Review Artical

Obesity in the Pathogenesis of type 2 Diabetes

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Abstract

The article reviews the relationship between type 2 diabetes and obesity. This also includes types of obesity and it's genetic predisposition. The modern generalization of sedentary life style and caloric abundance has created new physiological conditions capable of changing the level of expression of a number of genes involved in fuel metabolism and body weight regulation. In this article, we underscore the importance of obesity in relation to disorders of diverse etiologies characterized by disturbances of free fatty acids, visceral adiposity and insulin resistance. Further, we have investigated the role of selecting the traits to be subjected to quantitative genetic analysis in the occurrence of obesity.

Keywords *T 2 DM, Obesity, Visceral adiposity.*

Introduction

Diabetes mellitus type 2 is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency[1]. This is in contrast to Diabetes type 1 in which there is an absolute insulin deficiency due to destruction of islet cells in the pancreas and gestational diabetes mellitus that is a new onset of high blood sugars in associated with pregnancy[2]. The classic symptoms are excess thirst, polyuria polydipsia, polyphagia, and weight loss. Type 2 diabetes makes up about 90% of cases of diabetes with the other 10% due primarily to diabetes mellitus type 1 and gestational diabetes. Obesity is thought to be the primary cause of type 2 diabetes, in people who are genetically predisposed to the disease. Antibody testing may be useful to confirm type 1 diabetes and C-peptide levels may be useful to confirm type 2 diabetes[1], with C-peptide levels normal or high in type 2 diabetes, but low in type 1 diabetes.

Pathophysiology

Type 2 diabetes is due to insufficient insulin production from beta cells in the setting of insulin resistance. Insulin resistance, which is the inability of cells to respond adequately to normal levels of insulin, occurs primarily within the muscles, liver, and fat tissue[3]. In the liver, insulin normally suppresses glucose release. However, in the setting of insulin resistance, the liver inappropriately releases glucose into the blood[4]. The proportion of insulin resistance versus beta cell dysfunction differs among individuals, with some having primarily insulin resistance and only a minor defect in insulin secretion and others with slight insulin resistance and primarily a lack of insulin secretion. Other potentially important mechanisms associated with type 2 diabetes and insulin resistance include: increased breakdown of lipids within fat cells, resistance to and lack of incretin, high glucagon levels in the blood, increased retention of salt and water by the kidneys, and

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inappropriate regulation of metabolism by the central nervous system[4] However, not all people with insulin resistance develop diabetes, since an impairment of insulin secretion by pancreatic beta cells is also required.

Free Fatty Acids And Triglycerides In The Development Of T2DM

Free fatty acids (FFA) are a major source of energy for liver, kidney and skeletal muscle and a key substrate for triglyceride production by the liver. In periods of prolonged fasting, FFA provide an alternative energy source to glucose, preserving glucose for cerebral requirements and also preserving body proteins, which can serve as substrates for gluconeogenesis. FFA are stored in the body in the form of triglycerides, the vast majority of which are located in white adipose tissue, and are released from triglycerides by the process of lipolysis. After transportation into the tissue, FFA are mainly oxidized in muscle cells to release energy, or converted into lipoproteins by the liver. The enzyme that controls the rate-limiting step for mobilization of triglycerides in adipose tissue is hormonally regulated. Insulin is one of the main hormones involved in this regulatory process[5], and the most potent anti lipolytic hormone. In insulin resistance, the insensitivity of adipocytes to insulin, results in elevated FFA[7,8] which is a characteristic feature of Type 2 DM[10,11] and is strongly implicated in the development of insulin resistance and beta-cell dysfunction. Thus, it is becoming increasingly apparent that reducing FFA levels is an important goal in the management of patients with Type 2 DM. Prospective epidemiological studies have shown that an elevated FFA level is a risk marker for long-term development of glucose intolerance and progression to, in addition to being associated with several other independent[7] Type 2 DM risk factors for cardiovascular diseases[1-3,8,14].

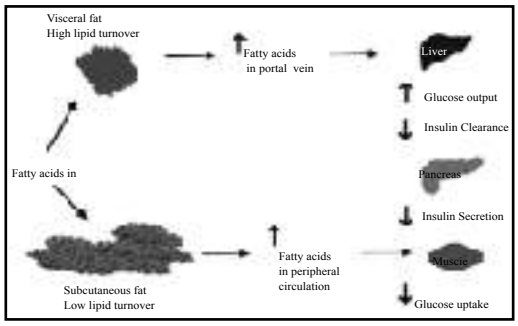

Figure 1: FFA turnover in visceral and subcutaneous Adipose tissues: Arner p. Diabetes obesity and Metabolism[5] 3(s1) 11-19, 2001.

It is becoming increasingly clear that management of dyslipidaemia is of equal importance to control of hyperglycaemia and hypertension in the care of patients with Type 2 DM. The majorities of the patients is obese and have elevated plasma FFA levels[10]. It has been suggested that FFA may be an important link between obesity & Type 2 DM

WHO Diabetes diagnostic criteria

Condition	2 hour glucose mmol/l(mg/dl)	Fasting glucose mmol/l(mg/dl)	HbA
Normal	<7.8 (<140)	<6.1 (<110)	<6.0
Impaired fasting glycaemia	<7.8 (<140)	≥ 6.1(≥ 110) & <7.0(<126)	6.0
Impaired glucose tolerance	> 7.8 (> 140)	<7.0 (<126)	6.0
Diabetes mellitus	≥11.1 (≥ 200)	≥7.0 (≥ 126)	≥ 6.5

Mechanisms of progressive ß-cell dysfunction in obese individuals

Obesity, and especially visceral adiposity, escalates the development of insulin resistance and type 2 diabetes. Excess adipose tissue contributes to a chronic increase in circulating fatty acids reducing the usage of glucose as a source of cellular energy. Excess fatty acids also result in increased deposition of fat in muscle and liver, and increased metabolites such as diacylglycerol which activate iso forms of protein kinase C that impede cellular insulin signaling. Chronically raised lipid levels also impair islet beta cell function, acting in conjunction with insulin resistance to aggravate hyperglycaemia. When insulin resistance is accompanied by dysfunction of pancreatic islet ß-cells, the cells that release insulin failure to control blood glucose levels. 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[4], that contribute to insulin resistance as well as reduced levels of adiponectin[12], 2) ectopic fat deposition, particularly in the liver and perhaps also in skeletal muscle, and the dysmetabolic sequelae[13]; and 3) mitochondrial dysfunction, evident by decreased mitochondrial mass and/or function[14]. Mitochondrial dysfunction could be one of many important underlying defects linking obesity to diabetes, both by decreasing insulin sensitivity and by compromising ß-cell function. Impaired insulin secretion results in decreased insulin levels and decreased signaling in the hypothalamus, leading to increased food intake and weight gain,decreased inhibition of hepatic glucose production, reduced efficiency of glucose uptake in muscle,

and increased lipolysis in the adipocyte, resulting in increased plasma NEFA levels. The increase in body weight and NEFAs contribute to insulin resistance, and the increased NEFAs also suppress the ß-cell's adaptive response to insulin resistance. The increased glucose levels together with the elevated NEFA levels can synergize to further adversely affect ß-cell health and insulin action, often referred to as 'glucolipotoxicity'.

There are a number of medications and other health problems that can predispose to diabetes[15]. Some of the medications include glucocorticoids, thiazides, beta blockers, atypical antipsychotics[16] and statins[17]. Those who have previously had gestational diabetes are at a higher risk of developing type 2 diabetes[20] Other health problems that are associated include: acromegaly, Cushing's syndrome, hyperthyroidism, pheochromocytoma, and certain cancers such as glucagonomas[15]. Testosterone deficiency is also associated with type 2 diabetes[18,19].

Managing body weight by behavioral change and medications

The dramatic increase in incidence and prevalence of obesity over the past 50 years, associated in part with major worldwide changes in caloric intake and dietary composition, has focused attention on lifestyle intervention to reverse or ameliorate caloric imbalance. A number of lifestyle factors are known to be important to the development of type 2 diabetes, including: obesity (defined by a body mass index of greater than thirty), lack of physical activity, poor diet, stress, and urbanization[21]. Dietary factors also influence the risk of developing type 2 diabetes. Consumption of sugar-sweetened drinks in excess is associated with an increased risk[22,23].

The type of fats in the diet are also important, with saturated fats and trans fatty acids increasing the risk and polyunsaturated and monounsaturated fat decreasing the risk[28]. Eating lots of white rice appears to also play a role in increasing risk[25]. A lack of exercise is believed to cause 7% of cases[26]. A proper diet and exercise are the foundations of diabetic care [26] with a greater amount of exercise yielding better results[32]. Aerobic exercise leads to a decrease in HbA1c and improved insulin sensitivity[32]. Onset of type 2 diabetes can be delayed or prevented through proper nutrition and regular exercise[29,30]. Intensive lifestyle measures may reduce the risk by over half[27]. The benefit of exercise occurs regardless of the person's initial weight or subsequent weight loss[31].Onset of type 2 diabetes can be delayed or prevented through proper nutrition and regular exercise. Intensive lifestyle measures may reduce the risk by over half [8]. The benefit of exercise occurs regardless of the person`s initial weight or subsequent weight loss.

Pharmacologic prevention

Metformin is the gold standard in type 2 diabetes. The ADA recommends that, in addition to lifestyle counseling, metformin be considered in selected patients with pre diabetes[3]. ADA criteria for preventive metformin therapy are as follows:

- Obesity
- Age younger than 60 years
- Both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT)
- Other risk factors (eg, HbA1C >6%, hypertension, low HDL cholesterol, elevated triglycerides, or a family history of diabetes in a first-degree relative)

Metformin is a biguanide that can use alone or in combination with sulfonylureas or insulin in the treatment of non-insulin-dependent diabetes mellitus (NIDDM). Since biguanides do not increase pancreatic insulin secretion, they are referred to as anti hyperglycemic agents, as opposed to hypoglycemic agents. Type 2 diabetes mellitus results from impaired insulin secretion and reduced peripheral insulin sensitivity. Treatment options include diet, oral anti hyperglycemic agents, and insulin. Metformin is a cornerstone of oral anti diabetic treatment. Recent joint American and European guidelines recommend instituting metformin therapy along with lifestyle modification at the time type 2 diabetes mellitus (T2DM) is diagnosed.

Metformin acts to reduce hepatic gluconeogenesis and improve glucose uptake, and it may exert protective effects on pancreatic islet cells because it reduces blood glucose levels predominantly by decreasing hepatic glucose production and release and also by increasing peripheral tissue sensitivity to insulin; it does not stimulate insulin secretion from the beta cells in the pancreas. Metformin acts to decrease preprandial and postprandial blood glucose concentrations by increasing skeletal muscle uptake of glucose Although metformin therapy produces substantial reductions in HbA1c, it does not produce body weight gain, is not associated with substantial risk for hypoglycaemia and has neutral to positive effects on lipids and blood pressure. In lean or overweight type 2 diabetic patients uncontrolled by

diet, metformin monotherapy significantly improves glycemic control, The addition of metformin to maximum dosages of a sulfonylurea may synergistically improve glucose control. The drug may offer other potential benefits, such as weight loss or minimal weight gain, improved blood flow in patients with peripheral vascular disease, reduction of tissue plasminogen activator inhibitor. In patients who are not getting the desired effect with sulfonylureas, it is useful to combine sulfonylureas with metformin therapy. Metformin should be considered a first-line agent, particularly in obese and/or hyperlipidemic NIDDM patients.

Summary

Visceral obesity plays an important role in the development of diabetes by mobilizing free fatty acids and certain inflammatory cytokines promoting insulin resistance. Management of type 2 diabetes focuses on lifestyle interventions, lowering other cardiovascular risk factors, and maintaining blood glucose levels in the normal range Type 2 diabetes is initially managed by increasing exercise and dietary modification. If blood glucose levels are not adequately lowered by these measures, medications such as metformin or insulin may be needed. In those on insulin, there is typically the requirement to routinely check blood sugar levels long[5] term complications from high blood sugar can include heart disease, strokes, diabetic retinopathy where eyesight is affected, kidney failure which may require dialysis, and poor circulation of limbs leading to amputations. The acute complication of ketoacidosis, a feature of type 1 diabetes, is uncommon in NIDDM[6]. However, non ketotic hyper osmolar coma may occur. The goal of treatment is typically an HbA1c of less than 7% or a fasting glucose of less than 6.1 mmol/L (110 mg/dl)[7] -It is recommended that all people with type 2 diabetes get regular ophthalmology examination[3].

Conclusion

Metformin is generally recommended as a first line treatment as there is some evidence that it decreases mortality. Evidence for the benefit of dietary changes alone, however, is limited with some evidence for a diet high in green leafy vegetables and some for limiting the intake of sugary drinks.in those with impaired glucose tolerance, diet and exercise either alone or in combination with metformin or acarbose may decrease the risk of developing diabetes Lifestyle interventions are more effective than metformin.

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