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Insulin Resistance and Its Associations

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ABSTRACT

Insulin resistance occurs when a given amount of artificial or natural (endogenous) insulin fails to make the cell absorb and utilize the glucose as same level as it does in the general population (Normal level of insulin in our bodies is about 5-15ul/ml of blood) .insulin acts by binding to a particular receptor present on the plasma membrane of target tissue. Which is subsequently transported into the cell via a sequence of protein-protein interactions. Intracellular insulin action is mediated by two primary protein-protein interaction cascades: one is related to regulate intermediate metabolism, and the other is involved in controlling the process of growth as well as mitosis of cell. It is possible to separate the regulation of these two different pathways. Indeed, some evidence suggests that in type 2 diabetes, the system governing intermediate metabolism is impaired, but the pathway regulating mitosis and growth processes is normal. Many pathways are being identified as potential reasons for insulin resistance and its syndrome's development. Congenital anomalies of one or many proteins action cascade of insulin, prenatal nutritional deficiency and elevations in the visceral adiposity are among them. This is a symptom seen in a group of cardiovascular metabolic disorders which are basically the Insulin Resistance Syndrome and other is metabolic syndrome. Role of insulin in causing dyslipidemia and in pcos and in disease like Alzheimer's is under tremendous research and its affect in worsening these conditions are topic of utmost importance. Predisposition to insulin can be related to genetic factors or it may be caused by some kind of medication (glucosamine) or by the conditions mentioned above. Mostly people who are risk are obese specially those having age above 40 years. It is noticed that genetically Latino, African, native American and Asian American are predisposed to it. Some patients having atherosclerosis and hypertensive history are also at risk.

Key words: Insulin, Insulin resistance, Metabolic syndrome, Cardiovascular metabolic disorders

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INTRODUCTION

Insulin

Pancreas is an endocrine gland in our body that secretes two hormones, insulin and glucagon. Both of these hormones are related two glucose metabolism, they regulate the amount of glucose in the blood at any time of the day [1]. Insulin is not important just for monitoring the glucose but also to store glucose in the liver, fat, and muscles. Finally, it regulates metabolism of carbohydrates, fats, and proteins human body. Without the appropriate functioning of the insulin, there is no storage of glucose in the muscles or liver, but there is no fat production either. Rather, there is fat breakdown and ketoacid production. If there is too much acid production, there is imbalance that precipitates diabetic ketoacidosis, which is a potentially fatal condition [2]. The origin of two major diseases are believed to be because of underlying increased plasma insulin and glucose levels.

- ✓ Metabolic syndrome.
- ✓ Type two diabetes.

Insulin-resistance

It occurs when fat, muscles and liver cells do not give an appropriate response to insulin and are inefficient for glucose uptake from blood. The outcome of this is that

the pancreas have to produce more insulin to facilitate glucose entry into the cell [3]. Till the pancreas are making a responsive quantity of insulin to overdo the cells that give poor feedback to insulin, the blood sugar or glucose levels are proved toulter in the tolerable level.

Prediabetes

This is basically when the glucose level of blood is higher than the normal range but not too an extent that is sufficient to be diagnosed as diabetes. Prediabetes usually occurs either in individual shaving defective beta cells which are not capable to form enough insulin to maintain normal blood glucose levelorwho already have some insulin resistance [4]. Insufficient insulin results in extra glucose that then stays in the bloodstream instead of entering the cells.

Insulin- resistance and kidney

The substantial link between salt-sensitive arterial hypertension and insulin resistance suggests that the kidney do play a very important function in the insulin resistance syndrome. Insulin signalling is essential for the viability of podocyte and the tubular function, and its receptor is expressed in the podocytes and renal tubular cells. In insulin- resistance, the renal sodium transport is intact, and it contributes to blood pressure salt sensitivity in hyperinsulinemia. An integrated approach focused at the bringing back the overall sensitivity to insulin and enhancement of insulin signalling also can be used to treat renal and vascular insulin resistance Understanding of the molecular mechanisms of this disease or insensitivity to insulin opens the door to better treatments. Type two diabetes is one of the major source of mortality and morbidity in most of the countries, and its incidence is expected to skyrocket in the future decades [5].

As a result of this tackling the metabolic path-ways that contributes to diabetes type two is an primary healthcare goal that must be achieved. New investigating ways on the bases of magnetic resonance spectroscopy or (MRS) provide live understanding of the defective points at molecular level in the person having diabetes type two, which reveals that insulin insensitivity occurs due to the decrease in the insulin induced skeletal glycogen synthesis in muscles, which is primarily because of the decreased insulin stimulated skeletal muscle glycogen synthesis [6].

Insulin resistance and lipodystrohy

Observations in people and mice models of lip dystrophy support the concept that insulin resistance is caused by an increase of intra-cellular lipid metabolites (e.g., fatty acyl CoAs, diacylglycerol) in hepatocytes and the skeletal musculature. In addition, weight loss leads to an increase in hepatic insulin sensitivity as well as a considerable decrease in intra-hepatic fat without any specific changes in the circulating adipocytokines in patients with type 2 diabetes (interleukin-6, leptin, resistin) [7]. The recent MRS studies in the adults of type 2 diabetes have shown thatthe decrease in mitochondria is linked to type 2 diabetes.

Contribution of glucocorticoids and insulin resistance to dyslipidaemias

Insulin resistance is a central feature of android (visceral) obesity, and it is associated with hypertension, higher concentrations of both very low-density lipoproteins (VLDL) and low-density lipoproteins (LDL), and lower concentrations of high-density lipoproteins (HDL). Cortisol produces insulin resistance in tissues and the sensitivity of adipose tissue to lipolytic hormones is thereby increased [8]. This intern results in an accelerated release of fatty acids from adipose tissue, and greater delivery to the liver because of higher visceral massed adipose tissue. Fatty acids all by themselves cause further insulin resistance in the liver, and end up stimulating gluconeogenesis as well as synthesis of triacylglycerol. Glucocorticoids and insulin also stimulate fatty acid synthesis synergistically. The increased presence of glucocorticoids and the fatty acids provide strengthened stimuli for the release of VLDL. Dexamethasone is a synthetic glucocorticoid known to stimulate triacylglycerol secretion, Apo lipoprotein B (apoB) secretion from the isolated hepatocytes. The resultant effects are antagonized by insulin. The mechanism for Apo lipoprotein's increased secretion involves increased production and decreased breakdown of same, causing effects that are opposite to those of insulin. This increased secretion means that cortisol influences the production of VLDL. This cause's atherosclerotic plaque formation, as each VLDL particle is turned either to an intermediate density lipoprotein or to LDL. Glucocorticoids decrease the uptake of these particles through down-regulation of the hepatic apoB/E receptor [9]. Resultant, both insulin resistance and higher activity of glucocorticoids produceshyper-apo-beta-lipoproteinemia. This partly explains the association of dyslipidaemia with stress, android obesity, diabetes and so as to why these are predisposing conditions to premature atherosclerosis.

Insulin resistance in PCOS

It may be at the heart of PCOS, causing both the production and deterioration of the condition. PCOS is a marked risk factor for diabetes. Inspite of the fact that the signs and symptoms of insulin resistance appear much after that of the PCOS, it is thought that insulin resistance may have a role in the development of PCOS and is not the other way round. Inflammation and other metabolic problems linked with PCOS may be exacerbated by high insulin levels. While the link between the two illnesses is well understood, the causes of the relationship are less so. Most importantly, insulin resistance affects people differently, and a few women with insulin resistance develop PCOS whereas the others do not [10]. Obesity-related insulin resistance, according to some experts, modifies the mechanism of action of pituitary gland and hypothalamus in the brain, boosting the formation of androgenic hormones, in turn leading to PCOS. Over produced androgenic hormone, which may or may not

be associated with PCOS, is another unconventional risk factor for dysfunctional ovaries and infertility in females.

Pre-diabetes or diabetes

This increases the risk of diabetes type two and other associated metabolic conditions. This stage, which lasts as long asupto12 years, there is no optimal sensitivity to insulin [7]. This produces higherpost meal blood sugar levels, the symptoms of which mainly include easy fatigability, polyuria andpolydipsia, neuropathy, blindness depending on the severity and other vascular diseases.

Screening

Women with PCOS are suggested tobe evaluated for the same on a regular basis so that detection and treatment can begin sooner [11].

- ✓ Fasting Blood Glucose Test: Before the blood is used to check the blood sugar level, it is usually instructed to fast for a certain length of time. If the sugar levels are high, more tests to assess how the body handles sugar are done.
- ✓ Glucose Tolerance Test: The blood sugar level is measured, then a sugary drink is given. After taking the drink, the blood sugar is measured at certain intervals to assess how long it takes for the cells to metabolise the sugar. If the blood glucose levels remain raised for even a bit longer than the normal, the body may develop insulin resistance.
- ✓ Glycosylated Haemoglobin, A1C: This measures the three-month average glucose levels.

Insulin resistance and pancreatic cancer

Diabetes in patients having cancer of pancreas is easily noticed as severe insulin resistance usually peripheral. In the skeletal muscular samples from known cases of the patients having pancreatic cancer which may be with diabetes or without it and volunteers as the control group, the molecular mechanism of insulin resistance was studied. In patients having cancer of the pancreas insulin receptor binding capacity, themRNA, tyrosine kinase activity, IR substrate-1 content, GLUT-4, and its mRNA content were found normal. Multiple abnormalities in glycogen synthesis, on the other hand, were discovered in patients having cancer of pancreas. Particularly those having diabetes. When we compare them with controls, pancreatic cancer patients had significantly lower low activity of enzyme glycogen synthase one, overall activity, and level of mRna .Only the diabetic pancreatic cancer group saw a decrease in fractional velocity of glycogen synthase.

In the known cases of diabetic pancreatic cancers, both glycogen phosphorylases a and glycogen phosphorylases b were elevated, whereas the levels of glycogen phosphorylase mRNA showed no significant difference. This is linked to a post-IR impairment in skeletal muscle glycogen production and storage, which is connected with pancreatic cancer.

Contributions of insulin resistance in causing amyloidrelated neurodegeneration in alzheimer's disease

This disease is one of the most common cause for dementia. It's is basically a metabolic disease characterised by gradual defacement in brains ability to use glucose for energy needs and its ability to respond to insulin like growth factor and natural insulin. Furthermore, proclivity of the brain to collect misfolded, atypically processed and groupedoligomericproteins, such as hyper phosphorylated tau and amyloid peptides, explains just a portion of the heterogeneity in AD [12].

According to evidences, various other factors such as oxidative stress, impairment in metabolism of energy, neuro inflammation, insulin and IGF resistance as well as its deficiency in the brain, are included in an hypothesis to develop more practical approach to diagnosis and therapy. The link between poor insulin and IGF signalling and amyloid pathology, as well as prospective treatment methods, is reviewed in this review. Increased production of amyloid-precursor protein (APP) and buildup of APP-A are caused by impairments in brain insulin/IGF signalling. Furthermore, they cause oxidative stress and energy metabolic deficiencies, resulting in the activation of proAβPP-Aβmediated neuro degeneration cascade.

Although primary and secondary disease processes can cause insulin/IGF resistance and insufficiency in the brain.A key part in the current AD epidemic showing the rise in the rate of peripheral insulin resistance, is associated with metabolic syndrome and infact type 2 DM.

Chronic hyperinsulinemia has been associated to consequent impairment degeneration in the CNS, with a slight increase in APP-A and slower clearance, according to both clinical and experimental studies. As a result, both restoring insulin response and using the insulin therapy technique that can improve the cognitive performances, but along with varying impact on APP-A load in brain. Whereas, experimental evidencesupports the idea that APP-toxic A's actions do increase resistance against insulin.

The mentioned findings depicts as if insulin resistance causes APP-A gathering, and APP-A toxicity causes insulin resistance in brain, ultimately resulting in progressive neurodegeneration. This phenomenon explains why assessing APP-Aamount in CSF fluid has been shown to be single inefficient biomarker to diagnose AD, and also the reason as to why anti-APP-A monotherapy clinical trial results have been unsatisfactory. Instead, the evidence suggests that insulin resistance in brain and it's insufficiency should be targeted correctively to slow or reverse the progression of Alzheimer's disease.

Various positive effects of various treatments affecting the role of brain insulin/IGF resistance and it's deficiency, such as intranasal delivery of insulin, insulin sensitizer agents and incretions, as well as the benefits of changes in lifestyle to reduce the risk of mild impairment or AD, are discussed. Overall, the evidence clearly suggests that we should use multimodal instead of unimodal

diagnostic practices and various corrective procedures for AD [13-17].

Drug mimetic for exercise

MS and its related risk factors have been treated with drug therapy and exercise training/physical activity. Drug therapy is compared. Numerous impediments have been identified in studies that usually lead to the discontinuation of exercise training programs and regular physical activity, resulting in MS, T2D, and CVD. It is obvious that translating effectiveness studies proving the benefits of a wide range of exercise and activity modalities is critical. Studies show that supervised training programs [often used in random controlled trials (RCTs)] produce better results than unsupervised training programs. Alternatively, because exercise (and other lifestyle therapies, such as food) is difficult to maintain, it is anticipated that individuals will find it simpler to maintain health benefits through pharmacological therapy. Even a simple therapy like taking a medication instead of modifying one's physical activity is prone to significant levels of noncompliance [13]. Loss of weight many of the differences in phenotypic results have been described previously.

Physical activity and increased fitness appear to play a key impact in preventing the metabolic syndrome in both observational and interventional studies. Physical activity-based therapies provide with +ve effects on each component of the metabolic problems or syndrome to some extent. Due to the presence of the metabolic syndrome and its individual components (which underlay obesity and insulin resistance) have recently risen dramatically, many professional organisations have issued guidelines urging immediate and more work to combat the prevalence of this.

While physical activities that improve fitness are improbable to bring insulin resistance under the normal range, lipid disorders, obesity, fitness improvement and synergistic effects by increasing activity on these risk markers, or both have shown a significant effect on health outcomes related to metabolic syndrome.

Performing exercise on daily basis is a cost-effective way for preventing and reducing the effects of metabolic syndrome, although it is still neglected. This article gives an understanding about the effects of more physically active exercise and role of fitness in metabolic syndrome and also the understanding of various mechanisms marking the advantages of being much more physically active and being fit.

CONCLUSION

The significance of this field, as well as scientific and social interest in it is not decreased in the century or so since research began in earnest. Instead, as low physical activity and convenience of foods reveal hidden already present genetic features, fast urbanisation, industrialization and globalisation have generated outbreaks of diabetes and its related diseases and obesity. The biological systems are intricate and complex, and their workings are still a mystery. Now that we look back, we might need to evaluate the previous years' major lifestyle changes in terms of socialization, job, daily physical activity and daily nutrition intake and sleep schedule. Aside from the problems that remain unsolved.

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