SURVEILLANCE

Diabetes type 2 pandemic in 21st century

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Abstract: In the second half of the 20th century it became obvious that a relentless increase in diabetes type 2 (DM) affecting the economically affluent countries, is gradually afflicting also the developing world. This review juxtaposes the threat that the DM epidemic represents to mankind, with the astonishing recent discoveries on the role of obesity and of the body fat in this metabolic disorder.

Presently, the highest prevalence of DM is in Saudi Arabia, a country deep in riches generated by its oil wells. DM is very high, in over 10 % of adults in the USA, Switzerland and Austria. Prevalence is low in Norway, China and in Iceland. Predictions of epidemiologists for the first third of the 21st century claim up to 2.5 times increase in DM in the Middle East, Sub-Saharan Africa, India, rest of Asia and in the Latin America. In China the number of patients with DM will double but in the economically advanced countries that experienced rise in DM in the 20th century, the increase will be only about 50 %. Remarkably, a lowest increase in DM is expected in the countries that formerly belonged to the Soviet political space. Increasing urbanization, aging populations, obesity, and falling levels of physical activity are all contributing to the rise of DM worldwide.

The main cause of DM pandemic is growing prevalence of obesity, in Europe and in the Latin America. In the North America obesity is considered to be responsible for 90 % of DM in females. Male obesity is associated with DM slightly less, at 70–80 % in the European Union and in the US. The precise mechanism by which obesity leads to insulin resistance and to DM is not completely described but it may be related to several biochemical factors, such as abnormalities in free fatty acids, adipokines, leptin and other substances (Tab. 1, Fig. 4, Ref. 24). Full Text (Free, PDF) www.bmj.sk.

Key words: diabetes type 2, increased prevalence, obesity, free fatty acids, adipokines, leptin.

Present prevalence of diabetes

DM is a costly disease what regards human suffering and public expense. Disease onset tends to be insidious, delaying the diagnosis and management. Complications are microvascular (nephropathy, retinopathy, neuropathy) and macrovascular (atherosclerosis, myocardial infarction, stroke). DM accounts for almost 14 % of US health care expenditures. Direct medical and indirect expenditures attributable to DM in 2002 were in the US estimated at 132 billion dollars.

According to the International Diabetes Federation (1), highest prevalence of DM is in Saudi Arabia where wealth derived from oil is accompanied with frequent obesity. A dramatic rise in obesity in the US resulted in 11 % of adults being diabetics. In Europe, most DM is in the central region: Switzerland, Austria, Hungary and the Czech Republic (Fig. 1). One in ten adult Czechs is a diabetic. Slovak Republic and Italy have only little more DM than Poland and Russia. Scandinavians are less affected and least DM (only 2 %) is reported from Iceland.

Future trends in diabetes to year 2030

Increasing urbanization, aging populations, rise in obesity and falling levels of physical activity are all contributing to increases in DM worldwide (2). In the year 2000 there were about 170 million people in the world who had DM and this is projected to increase to 366 million diabetics by 2030 (3) (Tab. 1). Highest rise in DM is expected in the Middle East. DM will more than double in India, China, in Sub-Saharan Africa and in the Latin America. Less DM will cumulate in the economically af-

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fluent countries that already experienced a sharp rise in DM during the second half of the 20th century. These countries have public policies aimed at preventive measures.

Remarkably, least prominent will be DM increase in the post-communist countries. Demographic factors contributing to this trend may have roots in slower population growth and also in lower medium life expectancy. In the Eastern Europe and specifically in the Russian Federation and in Ukraine, sizeable proportion of the population dies of other causes before the impaired metabolism fully develops into glucose intolerance and DM.

Causes of the diabetes pandemic

Main factors contributing to DM is not only aging of the population but also increasing obesity and falling levels of physical activity. As the populations age, the prevalence of DM prominently increases (Fig. 2) (4).

Thus it is obvious that in the societies where affluence is a component of life style, living longer is associated with increased prevalence of DM. Life expectancy improved remarkably in the wealthy parts of the world during the 20th century. Populations started to live longer also in the less developed parts of the globe. In India the medium life expectancy in males was only 45 years in 1960. In 2005 it increased to 63 years.

However, we now recognize the body overweight and obesity to be the all important cause of DM and its metabolic consequences. Over recent years prevalence of obesity has escalated rapidly not only in the USA but also in many other countries to epidemic proportions, reflecting increased consumption of energy dense diets, compounded by declining levels of physical activity. Figure 3 illustrates the relationship of obesity with DM. It appears that in the US, up to 90% of DM in women is attributable to significant overweight. Likewise, women in the Latin America and in Central Europe have the body overweight clearly associated with DM. The antique ideal of female beauty, body fatness, takes its metabolic toll. While men with their predominantly abdominal obesity are relatively less prone to develop DM, the association with overweight is still remarkable, being at 70–85% in Europe and in North America.

From diabetes epidemiology to metabolic research

Fortunately, the alarming rise in DM has been met with important advances in our understanding of the pathogenesis of DM. Role of free fatty acids in hyperglycemia and diabetes

![Diagram of metabolic pathways](image-url)
glucose intolerance and DM. It has been well documented that excessive storage of body fat, especially in males along the waist is strongly associated with a metabolic syndrome, lipid abnormalities, decreased insulin sensitivity, atherosclerosis and DM.

Abdominal obesity is thus associated with development of DM which is characterized by an abnormal glucose and lipid metabolism due in part to resistance to the actions of insulin in skeletal muscle, liver and fat. The precise mechanism by which obesity leads to insulin resistance is not completely understood but may be related to several biochemical factors, such as free fatty acids, adipokines, leptin and other substances.

1) Free fatty acids

Free fatty acids (FFA) serve as physiologically important energy substrates and their release from the adipose tissue by lipolysis is regulated according to the energy demands of the body. FFA are increased in obese patients and contribute to diabetes. There are various mechanisms by which FFA promote glucose intolerance (Fig. 4). In the striated muscle which we now consider an important component of overall metabolic regulation, the consequence of excessive lipolysis is an increased FFA oxidation followed by reduced glucose utilization. Similar processes occur in the liver: FFA oxidation is increased, leading to enhanced gluconeogenesis.

FFA contribute to insulin resistance in all major insulin target organs (skeletal muscle, liver, endothelial cells). FFA also produce low-grade inflammation in skeletal muscle, liver, and fat, through activation of nuclear factor-kappaB, resulting in release of several proinflammatory cytokines which may contribute to DM (7). The mechanism through which FFA induce insulin resistance involves accumulation of triglycerides and activation of several serine/threonine kinases. Thus, increased supply of FFA causes insulin resistance in skeletal muscle and liver, which contributes to the development of DM (8). FFA mobilization influences release of tumor necrosis factor-alpha (TNF-alpha) and of adiponectin from adipose tissue. These metabolites also modulate insulin resistance (9, 10).

2) Adipokines

The adipose tissue in the body consists predominantly of the “white” fat that contributes to energy storage and wide ranging metabolic regulations. More recently there has been renewed interest in the “brown” fat that is present in much smaller focal deposits. Brown fat is affected by environmental temperature and has potentially beneficial effects. Most of metabolic research is related to the white fat.

White adipose tissue is now recognized to be an active participant in energy homeostasis and physiological functions. Macrophages are components of adipose tissue and actively participate in its activities. Adipose tissue is known to express and secrete a variety of products known as adipokines. The adipokines are cytokines (cell-to-cell signalling proteins). They include chemerin, interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), retinol binding protein 4 (RBP4), tumor necrosis factor-alpha (TNFα) and visfatin.

The current terminology refers to a cytokine as an immunomodulating agent. However, conflicting data exists about what is termed a cytokine and what is termed a hormone. Under the current terminology, adiponectin, leptin and resistin are not appropriately considered adipokines (cytokines) as they do not act on the immune system. The definition of an adipokine is a cytokine produced by an adipocyte.

Different adipocytokines have roles in the pathogenesis of insulin resistance. Obesity promotes inflammatory processes in the adipose tissue. This stimulates secretion of an array of proteins implicated in the impairment of insulin signaling (11). These proteins can be generally classified as proinflammatory or anti-inflammatory and they allow the organism to respond rapidly to an immune challenge by coordinating an appropriate immune response. In DM, the balance between proinflammatory and anti-inflammatory cytokines is shifted toward proinflammation (12, 13). The release of adipokines by either adipocytes or adipose tissue-infiltrated macrophages leads to a chronic subinflammatory state that could play a central role in the development of diabetes (14).

Lately, much attention has been focused on leptin (15). Leptin is an adipocyte-derived hormone that regulates energy balance through a wide range of functions. Increased circulating leptin, a marker of leptin resistance, is common in obesity and independently associated with insulin resistance. Obesity-induced leptin resistance injures numerous peripheral tissues, including pancreas and liver. In peripheral tissues, leptin induces fatty acid oxidation and glucose uptake. These metabolic responses are also triggered by adenosine monophosphate-activated protein kinase (AMPK) activation; this implices AMPK kinase as a candidate in the mediation of leptin responses.

3) Adenosine monophosphate-activated protein kinase (AMPK)

AMPK is an that enzyme plays a role in cellular energy homeostasis. The net effect of AMPK activation is stimulation of fatty acid oxidation, inhibition of adipocyte and lipogenesis, stimulation of skeletal muscle fatty acid oxidation and muscle glucose uptake, and modulation of insulin secretion by AMPK regulates the coordination of anabolic (synthesis and storage of glucose and fatty acids) and catabolic (oxidation of glucose and fatty acids) metabolic processes (16, 17). AMPK controls whole-body glucose homeostasis by regulating metabolism in multiple peripheral tissues, such as skeletal muscle, liver, adipose tissues, and pancreas – key tissues in the pathogenesis of DM.

Changes in AMPK signaling are important in the pathogenesis of diabetes. Sedentary life style impairs the AMPK signaling system, predictably leading to metabolic perturbations observed in DM. Increased recruitment of the AMPK signaling system, either by exercise or pharmaceutical activators, may be effective in correcting insulin resistance in patients where impaired glucose tolerance and diabetes result from defects in the insulin signaling cascade (18). Physical exercise and two major classes of antidiabetic drugs (biguanides and thiazolidinediones) have recently been reported to activate AMPK (16, 19). Pharmacological activation of AMPK makes this protein kinase a novel therapeutic target in the treatment of diabetes.
Conclusion

This review focuses on links between obesity, DM and recently described abnormalities in immune and cytokine responses of metabolism in a fat cell. Most effective intervention to block the pandemic of DM is to block the globalization of body mass increase in world populations (20). This is a very tall order, considering the rapid rise in childhood and adolescent obesity (21). World pandemic of DM is related to globalization of wealth. That includes mechanical devices to spare mankind from neck-breaking physical strain, a curse of the past millenia. Automobiles, television and computers, bringing convenience and comfort are formidable opponents of the struggle to return to a healthy life style. It is of interest that active commuting to work (walking, bicycling) resulted not only in better physical fitness in men and women but was also inversely associated with the body mass index, obesity, triglyceride and insulin levels (22).

Prevention that promotes a healthy life style is of primary importance but it clearly has to be supported by effective medications. Pharmacological research has an immense role to ameliorate the dire metabolic consequences of glucose intolerance and DM. Better understanding of both the physiology and pathophysiology of glucose and fat metabolism resulted in renewed scientific interest in fat metabolism and in gut hormones (23) and their role in regulation of pancreatic beta cells. Explosion of information on incretin hormones indicates their favorable potential. Mediating the beta cell function, incretins may counter progressive loss of beta cells and possibly reverse/halt progression of DM (24).

References


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