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RECENT UPDATES IN DIABETES MELLITUS AND INSULIN RESISTANCE

BLESSY PUSHPARATHNA S[1], ANITHA ROY[2*] AND MURALIDHARAN NP[3]

1: Research associate, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and technical Sciences, Saveetha University, Chennai, India

2: Associate Professor, Department of Pharmacology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and technical Sciences, Saveetha University, Chennai, India

3: Associate Professor, Department of Microbiology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and technical Sciences, Saveetha University, Chennai, India

***Corresponding Author: E Mail: Dr. Anitha Roy: anitharoy@saveetha.com**

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ABSTRACT

Insulin resistance occurs when body cells do not respond to insulin properly so that blood glucose will be increased. This increases the potential of developing prediabetes which may eventually lead to type 2 diabetes. Prediabetes occurs in people with high insulin resistance. Around 1 in 3 people in the United States have prediabetes, according to figures from the Centers for Disease Control and Prevention (CDC). Insulin usually helps the body maintain a good balance of energy, therefore it is important to never allow the level of blood glucose to spike for too long. Insulin resistance can lead to several health issues like Acanthosis nigricans, Polycystic ovary syndrome (PCOS), increased risk of vascular diseases, such as heart disease etc. The risk factors for insulin resistance, prediabetes, and diabetes include obesity, a sedentary lifestyle or one that is low in exercise, smoking, sleep issues and high blood pressure. Several tests can help diagnose prediabetes and diabetes-like A1C test, Fasting blood glucose test and Random glucose test. Studies report that individuals can reduce the risk of type 2 diabetes by following some preventive lifestyle changes which

primarily includes losing weight and increasing physical activity. Physical activities must be done regularly and healthful low carbohydrate diets must be followed as preventive measures. The most effective way to reduce insulin resistance is to make sustainable changes by altering our daily habits. The starting point for living well with diabetes is an early diagnosis. Regular screening tests for complications is also required. Easy access to basic diagnostics, such as blood glucose testing, should, therefore, be made available by the government in primary health care settings.

Keywords: Diabetes; Insulin resistance; complications; etiology

INTRODUCTION

Diabetes mellitus is a chronic non-communicable condition that results in high blood glucose levels. It is a complex metabolic disorder characterized by defective processing of blood sugar in our body. It is a condition primarily defined by the level of glucose giving rise to a risk of microvascular damage, retinopathy, nephropathy, neuropathy and other notable clinical conditions. 95% of the cases are type 2 diabetes requiring close monitoring of blood sugar levels regularly. It is estimated that 72.96 million adult population of India are diabetic **[1]**. According to the statistics of 2019 over 463 million adults of age ranging from 20 to 79 years are living with diabetes and it was predicted to rise to 700 million in 2030 **[2, 3]**. It is associated with reduced life expectancy, significant morbidity due to specific diabetes-related microvascular complications, increased risk of macrovascular complications leading to ischaemic heart disease, stroke and peripheral vascular disease, and diminished quality of life **[4]**. Therefore without undertaking careful management, diabetes can increase the risk of complications like stroke and heart disease **[5]**. Healthy eating and developing and maintaining active lifestyles can ward off this condition. Diabetes management is a large economic burden on society. It can increase the risks of other long term conditions if proper management of diabetes is taken **[6]**. The International Diabetes Federation (IDF) has concluded 14th of November each year as World Diabetes Day primarily to create global awareness due to its rapidly increasing numbers worldwide. This campaign acts as a platform to draw attention and reach a global audience of over 1 billion people in more than 160 countries **[7]**.

Insulin is a peptide hormone produced by beta cells of the islets of Langerhans. It plays a central role in controlling blood sugar, breaking down the carbohydrates

into sugar in the form of glucose. It helps in the transportation of glucose from the blood into the cells **[8]**. Insulin is essential for staying alive. Insulin resistance is a condition in which the body is resistant to insulin resulting in increased blood sugar. This affects the glucose balance and deteriorates the normal response of the body cells towards insulin **[9]**. There is a peak decrease in the entry of glucose into the cells paving way for its accumulation in the bloodstream. Insulin resistance is thus a major feature of prediabetes. Incase of Prediabetes the blood sugar is high, but not high enough to cause type 2 diabetes. It is a very common condition, more than 10 million cases are prediabetic in India. Physical inactivity is linked to prediabetes. Prediabetic people usually don't have any symptoms. Progression from prediabetes to type 2 diabetes is therefore not prominent. Proven lifestyle changes can prevent or delay prediabetes from developing into type 2 diabetes **[10]**. This article gives us a brief idea about the recent updates in diabetes mellitus and insulin resistance. Many hormones can induce insulin resistance including cortisol, growth hormone, and human placental lactogen.

2. INSULIN RESISTANCE:

2.1 Molecular mechanisms of insulin resistance

Diabetes is a complex metabolic disorder that defines a single etiological pathway. Accumulation of lipid metabolites, activation of unfolded protein response (UPR pathway) and innate immune pathways have all been implicated in the pathogenesis of insulin resistance **[11]**. The excess lipids are driven into alternate non-oxidative pathways which interns result in lipotoxicity and lipoapoptosis **[12]**. As the age goes up there is a gradual development of carbohydrate intolerance. This carbohydrate intolerance acts as a consequence of peripheral insulin resistance caused by a post-receptor defect in target tissue insulin action. Thus in elderly subjects, the severity of the abnormality in carbohydrate intolerance is directly associated with the degree of peripheral insulin resistance. There are various theories explaining insulin resistance, the new energy-based concept of insulin resistance states that insulin resistance is due to the surplus amount of energy in our cells. This is mediated by ATP via adenosine monophosphate-activated protein kinase signalling pathway. Decreasing the ATP level is a promising approach to treating insulin resistance according to this theory **[13]**. Thus weight loss exercise and calorie restriction reduce the ATP released by the insulin-sensitive cells. Recent studies demonstrated that a

reduced strength of insulin signalling via the IRS-PI3-Kinase pathway results in diminished glucose uptake and utilisation in an insulin target tissue of an insulin-resistant individual **[14, 15]**. Other mechanisms include an imbalance between free radical production and antioxidant sensitivity leading to reduction of peripheral insulin sensitivity and contributing to insulin resistance **[16]**.

2.2 Etiology of insulin resistance

Genetics, ageing and ethnicity play a vital role in developing insulin sensitivity. Primary factors behind it include obesity, belly fat, lack of excise, smoking and even lack of sleep. In skeletal muscles, it is manifested as reduced insulin-stimulated glycogen synthesis due to reduced glucose transport **[17]**. Candidate causal genes for insulin resistance were screened in human preadipocytes and adipocytes. Studies identified the Twelve genes which showed diverse phenotypes indicating differential roles in insulin sensitisation. This suggests the bridging mechanisms and the association of their genomic loci with insulin resistance. Short term best rest can induce insulin resistance in a person **[18]**. Some medications like corticosteroids, protease inhibitors and atypical antipsychotics are associated with insulin resistance. Many hormones including cortisol, growth hormone and human placental lactogen can induce insulin resistance. Acute or chronic inflammation, polycystic ovary syndrome and non-alcoholic fatty liver disease (NAFLD) can also be etiological factors of insulin resistance.

2.3 Complications of insulin resistance

Potential complications of insulin resistance include the development of cardiovascular diseases, renal diseases and ocular complications. Many patients do not develop diabetes even in extreme cases, to its contrast others develop multiple complications and people may be manifested with classic symptoms of diabetes mellitus such as polydipsia, polyuria, polyphagia and weight loss. During insulin resistance, several metabolic alterations induced the development of cardiovascular diseases. Insulin resistance can induce an imbalance in glucose metabolism that can lead to chronic hyperglycemia, which can trigger the oxidative stress and can cause an inflammatory response leading to cell damage **[19]**. Insulin resistance can alter a systematic lipid metabolism which leads to the development of dyslipidemia. This is often characterised by a well-known lipid triad **[20]**. Endothelial dysfunction due to insulin resistance paves way for atherosclerotic plaque formation **[21]**. In an insulin-resistant state, NO Synthesis is

selectively impaired and the compensatory hyperinsulinemia may activate the MAPK pathway resulting in the elevation of blood pressure **[22]**. A killer complications associated with insulin resistance include diabetic retinopathy, papillopathy, cataract, glaucoma and ocular surface disease **[23]**. Insulin resistance also leads to diabetic renal complications like renal nephropathy **[24]**. Type 2 diabetes is primarily associated with liver disorders including liver cirrhosis, hepatic fibrosis **[25]**, hepatocellular carcinoma and acute liver failure **[26, 27]**. As type 2 diabetes starts to prolong the body cells become less sensitive to insulin. This resulting insulin resistance is accompanied by inflammation **[28]** . These conditions can be treated if detected early and thus there is a possible decrease in risks due to insulin resistance.

2.4 Clinical manifestations of insulin resistance

Insulin resistance increases the risks of developing prediabetes which eventually leads to type 2 diabetes. Some do not develop diabetes even in extreme conditions. The primary condition includes obesity leading to raised BMI, which may be due to social demographic and lifestyle effects such as deprivation, smoking, ethnicity and gender **[29]**. Adipose tissue and peripheral tissue insulin resistance can generate pre-diabetes thus adipose tissue insulin resistance is a primary factor causing prediabetes **[30]**. It was demonstrated that thigh adipose tissue distribution is associated with insulin resistance in obesity and type 2 diabetes **[31]**. Metabolic syndrome is often associated with insulin resistance thus strength training and exercise may improve glucose sensitivity and reduce elevated insulin levels **[32]**. Other clinical conditions include polycystic ovary syndrome bracket (PCOS) **[33]**, Acanthosis nigricans **[34]**, linear and acral growth, hyperandrogenism and reproductive abnormalities **[35]**.

2.5 Psychological and economic aspects

This can often lead to symptoms of depression leading to disruptions in the brain's ability to signal satiation exhibiting increased levels of anhedonia food and seeking behaviour **[36]**. Psychological insulin resistance phenomenon is often observed in type 2 diabetes patients with proper social support and management can reduce the complications. Dispelling the insulin myths, demonstrating the injection process, collaborative style and authoritative can act as key procedures to reduce psychological insulin resistance **[37]**. Insulin resistance is associated with high rates of cardiovascular diseases, thus hospitalisation and healthcare expenditure also comes into play. The impact of obesity also leads to economic burden **[38]**.

2.6 General Management of Diabetes

Type 1 diabetes cannot be caused by insulin resistance but people with type 1 diabetes with insulin resistance will require large amounts of insulin doses to keep their blood sugar in control. Insulin resistance has been one of the reasons for suboptimal glycemic control in type 1 diabetes. These people are more prone to cardiovascular diseases and are usually obese. It is associated with the requirement of more insulin and further increased weight gain. It causes concerns about weight gain among teenagers psychologically. Hence prevention of weight gain by maintaining a proper diet and exercise is important. Thus long-term weight management should be considered in the treatment plan and methods to encounter microvascular diseases are often considered.

The management of type 2 diabetes hypoglycemic agents like sulphonylureas, meglitinides, biguanides, thiazolidinediones and alpha-glucosidase. If adequate control is not obtained by using a single therapeutic agent, physicians recommend therapy combining multiple oral hypoglycemic agents. Thus type 2 diabetes can be maintained by regular exercise, weight management, healthy eating, regular blood sugar monitoring and use of possible diabetes medication and insulin therapy **[39-40]**.

Several oral hypoglycemic agents used for the treatment of diabetes are reported to have an adverse effect which includes severe liver damage, lactic acidosis and diarrhoea. Hence new plants are explored for their various pharmacological activities. Plants with cytotoxic effect are used for the treatment of cancer **[41]**. Research is being done to discover therapeutic agents with least side effects and has been a subject of great interest these years **[42-45]**. There are several hypoglycemic drugs in nanotechnology engineered to control diabetes **[46]**. It is an attractive field of science with controlled dispersity as well as possible clinical approaches and using natural sources as therapeutic agents. Recent approaches in drug discovery are based on Incretin mimetics, amylin analogues, gip analogues, peroxisome proliferator receptor **[47]**. Efforts are being made to educate the people about diabetes to reduce the impact of the disease. Health care professionals should be more active in spreading the knowledge about diabetes especially among the aged people **[49]**.

3.CONCLUSION

Diabetes is a chronic, metabolic disease characterized by elevated levels of blood glucose which leads over time to serious damage to the heart, blood vessels, eyes, kidneys and nerves. The most common is type 2 diabetes which occurs when the

body becomes resistant to insulin or doesn't synthesize enough insulin. Globally the number of people with diabetes mellitus has quadrupled in the past three decades and is the ninth major cause of death about 1 in 11 adults worldwide now have diabetes mellitus. The most common etiology of diabetes is due to insulin resistance. Controlling blood sugar level with oral medication or insulin is the main treatment. It is better to take preventive measures to avoid diabetes with proper exercise and diet.

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5. CONFLICT OF INTEREST: Nil

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