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An update on Diabetes Mellitus

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Abstract

The paper introduced diabetes mellitus and differentiated it with diabetes insipidus. The paper discussed epidemiology of type 1 and type 2 diabetes mellitus, pathogenesis, pathophysiology, complications. Diabetes mellitus has been increasing at alarming rate with ravaging consequence on the health of the patients and economic loss to the society.

Keywords: diabetes mellitus, pathogenesis, pathophysiology, complications.

Diabetes Mellitus

Diabetes mellitus (DM) is a disease condition in which the pancreas produces insufficient amount of insulin or in which the body cells fail to respond appropriately to insulin. Insulin is a hormone that helps the body's cells absorbs glucose (sugar) so it can be used as source of energy. People suffering from diabetes have high accumulation of sugar in their urine and blood causing problems associated with protein and fat metabolism which leads to excessive hunger, thirst, and urination. Diabetes insipidus, which is caused by lack of the hormone vasopressin, which controls the amount of urine secreted, is different from diabetes mellitus. Diabetes mellitus is characterized by decreased glucose tolerance resulting from a relative deficiency of insulin or a lack of sensitivity to the endogenous hormone. Insufficient insulin, or decreased insulin sensitivity, results in hyperglycemia. Long-term exposure of tissues to elevated ambient glucose concentrations is associated with the development of complications, including macro- and microvascular disease. Of particular concern are coronary heart disease, cerebrovascular disease, and the characteristic retinopathy, nephropathy, and neuropathy of this disorder.

In diabetes mellitus low insulin levels or poor responses to insulin prevent cells from absorbing glucose resulting to increase in the blood sugar level, when sugar level in the blood passes through the kidney, the organs that remove blood impurities, the kidneys cannot absorb all the excess glucose. The excessive glucose move to the urine, accompanied by water and electrolytes which are required by the cells to regulate the electric charge and low flow of water molecule across the cell membrane. This causes frequent urination to get rid of the additional water drawn into urine; excessive thirst to trigger replacement

of loss of water, and hunger to replace the glucose lost in urination. Additional symptoms may include blurred vision, nausea, vomiting, irritability weight loss, weakness and fatigue.

Epidemiology and etiology of type 1 diabetes mellitus (IDDM)

Type 1 diabetes represents around 10% of all cases of diabetes, affecting approximately 20 million people worldwide (American Diabetes Association, 2001).Although type 1 diabetes affects all age groups, the majority of individuals are diagnosed either at around the age of 4 to 5 years, or in their teens and early adulthood (Blood *et al*., 1975). The incidence of type 1 diabetes is rising. Across Europe, the average annual increase in the incidence in children under 15 years is 3.4% (EURODIABACE study Group, 2000), with the steepest rise in those under 5 years old (Karvonen *et al*., 1999). Type 1 diabetes is the result of an autoimmune reaction to proteins of the islets cells of the pancreas (Holt, 2004).There is a strong association between IDDM and other endocrine autoimmunity (for example, Addison disease) and an increased incidence of autoimmune diseases are seen in family members of IDDM patients. The three types of auto antibodies known are:

i) Islet cell cytoplasmic antibodies (ICCA): The primary antibodies found in 90% of type 1 diabetics are against islet cell cytoplasmic proteins. The presence of ICCA is a highly accurate predictor of future development of IDDM.

ii) Islet cell surface antibodies (ICSA): Auto antibodies directed against islets cell surface antigens (ICSA) have also been described in as many as 80% of type 1 diabetics. Some patients with type 2 diabetes have been identified, which are ICSA positive.

iii) Specific antigenic targets of islet cells: Antibodies to glutamic acid decarboxylase (GAD) have been identified in over 80% of patients newly diagnosed with IDDM. Anti GAD antibodies decline over time in type 1 diabetics. The presence of anti GAD antibodies is a strong predictor of the future development of IDDM in high risk populations. Anti insulin antibodies (IAAs) have been identified in IDDM patients and in relatives at risk to developing IDDM. These IAAs are detectable even before the onset of insulin therapy in type 1 diabetics. IAA is

iv) detectable in around 40% of young children with IDDM (Raju and Raju, 2010).

Pathogenesis of type 1 diabetes mellitus

Type 1 diabetes mellitus is a chronic autoimmune disease associated with selective destruction of insulin-producing pancreatic β-cells. The onset of clinical disease represents the end stage of β-cell destruction leading to type 1 diabetes mellitus. Al Homsi and Lukic (1992) explained that several features characterize type 1 diabetes mellitus as an autoimmune disease:

1. Presence of immuno-competent and accessory cells in infiltrated pancreatic islets;
2. Association of susceptibility to disease with the class II (immune response) genes of the major histocompatibility complex (MHC; human leucocyte antigens HLA);
3. Presence of islet cell specific autoantibodies;
4. Alterations of T cell mediated immunoregulation, in particular in CD4+ T cell compartment;
5. The involvement of monokines and TH1 cells producing interleukins in the disease process;
6. Response to immunotherapy and;
7. Frequent occurrence of other organ specific auto- immune diseases in affected individuals or in their family members.

The pathogenesis of selective β-cell destruction within the islet in type 1 DM is difficult to follow due to marked heterogeneity of the pancreatic lesions. At the onset of overt hyperglycemia, a mixture of pseudoatrophic islets with cells producing glycogen (a cells), somatostatin (d cells) and pancreatic poly-peptide (PP cells), normal islets, and islets containing both b-cells and infiltrating lymphocytes and monocytes may be seen (Al-Homsi and Lukic, 1992). Lymphocytic infiltration is found only in the islet containing residual β-cells and is likely that the chronicity with which type 1 DM develops reflects this heterogeneity of islet lesions (Al-Homsi and Lukic, 1992). In contrast to this chronicity in the natural history of the disease, β-cells are rapidly destroyed when pancreas is transplanted from identical twin donors into their long term diabetic twin mates in the absence of

immunosuppression. In these cases, massive insulitis develops rapidly with infiltrating T lympocytes indicating an anamnestic autoimmune reaction (Al Homsi and Lukic, 1992). In addition, this observation also indicates that the chronic time course in type 1 DM (but not in a transplanted pancreas) is a consequence of down regulatory phenomena taking part in immunopatho-genesis of the disease (Al Homsi and Lukic, 1992). Activation of islet antigen - specific CD4+ Tcells appear to be absolute prerequisite for the development of diabetes in all animal models of type 1 DM (Gill and Haskins, 1993). CD4+ islet specific T-cell clones derived from diabetic NOD mice, when injected into prediabetic or non diabetes prone Fl mice, induce insulitis and diabetes. It was also reported that CD4+ T cells are sufficient to induce insulitis while CD8+ T cells contribute to the severity of the damage.These findings together with the evidence that insulitis in chronic graft versus host disease may occur in the absence of CD8+ T cells suggest that CD4+ T cells may be the only immunocompetent cells required in the disease process. However, it seems that only one subset of CD4+ T cells are responsible for disease induction. CD4+T cell bearing alloantigen RT6 are absent in diabetes prone BB rats and appear to protect AO rats from MLD-STZ induced diabetes. Down-regulation of diabetogenic autoimmune response by the spleen cells derived from animals treated with adjuvants could also be explained by CD4+ T cell subsets interplay (Ulaeto *et al*., 1992). High level of THI type cytokines IL-2 and interferon g are found to correlate or/and to enhance induction of autoimmune diabetes in experimental models (Fowell *et al*., 1991; Campbell *et al*., 1991). The TH-1 type cells, and in particular their product IFN-g, activate macrophages. In animal, models of type 1 DM electron microscopic studies of pancreata showed that macrophages are the first cell type invading the islets (Kolb-Bachofen *et al*., 1988). In vitro studies and studies on perfused pancreas suggest that Interleukin 1 (IL-1) and tumor necrosis factor (TNFa), two cytokines mainly produced by macrophages, induce structural changes of β-cells and suppression of their insulin releasing capacity (Mandrup-Poulsen *et al*., 1987). However, it seems that IL-1 and TNF do not contribute appreciably to the cytotoxic activity of macrophages (Kroncke *et al*., 1991). Interferon g is also a powerful activator of macrophages for nitric oxide synthesis. Recently, evidence has been provided indicating that NO synthase activity is involved in diabetes development (Lukic *et al*., 1991). These data indicated, for the first time, that nitric oxide may be a pathogenic factor in autoimmunity and suggested a possibility that a new class of immunopharmacological agents, capable of modulating nitric oxide secretion may be tested in the prevention of type 1 DM development (Kolb and Kolb-Bachofen, 1992).

Pathophysiology of type 1 diabetes- insulin dependent diabetes mellitus (IDDM)

The autoimmune destruction of pancreatic β-cells, leads to a deficiency of insulin secretion which results in the metabolic derangements associated with IDDM. In addition to the loss of insulin secretion, the function of pancreatic α-cells is also abnormal and there is excessive secretion of glucagon in IDDM patients. Normally, hyperglycemia leads to reduced glucagon secretion; however, in patients with IDDM, glucagon secretion is not suppressed by hyperglycemia (Raju and Raju, 2010). The resultant inappropriately elevated glucagon levels exacerbate the metabolic defects due to insulin deficiency. The most pronounced example of this metabolic disruption is that patients with IDDM rapidly develop diabetic ketoacidosis in the absence of insulin administration. Although insulin deficiency is the primary defect in IDDM, there is also a defect in the administration of insulin. There are multiple biochemical mechanisms that account for impairment of tissue's response to insulin. Deficiency in insulin leads to uncontrolled lipolysis and elevated levels of free fatty acids in the plasma, which suppresses glucose metabolism in peripheral tissues such as skeletal muscle (Raju and Raju, 2010). This impairs glucose utilization and insulin deficiency also decreases the expression of a number of genes necessary for target tissues to respond normally to insulin such as glucokinase in liver and the GLUT 4 class of glucose transporters in adipose tissue. Raju and Raju (2010) explained

that the major metabolic derangements, which result from insulin deficiency in IDDM, are impaired glucose, lipid and protein metabolism which are explained in details as follows:

Effects of type 1 diabetes on glucose metabolism

Uncontrolled IDDM leads to increased hepatic glucose output. First, liver glycogen stores are mobilized then hepatic gluconeogenesis is used to produce glucose. Insulin deficiency also impairs non hepatic tissue utilization of glucose. In particular in adipose tissue and skeletal muscle, insulin stimulates glucose uptake. This is accomplished by insulin mediated movement of glucose transporters proteins to the plasma membrane of these tissues. Reduced glucose uptake by peripheral tissues in turn leads to a reduced rate of glucose metabolism. In addition, the level of hepatic glucokinase is regulated by insulin. Therefore, a reduced rate of glucose Phosphorylation in hepatocytes leads to increased delivery to the blood. Other enzymes involved in anabolic metabolic metabolism of glucose are affected by insulin.The combination of increased hepatic glucose production and reduced peripheral tissues metabolism leads to elevated plasma glucose levels. When the capacity of the kidneys to absorb glucose is suppressed, glucosuria ensues. Glucose is an osmotic diuretic and an increase in renal loss of glucose is accompanied by loss of water and electrolyte. The result of the loss of water (and overall volume) leads to the activation of the thirst mechanism (polydipsia). The negative caloric balance, which results from the glucosuria and tissue catabolism leads to an increase in appetite and food intake that is polyphagia (Raju and Raju, 2010).

Effect on lipid metabolism

One major role of insulin is to stimulate the storage of food energy in the form of glycogen in hepatocytes and skeletal muscle, following the consumption of a meal. In addition, insulin stimulates hepatocytes to synthesize and store triglycerides in adipose tissue. In uncontrolled IDDM there is a rapid mobilization of triglycerides leading to increased levels of plasma free fatty acids. The free fatty acids are taken up by numerous tissues (except the brain) and metabolized to provide energy. In the absence of insulin, malonyl COA levels fall, and transport of fatty acyl-COA into the mitochondria increases. Mitochondrial oxidation of fatty acids generates acetyl COA that can be further oxidized in the TCA cycle. However, in hepatocytes the majority of the acetyl COA is not oxidized by the TCA cycle but is metabolized into the ketone bodies (acetoacetate and b-hydroxybutyrate). These ketone bodies are used for energy production by the brain, heart and skeletal muscle. In IDDM, the increased availability of free fatty acids and ketone bodies exacerbates the reduced utilization of glucose, furthering the ensuring hyperglycaemia. Production of ketone bodies in excess of the body's ability to utilize them leads to ketoacidosis. A spontaneous breakdown product of acetoacetate is the acetone that is exhaled by the lungs, which gives a distinctive odor to the breath. Normally, plasma triglycerides are acted upon by lipoprotein lipase (LPL) that requires insulin. LPL is a membrane bound enzyme on the surface of the endothelial cells lining the vessels, which allows fatty acids to be taken from circulating triglycerides for storage in adipocytes (Raju and Raju, 2010). The absence of insulin results in hypertriglyceridemia. Insulin regulates the synthesis of many genes, either positively or negatively, which affect overall metabolism. Insulin has an overall effect on protein metabolism, increasing the rate of protein synthesis and decreasing the rate of protein degradation. Thus insulin deficiency will lead to increased catabolism of protein. The increased rate of proteolysis leads to elevated concen-tration of amino acids in plasma (Raju and Raju, 2010).Glucogenic amino acids serve as precursors for hepatic and renal glyconeogenesis, which further contributes to the hyperglycaemia seen in IDDM.

Epidemiology And Etiology Of Type 2 Diabetes (NIDDM)

Type 2 diabetes is the predominant form of diabetes and accounts for at least 90% of all cases of diabetes mellitus. The rise in prevalence is predicted to be much greater in developing than in

developed countries (69 versus 20%) (Shaw *et al*., 2010).

In developing countries, people aged 40 to 60 years (that is, working age) are affected most, compared with those older than 60 years in developed countries (Shaw *et al*., 2010). This increase in type 2 diabetes is inextricably linked to changes towards a Western lifestyle (high diet with reduced physical activity) in developing countries and the rise in prevalence of overweight and obesity (Chan *et al*., 2009; Colagiuri, 2010). There are approximately 1.4 million people with diagnosed type 2 diabetes in the UK (Bennett *et al*., 1995).

The incidence of diabetes increases with age, with most cases being diagnosed after the age of 40 years. This equates to a lifetime risk of developing diabetes of 1 in 10 (Neil *et al*., 1987). Type 2 diabetes is a heterogeneous disorder caused by a combination of genetic factors related to impaired insulin secretion, insulin resistance and environmental factors such as obesity, over eating, lack of exercise, and stress as well as aging (Kaku, 2010). It is typically a multifactorial disease involving multiple genes and environmental factors to varying extents (Holt, 2004).

Type 2 diabetes is the common form of idiopathic diabetes and is characterized by a lack of the need for insulin to prevent ketoacidosis. It is not an autoimmune disorder and the susceptible genes that predispose to NIDDM have not been identified in most patients. This could be due to the heterogeneity of the genes responsible for the susceptibility to NIDDM.

Pathogenesis of type 2 diabetes Mellitus

Under normal physiological conditions, plasma glucose concentrations are maintained within a narrow range, despite wide fluctuations in supply and demand, through a tightly regulated and dynamic interaction between tissue sensitivity to insulin (especially in liver) and insulin secretion (DeFronzo, 1988). In type 2 diabetes these mechanisms break down, with the consequence that the two main pathological defects in type 2 Diabetes are impaired insulin secretion through a dysfunction of the pancreatic β-cell, and impaired insulin action through insulin resistance (Holt, 2004). Type 2 diabetes mellitus has a greater genetic association than type 1 DM, the pathogenesis of type 2 diabetes mellitus is characterized by impaired insulin secretion and insulin resistance as shown in Figure 2. The 100% concordance rate in identical twins is thought to be over-estimated, due to a selection or reporting bias. A population based twin study in Finland has shown a concordance rate of 40%, and environmental effect may be a possible reason for the higher concordance rate for type 2 diabetes mellitus than for type 1 diabetes mellitus (Kaprio *et al*., 1992). Type 2 diabetes mellitus affects 1 to 2% of Caucasians (Cook *et al*., 1993) but it is much higher in some ethnic groups such as Pima Indians (Knowler *et al*., 1990) and Arabs (Richens *et al*., 1988) and approaches 50% in South India. This indicates that genetic factors are more important than environmental factors. Except for the onset of maturity diabetes in young (MODY) individuals, the mode of inheritance for type 2 diabetes mellitus is unclear. MODY, inherited as an autosomal dominant trait, may result from mutations in glucokinase gene on chromosome 7p. Glucokinase is a key enzyme of glucose metabolism in beta cells and the liver (Froguel *et al*., 1993; Hattersley *et al*., 1992). MODY is defined as hyperglycemia diagnosed before the age of twenty-five years and treatable for over five years without insulin in cases where islet cell antibodies (ICA) are negative and HLA-DR3 and DR4 are heterozygous. MODY is rare in Caucasians, less than 1%, and more common in blacks and Indians, more than 10% of diabetics. Chronic complications in MODY were thought to be uncommon but later were found to be more common, indicating its heterogeneity.

Considering MODY as a separate entity may masquerade its association with specific genetic diseases; and without a definite genetic marker, it should be treated as type 1 DM (Tattershall, 1991). Identification of a nonsense mutation in the glucokinase gene and its linkage with MODY was reported for the first time in a French family, implicating a mutation in a gene involved in glucose metabolism in the pathogenesis of type 2

diabetes mellitus (Vionnet *et al*., 1992). Later, sixteen mutations were identified in 18 MODY families. They included 10 mutations that resulted in an amino acid substitution, 3 that resulted in the synthesis of truncated protein, and 3 that affected RNA processing. Hyperglycemia in these families was usually mild and began in childhood, whereas the hyperglycemia of MODY families without glucokinase mutations usually appeared after puberty (Froguel *et al*., 1993).

Molecular genetic studies in type 2 diabetes mellitus, with the exception of MODY, have not been as successful as in type 1 diabetes mellitus. Mutations in the insulin gene lead to the synthesis and secretion of abnormal gene products, leading to what are called insulinopathies (Gabbay, 1980). Most of the patients with insulinopathies have hyperinsulinemia, inherited in autosomal fashion, heterozygous for normal and mutant alleles, and normally respond to exogenous insulin administration. Al Homsi and Lukic (1992) explained that most insulin gene mutations lead to:

(a) Abnormal insulins - Such as insulins Chicago and Wakayama where the mutation leads to an amino acid replacement at an important site for receptor interaction; or

(b) The mutation may interfere in the proinsulin processing to insulin (Chan *et al*., 2009).

The association of the polymorphic (hypervariable) 5' flanking region of the human insulin gene and type 2 diabetes mellitus is lacking in some population groups, indicating that it may be one of many factors in a multifactorial disease. Even MODY patients have shown no association with this region. It was mentioned earlier that there is a strong association between HLA-DR3/4 and type 1 diabetes mellitus. It was also reported that such an association is present with type 2 diabetes mellitus, rendering HLA-DR3/4 markers for beta cell destruction in these patients (Richens *et al*., 1988; Tattershall, 1991). Pancreatic abnormalities in islet secretory cells in type 2 diabetes mellitus are noted in beta, alpha and delta cells of the islets. Defects involving insulin secretion include relative decrease in basal secretion, decreased first and second phases of insulin response, glucose insensitivity and amino acid hypersensitivity of insulin release. The number and volume of beta cells are usually decreased to half the normal and the alpha cell mass is increased leading to hyperglucagonemia. The islets exhibit hyalinization and amyloid deposition, containing islet amyloid polypeptide (IAPP) or amylin. This is a minor secretory peptide of the beta cells released along with insulin and C-peptide, but its role in the pathogenesis of type 2 DM is not well understood (Steiner *et al*., 1991). This amylin is thought to produce insulin resistance (Molina *et al*., 1990). IAAP is reduced with progression of type 2 DM (Enoki *et al*., 1992). Intimate contact between beta cells and Amyloid deposit in type 2 DM is noted by electron microscopy (Westermark, 1973). Away from the islets in the exocrine pancreas, fatty infiltration and diffuse fibrosis are evident. Defective islet cell function is the primary event which may be due to an autoimmune reaction producing hyperglycemia in type 2 DM (Zawala *et al*., 1992). The insulin receptor gene is located on chromosome 19 and it encodes a protein having alpha and beta subunits including the transmembrane domain and the tyrosine kinase domain (Kahu and White, 1988). Mutations affecting the insulin receptor gene have been identified and their association with type 2 diabetes mellitus and type A insulin resistance is recognized. Type A insulin resistance is hereditary and type B is an autoimmune disorder (Levy and Hug, 1993). Restriction fragment length polymorphism (RFLP) analysis of the insulin receptor gene (Ohagi *et al*., 1992), erythrocyte glucose transporter gene, and HLA genes, were not found useful as genetic markers for type 2 DM. Insulin resistance is insufficient to cause overt glucose intolerance, but may play a significant role in cases of obesity where there is known impairment of insulin action. Insulin resistance by itself may be a secondary event in type 2 DM, since it is also found in non-diabetic obese individuals. Insulin secretion defect may be the primary event, presenting as impaired pulsatile secretion of insulin. Hence, hyperglycemia is an inducer as well as a consequence of impaired islet cell function and insulin resistance. Many factors contribute to the

insulin insensitivity including obesity and its duration (Evephart *et al*., 1992), age, lack of exercise, increased dietary fat and decreased fibres and genetic factors.

Fish oil is found to prevent insulin resistance in animals, but not in humans. It has a protective effect against thrombosis and vasospasm in type 2 DM (McVeigh *et al*., 1993). Insulin resistance in type 2 DM is not totally clear, it may involve reduced insulin receptor number, it may be secondary to hyperinsulinemia and hyperglycemia, (Vuorinen-Markkola *et al*., 1992) or it may result from reduced tyrosine kinase activity (Comi *et al*., 1987; Bonadonna *et al*., 1993; Sten-linder *et al*., 1993) or even abnormalities distal to the receptor involving glucose transporter proteins through a family of glucose transporter genes (Muechler,1990). The GLUT2 gene expressed in liver and pancreatic beta cells, and GLUT4, expressed in skeletal muscle and adipocytes, are strong candidate genes for the genetic susceptibility to type 2 DM. Analysis of these two glucose transporter genes, in addition to GLUT1, encoding for the brain/erythrocyte glucose transporter, has yielded, in Caucasians, no association of any RFLP marker on haplotype with either type 2 DM or obesity (Oelbaum, 1992). Obesity has genetic as well as environmental causes. It has a strong effect on the development of type 2 DM (Bjorntorp, 1992; Haffner *et al*., 1992) as it is found in Western countries (NDDG, 1979; Wilson *et al*., 1981) and some ethnic groups such as Pima Indians (Joffe *et al*., 1992; Knowler *et al*., 1993). Obesity is more than just a risk factor; it has a causal effect in the development of type 2 DM against a genetic background. The evolution from obesity to type DM results from a succession of pathophysiological events:

(a) Augmentation of the adipose tissue mass, leading to increased lipid oxidation;
(b) Insulin resistance noted early in obesity, revealed by euglycemic clamp, as a resistance to insulin mediated glucose storage and oxidation, blocking the function of the glycogen cycle;
(c) Despite maintained insulin secretion, unused glycogen prevents further glucose storage leading to type 2 DM;
(d) Complete b-cell exhaustion appears later (Felber, 1992). Type 2 DM patients have a characteristic shoulder, girdle-truncal obesity. Nutrient composition has also been found to be a risk factor for developing type 2 DM, where increased fat and decreased carbohydrate consumption have contributed to hyperinsulinemia of obesity. Dietary fibres, both soluble and insoluble, improve type 2 DM. It is also found that simple sugars do not directly cause diabetes. Deficiency of micronutrients, such as chromium and copper, is found to be an important cause of type 2 DM in a minority of cases. Stress has also been thought to induce type 2 DM. Actually, obesity and over availability of food rather than stress are the contributing factors to type 2 DM. Therefore, when permanent change in dietary habits is established, some people should be allowed to escape the "life-long" diagnosis of type 2 DM (Akinmokun *et al*., 1992).

Environmental factors in the pathogenesis type 2 diabetes

Aging, obesity, insufficient energy consumption, alcohol drinking, smoking, etc are independent risk factors of pathogenesis of type 2 diabetes. Obesity (particularly visceral fat obesity) due to a lack of exercise is accompanied by a decrease in muscle mass, induces insulin resistance, and is closely associated with the rapid increase in the number of middle and high aged patients. The changes in dietary energy sources, particularly the increase in fat intake, the decrease in starch intake, the increase in the consumption of simple sugars, and the decrease in dietary fiber intake, contribute to obesity and cause deterioration of glucose tolerance. Even mild obesity (Body mass index (BMI) < 25) causes a 4 to 5 fold increase in risk of developing diabetes, if accompanied by the increase in visceral fat mass. People prone to visceral fat accumulation due to hyperalimentation, and risk factors for diabetes are linked to the accumulation of visceral fat.

Pathophysiology of type 2 diabetes (NIDDM)

On the basis of oral glucose tolerance testing the essential elements of NIDDM can be divided into four distinct groups:

i) Those with normal glucose tolerance.
ii) Clinical diabetes (called impaired glucose tolerance)
iii) Diabetes with minimal fasting hyperglycemia (fasting plasma glucose less than 140 mg/dl)
iv) Diabetes mellitus in association with overt fasting hyperglycemia (fasting plasma glucose greater than 140 mg/dl).

The individuals with impaired glucose tolerance have hyperglycemia inspite of having highest levels of plasma insulin, indicating that they are resistant to the action of insulin. In the progression from impaired glucose tolerance to diabetes mellitus, the level of insulin declines indicating that patients with NIDDM have decreased insulin secretion. Insulin resistance and insulin deficiency are common in the average NIDDM patients (Holt, 2004).

Insulin resistance is the primary cause of NIDDM, however some researcher contend that insulin deficiency is the primary cause because a moderate degree of insulin resistance is not sufficient to cause NIDDM (Raju and Raju, 2010). Most patients with the common form of NIDDM have both defects. Recent evidence has demonstrated a role for a member of the nuclear hormone receptor super family of proteins in the etiology of type 2 diabetes (Raju and Raju, 2010). Relatively new classes of drugs used to increase the sensitivity of the body to insulin are the thiazolidinedione drugs. These compounds bind to and alter the function of the peroxisome proliferators-activated receptor g (PPARg). PPARg is also a transcription factor and when activated, binds to another transcription factor known as the retinoid x receptor (RXR). When these two proteins are complexed a specific set of genes becomes activated.

PPARg is a key regulator of adipocyte differentiation; it can induce the differentiation of fibroblasts or other undifferentiated cells into mature fat cells. PPARg is also involved in the synthesis of biologically active compounds from vascular endothelial cells and immune cells (Raju and Raju, 2010).

Conclusion

Diabetes mellitus is a disease condition in which the pancreas produces insufficient amount of insulin or in which the body cells fail to respond appropriately to insulin. Insulin is a hormone that helps the body's cells absorbs glucose (sugar) so it can be used as source of energy. People suffering from diabetes have high accumulation of sugar in their urine and blood causing problems associated with protein and fat metabolism which leads to excessive hunger, thirst, and urination. There should more researches targeting permanent cure and prevention of diabetes mellitus because of high morbidity and mortality rate.

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