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REVIEW ARTICLE

RECENT ADVANCES ON OBESITY INDUCED DIABETES

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ABSTRACT

The relationship between obesity and diabetes is of such interdependence that the term 'diabesity' has been coined. The passage from obesity to diabetes is made by a progressive defect in insulin secretion coupled with a progressive rise in insulin resistance. Both insulin resistance and defective insulin secretion appear very prematurely in obese patients, and both worsen similarly towards diabetes. Thus, the classic 'hyperbolic relationship' between insulin resistance and insulin secretion and the 'glucose allostasis concept' remain prevailing concepts in this particular field of knowledge. An increase in overall fatness, preferentially of visceral as well as ectopic fat depots, is specifically associated with insulin resistance. The accumulation of intra myocellular lipids may be due to reduced lipid oxidation capacity. The ability to lose weight is related to the capacity to oxidize fat. Thus, a relative defect in fat oxidation capacity is responsible for energy economy and hampered weight loss.

Despite many herbs having both antidiabetic as well as antiobesity activity; there is no marketed formulation for obesity associated diabetes. The antidiabetic and antiobesity effect of the formulation was found to be nearly similar to that observed for glibenclamide and sibutramine respectively. It can be concluded that, the formulation should be considered as an excellent candidate for future studies of obesity associated diabetes.

Key words: Obesity, diabetis, Insulin, intra myocellular lipids

INTRODUCTION

OBESITY:

Obesity is a condition in which excess body fat is accumulated to an extent that health may be negatively affected. Obesity is commonly defined as a body mass index (BMI) of 30 kg/m^2 or higher. This definition distinguishes obesity from being pre-obese or overweight, which is classified as a BMI of 25 kg/m^2 but less than 30 kg/m^2 [1].The excessive storage that creates obesity eventually leads to the release of excessive fatty acids from enhanced lipolysis, which is stimulated by the enhanced sympathetic state existing in obesity. The release of these excessive free fatty acids then incites lipotoxicity, as lipids and their metabolites create oxidative stress to the endoplasmic reticulum and mitochondria. This affects adipose as well as nonadipose tissue[2] .Obesity increases the risk of type 2 diabetes, cardiovascular disease, cancer, and premature death. More than 1.1 billion people are estimated to be overweight of which around 320 million are calculated to be obese. More than 2.5 million deaths each year are attributed to higher BMI, a figure that is expected to double by 2030. Incidence rate of obesity is about 300 million adult's worldwide [3] .At an individual level, a combination of excessive caloric intake, lack of physical activity, and genetic susceptibility is thought to explain most cases of obesity, with a limited number of cases due solely to genetics, medical reasons, or psychiatric illness [4, 5].

DIABETES:

Type 2 diabetes mellitus is characterized differently and is due to insulin resistance or reduced insulin sensitivity, combined with relatively reduced insulin secretion which in some cases becomes absolute. The defective responsiveness of body tissues to insulin almost certainly involves the insulin receptor in cell membranes. The predominant abnormality is reduced insulin sensitivity, characterized by elevated levels of insulin in the blood [6]. The

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prevalence of diabetes worldwide was estimated to be 2.8% in 2003 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 [7]. The international diabetes federation (IDF) estimates total number of diabetics to be around 40.9 million in India and this is further set to rise 69.9 million by year 2025 [8] . Insulin production is more or less constant within the beta cells, irrespective of blood glucose levels. It is stored within vacuoles pending release, via exocytosis, which is primarily triggered by food, chiefly food containing absorbable glucose. The chief trigger is a rise in blood glucose levels after eating. Insulin is the principal hormone that regulates uptake of glucose from the blood into most cells (primarily muscle and fat cells, but not central nervous system cells). Therefore deficiency of insulin or the insensitivity of its receptors plays a central role in all forms of diabetes mellitus. Most of the carbohydrates in food are converted within a few hours to the monosaccharide glucose, the principal carbohydrate found in blood and used by the body as fuel. Insulin is released into the blood by beta cells (β-cells), found in the Islets of Langerhans of pancreas, in response to rising levels of blood glucose, typically after eating. Insulin is used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel, for conversion to other needed molecules, or for the storage [9].

OBESITY INDUCED DIABETES:

Obesity and diabetes are closely related to each other as about 80% diabetics are obese. Obesity is a common finding in Type-II diabetes. There is impaired insulin sensitivity of peripheral tissues such as muscle and fat cells to the action of insulin in obese individuals (insulin resistance). Weight reduction in such obese patients produces improvement in the diabetic state [10]. Obesity increases the risk of type 2 diabetes, cardiovascular disease, cancer, and premature death [11]. Pharmacological factor involved in obesity and diabetes includes lipoprotein lipase (LL), having a central role in the metabolism of both triglyceride-rich particles and high density lipoproteins (HDL). LL is determinant of serum triglyceride and HDL concentrations [12].

OBESITY CAUSE TYPE 2 DIABETES:

It is a well known fact that if you are overweight or obese, you are at greater risk of developing type 2 diabetes, particularly if you have excess weight around your tummy (abdomen).

Inflammatory Response:

Studies suggest that abdominal fat causes fat cells to releases 'pro-inflammatory' chemicals, which can make the body less sensitive to the insulin it produces by disrupting the function of insulin responsive cells and their ability to respond to insulin. This is known as insulin resistance - a major trigger for type 2 diabetes. Having excess abdominal fat (i.e. a large waistline) is known as central or abdominal obesity, a particularly high-risk form of obesity.

Disruption in fat metabolism

Obesity is also thought to trigger changes to the body's metabolism. These changes cause fat tissue (adipose tissue) to release fat molecules into the blood, which can affect insulin responsive cells and lead to reduced insulin sensitivity. Another theory put forward by scientists into how obesity could lead to type 2 diabetes is that obesity causes prediabetes, a metabolic condition that almost always develops into type 2 diabetes.

Preventing obesity

The links between obesity and type 2 diabetes are firmly established - without the intervention of a healthy diet and appropriate exercise, obesity can lead to type 2 diabetes over a relatively short period of time. The good news is that by reducing your body weight, by even a small amount, can help improve your body's insulin sensitivity and lower your risk of developing cardiovascular and metabolic conditions such as type 2 diabetes, heart disease and types of cancer. According to the NHS, a 5% reduction in body weight followed up by regular moderate intensity exercise could reduce your type 2 diabetes risk by more than 50% [13].

MECHANISM O F O BESTIY I NDUCED DIABETES:

Mechanisms of ob esity-associated i nsulin resistance:

The influence of obesity on type 2 diabetes risk is determined not only by the degree of obesity but also by where fat accumulates. Increased upper body fat including visceral adiposity, as reflected in increased abdominal girth or waist-to hip ratio, is associated with the metabolic syndrome, type 2 diabetes, and cardiovascular disease [14], although underlying mechanisms remain uncertain.

Whether subcutaneous fat lacks the pathological effects of visceral fat or is simply a more neutral storage location, for example, requires further study. Beyond differences in body fat distribution, emerging evidence suggests that different subtypes of adipose tissue may be functionally distinct and affect glucose homeostasis differentially. Adult humans have limited and variable numbers of brown fat cells [15], which play a role in thermo genesis and potentially influence energy expenditure and obesity susceptibility [16]. Improved understanding of the function of different fat cell types and depots and their roles in metabolic homeostasis is a priority for investigation into the pathogenesis and complications of obesity. Likewise, adipose tissue is composed of heterogeneous cell types. Immune cells within adipose tissue also likely contribute to systemic metabolic processes. As the study of adipose biology progresses, it will be important to consider whether additional subtypes of adipocytes or other cell types can be identified to refine our understanding of obesity complications and generate novel approaches to prevention.

At least three distinct mechanisms have been proposed to link obesity to insulin resistance and predispose to type 2 diabetes:

1. Increased production of adipokines /cytokines, including tumor necrosis factor-a, resistin, and retinol binding protein, that contribute to insulin resistance as well as reduced levels of adiponectin [17];
2. Ectopic fat deposition, particularly in the liver and perhaps also in skeletal muscle, and the dysmetabolic sequelae [18]; and
3. Mitochondrial dysfunction, evident by decreased mitochondrial mass and/or function [19]. Mitochondrial dysfunction could be one of many important underlying defects linking obesity to diabetes, both by decreasing insulin sensitivity and by compromising b-cell function.

Mechanisms of p rogressive b -cell dys function in obese individuals:

The link between obesity and hyperinsulinemia first identified; 50 years ago [20], reflects compensation by insulin-secreting b-cells to systemic insulin resistance. Although mechanisms underlying this coupling (e.g., mild hyperglycemia and raised levels of circulating free fatty acids) remain elusive, obese normoglycemic individuals have both increased b-cell mass and function [21-24]. Obesity-induced glucose intolerance reflects failure to mount one or more of these compensatory responses [25]. Factors predisposing to b-cell decompensation could also be primarily genetic or epigenetic. A clear, mechanistic basis for this decompensation has remained elusive. Genetic studies have helped identify the role of some key molecules in b-cell biology that may be important in this regard. For example, recent rodent studies have demonstrate diabetogenic effects of reduced pancreatic expression of the Pdx1 gene [26, 27]. While these animal studies have demonstrated that PDX1 deficiency relates mechanistically to diabetes through b-cell apoptosis, and PDX1 deficiency is linked to MODY4 [28], it is not clear yet that PDX1 deficiency has a role in common forms of type 2 diabetes in humans. This example illustrates how a growing understanding of genetics and cellular function of the b-cell can identify potential mediators predisposing obese individuals to type 2 diabetes and further may provide insights for the development of new therapeutic agents.

Genetic factors linking obesity and diabetes:

Genome-wide association scans (GWAS) and candidate gene approaches now have identified; 40 genes associated with type 2 diabetes [29, 30] and a similar number, albeit largely different, with obesity. Most type 2 diabetes genes appear to be related to b-cell dysfunction, with many fewer involved in pathways related to insulin resistance independent of obesity [31]. Not surprisingly, many obesity gene variants appear to be involved in pathways affecting energy homeostasis. Although numerous diabetes- and obesity-associated genes have been identified, the known genes are estimated to predict only 15% of type 2 diabetes and 5% of obesity risk [32]. Although additional genes with important roles will undoubtedly be discovered, this low predictive power may reflect the importance of environmental factors, less frequent genetic variants with stronger effects, or gene-environment, gene and epigenetic interactions that are not readily identified through methods based on population genetics. Methods for detecting gene-gene interactions exist, but the population size needed to detect them is substantially greater than is required for detection of single genes of relatively small effect.

Alternatively, pathway analyses or a systems biology approach combining information from DNA variations with transcript, protein, and metabolite profiles may better capture the genetic influences on metabolism than studying single genes. One should also keep in mind that the missing heritability could be an illusion of inferring additive genetic effects from epidemiological data [33].

SYMPTOMS & DIAGNOSIS:

- ✓ Excessive body weight,
- ✓ Large waist, hips,
- ✓ Buttocks and thighs,
- ✓ Fatigue and
- ✓ Asphyxia.

BMI (Body Mass Index) more than 30 or body fat levels greater than 25 and 32 for males & females respectively [10].

TREATMENT:

Antihyperlipidemic drugs are used only if diet modification & exercise programs fail to lower LDL to normal levels. These are the group of drugs prescribed in adjuvant therapy to reduce elevated cholesterol levels in patients with high cholesterol and LDL levels in the blood.

COMMON H ERBS US ED I N T HE TREATMENT O F B OTH O BESITY A ND DIABETES:

Many traditional plant remedies for obesity and diabetes are used throughout the world. Plant drugs and herbal formulation are frequently considered being less toxic and devoid of any side effects than synthetic one. Few of the traditional plant treatments for diabetes have received scientific scrutiny and the World Health Organization (WHO) has recommended that this area warrants attention [34- 36].

1. Momordica charantia Linn.
2. Gymnema sylvester R.
3. Eugenia Jambolana Willd.
4. Acacia Catechu Linn.
5. Ziziphus maurantiana Linn.
6. Ginger officinalis Gearth
7. Cinnamon
8. Garcinia cambogia
9. Lagerstromia speciosa L.
10. Allium sativum
11. Ocimum sanctum
12. Phyllanthus amarus
13. Pterocarpus marsupium
14. Tinospora cordifolia
15. Trigonella foenum graecum
16. Withania somnifera

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