UNIVERSITY OF BASRAH

College of pharmacy

RESEARCH ON INSULIN RESISTANCE

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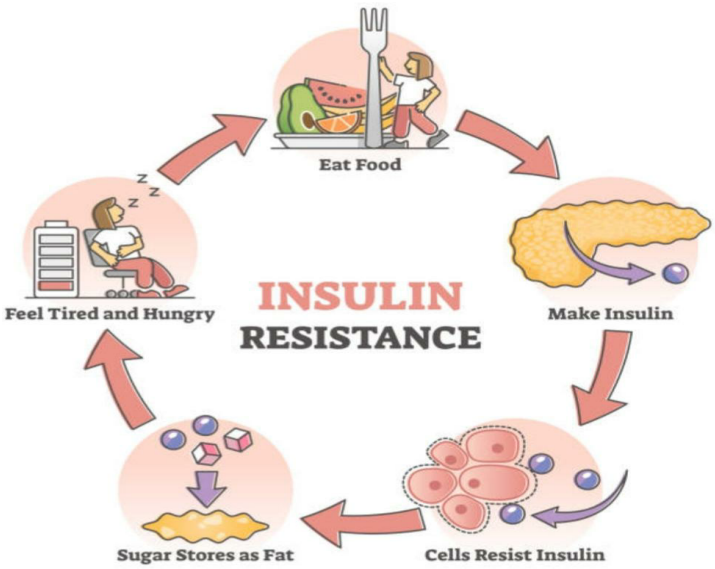


Introduction_____

Insulin resistance is the name given to when cells of the body don’t respond properly to the hormone insulin.

Insulin resistance is the driving factor that leads to type 2 diabetes, gestational diabetes and prediabetes Insulin resistance is closely associated with obesity; however, it is possible to be insulin resistant without being overweight or obese.

Modern research has shown that insulin resistance can be combated by treatment methods that reduce how much insulin the body is producing or taking via insulin injections or insulin pumps.

Reducing insulin resistance can be achieved by following low-carbohydrate and ketogenic diets.

What is insulin resistance?_____

The role of insulin is to allow cells of the body to take glucose to be used as fuel or stored as body fat. It also means that glucose is more likely to build up in the blood and this can lead to too high blood sugar levels.When the body becomes resistant to insulin, it tries to cope by producing more insulin. People with insulin resistance are often producing too much insulin than healthy people.Producing too much insulin is known as hyperinsulinemia.

clinical features of insulin resistance___

Insulin resistance is associated with a wide variety of clinical presentations. Factors to consider include :

Obesity, particularly abdominal obesity: obesity can lead to

insulin resistance through increased production of free fatty acids and adipocyte cytokines, which modulate insulin sensitivity and are pro-inflammatory.

Abnormal glucose metabolism: this spectrum may range from hyperinsulinemia with average glucose concentrations, to insulin dependent type 2 diabetes mellitus requiring large doses of insulin to control blood glucose.

Metabolic syndrome: the metabolic syndrome is the combination of obesity, hypertension, dyslipidemia and hyperglycemia Hyperandrogenism and reproductive abnormalities: women with severe tissue resistance to insulin may present with virilisation, hirsutism, amenorrhoea or Infertility is often associated with polycystic ovarian syndrome .

HIGH TESTOSTERONE LEVELS: High insulin levels cause the ovaries to overproduce male-sex hormones, called androgens. This leads to an excessive amount of testosterone in the female body, causing issues such as acne, male-like hair growth, and male-like hair loss.

Insulin also reduces the production of SHBG (sex-hormone binding globulin), a protein that attaches itself to free testosterone in your bloodstream which helps to regulate testosterone levels. Less SHBG means higher testosterone.

Musculoskeletal changes: some patients report muscle cramps unrelated to exercise.

Autoimmunity:autoimmune disorders, such as systemic lupus

erythematosus or systemic sclerosis Symptoms associated with insulin resistance include :

• Fatigue

• Lethargy

• Increased hunger

• Brain fog and difficulty concentrating

• Weight gain, especially around your midsection

• High blood pressure

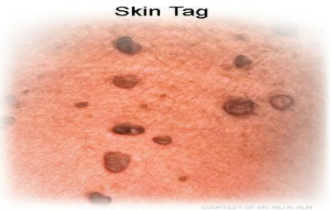
• High cholesterol levels

Dermatological Symptoms of IR_____

Insulin resistance is thought to induce skin changes through hyperinsulinemia, which activates insulin growth factor-1 (IGF-1) receptors in fibroblasts and keratinocytes stimulate their proliferation.The skin manifestations of IR can help to diagnose the condition and its complications. Skin manifestations can include:

• Acanthosis nigricans

• Acrochordons (skin tags)



• Acne

• Hirsutism

• Androgenetic alopecia (male pattern hair loss).

Skin diseases that have commonly been associated with insulin resistance and metabolic syndrome include:

• Psoriasis.

• Hidradenitis suppurativa.

• Vitiligo.

Mechanisms Of Insulin Resistance _____

Insulin Resistance and Muscle Glucose Metabolism

13C MRS21 studies of glucose disposal in normal humans suggested that skeletal muscle accounts for the majority of insulin-stimulated glucose uptake and that >80% of this glucose is then stored as glycogen.The rate of glycogen synthesis in skeletal muscle was ≈50% lower in diabetic subjects than in normal volunteers.The only other organ capable of storing a significant amount of glycogen is the liver, and here again, glycogen stores were reduced in diabetics.Subsequent studies focused on the rate-controlling steps in this pathway. 13C and 31P MRS were used together to monitor intracellular glucose-6-phosphate concentration and intramuscular glycogen synthesis during hyperinsulinemic-hyperglycemic clamps. Glucose-6-phosphate is an intermediate between glucose transport into the cell and its subsequent phosphorylation by hexokinase and glycogen synthesis . The increment in glucose-6-phosphate concentration was significantly reduced in type 2 diabetics, suggesting that glucose transport or phosphorylation must be the rate-controlling step in insulin-stimulated glucose disposal in skeletal muscle rather than glycogen synthase.Similar observations were also made in insulin-resistant offspring of type 2 diabetics, suggesting that this defect precedes the development of type 2 diabetes. Glucose transport in skeletal muscle is largely mediated by a specific insulin-responsive transporter known as glucose transporter 4 (GLUT4), whereas glucose phosphorylation is catalyzed by hexokinase. To determine which of these 2 steps was defective, we used a novel 13C MRS method to assess intracellular-free glucose in muscle,the idea being that if

hexokinase were rate controlling in insulin-resistant type 2 diabetics, intracellular glucose concentrations should increase substantially.

The fact that intracellular glucose concentrations in skeletal muscle from type 2 diabetics (during a hyperinsulinemic-hyperglycemic clamp) were 1/25 what they would have been if hexokinase were the primary rate-controlling enzyme suggested that glucose transport was rate controlling as opposed to hexokinase. Together, these data indicate that glucose transport into muscle is the rate-controlling step for insulin-stimulated muscle glycogen synthesis in patients with type 2 diabetes.

Mechanisms of Lipid Accumulation in Skeletal Muscle and Liver

Lipid accumulation in ectopic sites can occur in 3 ways: increased uptake of fatty acids, increased synthesis within the tissue involved, or reduced fatty acid oxidation/disposal. As alluded to above, it is clear that lipid infusion leads to lipid accumulation in skeletal muscle and short-term high-fat feeding elevates liver triglycerides; in both cases, insulin resistance ensues. Thiazolidinediones , now widely used as insulin sensitizers in the treatment of type 2 diabetes, act, at least in part, by lowering plasma free fatty acids and reversing the tendency to accumulate lipids in ectopic sites .Increased fatty acid concentrations are typical of a number of insulin-resistant states, including obesity, type 2 diabetes, and insulin-resistant offspring of type 2 diabetics, suggesting that this may well contribute to ectopic lipid accumulation .We have also shown that mice overexpressing lipoprotein lipase in either skeletal muscle or liver accumulate lipid in the corresponding tissue and go on to manifest insulin resistance in a tissue-specific manner .An interesting hypothesis suggests that hyperinsulinemia may be involved in driving lipogenesis in muscle and liver by increasing sterol regulatory element-binding protein 1c (SREBP1c) expression. SREBP1c is a key transcriptional regulator of de novo lipogenesis. Finally, any defect in fatty acid oxidation would be expected to induce lipid accumulation. We demonstrated recently that insulin resistance in the elderly and in lean healthy insulin-resistant offspring of type 2 diabetics is associated with IMCL accumulation, which in turn was linked to

a reduction in mitochondrial oxidative phosphorylation activity assessed by 13C/31P MRS. In the case of the elderly, this is likely to be a consequence of acquired mitochondrial mutations, a phenomenon known to occur with aging, whereas in the insulin-resistant offspring, it is more likely that the reduction in mitochondrial oxidative phosphorylation is a primary genetic defect. Enzyme defects have also been described in isolated mitochondria derived from human skeletal muscle biopsies from type 2 diabetics. Together, these data suggest that alterations in nuclear-encoded genes that regulate mitochondrial biogenesis, such as peroxisome proliferator-activated receptor γ-coactivator 1α (PGC-1α), AMP kinase, and Ca2+/calmodulin dependent-protein kinase IV (CAMKIV), may form the genetic basis for inheritance of at least some forms of type 2 diabetes. This notion is further supported by 2 microarray studies that revealed a reduction in PGC-1α–responsive transcripts in patients with type 2 diabetes and their first-degree relatives. PGC-1α is a key regulator of mitochondrial biogenesis.

Inflammation And Insulin Resistance

Obesity is a very common cause of insulin resistance. As mentioned above, a potential mechanism for this relationship is ectopic lipid accumulation. However, obesity is also associated with a systemic chronic inflammatory response characterized by altered cytokine production and activation of inflammatory signaling pathways. Recent reports have linked this inflammatory response to the development of insulin resistance in 2 different ways. First, activation of inflammatory signaling intermediates may be directly involved in serine phosphorylation of IRS-1 within insulin-sensitive cell types such as hepatocytes and myocytes and thereby inducing insulin resistance. Second, inflammatory cell infiltration within adipose tissue may be involved in altering adipocyte lipid metabolism (for example, tumor necrosis factor-α [TNF-α] is reported to promote lipolysis) as well as altering cytokine production by adipose tissue, which may in turn have downstream effects in other metabolically important tissues.

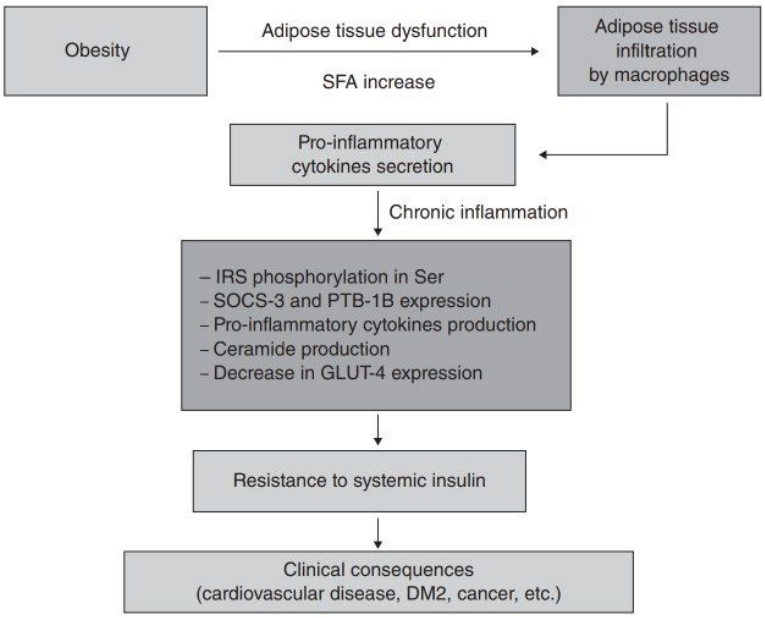


Figure 1. Inflammation and insulin resistance. Obesity promotes a state of low-grade chronic inflammation, due to an increase in the number of macrophages infiltrating the adipose tissue, which promotes the secretion of inflammation mediators. On one hand, these factors contribute to local and generalized obesity-associated inflammation state, and on the other, they can directly induce insulin resistance by promoting IRS's Ser residues phosphorylation, SOCS-3 expression, pro-inflammatory cytokines and ceramides production and a decrease in the expression of GLUT-4 and glucose transport. Insulin resistance is associated with the development of cardiovascular disease, DM2 and cancer, among other diseases.

Causes Of Insulin Resistance_____

the primary causes of insulin resistance are

- **Obesity** ,especially belly fat Obesity is associated with an increased risk of developing insulin resistance and type 2 diabetes. 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 developmen of insulin resistance .

- **sedentary lifestyle** physical inactivity
- **Nutritional imbalance** e.g Diet high in carbohydrates and Increased sodium diets.
- **Health conditions:** Nonalcoholic fatty liver disease(NAFLD)and polycystic ovary syndrome(PCOS) are associated with insulin resistance . Hepatitis C also makes people three to four times more likely to develop type 2 diabetes and insulin resistance.
- **Gestational diabetes**

Risk factors are associated with IR_____

- **A family history** of diabetes.
- **Age ;** it's more likely after 45 .This is related to increased prevalence of central obesity in the aging population. Imbalance of sex hormone and lack of physical exercise contribute to the central obesity in aging people .
- **Ethnicity** -- it's more likely if your ancestry is African, Latino, or Native American**.**
- **Hormonal disorders ;like**
    1. **Cushing's syndrome,** which is a serious condition characterized by long-term exposure to high cortisol levels .Cortisol counteracts insulin and can lead to increased hepatic gluconeogenesis, reduced peripheral utilization of glucose, and increased insulin resistance. It does this by decreasing the translocation of glucose transporters (especially GLUT4) to the cell membrane
    2. **Acromegaly :** is a disorder that results from excess growth hormone (GH) after the growth plates have closed.

- **Medications:** Some medications are associated with insulin resistance

  Including glucocorticoids, anti-adrenergic, protease inhibitors(which are types of HIV medications) , atypical antipsychotics, and some exogenous insulin.

- **Sleep problems** like sleep apnea
- **Smoking**
- **Inflammation:** Acute or chronic inflammation, such as in infections, can cause insulin resistance . TNF-α is a cytokine that may promote insulin resistance by promoting lipolysis, disrupting insulin signaling, and reducing the expression of GLUT4.

Diagnosis

In an effort to clinically identify patients with insulin resistance, various organizations have developed diagnostic criteria. The most commonly used criteria are those of the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III).

NCEP/ATP III criteria for the diagnosis of the metabolic syndrome include the following ,diagnosis is made when three or more are present:

- Waist circumference of more than 102 cm in men or more than 88 cm in women.
- Fasting triglyceride level of 150 mg/dL or higher.
- Blood pressure level of 130/85 mm Hg or higher.
- High-density lipoprotein cholesterol (HDL-C) level of less than 40 mg/dL in men or less than 50 mg/dL in women.
- Fasting glucose level of 110 mg/dL or higher .

Complications of Insulin Resistance

If metabolic syndrome goes untreated, it could lead to:

- Severe high blood sugar
- Severe low blood sugar
- Heart attack
- Stroke
- Kidney disease
- Eye problems
- Cancer
- Alzheimer's disease

Management_____

There are no published guidelines on the management of insulin resistance. Treatment that has been shown to decrease insulin resistance includes: Weight reduction • Increased physical activity • A Mediterranean diet, with an emphasis on fruits, vegetables, nuts and whole grains.

Dietary management

The objectives of dietary management for insulin resistance are:

• Improvement of the insulin sensitivity by restriction of the carbohydrate content of the diet.

• Improving and normalization of parameters of metabolic health.

• Weight loss of 10-15% (20% in case of obesity stage 3) and weight maintenance of 2-5 years.

• Sustaining or improving muscle mass.

• Maximum satiation through protein, fat and fiber.

• Optimal supply of vitamins and minerals.

• Improvement of quality of life.

Carbohydrates

A carbohydrate restriction has a greater effect on lowering serum glucose values than a caloric restriction and should be the first choice.A low carbohydrate diet is effective in improving lipid profile in insulin resistance Replacing carbohydrates by protein and fat leads to more satiety and satiation .These recommendations are guidelines which will be adjusted per patient, dependent on dietary diagnosis, including

anthropometric measurements, and dietary history .

Dietary proteins

have an insulinotropic effect and thus promote insulin secretion, which indeed leads to enhanced glucose clearance from the blood. In the long term, however, a high dietary protein intake is associated with an increased risk of type 2 diabetes.

Fat

A lower-carbohydrate, higher-fat diet reduces abdominal and intramuscular fat and increases insulin sensitivity in adults at risk of type 2 diabetes. It leads to better weight loss, larger decrease of intramuscular and intra-abdominal fat and decrease of the insulin secretion.

Vitamins and Minerals

The objectives for supplementation are prevention of deficiencies, improvement of micronutrient status and restoration of the insulin sensitivity.

- Magnesium reduces IR and improves insulin production .
- Extra vitamin D reduces IR, improves insulin production and is essential to sustain muscle mass; it also prevents infections .
- Zinc reduces and stabilizes serum glucose.
- Chromium diminishes IR and improves the effect of insulin.

- Biguanides (metformin) reduce the absorption of hydroxocobalamin (vitamin B12) and folic acid.

Physical Exercise

Physical exercise is essential to reduce IR and to achieve weight loss.

Constant exercise causes strong anti-inflammatory effects , probably

because of the influence of exercise on the immune system, and through the reduction of visceral fat. During training muscle cells probably release many anti-inflammatory cytokines .

Sleep

Sleep deprivation leads to insulin resistance. Sleep plays a key role in homeostasis of the glucose metabolism. Sleep deprivation leads to an increase of the glucose production with 22%, suggesting hepatic insulin resistance .

Summary

Insulin resistance is a serious condition caused by a too large fat mass, especially when located in the abdomen, leading to metabolic disease, such as hypertension, glucose intolerance, dyslipidemia, type 2 diabetes and cardiovascular disease. It is best diagnosed by measuring fasting glucose levels. Measuring waist circumference and calculating BMI are additional instruments. Management should focus on weight loss through a low carbohydrate diet, with sufficient fat, protein, vitamins and minerals. Exercise is an essential part of management and relapse prevention. Persons that are insulin resistant may regain their health through these measures. ey will always stay insulin resistant to a certain extent, and cannot eat normal quantities of carbohydrates that are commonly used and advised in general dietary guidelines

Reference

- Prediabetes & Insulin Resistance. – The National Institute of Diabetes and Digestive and Kidney Diseases Health
- Information Center. Retrieved: March 01, 2017 Guideline for the Management of Insulin Resistance.