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Review Article

OBESITY AND INSULIN RESISTANCE: AN OVERVIEW

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ABSTRACT

Central obesity is a leading preventable cause of death worldwide, with increasing prevalence in adults and children and authorities view it as one of the most serious public health problems of the 21st century. It is defined as to the presence of excess fat in the abdominal area. Of late, it has been shown that it has positive correlation with insulin resistance and is a strong risk factor for cardiovascular diseases and a strong predictor of future diabetes mellitus. This realization has brought the concept of measuring waist circumference as an indicator of insulin resistance. It is estimated that 20 % – 25 % of south Asians have developed metabolic syndrome and many more may be prone to it. There is currently no treatment to manage the metabolic syndrome. Many studies are looking at treatment that might improve some of the symptoms of metabolic syndrome.

Keywords: Obesity, Insulin resistance, Metabolic Syndrome

INTRODUCTION

Internationally obesity and overweight have become health concern. They are the fifth leading risk of global death[1] with increasing prevalence in adults and children. It has become the most serious public health problem of 21st century.[2] Of particular worry is central obesity which is defined as presence of excess fat in abdominal area.[3] Of late it has been shown that it has positive correlation with insulin resistance, which is astrong risk factor for vascular disorders and a strong predictor for future type 2 diabetes mellitus. This realization has brought the concept of measuring waist circumference as an indicator of insulin resistance.[4]

Obesity and Overweight

WHO defines it as excess fat accumulation that is detrimental to health. It is determined by measuring body mass index (BMI), waist circumference and/or waist hip ratio.[5] It can also beassessed by trained personnel measuring skin fold thickness using calipers[6]

Body Mass Index (BMI)

Body mass index was described in the 19th century by Belgian statistician and anthropometrist Adolphe[7]. Body mass index is measured by calculating the weight of individual divided by height in meter square i.e. kg/m^2. The WHO classifies obesity as class 1, 2 and 3 by BMI.

Table 1

BMI (kg/m^2)	Obesity Class
> 25-29.9	Overweight
>30-34.9	Class 1
>35-39.9	Class 2
>40	Class 3

BMI is a useful measurement for most people however it does not distinguish between fat mass and muscle mass nor does it give information about body shape. Other methods are therefore used to give detail of central obesity.

Abdominal (Central) Obesity

The presence of excess fat over the abdominal area determines central obesity and it is estimated by measuring waist circumference and/or waist hip ratio. Carr *et al*. (2004) showed that waist circumference was independently associated with each of the components of metabolic syndrome including insulin resistance[8]. Metabolic syndrome is associated with an increased risk for CV complications and is defined by The American Heart Association (AHA), the National Heart, Lung and Blood Institute (NHLBI) and the International Diabetes Federation as any three of: increased waist circumference (see below), elevated triglycerides (≥ 1.7 mmol/L), decreased HDL cholesterol (< 1.03 mmol/L for men, < 1.29 mmol/L for women), blood pressure > 130/85 mmHg or active treatment for hypertension and fasting plasma glucose level > 5.6 mmol/L or active treatment for hyperglycaemia (SIGN guideline 97). The International

diabetes federation (IDF) has determined central obesity via waist circumference based on the ethnic group.[9]

Table 2

Ethnic group	Waist circumference (centimeters)
Europids	Male - > 94 Female - >80
South Asians	Male - > 90 Female - > 80
Chinese	Male - > 90 Female - > 80
Japanese	Male - >85 Female - >90
Others Sub Saharans and eastern Mediaterrean	As per Europids

Central Obesity and its relationship with Insulin Resistance

Lack of exercise is independent risk factor for obesity and type 2 diabetes. Sedentary life style and dietary habits are the main factors in obesity which may lead to insulin resistance. Among obesity types, the most clinical important is visceral obesity and/or ectopic fat in comparison to the total obesity[10,11]

Insulin Resistance

Insulin normally acts to stimulate the uptake of glucose into muscle and adipose tissue, the formation of proteins and glycogen in muscle and liver and the formation and deposition of lipids in adipose tissue. It also inhibits the breakdown of glycogen, fatty acid oxidation and inhibits gluconeogenesis. Effectively in puts nutrition in stores and works to keep them there. Based on their response to an oral glucose challenge an individual can be determined as insulin resistant or insulin sensitive. In insulin sensitive individuals, glucose load stimulatesinsulin secretion from the pancreas and glucose uptake by the peripheral tissues. In insulin insensitive individuals insulin secretion is initially increased and glucose clearance may be normal[12]. Diabetes ensues when beta cells cannot compensate meaning insulin levels fall and blood glucose levels rise. Chronic hyperglycemia is associated with diabetes complications such as neuropathy, retinopathy, nephropathy and sexual dysfunction, cerebrovascular, cardiovascular and peripheral vascular disease.

Complications of Adiposity and Insulin Resistance

Obesity can affect social and personal life both in terms of self-esteem and mental health but also in terms of the risk of future type 2 diabetes mellitus, dyslipidaemia, hypertension and cardiovascular disease.[13] It can also lead to diseases of the pulmonary system, gall bladder and skin as well as causing non-alcoholic fatty liver disease, various cancers, increased risk of cataracts, gynecological disorders, gout and osteoarthritis. It is estimated that life expectancy of obesity with BMI > 30 is decreased by approximately 4 years[14] Due to its effect on multiple systems diabetes has a high morbidity and mortality rate[15]

Pathogenesis

Hyperinsulinaemia

The hyperinsulinaemia that occurs as early stages of insulin resistance in obesity has a knock on effect of promoting insulin resistance. This effect is by preventing the glucose transporter GLUT-4 from moving to the membrane, by inhibiting the expression of the gene for the insulin receptor, by inhibiting intracellular messengers and by evoking mitochondrial damage and oxidative stress.[16]

Inflammation

An excess of visceral fat in obesity leads to alteration in the release of cytokines and adipokines from this endocrine tissue – obesity is essentially a chronic inflammatory disorder. In obesity, levels of tumor necrosis factor alpha (TNFα), interleukin- 6 (IL-6) resistin and leptin are all elevated, whilst levels of adiponectin are reduced. Adiponectin normally acts to enhance insulin sensitivity and has an anti-inflammatory effect. TNFα, leptin, resistin and, at high levels, IL-6 increase hepatic insulin resistance and altering the balance of these compounds in obesity leads to insulin resistance. [17]

Dyslipidaemia

Important to the development of insulin resistance is the elevation of levels of free fatty acids and triglycerides that occurs with obesity. VLDL triglycerides deposit in peripheral muscle adding to insulin resistance. They also accumulate in the liver where they encourage insulin resistance. Accumulation in the liver may lead to non-alcoholic fatty liver disease which may progress to hepatitis and cirrhosis[18]. Furthermore, the deposition of triglycerides in the pancreas encourages beta cell failure and the eventual decline in compensatory insulin release.

The effects of diet

Another theory regarding the link between obesity and insulin resistance is that metabolites of fat and protein can induce insulin resistance. Obesity is associated with elevated levels of amino acids in the blood. For example branched chain amino acid (BCAA) has been shown to interfere with the intracellular pathways triggered by insulin. In rats fed with a high fat diet this effect is further enhanced and is associated with incomplete fatty acid oxidation. A high fat, high protein diet might therefore lead to insulin resistance by these mechanisms and removal of the products of incomplete fatty acid oxidation by, for example, exercise, increases insulin's effectiveness.[19]

Fructose

Consumption of fructose, often in the form of high-fructose cornstarch being used as a sweetener, has been linked to metabolic derangement. In older obese and overweight subjects fructose increased visceral adiposity, lipogenesis, dyslipidaemia, and decreased insulin sensitivity, all of which are associated with metabolic syndrome and type 2 diabetes. Consumption of glucose did not have the same effect. The mechanism for fructose causing insulin resistance is likely to be via the elevation intrahepatic lipids resulting from lipogenesis.[20]

Trans fatty acids (TFA)

TFAs have been implicated in obesity and insulin resistance. They are available in natural forms but often come from the food industry as a component of partially hydrogenated vegetable oil(s). TFAs damage the

endothelium and increase levels of very low density lipoprotein-cholesterol (VLDL-c) and low density lipoprotein-cholesterol (LDL-c) leading to the formation of atherosclerosis as well as lowering high density lipoprotein-cholesterol (HDL-c) which is normally cardio protective. TFAs also evoke reduced Triglyceride uptake and production of free fatty acids which will lead to insulin resistance. TFAs further promote inflammation which will add to the already inflammatory state of obesity. They directly increase insulin resistance.[21] It can be seen that a number of these mechanisms can be tied back to the role of the liver in obesity and insulin resistance. Insulin resistance in the liver is emerging as the likely primary lesion in the syndrome pathogenesis[22].

Prevention of Insulin Resistance

Liver fat content is directly correlated with insulin sensitivity and is therefore a target in increasing insulin sensitivity. Calorie restriction, particularly of lipogenic substrates improves insulin sensitivity and reduces liver fat accumulation[23]. Lipogenesis and hepatic lipid load can be decreased by high fiber diet and exercise and fitness lowers hepatic fat content, Important in terms of cardiovascular risk is the fact that there is a significant correlation between liver fat content and intra-abdominal fat mass. Exercise also helps reduction by burningacetyl co enzyme and further prevents the buildup of fatty acids which improves insulin sensitivity in muscles[24]

Treatment Protocol of Obesity and Insulin Resistance

The lifestyle management of diabetes and obesity associated insulin resistancecan be divided into phases.

Primary Phase

- Moderate calorie restriction to induced 5-10 % of weight loss
- Moderate increases in physical activity
- Change in dietary composition
- Smoking cessation

It is estimated that only a small amount of weight reduction, resulting from a small negative energy balance over a long period, is better than rapid weight loss in the short term, to prevent diabetes or delay the onset of the disease[25]

Education

Proper education to the patient with regards to their condition helps in preventing diabetes complications[26].

Secondary phase

This is where drug intervention is required due to insufficient management by dietary or life style changes. It is essential in this stage to treat the individual components of metabolic syndrome in order to reduce the individual risk.

Dyslipidemia

The aim of the therapy is to increase the level of HDL-c and decrease the levels of VLDL-c. LDL-c and triglycerides, Statins are routinely used to lower LDL-c and act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. They suppress cholesterol biosynthesis, which results in increased LDL receptor activity and/or number. They have a smaller effect of raising levels of HDL-c and reducing triglycerides[27]. Fibrates activate peroxisome proliferator-activated receptors alpha (PPAR-alpha). They stimulate oxidation of fatty acids and therefore lower plasma levels of free fatty acids and triacylglycerol and increase HDL-c. Fibrates may also improve insulin sensitivity[28]. In addition, cholesterol absorption inhibitors, resins and niacin are available and may be used along with statins to reach the LDL goal or in the case of statin intolerance

Hypertension

Anti hypertensive are administered at the level of the 130/80 mmHg in diabetic patients. Thiazide diuretics (TD), angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, calcium channel blockers (CCB) and beta-blockers all lower blood pressure (BP) and patients often need polypharmacy to achieve control. ACE inhibitors are first line in most patients under 55years. The exception being black patients who would normally be commenced on CCBs or TDs. All receptor antagonists can be used in cough or rash from ACE inhibitors but not proven to improve CV outcomes. ACE inhibitors have an additional benefit on renal function. It is of note that a combination of beta blockers and diuretics may induce the onset of diabetes[29]

Hyperglycemia

The Diabetes prevention programme showed that Metformin therapy in pre diabetes subject will prevent or delay the onset[30]. Thiazolidinediones and acarbose have also been shown to delay in onset of diabetes[31-32]

Bariatric surgery

When obesity is not managed by the diet and lifestyle then bariatric surgery may be performed. It doesn't only reduce the weight but also delays the onset of Diabetes. It is usually performed in adults with a BMI > 40 kg/m^2[33]

CONCLUSION

Insulin resistance is increasing due to increase in rates of obesity. Metabolic syndrome may overtake smoking as the leading factor for the heart disease. The processes involved in obesity and insulin resistance include diet, inflammation, dyslipidaemia and impaired liver metabolism. Managing the subjects at this particular juncture may not only prevent diabetes also reduce all possible complications due to its effect on multiple systems. Increased incidence and prevalence rate of Diabetes worldwide is the prime factor for this therefore proper screening, education, and assessment of patient is extremely important in obesity. This will not only have impact on the patient but will also significantly improve healthcare budget and the workload of Health Care Professionals.

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