INSULIN RESISTANCE: CAUSES AND METABOLIC IMPLICATIONS

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ABSTRACT

Insulin is an anabolic hormone that plays key roles in glucose metabolism. Insulin resistance is a decreased biological response to normal concentration of circulating insulin. In insulin resistance, normal amounts of insulin are inadequate to produce a normal insulin response from fat, muscle and liver cells. Insulin resistance in fat cells results in hydrolysis of stored triglycerides, which elevates free fatty acids in the blood plasma. In muscles, it reduces glucose uptake, whereas in the liver, it reduces glucose storage with both effects serving to elevate blood glucose. High plasma levels of Insulin and glucose due to Insulin resistance often lead to metabolic syndrome and type 2 diabetes mellitus. The cause of the vast majority of cases of insulin resistance remains unknown. However, it is claimed that insulin resistance might be caused by a high carbohydrate diet. Studies have shown that glucosamine (often prescribed for joint problems) may cause Insulin resistance. It is also reported that insulin resistance occurrence in a population increased as sugar consumption and addition of high fructose corn syrup to diets increased. Physical inactivity and obesity have been implicated as factors, which aggravate insulin resistance. The presumption that a defect in specific gene may cause insulin resistance is still under investigation.

Key words: Insulin, diabetes, hypertension, hypertriglyceridemia, hypoglycemia, syndrome X, cholesterol.

INTRODUCTION

Insulin is a protein produced by the ß-cells of the islets of langerhans in the pancreas. Insulin was the first protein hormone to be sequenced, the first substance to be measured by radio-immunoassay (RIA) and the first compound produced by recombinant DNA technology for practical use[1,2]. It is an anabolic hormone that stimulates the uptake of glucose into fat and muscle, promotes the conversion of glucose to glycogen or fat for storage, inhibits glucose production on by the liver, stimulates protein synthesis, and inhibit protein breakdown. Human Insulin (molecular mass 6000D) consists of 51 amino acids in two chains (A & B) joined by two disulfide bridges with a third disulfide bridge within the A chain[2].

INSULIN RESISTANCE

Insulin resistance is defined as a decreased biological response to normal concentrations of circulating

insulin. A situation where the normal amount of insulin secreted by the pancreas is not able to unlock the door to cells. Hence normal insulin response from fat, muscle and liver cells will not be produced.

Insulin resistance is found in both obese, non-diabetic individuals and those with type 2 diabetes[1].

CAUSES

It is claimed that the cause of the vast majority of insulin resistance are unknown. However, some of the listed/suspected causes are: diet, drugs, obesity and physical inactivity, insulin therapy, etc.

DIETS

HIGH CARBOHYDRATE DIET: Some studies have established that Insulin resistance occurrence in a population increased as sugar consumption and the addition of high fructose corn syrup (HFCS) to diet increased. It is also reported that some types of Mono-unsaturated fatty acids and saturated fats appear to promote insulin resistance, whereas some types of polyunsaturated fatty acids (Omega-3) can increase Insulin sensitivity[3,4].

DRUGS

It was shown in an American study that glucosamine (often prescribed for joint problems) may cause insulin resistance. In addition, drugs like glucocorticoids, isoniazid, are listed to be associated with insulin resistance[5,6].

OBESITY& PHYSICAL INACTIVITY

Reports show that obesity and physical inactivity aggravates insulin resistance[7].

USE OF (ANIMAL) INSULINS

Insulin resistance is also occasionally found in patients who use insulin. In this case, the production of antibodies against insulin leads to lower than expected fall of glucose level after a given dose of insulin. With the development of human insulin and analogues in the 1980s and the decline in the use of animal insulin (e.g. pork, beef), this type of insulin resistance has become very uncommon[1].

DEFECTS OR MUTATIONS IN INSULIN RECEPTORS

Insulin receptor mutation (Donohue syndrome)

Insulin resistance may also be caused by the damage of liver cells having undergone a defect of insulin receptors in hepatocytes[1].

SYMPTOMS, PATHOPHYSIOLOGY AND METABOLIC IMPLICATIONS

SYMPTOMS OF INSULIN RESISTANCE

1. Fatigue
2. Brain fogginess and inability of focus
3. Low blood sugar: Mild, brief period of low blood sugar are normal during the day, especially if meals are not eaten on a regular schedule. But prolonged hypoglycemia with some of the symptoms listed here, especially physical and mental fatigue, are not normal.
4. Intestinal bloating: Most intestinal gas is produced from Carbohydrates in the diet. Sufferers who eat carbohydrates suffer from gas, lots of it.
5. Sleepiness: Many people with insulin resistance get sleepy immediately after eating a meal containing more than 20% or 30% carbohydrate.
6. Weight gain, fat storage, difficulty loosing weight. For most people, too much weight is too much fat.
7. Increased triglycerides.

8. Increased blood pressure.
9. Depression: Because carbohydrates are a natural "downer", depressing the brain, it is not uncommon to see may depressed persons who also have insulin resistance[5].

PATHOPHYSIOLOGY AND METABOLIC IMPLICATIONS

In a person with normal metabolism, insulin is released from the ß-cells of the islets of langerhans after eating, and it signals insulin-sensitive tissues in the body (e.g. muscle, adipose) to absorb glucose to lower blood glucose to normal level (approximately 5mmol/l or 90mg/dl)[2].

In an insulin-resistant person, normal levels of insulin do not trigger the signal for glucose absorption by muscle and adipose cells. To compensate for this the pancreas in an insulin-resistant individual releases much more insulin such that the cells are adequately triggered to absorb glucose.

This can lead to a steep drop in blood sugar and a hypoglycemic reaction several hours after the meal. In some case (about 1/3 of people with insulin resistance), when the body cells resist or do not respond to even high levels of insulin, glucose builds up in the blood resulting in high blood glucose or type 2 diabetes. Even people with diabetes who take oral medication or require insulin injection to control their glucose levels can have higher than normal blood insulin levels due to insulin resistance[4].

Insulin resistance in fat cells results in hydrolysis of stored triglycerides, which elevate free fatty acids in the blood plasma[3]. Insulin resistance in muscle reduces glucose uptake.

Whereas, insulin resistance in the liver reduces glucose storage, with both effects serving to elevate blood glucose.

High plasma levels of insulin and glucose often lead to metabolic syndrome and type-2 diabetes[2]. The inability of the ß – cells to produce more insulin in a condition of hyperglycemia is what characterizes the transition from insulin resistance to type-2 diabetes.

People who are insulin resistant typically have an imbalance in their blood lipids (blood fat). They have an increased level of triglycerides and a decreased level of HDL (good) cholesterol. Imbalances in triglycerides and HDL cholesterol increase the risk for heart disease[3,8].

IMPLICATIONS OF INSULIN RESISTANCE FOR NIGERIANS.

It is very obvious that many factors leading to insulin resistance are seen in the lifestyles of diabetic and non-diabetic Nigerians. Over-use of therapeutic insulin, poor exercise culture, consumption of food/ pastries/drinks containing high sugar contents, high – fructose corn syrup and some unsaturated fatty acids are possible predisposing factors. The fact that various fruit juices and sugar containing beverages are introduced into Nigerian market daily is quite tempting to Nigerians as their acceptance and over consumption may gradually cause insulin insensitivity, and subsequently type -2 diabetes mellitus. Bakari and Onyemelukwe reported that about 40% of type-2 diabetic Nigerians exhibit insulin resistance[9]. It was reported by martins et al. that a decrease in insulin sensitivity precedes and strongly predicts the development of type-2 diabetes[10,11].

SYNDROME X

In insulin resistance, there are risk factors for heart disease.

Syndrome X is a cluster of risk factors for heart disease associated with insulin resistance. These risk factors include: hypertriglyceridemia (high blood lipid), low HDL-cholesterol, hyperinsulinemia, often hyperglycemia and hypertension. Reports show that it is often possible to show a direct relationship between the level of insulin and blood pressure; as insulin level elevate, so does blood pressure[12].

SOME DIAGNOSTIC CRITERIA FOR SYNDROME X

Different professional and research authorities have given some criteria to establish a case definition for syndrome X. The International diabetic federation (IDF) for example maintains that if Body Mass Index (BMI) is greater than 30Kg/m^3, central obesity can be assumed and waist circumference does not need to be measured, however, this potentially excludes any subject without increased waist circumference if BMI is less than 30Kg/m^3.Another authority – National Cholesterol Education Program (NCEP) maintains that metabolic syndrome can be diagnosed based on other criteria. The IDF uses geography – specific cut points for waist circumference, while NCEP uses only one set of cut points for waist circumference regardless of geography[10,12].

IDF CRITERIA

Central obesity and any two of the following:

1. Raised triglycerides: > 150 mg/dl (1.7mmol/L) or specific treatment for this lipid abnormality.
2. Reduced HDL cholesterol: < 40mg/dL (1.03 mmol/L) in males < 50mg/dL (1.2gmmol/L) in females, or specific treatment for this lipid abnormality.
3. Raised fasting plasma glucose: > 100mg/dL (5.6mmol/L), or previously diagnosed type 2 diabetes. If fasting plasma glucose >5.6mmol/L or 100mg/dL, oral glucose tolerance test is strongly recommended but is not necessary to define presence of the syndrome[10].

WHO CRITERIA

The World Health Organization criteria (1999) require presence of diabetes mellitus, impaired glucose tolerance, impaired fasting glucose or insulin resistance, and two of the following[10];

1. Blood pressure: ≥ 140/90mmHg
2. Dyslipidaemia: triglycerides (TG): ≥ 1.695mmol/L, and high – density (Lipoprotein cholesterol (HDL – cholesterol) ≤ 0.9 mmol/L (male), ≤ 1.0mmol/L (female).
3. Central obesity: waist: hip ratio > 0.90 (male); > 0.85 (female), and or body mass index > 30kg/m^3.
4. Microalbuminuria: urinary albumin excretion ratio ≥ 20mg/min or albumin: creatimne ratio ≥ 30mg/g.

The US National Cholesterol Education Program Adult Treatment panel 111 (2001) – NCEP ATP 111 – requires at:

1. Central obesity: waist circumference ≥ 102cm or 40inches (male), ≥ 88cm or 36inches (female).
2. Dyslipideamia: TG ≥ 1.695 mmol/L (150mg/dL)
3. Dyslipideamia: HDL – Cholesterol < 40 mg/dL (male), < 5omg/dL (female).
4. Blood pressure ≥ 130/85mmHg.
5. Fasting plasma glucose ≥ 6.1 mmol/dL

OTHER CRITERIA

High – sensitivity c – reactive protein (hs – CRP) has been developed and used as a marker to predict coronary vascular diseases in

metabolic syndrome, and it was recently used as a predictor for non – alcoholic fatty liver disease in correlation with serum markers that indicated lipid and glucose metabolism[13].

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