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Insulin resistance: A review

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Abstract
Insulin resistance is a state in which there are impaired biological and physiological responses to insulin in tissue. In its early stages, there is a compensatory increase in insulin concentrations. Although hyperinsulinemia may compensate for resistance to some biological actions of insulin, it may result in over expression of actions in tissues that retain normal or minimally impaired sensitivity to insulin. This metabolic dysfunction leads to a cluster of abnormalities with serious clinical consequences – most importantly, cardiovascular disease (CVD), chronic kidney disease and type 2 diabetes.

Keywords: diabetic, insulin, résistance

Introduction

Insulin Resistance (IR) is considered as a pathological condition in which cells fail to respond normally to the hormones insulin. To prevent hyperglycemia and noticeable organ damage over time, the body produces insulin when glucose starts to be released in to the blood stream, primarily from the digestion of carbohydrates in the diet. Under normal conditions of insulin reactivity, this insulin response triggers glucose being taken in to body cells, to be used for energy and inhibits the body from using fat for energy, thereby causing the concentration of glucose in the blood to decrease as a result, staying within the normal range even when a large amount of carbohydrates is consumed. Carbohydrates comprise simple sugar, i.e. monosaccharides, such as glucose and fructose, disaccharides, such as cane sugar, and polysaccharides, e.g. starches [1, 2].
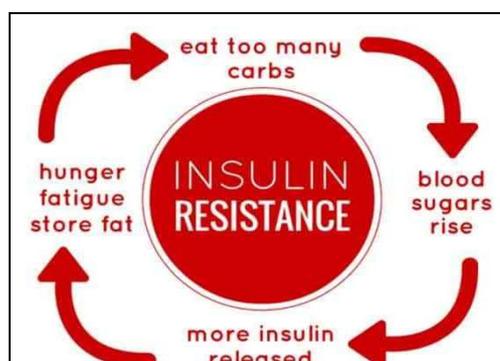
Fig 1: Insulin Resistance

Fructose, which is metabolized in to triglycerides in the liver, stimulates insulin production through another mechanism and can have a more potent effect than other carbohydrates [3]. A habitually high intake of carbohydrates and particularly fructose, e.g. with sweetened beverage, contributes to insulin resistance and has been linked to weight gain and obesity [4, 5]. If excess blood sugar is not sufficiently absorbed by cell even in the presence of insulin, the increase in the levels of blood sugar can result in the classic hyperglycemia triad of polyphagia (increased appetite), polydipsia (increase thirst) and Polyuria (increase urination). Avoiding carbohydrates and sugar, a no carbohydrate diet or fasting can reverse insulin resistance [6].

History

In 1889 German scientists Minkowski and von Mering noted, from their experimental work with animals, that total pancreatectomy led to the development of severe diabetes.

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They hypothesised that a substance secreted by the pancreas was responsible for metabolic control. Others later refined this hypothesis, noting diabetes to be associated with destruction of the islets of Langerhans. While Minkowski, as well as Zuelzer in Germany and Scott in the USA attempted, with inconsistent results, to isolate and administer the missing pancreatic islet substance, Belgian investigator de Meyer in 1909 proposed the name "insuline", as did British researcher Schaefer in 1916. Finally in 1921, a decade later, insulin was finally isolated, purified and available in a form capable of therapeutic administration. In May 1921, Toronto surgeon Banting, assisted by medical student Best, and under the supervision of McLeod, Professor of Carbohydrate Metabolism, began experiments in dogs. They administered chilled saline extracts of pancreas intravenously to dogs rendered diabetic by pancreatectomy and observed lowering of blood glucose. In December 1921 this work was presented to the American Physiological Association, and biochemist Collip, who had joined the team, further demonstrated that this extract also restored hepatic glycogen mobilisation and the capacity to clear ketones. One month later, in January 1922 the fi rst human experiments began on a 14 year old diabetic boy whose clinical symptoms and biochemical abnormalities were essentially reversed by administration of the pancreatic isolate.

In May 1922, the active component had been named insulin, and the results of these experiments presented to the Association of American Physicians. Eli Lilly subsequently began production of porcine insulin, enhancing purification through iso electric precipitation, making commercial quantities by early 1923. The Nobel Prize was awarded in 1923 to Banting and McLeod [7].

Causes
There are many factors lead to development of insulin resistance. The major leading causes are overweight, sedentary life style and genetic factors. Some other factors contribute in some ways of development of insulin resistance. Most important are obesity, physical inactivity, and genetic factors. Other factors that may affect the degree of insulin resistance are diet composition, aging, and hormones (particularly glucocorticoids and androgens). High carbohydrate diets reproduce some of the features of the metabolic syndrome [8]. There are several factors that are postulated after several studies that cause insulin resistance. There are three main ones that converge on common pathways that inhibit insulin action. They are:
1. The accumulation of ectopic lipids and its metabolites.
2. The development of 'ER stress' and the activation of the unfolded Protein response.
3. The contribution of systemic low grade inflammation. These are complex metabolic processes that have been extensively studied.

Association of ectopic lipid accumulation and insulin resistance has been universally established. It acts at the glucose transport level GLUT4 at the cell membrane that responds to insulin signalling thereby impairing insulin signalling. The activation of the unfolded protein response (UPR) also known as endoplasm reticulum stress which positively gives cells the capacity to adapt to changes especially the b-cells of islet. But in liver and adipose tissue especially, activation of the Jun-N-Kinase 1(JNK1) causes the serine phosporylation of insulin receptor substrate 1 at a key serine, leading to impaired insulin signaling [9].

Pathophysiology
One of insulin's functions is to regulate delivery of glucose into cells to provide them with energy. Insulin resistant cells cannot take in glucose, amino acids and fatty acids. Thus, glucose, fatty acids and amino acids 'leak' out of the cells. A decrease in insulin/glucagon ratio inhibits glycolysis which in turn decreases energy production. The resulting increase in blood glucose may raise levels outside the normal range and cause adverse health effects, depending on dietary conditions. Certain cell types such as fat and muscle cells require insulin to absorb glucose. When these cells fail to respond adequately to circulating insulin, blood glucose levels rise [10]. The liver helps regulate glucose levels by reducing its secretion of glucose in the presence of insulin. The normal reduction in the liver's glucose production may not occur in people with insulin resistance [11-13].
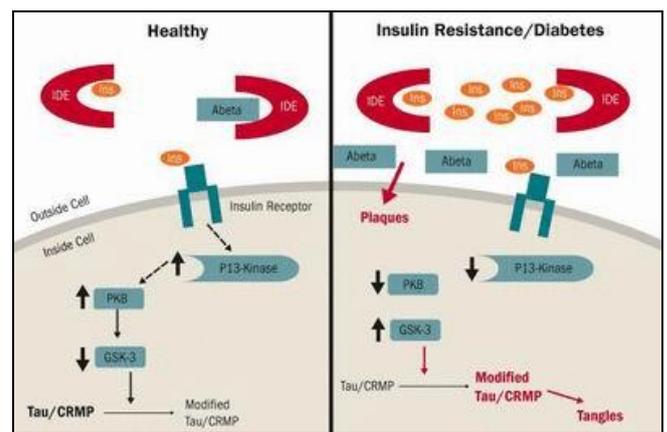

Fig 2: Healthy and Insulin resistance

Insulin resistance in muscle and fat cells reduces glucose uptake (and also local storage of glucose as glycogen and triglycerides, respectively), whereas insulin resistance in liver cells results in reduced glycogen synthesis and storage and also a failure to suppress glucose production and release in to the blood. Insulin resistance normally refers to reduced glucose lowering effects insulin. However, other functions of insulin can also be affected. For example, insulin resistance in fat cells reduces the normal effects of insulin on lipids and results in reduced up take 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 (associated with insulin resistance and diabetes mellitus type 2).], reduced muscle glucose uptake, and increased liver glucose production all contribute to elevated blood glucose levels. High plasma levels of insulin and glucose due to insulin resistance are a major component of the metabolic syndrome. If insulin resistance exists, more insulin needs to be secreted by the pancreas. If this compensatory increase does not occur, blood glucose concentrations increase and type 2 diabetes or latent autoimmune diabetes of adults occur [14].

Any food or drink containing glucose (or the digestible carbohydrates that contain it, such as sucrose, starch etc.,) causes blood glucose levels to increase. In normal metabolism, the elevated blood glucose level instructs beta cells in the islets of langerhans, located in the pancreas, to release insulin in to the blood. The insulin, in turn, makes

insulin sensitive tissues in the body (primarily skeletal muscle cells, adipose tissue and liver) absorb glucose, and thereby lower the blood glucose level. The beta cells reduce insulin out put as the blood glucose level falls, allowing blood glucose to settle at a constant of approximately 5 mmol/L (90mg/dL). In an insulin resistance person, 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 (impaired fasting glucose) or postprandial (impaired glucose tolerance) glucose concentration increase. Eventually, type 2 diabetes or latent autoimmune diabetes occurs when glucose levels become higher throughout the day as the resistance increases and compensatory insulin secretion fails. The elevated insulin levels also have additional effects that cause further abnormal biological effects throughout the body [15].

The most common type of insulin resistance is associated with overweight and obesity in a condition known as the metabolic syndrome. Insulin resistance often progresses to full type 2 diabetes mellitus or latent autoimmune diabetes of adults. This often is seen when hyperglycemia develops after a meal, when pancreatic beta cells are unable to produce sufficient insulin to maintain normal blood sugar levels in the face of insulin resistance. The inability of the beta cells to produce sufficient insulin in a condition of hyperglycemia is what characterizes the transition from insulin resistance to type 2 diabetes mellitus. Various disease states make body tissues more resistant to the actions of insulin. Examples include infection (mediated by the cytokine TNF alfa) and acidosis. Recent research is investigating the roles of adipokines (the cytokines produced by adipose tissue) in insulin resistance. Certain drugs also may be associated with insulin resistance (e.g. glucocorticoids).

The presence of insulin leads to a kind of insulin resistance every time a cell exposed to insulin, the production of GLUT4 (glucose transporter type 4) on the membrane of the cell decreases somewhat. In the presence of a higher than usual levels 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, but if it is left unchecked, it may contribute to insulin resistance. Elevated blood levels of glucose-regardless of cause-lead to increase glycation of proteins with changes, only a few of which are understood in any detail, in protein function throughout the body.

Insulin resistance often is 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 elevated triglycerides, small dense low density lipoprotein (SDLDL) particles and decreased HDL 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 experiment 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 beta/ NF kappa B pathway, a protein network that enhances transcription of inflammatory markers and mediators that may cause insulin resistance. Second, visceral adiposity is related to an accumulation of fat in the liver, a condition known as non-alcoholic 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 type 2 diabetes mellitus. Also, insulin resistance often is associated with a hypercoagulable state (impaired fibrinolysis) and increased inflammatory cytokine levels [16].

Diagnosis
Fasting insulin levels
A fasting serum insulin level greater than 25 mU/L or 174 pmol/L is considered insulin resistance. The same levels apply three hours after the last meal.

Glucose tolerance testing
During a glucose tolerance test (GTT), which may be used diagnose diabetes mellitus, a fasting patient takes a 75 gram oral dose of glucose. Then blood glucose levels are measured over the following two hours. Interpretation is base on world health organization guidelines. After two hours a glycemia less than 7.8 mmol/L (140 mg/dL) is considered normal, a glycemic of between 7.8 and 11.o mmol/L (140 to 197 mg/dl) is considered as impaired glucose tolerance (IGT), and a glycemia of greater than or equal to 11.1 mmol?L (200 mg/dL) is considered diabetes mellitus. An oral glucose tolerance test (OGTT) may be normal or mildly abnormal in simple insulin resistance. Often, there are raised glucose levels in the early measurements, reflecting the loss of a postprandial peak (after the meal) in insulin production. Extension of the testing (for several more hours) may reveal a hypoglycemic 'dip' that is a result of an overshoot in insulin production after the failure of the physiologic postprandial insulin response [17].

Conclusion
A century or more since research into this field began in earnest neither the significance nor the medical and scientific interest in this area has waned. Instead, rapid globalization, urbanization and industrialization have spawned epidemics of obesity, diabetes and their attendant co morbidities, as physical inactivity and "convenience" foods unmask latent predisposing genetic traits. The biological mechanisms are intricate and complex and incompletely understood. However, taking a step back, we may need to consider the dramatic social changes of the past century with respect to physical activity, diet, work, socialization and sleep patterns. Aside from the challenges that remain in unraveling the genetic and mechanistic factors, perhaps a greater challenge is creatively, to adapt contemporary lifestyles to our genetic makeup and physiological requirements.

Reference
1. Basciano, Heather, Federico, Lisa, Adeli, Khosrow Fructose, insulin resistance and metabolic dyslipidemia. Nut & Met. 2005; 2(1):5
2. Frank HU. Nutrition and Epidemiology Harvard school of public health. Obesity epidemiology. Oxford University press, 2008, 283-285.
3. Chiu HK, Tsai EC, Juneja R. "Equivalent insulin resistance". Diabetes Research and Clinical Practice 2007; 77(2):237-44.
4. Thorell A, Efendic S, Gutniak M, Häggmark T, Ljungqvist O. "Insulin resistance after abdominal surgery". British Journal of Surgery. 1994; 81(1):59-63.
5. Wang guanyu. "Tunable ultra-sensitivity: functional decoupling and biological insights". Sci Rep. 2016; 6:2034-2035.
6. Huang YJ, Fang VS, Juan CC, Chou YC, Kwok CF, Ho LT. "Amelioration of insulin resistance and hypertension in a fructose fed rat model with fish oil supplementation". Metab. Clin. Exp. 1997; 46(11):1252-58
7. Bliss M. The history of insulin Diabetes Care. 1993; 16(3):4-7.
8. Shulman, Gerald I. "Cellular mechanisms of insulin resistance." Journal of Clinical Investigation. 2000; 106(2):171.
9. Hirosumi, Jiro. "A central role for JNK in obesity and insulin resistance." Nature. 2002; 420(6913):333-336.
10. Home PD. Insulin therapy. In Alberti KGMM, Zimmet P, Defronzo RA editors & Keen H, International Textbook of Diabetes Mellitus. John Wiley & Sons, New York, 1997, 899-928.
11. Dodson G, Steiner D. The role of assembly in insulin's biosynthesis. Curr Opin Struct Biol. 1998; 8:189-94.
12. Malaisse WJ. Insulin biosynthesis and secretion *in vitro*. In: Alberti KGMM, Zimmet P, Defronzo RA & Keen H (Hon) editors. International Textbook of Diabetes Mellitus. John Wiley & Sons, New York, 1997, 315-36.
13. Porksen N, Hollingdal M, Juhl C, Butler P, Veldhuis JD, Schmitz O. Pulsatile insulin secretion: detection, regulation, and role in diabetes. Diabetes. 2002; 51(1):245-54.
14. MacDonald PE, El Kholy W, Riedel MJ, Salapatek AM, Light PE, Wheeler MB. The multiple actions of GLP-1on the process of glucose stimulated insulin secretion. Diabetes. 2002; 51(4):34-42.
15. Kahn SE, McCulloch DK, Porte D. Insulin secretion in the normal and diabetic human. In: Alberti KGMM, Zimmet P, Defronzo RA, editors & Keen H. International Textbook of Diabetes Mellitus. John Wiley & Sons, New York. 1997, 337-54.
16. Wheatcroft SB, Williams IL, Shah AM, Kearney MT. Pathophysiological implications of insulin resistance on vascular endothelial function. Diabet Med. 2003; 20:255-68.
17. McAuley KA, Williams SM, Mann JI, Walker RJ, Lewisv Barned NJ, Temple LA. Diagnosing Insulin Resistance in the General Population. Diabetes Care; 2015; 24(3):460-4.