

Visceral Obesity and Diabetes Mellitus

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SUMMARY

- The pathogenetic mechanisms linking obesity and type 2 diabetes is explained by the observation that excessive amounts of adipocytes are associated with an impairment of insulin sensitivity.
- Hepatic insulin resistance is exacerbated by systemic insulin resistance and impaired handling by skeletal muscle and adipose tissue of both glucose and free fatty acids.
- Besides releasing free fatty acids, adipocytes secrete substances that contribute to peripheral insulin resistance, including adiponectin, resistin, TNF-alpha and interleukin 6. The decline in β -cell function is driven at least in part by glucotoxicity and lipotoxicity, which in turn are driven by insulin resistance. Anti-inflammatory and proinflammatory molecules play a role in developing the syndrome.
- “Prediabetes” is defined as the presence of impaired fasting glucose and/or impaired glucose tolerance. Even at these blood glucose levels, significant risk exists for both micro and macrovascular complications.
- There is beneficial effect of diet & exercise on prevention of T2DM. Besides, four pharmacologic agents have been tried to prevent/delay diabetes in prediabetics. These are metformin, thiazolidinediones, acarbose and orlistat with various degrees of risk reductions.

AIM OF THIS REVIEW

The aim of this review is to delineate some aspects of the interrelation of visceral obesity and diabetes mellitus. It also revises modalities for prevention of dysglycemia.

EPIDEMIOLOGY AND PREVALENCE

- In the Mediterranean region a multicentre study was done on 4254 subjects, 2090 non-diabetic and 2163 with T2DM recruited from 6 countries, Algeria, Bulgaria, Egypt, Italy, Greece and Serbia-Montenegro. MetS was diagnosed by the National Cholesterol Education Program (NCEP) criteria. The prevalence of MetS in the population studied was 27.2% but varied greatly among centers, from 5.8% in Algeria to 20.6% in Egypt and 37.3% in Greece. In Egypt the

prevalence of MetS was 10.8% in males and 30.4 in females and that of obesity was 25.6 % and 26.8 % respectively. Hyperglycemia was observed in 14% of MetS positive subjects, in only 2.2% of MetS-negative subjects and in 5.5% of the population as a whole, being the less frequently observed characteristic of MetS (3).

- In Iran, diabetes mellitus was reported in 6.2% of participants. Prevalence of diabetes mellitus in men and women was 4.4% and 7.4%, respectively. The prevalence rates of high WHR were 54.7% among men and 88.9% among women (4).
- In the USA, data from Centers for Disease Control and Prevention (CDC) in 2000, revealed a prevalence of obesity among US adults of approximately 20%, a 61% increase from the 1991 prevalence rate. Currently, most adults (>56%) are overweight, approximately 1 in 5 is obese, and 7.3% have diabetes (5).

DIAGNOSTIC CRITERIA

Table I. AACE Clinical Criteria for Diagnosis of the Insulin Resistance Syndrome (8)

Risk Factor Components	Cut points for Abnormality
Overweight/obesity	BMI \geq 25 kg/m ²
Elevated triglycerides	\geq 150 mg/dL (1.69 mmol/L)
Low HDL cholesterol	Men <40 mg/dL (1.04 mmol/L) Women <50 mg/dL (1.29 mmol/L)
Elevated blood pressure	\geq 130/85 mm Hg
2-Hour post-glucose challenge	>140 mg/dL
Fasting glucose	Between 110 and 126 mg/dL
Other risk factors	
Family history of type 2 diabetes, hypertension, or CVD	
Polycystic ovary syndrome	
Sedentary lifestyle	
Advancing age	
Ethnic groups having high risk for type 2 diabetes or CVD	

PATHOGENESIS

- Current explanations for obesity center around a predisposition in genotype and phenotype, possibly triggered by an inflammatory process or event, and exacerbated by environmental and psychological factors.
- Leptin resistance may be an important neurochemical cause of obesity.
- Genetic studies support the postulate that a gene originating with our cave-dwelling ancestors, critical to survival when food was scarce, has evolved into a trigger for obesity and related diseases.
- C-reactive protein, interleukin-6, and others are elevated in obesity, supporting the hypothesis that inflammation plays a role in the condition. Tumor necrosis factor alpha is over expressed in obesity and diabetes, suggesting that it may be part of the link between the 2 conditions (12).

INSULIN RESISTANCE (see also chapter 8)

- The major defect in T2DM is the signaling pathway between the insulin receptor and stimulation of GLUT4 translocation. This defect is caused by insulin resistance. There are multiple sites of abnormal cellular signaling due to insulin resistance (13): IRS- 1, 2; GLUT- 4; P - 85 and p - 110 subunits of PI-3 kinase & C - AMP dependent kinase.
- Some of the signaling abnormalities originate in insulin receptor itself and affects the action of the post receptor functions including: 1. Insulin receptor coupling; 2. Insulin receptor b subunit and 3. Insulin receptor tyrosine kinase.
- Insulin has two pathways of action. The phosphatidyl-inositol-3 (PI-3) kinase pathway is vasculoprotective by mediating nitric oxide transport and potentially reversing insulin resistance, and, thus, components of the dysmetabolic syndrome.
- MAP kinase pathway mediates effects in vascular smooth muscle cells, which are proatherogenic.
- In type 2 diabetes, due to deficient insulin signaling, PI-3 kinase activity is reduced. MAP kinase pathway is not significantly affected. Therefore, promotional effects of insulin on vascular smooth muscle and promotion of atherosclerosis are not counterbalanced by atheroprotective downstream effects of PI-3 kinase (14).

- Recent data clearly implicate hepatic insulin resistance as a culprit in accumulation of FFAs as triglycerides in hepatocytes. The key consequence of hepatic insulin resistance, impaired hepatocyte insulin signal transduction, results in adverse cellular and molecular changes exacerbating hepatocyte triglyceride storage (15).

INCREASED FFA AND LIPOTOXICITY

- Impairments in glucose metabolism are associated with molecular alterations of insulin signaling, which are particularly well characterized in muscle (20). An increased content of fatty acids appears to favor serine phosphorylation of insulin receptor substrate 1 (IRS-1), and to block IRS-1 tyrosine phosphorylation and the associated activation of phosphatidylinositol-3' kinase activity. This results in a decreased translocation of the glucose transporter GLUT4 to muscle membranes (21). A similar mechanism involving IRS-2 is suggested to occur in liver (22).

HYPERGLYCEMIA

- The pathogenesis of T2DM is complex and arises from a combination of both insulin resistance and β -cell dysfunction. Loss of β -cell dysfunction arises from a complex interaction of a number of factors; besides it is driven at least in part by glucotoxicity and lipotoxicity, which in turn are driven by insulin resistance.
- The consequences of insulin resistance at the tissue level include decreased insulin-dependent glucose uptake into adipose tissue and muscle. Combined with excessive insulin-sensitive glucose production by the liver, this leads to hyperglycemia, which in turn causes a compensatory increase in insulin secretion.
- In addition, excessive breakdown of triglycerides in the adipose tissue leads to increased circulating FFAs. FFAs not only compete for glucose during metabolism, but their rise is associated with loss of pancreatic β -cell function (24).
- Elevated plasma FFA's lead to:
 - Increased hepatic gluconeogenesis

- Impairment of glucose-stimulated insulin secretion by pancreatic β -cells
- Decreased glucose uptake, glycogenolysis and glucose oxidation by skeletal muscle.
- In the insulin-resistant state, the pancreas is able to initially compensate for insulin resistance via increased production. With time, the β -cells fail to maintain the high rate of insulin secretion leading to the development of IGT and then frank diabetes.
- Glucotoxicity is the ability of glucose to stimulate the death of β -cells. Similarly, chronically elevated free fatty acids have a lipotoxic effect upon the pancreas, inducing β -cell dysfunction. Lipotoxicity is the ability of free fatty acids to stimulate the death of β -cells. Oversecretion of insulin also contributes to β -cell dysfunction.

PROINFLAMMATORY FACTORS (26)

- There is a correlation between levels of CRP and the number of metabolic disorders present.
- Following activation by cytokines, the active part of NF κ B is translocated to the nucleus, where it induces the synthesis of pro-inflammatory proteins (e.g. IL-6, COX-2, TNF α , etc).
- The cytokines, in addition to amplifying the immune response, alter endothelial cell function towards a prothrombotic state, characterised by increased production of plasminogen activator inhibitor-1 (PAI-1), tissue factor expression (TFE) and activation of the extrinsic coagulation pathway), and release of PDGF.

DIABETIC DYSLIPIDEMIA

- The main lipid abnormalities in T2DM are reduced HDL cholesterol levels and elevated triglycerides. This leads to increases in total / HDL cholesterol. Besides, elevated levels of plasma FFAs are commonly observed in these patients.
- While total LDL levels tend to remain relatively unchanged, T2DM is associated with a preponderance of small, dense LDL particles, which are more susceptible to oxidation, and believed to be more atherogenic than unmodified LDL.

- HDL-C is lower in hyperinsulinemic patients. compared with normoinsulinaemic. The relationship holds true both in obese and non-obese patients. Small, dense LDL particle patterns are associated with a higher degree of insulin resistance.
- Compared with subjects with larger LDL particle patterns or intermediate patterns, subjects with small, dense LDL particle patterns are more insulin resistant, have higher glucose, insulin and triglyceride levels, have lower HDL levels and have higher blood pressure.

PREDIABETES AND PREVENTION OF DIABETES

- “Prediabetes” is defined as the presence of impaired fasting glucose (IFG) (fasting glucose of 100-125 mg/dL) and/or impaired glucose tolerance (IGT) (2h post glucose load of 140-199 mg/dL).
- A single abnormal reading at formal testing is adequate to define prediabetes.
- People who have prediabetes are at increased risk of developing diabetes, although a proportion of those with prediabetes can revert to normal glucose tolerance (28).
- There is substantial evidence to suggest that even at these blood glucose levels, significant risk exists for both micro and macrovascular complications (29).

The effect of exercise

Some epidemiologic studies demonstrating reduced risk for developing Type Diabetes associated with increased physical activity.

- In the four studies that measured the incidence of diabetes as an outcome, the risk of diabetes was reduced by approximately 50%.
- Results indicate that the contribution of physical activity independent of dietary or weight loss changes to the prevention of T2DM prediabetics is equivocal (30).

TARGETING HYPERGLYCEMIA- PHARMACOLOGIC APPROACHES

The effect of pharmacotherapy

- Four main pharmacologic agents have been tried to prevent /delay diabetes in prediabetics. These are metformin, thiazolidinediones, acarbose and orlistat with various degrees of risk reductions (from 25 to 55%) (34-38).
- Early treatment with thiazolidinediones may significantly delay or prevent progression of impaired glucose tolerance or insulin resistance to T2DM (35).
- In the DREAM Study, Rosiglitazone 8 mg/day reduced new DM by > 60% in people with IGT or IFG. Yet this has been associated with increased risk of CHF (36).
- In the XENDOS Study, Orlistat decreased the incidence of T2DM from 9 to 6.2 % in all subjects and from 28.8 to 18.8 % in subjects with IGT (38).
- The detrimental effect of elevated FFAs on insulin sensitivity can be improved by TZDs in patients with type 2 diabetes mellitus.
- The release of the insulin-mimetic visfatin may represent a major mechanism of metabolic TZD action. The presence of FFA antagonizes this action, which may have implications for visfatin bioactivity (39).

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