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Insulin resistance

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ABSTRACT

Type 2 diabetes mellitus, obesity, genetic factors are linked to insulin resistance. The three factors are linked to each other or are independent in causing insulin resistance. Insulin resistance has a harmful effect on the body. It can lead to metabolic syndrome, cardiovascular disease patient to increase in number.Combination of drug and lifestyle modification are necessary to overcome it. Hence, the basis of treatment in insulin resistance is to introduce healthy lifestyle and exercise, as exercise increases the sensitivity of insulin receptor.

Keywords: Diabetes mellitus, insulin resistance, obesity, insulin receptors

Introduction

Insulin resistance is a physiological condition in which body produces normal amount of insulin, but the cells fail to respond to the normal actions of the hormone insulin effectively, leading to hyperglycemia.This leads toincrease production of insulin from β-cells in the pancreas, further contributing to hyperinsulinemic state.In general,it remains undetected and can contribute to a diagnosis of type 2 diabetes.

One of the important functions of insulin is to regulate delivery of glucose into cells to provide them with energy[1]. Insulin resistant cells cannot take in glucose, amino acids and fatty acids. A decrease in insulin/glucagon ratio inhibits glycolysis, which in turn decreases energyproduction. The resulting increase in blood glucose may raise levels outside the normal range and cause adverse health effects, depending on dietary conditions[2].

Certain cells like fat and muscle cells absorbs glucose in presence of insulin. When these cells fail to respond adequately to circulating insulin, blood glucose levels rise. The liver helps regulate glucose levels by reducing its secretion of glucose in the presence of insulin [3].

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Insulin resistance in muscle and fat cells reduces glucose uptake, whereas in liver cells it reduced glycogen synthesis and storage and a fails to suppress glucose production and release into the blood. Insulin resistance normally refers to reduced glucose-lowering effects of insulin. It also effects other functions of insulin, asin fat cells it results in reduced uptake of circulating lipids and increased hydrolysis of stored triglycerides. Increased mobilization of stored lipids in these cells elevates free fatty acids in the blood plasma. Elevated blood fatty-acid concentrations, reduced muscle glucose uptake, and increased liver glucose production all contribute to elevated blood glucose levels. Themajor component of the metabolic syndrome is high plasma levels of insulin and glucose due to insulin resistance. This insulin resistance will make the pancreas to increase the secretion of insulin by compensatory mechanism. If thiscompensatory mechanism fails, blood glucose levels increase and leads to development of type 2 diabetes mellitus (T2DM) [4].

Pathophysiology

Any food or drink containing glucose causes blood glucose levels to increase. In a normal metabolism, the elevated blood glucose level makes β-cells in the Islets of Langerhans, located in the pancreas, release insulin into the blood. The insulin, in turn, makes insulin-

sensitive tissues in the body absorb glucose, and thereby lower the blood glucose level. The β-cells reduce insulin output as the blood glucose level falls, allowing blood glucose to settle at a constant of. In an insulin-resistantperson, normal levels of insulin do not have the same effect in controlling blood glucose levels. During the compensated phase on insulin resistance insulin levels are higher, and blood glucose levels are still maintained. If compensatory insulin secretion fails, then either fasting or postprandial glucose concentrations increase. Eventually, type 2 diabetes occurs when glucose levels become higher throughout the day as the resistance increases and compensatory insulin secretion fails.

The most common type of insulin resistance is associated with overweight and obesity in a condition known as metabolic syndrome. Insulin resistance often progresses to full T2DM. This is often seen when hyperglycemia develops after a meal, when pancreatic β-cells are unable to produce sufficient insulin to maintain normal blood sugar levels (euglycemia) in the face of insulin resistance. The inability of the β-cells to produce sufficient insulin in a condition of hyperglycemia is what characterizes the transition from insulinresistance to T2DM [5].

Insulin itself leads to a kind of insulin resistance; every time a cell is exposed to insulin, the production of GLUT4 on the cell's membrane decreases somewhat [6].In the presence of a higher than usual level of insulin (generally caused by insulin resistance), this down-regulation acts as a kind of positive feedback, increasing the need for insulin. Exercise reverses this process in muscle tissue [7], but if it is left unchecked, it can contribute to insulin resistance.

Insulin resistance is often found in people with visceral adiposity (i.e., a high degree of fatty tissue within the abdomen – as distinct from subcutaneous adiposity or fat between the skin and the muscle wall, especially elsewhere on the body, such as hips or thighs), hypertension, hyperglycemia and dyslipidemia involving elevatedtriglycerides, small dense low-density lipoprotein (LDL) particles, and decreased high-density lipoprotein cholesterol levels. With respect to visceral adiposity, a great deal of evidence suggests two strong links with insulin resistance. First, unlike subcutaneous adipose tissue, visceral adipose cells produce significant amounts of proinflammatory cytokines such as tumor necrosis factor-alpha, and interleukins-1 and -6, etc. In numerous experimental models, these proinflammatory cytokines disrupt normal insulin action in fat and muscle cells, and may be a major factor in causing the whole-body insulin resistance observed in patients with visceral adiposity. Much of the attention on production of proinflammatory cytokines has focused on the IKK-β/NF-kappa-B pathway, a protein network that enhances transcription of inflammatory markers and mediators that can cause insulin resistance. Second, visceral adiposity is related to an accumulation of fat in the liver, a condition known as nonalcoholic fatty liver disease (NAFLD). The result of NAFLD is an excessive release of free fatty acids into the bloodstream (due to increased lipolysis), and an increase in hepatic glycogenolysis and hepatic glucose production, both of which have the effect of exacerbating peripheral insulin resistance and increasing the likelihood of T2DM.

Insulin resistance is also occasionally found in patients who use insulin. With the development of human insulin and analogues in the 1980s and the decline in the use of animal insulins(such as pork or beef), this type of insulin resistance has become less common. This form of insulin resistance is not what is being referred to in the metabolic syndrome.

Magnesium (Mg) is present in living cells and its plasma concentration is remarkably constant in healthy subjects. Plasma and intracellular Mg concentrations are tightly regulated. Among the controlling mechanisms, insulin seems to be one of the most important. *In vitro* and *in vivo* studies have demonstrated that insulin may modulate the shift of Mg from extracellular to intracellular space. Intracellular Mg concentration has also been shown to be effective in modulating insulin action (mainly oxidative glucose metabolism), offset calcium-related excitation contraction coupling, and decrease smooth cell responsiveness to depolarizing stimuli. Poor intracellular Mg concentrations, as found in T2DM and in hypertensive patients, may result in a defective tyrosine-kinase activity at the insulin receptor level and exaggerated intracellular calcium concentration. Both events are responsible for impairment in insulin action, and a worsening of insulin resistance in noninsulin dependent diabetic and hypertensive patients. By contrast, in T2DM patients daily Mg administration, restoring a more appropriate intracellular Mg concentration, contributes to improve insulin-mediated glucose uptake. The benefits deriving from daily Mg supplementation in T2DM patients are further supported by epidemiological studies showing that high daily Mg intake are predictive of a lower

incidence of T2DM.

Causes of Insulin Resistance

Molecular

Insulin resistance has been proposed at a molecular level to be a reaction to excess nutrition by superoxide dismutase in cell mitochondria that acts as an antioxidant defense mechanism. This link seems to exist under diverse causes of insulin resistance. It is also based on the finding that insulin resistance can be rapidly reversed by exposing cells to mitochondrial uncouplers, electron transport chain inhibitors, or mitochondrial superoxide dismutase mimetics [8].

Cellular

At the cellular level, much of the variance in insulin sensitivity between untrained, non-diabetic humans is explained by two mechanisms: Differences in phospholipid profiles of skeletal muscle cell membranes, and in intramyocellular lipid stores within these cells [9]. High levels of lipids in the bloodstream have thepotential to result in accumulation of triglycerides and their derivatives within muscle cells, which activate proteins Kinase C-ε and C-θ, ultimately reducing the glucose uptake at any given level of insulin[10,11]. This mechanism is quite fast-acting and can induce insulin resistance within days or even hours in response to a large lipid influx [12]. Draining the intracellular reserves, on the other hand, is more challenging: moderate caloric restriction alone, even over a period of several months, appears to be ineffective [13,14], and it must be combined with physical exercise to have any effect.

In the long term, diet has the potential to change the ratio of polyunsaturated to saturated phospholipids in cell membranes, correspondingly changing cell membrane fluidity; full impact of such changes is not fully understood, but it is known that the percentage of polyunsaturated phospholipids is strongly inversely correlated with insulin resistance [15]. It is hypothesized that increasing cell membrane fluidity by increasing polyunsaturated fatty acidconcentration might result in an enhanced number of insulin receptors, an increased affinity of insulin to its receptors and a reduced insulin resistance, and *vice versa* [16].Many stressing factors can lead to increased cortisol in the bloodstream. Cortisol counteracts insulin, and contributes to hyperglycemia-causing hepatic gluconeogenesis[17] and inhibits the peripheral utilization of glucose, which eventually leads to insulin resistance [17]. It does this by decreasing the translocation of glucosetransporters (especially GLUT4) to the cell membrane [18,19]. Although inflammation is often caused by cortisol, inflammation by itself also seems to be implicated in causing insulin resistance.

Diet

Insulin resistance and obesity commonly coexists. The, causal links between insulin resistance, obesity, and dietary factors are complex and controversial. It is possible that one of them arises first, and tends to cause the other. Itis also possible that insulin resistance and excess body weight might arise independently as aconsequence of a third factor, and at last reinforcing each other. Some population groups might be genetically predisposed to one or the other. Dietary fat has long been implicated as a driver of insulin resistance. Studies on animals observed significantinsulin resistance in rats after just 3 weeks on a high-fat diet[10], but saturated fat appears to be the most effective at producing insulin resistance[20]. In humans, statistical evidence is more equivocal. Being insensitive to insulin is positively correlated with fat intake, and negatively correlated with dietary fiber intake[21]. The effect of dietary fat is largely or completely overridden if the high-fat diet is modified to contain nontrivial quantities of polyunsaturated omega-3 fatty acids[20,22,23]. This protective effect is most established with regard to the so-called “marine long-chain omega-3 fatty acids,”eicosapentaenoic acid and docosahexaenoic acid, found in fish oil; evidence in favor of other omega-3's, in particular, the most common vegetable based omega-3 fatty acid, alpha-linolenic acid (ALA), also exists [24], but it is more limited; some studies find ALA only effective among people with insufficient long-chain omega-3 intake [25], and some studies fail to find any effect at all[26].

Elevated levels of free fatty acids and triglycerides in the blood stream and tissues have been found in many studies to contribute to diminished insulin sensitivity[20,27-29]. Triglyceride levels are driven by a variety of dietary factors. They are correlated with excess body weight [30]. They tend to rise due to overeating and fall during fat loss [31]. At constant energy intake, triglyceride levels are positively correlated with trans-fat intake and strongly inversely correlated with omega-3 intake. High-carbohydrate, low-fat diets were found by many studies to result in

elevated triglycerides [32], in part due to higher production of very LDL from fructose and sucrose, and in part because increased carbohydrate intake tends to displace some omega-3 from the diet. Several recent authors suggested that the intake of simple sugars, and particularly fructose, is also a factor that contributes to insulin resistance[33,34]. Fructose is metabolized by the liver into triglycerides, and, as mentioned above, tends to raise their levels in the blood stream. Therefore, it may contribute to insulin resistance through the same mechanisms as the dietary fat. Just like fat, high levels of fructose and/or sucrose induce insulin resistance in rats [35,36], and, just like with fat, this insulin resistance is ameliorated by fish oil supplementation[37]. One study observed that a low-fat diet high in simple sugars but not in complexcarbohydrates and starches significantly stimulates fatty acid synthesis, primarily of the saturated fatty acid palmitate, therefore, paradoxically, resulting in the plasma fatty acid pattern that is similar to that produced by a high-saturated-fat diet[38]. It should be pointed out that virtually all evidence of deleterious effects of simplesugars so far is limited to their concentrated formulations and sweetened beverages. In particular, very little is known about effects of simple sugars in whole fruit and vegetables. If anything, epidemiological studies suggest that their high consumption is associated with somewhat lower risk of IR and/or metabolic syndrome [39,40].

Some proposed mechanism involves the phenomenon known as leptin resistance. Leptin is a hormone that regulates long-term energy balance in many mammals. An important role of leptin is long-term inhibition of appetite in response to formation of body fat. This mechanism is known to be disrupted in many obese individuals: Even though their leptin levels are commonly elevated, this does not result in reduction of appetite and caloric intake [41].

As elevated blood glucose levels are the primary stimulus for insulin secretion and production, habitually excessive carbohydrate intake is another likely contributor. Furthermore, carbohydrates are not equally absorbed. Integrated blood glucose response to a fixed quantity of carbohydrates in a meal is known as glycemic index. Some diets are based on this concept, assuming that consumption of low-GI foods is less likely to result in insulin resistance and obesity. However, small to moderate amounts of simple sugars (i.e., sucrose, fructose, and glucose) in the typical developed-world diet seem to not have a causative effect on the development of insulin resistance [42].

Studies show that high levels of cortisol within the bloodstream from the digestion of animal protein can contribute to the development of insulin resistance [43,44].In addition, animal protein, because of its high content of purine, causes blood pH to become acidic. Several studies conclude that high uric acid levels, apart from other contributing factors, by itself may be a significant cause of insulin resistance [45]. Vitamin D deficiency is also associated with insulin resistance [46].

Insulin resistance can also be induced by a low carbohydrate high fat diet in which it is termed physiological insulin resistance. This form of insulin resistance is not considered a diabetes marker and can be recovered from by introducing a sufficient amount of carbohydrate to the diet for a few days (100-150 g of carbohydrates). Whiledieting, fatty muscle tissue breakdown releases non esterified fatty acids that are mostly taken by the muscle cells as fuel and automatically inducing insulin resistance in those muscles.

Sedentary lifestyle

Sedentary lifestyle increases the likelihood of development of insulin resistance[47,48]. A different study found that vigorous exercise at least once a week reduced the risk of type 2 diabetes in women by 33% [49].

Protease inhibitors

Protease inhibitors found in HIV drugs are linked to insulin resistance [50].

HCV and insulin resistance

Hepatitis C also makes people three to four times more likely to develop type 2 diabetes and insulin resistance[51]. In addition, “people with Hepatitis C who develop diabetes probably have susceptible insulinproducing cells, and would probably get it anyway - but much later in life [51]. The extra insulin resistance caused by Hepatitis C apparently brings on diabetes at 35 or 40, instead of 65 or 70[51].”

Diagnosis

Fasting insulin levels

A fasting serum insulin level of greater than the upper limit of normal for the assay is used which is approximately 60pmol/L

Glucose tolerance testing (GTT)

A fasting patient takes a 75 g oral dose of glucose. Blood glucose levels are then measured over the following 2h. Interpretation is based on WHO guidelines. After 2 h a glucose level<7.8 mmol/L (140 mg/dl) is considered normal, a glycemia of between 7.8 and 11.0 mmol/L (140-197 mg/dl) is considered as impairedglucose tolerance and a glycemia of ≥11.1 mmol/L (200 mg/dl) is considered diabetes mellitus.

An oral GTT can be normal or mildly abnormal in simple insulin resistance.

Measuring insulin resistance

Hyperinsulinemiceuglycemic clamp

The gold standard for investigating and quantifying insulin resistance is the "hyperinsulinemiceuglycemic clamp," so-called because it measures the amount of glucose necessary to compensate for an increased insulin level without causing hypoglycemia [52]. It is a type of glucose clamp technique. The test is rarely performed in clinical care, but is used in medical research, to assess the effects of different medications. The rate of glucose infusion is commonly referred to in diabetes literature as the GINF value [53]. The procedure takes about 2 h. Through a peripheral vein, insulin is infused at 10-120 mU/m^2/min. In order to compensate for the insulin infusion, glucose 20% is infused to maintain blood sugar levels between 5 and 5.5 mmol/l. The rate of glucose infusion is determined by checking the blood sugar levels every 5-10 min. Low-dose insulin infusions are more useful for assessing the response of the liver, whereas high dose insulin infusions are useful for assessing peripheral (i.e., muscle and fat) insulin action [53].

The rate of glucose infusion during the last 30 min of the test determines insulin sensitivity. If high levels (7.5 mg/min or higher) are required, the patient is insulin-sensitive. Very low levels (4.0 mg/min or lower) indicate that the body is resistant to insulin action. Levels between 4.0 and 7.5 mg/min are not definitive and suggest "impaired glucose tolerance," an early sign of insulin resistance [53].

This basic technique can be significantly enhanced by the use of glucose tracers. Glucose can be labeled witheither stable or radioactive atoms. Commonly-used tracers are 3-3H glucose (radioactive), 6,6 2H-glucose(stable) and 1-13C glucose (stable). Prior to beginning the hyperinsulinemic period, a 3h tracer infusion enablesone to determine the basal rate of glucose production. During the clamp, the plasma tracer concentrationsenable the calculation of whole-body insulin-stimulated glucose metabolism, as well as the production of glucoseby the body (i.e., endogenous glucose production) [53].

Alternatives

Given the complicated nature of the "clamp" technique (and the potential dangers of hypoglycemia in some patients), alternatives have been sought to simplify the measurement of insulin resistance. The first was the Homeostatic Model Assessment (HOMA), and a more recent method is the Quantitative insulin sensitivity check index (QUICKI). Both employ fasting insulin and glucose levels to calculate insulin resistance and both correlate reasonably with the results of clamping studies. Wallace *et al.* point out that QUICKI is the logarithm of the value from one of the HOMA equations [54].

Management

The primary treatment for insulin resistance is exercise and weight loss. Low-glycemic load diet has also been shown to help [55]. Both metformin and the thiazolidinediones improve insulin resistance, but are only approved therapies for type 2 diabetes, not insulin resistance. By contrast, growth hormone replacement therapy may be associated with increased insulin resistance [56].

Metformin has become one of the more commonly prescribed medications for insulin resistance, and currently a newer drug, exenatide, is being used. Exenatide has not been approved in the UK except for use in diabetics, but often improves insulin resistance in healthy individuals by the same mechanism as it doesin diabetics.

The diabetes prevention programshowed that exercise and diet were nearly twice as effective as metformin at reducing the risk of progressing to type 2 diabetes [57]. One 2009 study has found that carbohydrate deficit after exercise, but not energy deficit, contributed to

insulin sensitivity increase [58]. Resistant starch from high amylase corn has been shown to reduce insulin resistance in healthy individuals, and in individuals with type 2 diabetes [59,60]. Animal studies demonstrate that it cannot reverse insulin resistance, but that it reduces the development of insulin resistance [61].

Some types of monounsaturated fatty acids, saturated, and trans fats promote insulin resistance. Some types of polyunsaturated fatty acids (omega-3) can moderate the progression of insulin resistance into type 2 diabetes [62]. However, omega-3 fatty acids appear to have limited ability to reverse insulin resistance, and they cease to be efficacious once type 2 diabetes is established [63].

Caffeine intake limits insulin action, but not enough to increase blood sugar levels in healthy persons. People who already have diabetes II can see a small increase in levels if they take 2 or 21/2 cups of coffee per day [64].

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