose and monitor prediabetes or diabetes. (26)

Lipid panel (lipid profile)

A group of tests that measure specific lipids in the blood , which include :

Total cholesterol : Measures the overall cholesterol level.

LDL cholesterol : Type of cholesterol, known as "bad cholesterol," can collect in blood vessels and increase your risk of cardiovascular disease.

HDL cholesterol :- Type of "good cholesterol" helps reduce the buildup of LDL.

Triglycerides: Excess amounts of this type of fat are associated with cardiovascular disease and pancreatic inflammation.(31)

If the triglycerides are significantly elevated (e.g., greater than 400 mg/dL), LDL cholesterol should not be calculated and a direct LDL (direct measurement of the LDL cholesterol) can be performed.(26)
Desired or normal values:
Total cholesterol: Below 200 mg/dL
HDL (good) cholesterol: Above 60 mg/dL
LDL (bad) cholesterol: Below 100 mg/dL (For people with diabetes: Below 70 mg/dL)
Triglycerides: Below 150 mg/dL . (31)
In insulin resistance patients
Low HDL cholesterol
Increased LDL cholesterol
Elevated triglyceride levels and
Elevated "dense" LDL particles where the particles have a reduced cholesterol content. (26)

Polycystic ovary syndrome

Blood tests :
1- Check the higher-than-normal levels of male hormones (androgens) which evidence of this may include a high blood testosterone level, for example, or symptoms such as acne (sometimes severe) and excess hair growth, which can be on the face, stomach and/or back.(27)
Androgens are normally produced in small amounts in females by the ovaries and adrenal glands , the normal testosterone levels range from 15 to 70 nanograms per deciliter (ng/dL) of blood (Testosterone levels higher than 70 ng/dL may lead to PCOS) . (28)
2- For checking glucose tolerance , fasting cholesterol and triglyceride levels.(27)
An ultrasound (transvaginal ultrasound) : uses sound waves to look for abnormal follicles and other problems with your ovaries and uterus, checks the appearance of ovaries and the thickness
of the lining of the uterus .
A physical examination : Will include checking for signs of excess hair growth, and acne.(27)

- Transvaginal ultrasound : A wandlike device (transducer) is placed in a vagina . The transducer emits sound waves that are translated into images on a computer screen.(2)

Other tests

High-sensitivity CRP (hs-CRP) : Measurements can detect low levels of inflammation and may be done as part of an evaluation of cardiac risk. CRP may be increased with insulin resistance .

Insulin : The fasting insulin level can be measured. Insulin levels will usually be elevated in those with significant insulin resistance.

- ❖ However, this test is rarely needed and is not recommended in routine clinical practice. (26)

CLINICAL MANAGEMENT

Non_pharmacological treatment

Treatment of insulin resistance (and improving insulin sensitivity) primarily involves exercises and changes in lifestyle and diet .

Exercises

Regular exercise is one of the best ways to increase insulin sensitivity.

It helps move sugar into the muscles for storage and promotes an immediate increase in insulin sensitivity, which lasts 2–48 hours, depending on the exercise

Lifestyle change

More sleep : A lack of sleep can be harmful and increase the risk of infections, heart disease and type 2 diabetes and catching up on lost sleep can reverse the effects of poor sleep on insulin resistance .

So, a good night's sleep can reduce insulin resistance and enhance insulin sensitivity.

Reduce stress : Stress affects a body's ability to regulate blood sugar.

It encourages the body to go into "fight-or-flight" mode, which stimulates the production of stress hormones like cortisol and glucagon.

These hormones break down glycogen, a form of stored sugar, into glucose, which enters a bloodstream for the body to use as a quick source of energy.

So, ongoing stress keeps the stress hormone levels high which stimulates nutrient breakdown , increases blood sugar and makes the body more insulin resistant(high levels of stress hormones reduce insulin sensitivity).

Reduce Weight : Excess weight, especially in the belly area, reduces insulin sensitivity and increases the risk of type 2 diabetes.

Belly fat can do this in many ways, such as making hormones that promote insulin resistance in the muscles and liver .

So, higher amounts of belly fat lead to insulin resistance and lower insulin sensitivity .
Losing weight is an effective way to lose belly fat and increase insulin sensitivity. It may also reduce your risk of type 2 diabetes if you have prediabetes.

Diet

Eat More Soluble Fiber : Fiber can be divided into two broad categories : soluble and insoluble.
Insoluble fiber mostly acts as a bulking agent to help stool move through the bowels.
Meanwhile, soluble fiber is responsible for many of fiber's associated benefits, like lowering cholesterol and reducing appetite (high soluble fiber intake and increased insulin sensitivity)
Soluble fiber also helps feed the friendly bacteria in the gut, which have been linked to increased insulin sensitivity .
Eat More Colorful Fruit and Vegetables : Colorful fruits and vegetables are rich in plant compounds that have antioxidant properties .
Antioxidants bind to and neutralize molecules called free radicals, which can cause harmful inflammation throughout the body .
So, eating a diet rich in plant compounds is linked to higher insulin sensitivity .

Pharmacological treatment

Both children and adults can develop insulin resistance and metabolic syndrome.
Medications may also be necessary to treat co-existing conditions or diseases. Some examples include:

- ✓ Insulin sensitizers (Metformin)
- ✓ Blood pressure medication
- ✓ Lower Lipid profile

Insulin sensitizers

Diabetes's medications like metformin that can be used in diabetes mellitus and PCOS .
Metformin has been demonstrated to be effective in normalizing several parameters in women with PCOS , because the metformin is effective in improving ovulation rates in women with clomiphene resistance and resulted in fewer multiple pregnancies .

Advantage of metformin :

The treatment with metformin for at least 8 weeks will :-

1-Rreduced weight, fasting glucose, triglycerides and LDL by 4.5–5.6%

2- Reduce in fasting insulin by 14%, calculated insulin resistance (HOMA-IR) by 22%

3- Reduced new onset diabetes by 40%.

The treatment with metformin in PCOS for up to 6 months :-

1- Reduced hirsutism

2- Reduced androgen levels , with reductions in testosterone being between 25–50% .

- ❖ Metformin alone is not as effective in reduction in testosterone in a greater amount . So , metformin is used with a combined oral contraceptive to enhance responses .
- ❖ In women without evidence of renal or hepatic disease, metformin appears effective in reducing the negative effects of PCOS on both reproductive and metabolic health.

Disadvantages of metformin :

Including predominantly gastroenterological conditions consisting of

1- Bloating

2- Abdominal discomfort

3- Nausea

4- Diarrhea which is usually dose dependent and can be minimized by gradually building up the dose of metformin .

Dose for PCOS

Starting at 250–500mg / day taken just before the main meal and increasing over a period of 1–2 months, reaching doses of 2,000–2,500mg / day.

- ❖ If GI side effects intervene, reducing the dose for a period of 7–10 days, can often be followed by a resumption of the dosage increase . (35)

Dose for diabetes

Immediate-release tablet Initial : 500 mg PO q12hr or 850 mg PO qDay with meals .

Maintenance: 1500-2550 mg/day PO divided q8-12hr with meal , not exceed 2550 mg/day Extended-release

Tablet or suspension 500 mg PO qDay with dinner; titrated by 500 mg/day qWeek; not to exceed 2000 mg/day . (36)

Anti_hypertensive drugs

Only angiotensin-converting enzyme (ACE) inhibitors and angiotensin II (Ang II) receptor blocker (ARB) have been reported to enhance insulin sensitivity and reduce new onset of type II diabetes . They work by causing relaxation of blood vessels as well as a decrease in blood volume, which leads to lower blood pressure .

1) ACE inhibitors drugs include Captopril :

Dose :

Initial 25 mg PO q8-12hr, increase gradually based on response (may start lower in some patients)

Maintenance: 25-150 mg PO q8-12hr .

2) ARB drugs include Valsartan

Dose :

Initially; dosing range 80-320 mg qDay .

May increase to a maximum of 320 mg/day or a diuretic may be added if additional antihypertensive effect is required . (37)

Herbal therapy

Green Tea : It found that drinking green tea significantly reduced fasting blood sugar and increased insulin sensitivity. These beneficial effects of green tea could be due to its powerful antioxidant epigallocatechin gallate (EGCG), which many studies have found to increase insulin sensitivity .

Apple Cider Vinegar : Vinegar could help increase insulin sensitivity by reducing blood sugar and improving the effectiveness of insulin . It also appears to delay the stomach from releasing food into the intestines, giving the body more time to absorb sugar into the bloodstream .

Cinnamon : Cimmanon increases insulin sensitivity by helping receptors for glucose on muscle cells become more available and efficient at transporting sugar into the cells.

Herb and species added to Cooking

Fenugreek seeds : they’re high in soluble fiber, which helps make insulin more effective.

Turmeric : turmeric increases insulin sensitivity by reducing free fatty acids and sugar in the blood .

Ginger : ginger increases insulin sensitivity due to its active component gingerol makes sugar receptors on muscle cells more available and increases sugar uptake.

Garlic: garlic improves insulin secretion and has antioxidant properties that increase insulin sensitivity . (33)

CONCLUSION

Insulin resistance is a pathological condition in which cells fail to respond normally to the hormone insulin.

There are two types of insulin resistance : Type A (genetic in origin) and Type B (acquired) which is more common that type A.

Insulin resistance is a feature of a number of clinical disorders, including:

1. Type 2 diabetes mellitus
2. Dyslipidemia
3. Cardiac disease
4. Obesity & visceral obesity
5. Hypertension clustering in the so-called metabolic syndrome
6. PCOS .

These disorders of insulin resistance due to the ability of insulin to interact with plasminogen activator inhibitor-1 (PAI-1) and tissue factor (TF) gene expression, platelet activation and vascular tone .

There is no single test that can directly diagnose insulin resistance , so insulin resistance and it's outcome can be diagnosed by different type of laboratory tests:-

1. Fating blood sugar test , oral glucose tolerance test , glycated hemoglobin HbA1c , fasting insulin test
2. Test LDL cholesterol , Triglycerides ,VLDL and HDL cholesterol
3. Androgen level
4. An ultrasound
5. CRP
6. Blood pressure

These tests can do to find the disorders that causes by insulin resistance

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