Review Article

Natural Dietary System and Insulin Resistance

Santhi Priya S*, Kumar Ebenezar K**

*JRF, **Professor, Natural Medicine and Molecular Physiology Lab, Faculty of Allied Health Sciences, Chettinad Academy of Research & Education, Kelambakkam-603103, Chengalpattu Dt., TN. India.

Ms. S. Santhi Priya is a CARE-JRF pursuing Ph.D. degree in field of Genetics and Molecular biology at the Faculty of Allied Health Sciences, Chettinad Academy of Research and Education, Kelambakkam. She has completed her Master's degree in Medical Biochemistry from Dr. ALMPGIBMS, University of Madras, Chennai.

Corresponding author (The authors have equally contributed) - K. Kumar Ebenezar (jkebi23@gmail.com)

Chettinad Health City Medical Journal 2021; 10(1): 32 - 37

DOI: https://doi.org/10.36503/chcmj10(1)-05

Abstract

Natural diet or supplements may help fight insulin resistance, a health condition known to raise your risk of type 2 diabetes and heart disease. In people with insulin resistance, the body fails to respond properly to insulin. The body produces more and more insulin to help blood sugar (or "glucose") enters cells, but excess glucose builds up in the bloodstream and, in turn, promotes the onset of diabetes. But by pairing certain natural supplements with essential lifestyle changes, you may be able to protect against insulin resistance. Due to a lack of scientific support, the use of natural treatments for insulin resistance has been limited in regular practice. Current therapeutic approaches were largely developed in the absence of defined molecular targets or a solid understanding of disease pathogenesis. Within the past few years, our understanding of biochemical pathways related to the development of type 2 diabetes mellitus has expanded. This has opened the possibility for the development of potentially more-effective therapies, mainly focused on attenuating hepatic glucose production, enhancing glucose-dependent insulin secretion, enhancing the insulin signal transduction etc. Increasing knowledge on the biochemical and cellular alterations occurring in type 2 diabetes mellitus has led to the development of novel and potentially more effective therapeutic approaches to treat the disease. Insulin sensitivity changes with individuals with respect to their life style, dietary pattern and the supplements in diet which may benefit people with or at the risk of diabetes. This chapter brings some insights into the diabetes, insulin resistance and natural therapeutics, diets or supplements which may improve the health condition of an individual.

Keywords: Insulin resistance, diabetes mellitus, natural medicine, dietary system

Introduction

Diabetes is a chronic metabolic disorder affecting the glucose metabolism as its incidence is increasing rapid manner globally. As per world health organization (WHO) report, the prevalence of diabetes is anticipated to increase by 7.7% affecting 439 million adults in the year 2030. In India, it has been predicted that about 98 million people will suffer from diabetes in 2030.[1] The cause is multi-factorial in which insulin resistance plays an important role in the development of diabetes.[2] Insulin resistance or simply impaired glucose tolerance is a condition in which body does not respond or when cells do not react to the pancreatic hormone insulin and thus glucose uptake is hindered. When cells don't respond to insulin, pancreas secretes more insulin simultaneously body produce more and more insulin to help glucose enter the cell. Over a period of time pancreas won't be able to keep up with the increased secretion and leads to insulin resistance.[3]

At physiological level, insulin resistance leads to suppression of endogenous glucose production, lipolysis and glycogensis.[4,5] People with insulin resistance often progress to pre-diabetic condition which when left untreated leads to diabetes and subsequently associated with higher risk of heart diseases. Insulin resistance doubles the risk of having stroke and triples the danger of a heart attack.

During insulin resistance glucose tolerance remains normal due to the compensatory increase in the insulin secretion. Within the normal population which is glucose tolerant, the insulin secretion increases in proportion with the severity of insulin resistance. When insulin resistance is severe, the insulin secretion will also be greater. Approximately 25% of the population have insulin resistance in general but majority of them have normal glucose tolerance. It is estimated that in non-diabetic individual, 50% of the beta cell function would be

lost due to insulin resistance whereas in diabetic patients it is estimated to be 60-70%. Studies have demosntrated that the progression from normal to impaired glucose tolerance is related to development of severe insulin resistance. In short, insulin resistance is an increase in insulin EC50 or effective concentration with or without decrease in maximal response.[6,7]

Study with insulin dose response curve, a right shift due to decreasing surface receptors was shown whereas there was no decrease in the maximal response until 5-10% receptor has been reduced.[6] Insulin resistant individuals often have insulin resistance syndrome wherein the patients have glucose intolerance, dyslipidemia, endothelial dysfunction, etc. with clinical syndrome include diabetes, cardiovascular diseases, etc.[3] Insulin resistance is also commonly associated with clinical manifestations like visceral adiposity, hypertension, hypercoagulable state, and/or elevated markers of inflammation.

The effect of insulin resistance varies according to the function of the tissue and organ. Insulin resistance is mainly associated with the unresponsiveness of muscle, fat and liver cells (fig. 1 and 2) as they are coupled with the molecular mechanism of glucose uptake. Liver accounts for 30% of insulin mediated glucose disposal and is the major site of macronutrient metabolism.[7] Under normal condition, during glucose ingestion, insulin is secreted which is perceived by the liver and suppresses hepatic glucose production, gluconeogenesis, ketone body production and promotes glycogensis.[8] But during insulin resistance the insulin is not taken up by the liver and liver continues to release glucose which leads to hyperglycaemia.[8] Gluconeogeneis is increased due to decreased insulin uptake4 and thus hepatic insulin resistance is related to the level of glycemic control6. The major manifestation of hepatic insulin resistance is the alteration in lipoprotein metabolism and in adipocytes it causes increased free fatty acid (FFA) and decreased very low density lipoprotein (VLDL) catabolism which leads to increased hepatic release of triglycerides (TG) and VLDL.[9] Chronic hepatic insulin resistance was associated with increased fasting plasma insulin and increased gluconeogenic gene expression.[6,7]

Muscles are the major site for insulin mediated glucose uptake and accounts for nearly 60-70% of whole body glucose uptake.[7] Since muscles are the prime site, muscle insulin resistance have considerable effect on whole body glucose tolerance6. Insulin stimulated glycogensis and glycolysis in muscle are inhibited by the insulin resistance in muscle. There is a reduction in the GLUT4 (glucose transporter in muscle) translocation and decreased glycogen synthesis due to peripheral / muscle insulin resistance. In insulin resistant individuals, translocation of GLUT4 to plasma membrane is reduced.[8]

Apart from liver and muscles, adipocytes are also primarily related to insulin resistance and the mechanism of has not been elucidated fully. Insulin resistance in adipocytes are attributed to diminished insulin receptor activity and decreased insulin receptor concentration in the membrane.[7] Even though less than 5% of glucose is used by the adipocytes,

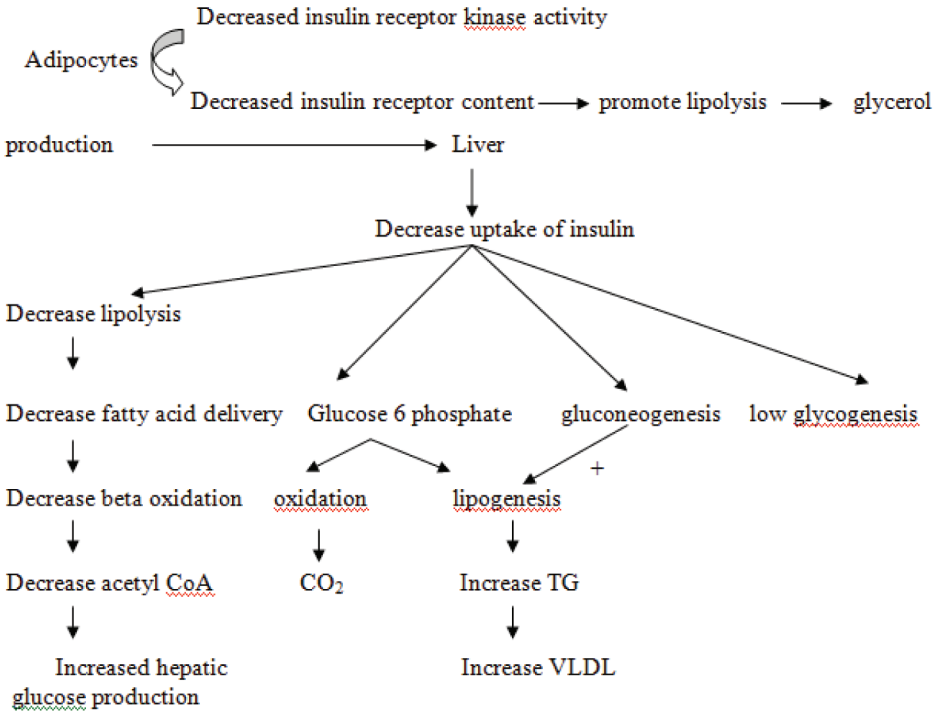

Figure 1: The schematic representation of insulin resistance in liver and adipocytes

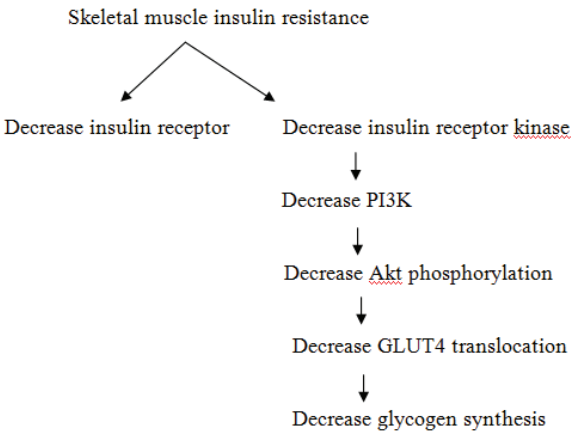

Figure 2: Insulin resistance in muscles

deletion of membrane bound glucose transporter leads to insulin resistance8 and affects both lipolysis and lipogenesis. Insulin resistance in adipocytes has been related to the inflammatory cytokines which impairs insulin signalling. Tumour necrotic factor (TNF)-α, Interleukin (IL)-6 and other cytokines promotes expression of numerous genes which are involved in insulin resistance.[6] Apart from that, brain, pancreas, kidneys, gonads and bone uses lower level of insulin dependent glucose uptake.[7]

The cellular mechanism behind the insulin resistance was elucidated and it can be owed to receptor defect or post receptor defect. Receptor defect is allied with decreased receptor expression and post receptor defect is related to impaired signal transduction. Decrease in insulin receptor causes reduction in insulin binding and not in the receptor affinity. But the insulin resistance due to receptor dysfunction is attributable to majorly liver and muscle.[7] In contrast the post receptor defect is associated with impaired Insulin receptor substrate (IRS)-1 and Phosphoinositide 3-kinases (PI3k) activity. Impaired PI3K activity with IRS-1 and its activation are characteristics of diabetes patients which are reduced in insulin resistant non diabetic individuals10. It is interesting to note that the mutation in glucose transporter (hexokinase) is not associated with insulin resistance. There was a decreased maximal insulin response in relation to whole body glucose uptake despite less than 90% loss of receptor which confirmed that both receptor and post receptor defect contribute to the insulin resistance.[11]

Insulin resistance has some common signs which include blood pressure of 130/80mmHg/higher, a fasting glucose of 100mmHg and over, fasting triglycerides of 150mg/dl, low HDL over 40-50mg/dl and skin tags which is called acanthosis nigricans.[12] There are several risk factors for insulin resistance which are listed below.[12]

- High fat diet
- Lack of exercise and physical activity
- Sedentary lifestyle
- Stress
- Sleep deprivation
- Obesity

High fat diet and lack of physical activity lead obesity is one the most important and foremost risk factor for insulin resistance. Tissue sensitivity to insulin is reduced in obese non-diabetic people and hyperinsulinemia is insufficient to overcome the insulin resistance and thus it leads to diabetic condition. Defective adipocytes function and certain genetic abnormalities also contribute to fat accumulation and also deficiency of perilipin which coats lipids droplets can also cause insulin resistance.

Therapeutics

Apart from insulin, the treatment for insulin resistance include concentrated insulin products, Metformin, Pramlintide, Glucagon like peptide-1 (GLP-1) receptor agonist and inhibitors like sodium glucose co-transporter 2 inhibitors. Concentrated insulin products are used to deliver large doses of insulin for patients with severe insulin resistance. Metformin is the initial pharmacological option and has positive impact on glycemic control and weight.[13] GLP1 agonist inhibits glucagon and Pramlintide is the analog of amylin, a substance co-secreted with insulin, deficient in diabetic patients. These therapeutics may help in the management of diabetes but comes with certain side effects as other synthetic drugs. The common side effects are diarrhoea, abdominal cramping, nausea, vomiting and hypoglycemia, etc. Metformin which is the commonly used drug is associated with gastrointestinal side effects[14] and the long term effect of these synthetic medications remains elusive. Here to alternate the above mentioned strategies, focus on natural remedies may help to overcome these drawbacks in many instance. Especially traditional natural remedies have known to have lesser side effects than the conventional medications. It is also easily available and much economical than the normal remedies[2] and hence discussing about some of the natural remedies used for insulin resistance would be useful.

Natural remedies

Ginseng refers to eleven varieties of fleshy root plant and has been believed to reduce blood glucose as well as HbA1c. Sugar lowering compound in it helped to improve insulin resistance and also affect the insulin production in pancreas11. Cinnamon is one such natural remedy for diabetes as it improves glucose metabolism by triggering the release of insulin. and also known to boost cholesterol metabolism. Study on cinnamon found that there

was 18% reduction in cholesterol level and 24% reduction in blood glucose level after the volunteers were given cinnamon for 40 days. It is anticipated that cinnamon works by increasing the number on glucose receptor on muscle cells.[15]

Fenugreek which is a common household item reported to have 4-hydroxyisoleucine which helps in the stimulation of insulin secretion and thereby decreasing blood sugar levels. Study suggested that fenugreek had effect on insulin resistance in diabetic patients.[16]

Numerous studies have found that green tea has a powerful antioxidant called epigallocatechin gallate (EGCG) which is known to increase insulin sensitivity and reduce blood sugar. A meta analysis of 17 studies found that EGCG significantly reduced blood glucose level. Eugenol, clove oil extract decreases blood glucose and also helps to maintain cholesterol level16.

Omega 3 fatty acid is known to have anti- inflammatory and prevent glucose intolerance[17] and it exert positive effect on insulin resistant individuals. Several studies have suggested that omega 3 fatty acid reduces the chances of metabolic disorders and enhances the anti-inflammatory properties.[18] Omega 3 fatty acid enhances the fatty acid oxidation and decreases fat deposition.[19] In a cohort study, Azadbakht et al (2011) found a significant association between fish oil and diabetes.[20] Fish oil has positive effect on insulin level and also independent of decreasing plasma triglycerides, erythrocyte membrane fatty acid composition and adiponectin concentration.[18] Fish oils which are rich in PUFA (poly unsaturated fatty acids) especially omega 3 fatty acid normalizes insulin action[21] and improvised HOMA-IR (homeostatic model assessment of insulin resistance).[22]

Berries, cocoa peanut and red grapes are used majorly in insulin resistant diets due to the presence of Trans resveratrol, a stilbene. Trans resveratrol counteract insulin resistance through NAD dependent histone deacetylases and activates SIRT1 AMPK pathway. Trans resveratrol also have a positive effect on HOMA IR and HbA1c.[23] Supplement of resveratrol helps in the managment of diabetes.[24] Almond consumption is associated with improved Hyperlipidemia, insulin sensitivity, reduce post prandial glucose level[25] and decreased inflammation cum oxidative stress. Presence of MUFA (mono unsaturated fatty acids), α tocopherol and dietary fiber in almonds helps to reduce insulin resistance. In a study by Lovejoy et al. (2002) found that patients in almond treated group had increased glycemic control in patients.[26]

Curcumin, a traditional supplement and a main ingredient of Turmeric in the oriental diet since ancient times has been capable of increasing insulin sensitivity and reduction of insulin resistance upon oral administration.[27] Clinical trials and In-vitro

S. No.	Natural compound	Major component	Efficacy of the compound
1.	Ginseng	Ginsenosides	Affect insulin production
2.	Cinnamon	Cinnamaldehyde	Increase insulin release Increase cholesterol metabolism
3.	Fenugreek	4-hydroxy Isoleucine	Increase insulin secretion
4.	Green Tea	Epigallocatechin gallate (EGCG)	Increase insulin sensitivity
5.	Clove	Eugenol	Decrease blood glucose Maintain cholesterol level
6.	Omega-3-fatty acid	Omega-3-fatty acid	Enhance fatty acid oxidation Prevent glucose intolerance
7.	Fish oil	Poly unsaturated fatty acid (PUFA)	Normalize insulin action Improve Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)
8.	Berries, Cocoa peanut, Red grapes	Trans- resveratrol	Improve HOMA-IR
9.	Almond	Monounsaturated fatty acids (MUFA), α tocopherol	Increase insulin sensitivity Decrease Postprandial glucose
10.	Tumeric	Curcumin	Increase insulin sensitivity Stabilize blood glucose level

Table 10: Qualitative Phytochemical analysis of Premna serratifolia

studies with curcumin supplementation and curcuminoids reported positive on fasting glycaemic parameters in high risk and individuals with diabetes and demonstrated potent inhibitory effect in improving insulin resistance.[28]

Diet also plays an important role in management of insulin resistance. A diet with 15 to 30% increased protein and decreased carbohydrate and fat significantly decreased the glycohemoglobin levels. A further reduced carbohydrate (40-20% of total energy) diet decreased fasting, post-meal glucose concentration and decreased HbA1c levels in participants strictly followed the diet29.[29]

Summary and conclusion

Insulin resistance is a characteristic feature of diabetes patients which is developed when the beta cells of pancreas cannot produce excess insulin. The consequence of insulin resistance and its link to diabetes has been well recognized. Further insight can provide invaluable information regarding the early prognosis and treatment of diabetes. Several synthetic drugs are used in the therapeutic strategy but the use has been limited with long term adverse effects. Natural remedies has been recommended as alternative for the management of diabetes and insulin resistance which is much more advantages than conventional therapies. Cost effectiveness, less side effect, strengthening of immunity and natural healing are some of the advantages of many natural compounds. Though these compounds are in practice as food supplements, taste or flavour enhancers and medicinal agents for a longer time, the bioavailability of these natural products remains elusive. An important direction need to be promoted for further studies in the field of natural remedies to optimize the oral bioavailabilities of these natural agents and realize their chemopreventive or chemotherapeutic effects.

Conflict of interest

No conflict of interest to declare among the authors.

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