Journal of Applied Pharmaceutical Science

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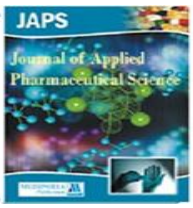

ISSN: 2231-3354
Received: 01-06-2011
Revised on: 04-06-2011
Accepted: 10-06-2011

Review: Cardio vascular complication of Diabetes Mellitus

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ABSTRACT

Now day diabetes is very common world wild disease. Basically two type of diabetes: Type-I and Type-II. Various short term complications like diabetec ketoacidosis, hyperosmolar nonketotic coma and hypoglycemia and long term complication like diabetec neuropathy, diabetec retinopathy, diabetec nepheropathy, diabetec microangiopathy, heart disease and stroke occur due to diabetes mellitus. Cardiovascular complication mainly occurs by either increase of glucose by activation of protein kinase, rennin angeotensin system, advance glycation end-product theory i.e. AGE-RAGE or by metabolic syndrome and insulin resistance mechanism which precipitates obesity, physical inactivity and genetic susceptibility. Insulin secretion is decreases with advancing age which may be accelerate by genetic factor. Insulin resistance led to onset of Type-II diabetes mellitus and is commonly associated with other cardio vascular risk factors like dysbetalipidema, hypertension and prothombic factor. Evaluation of these major risk factors is very necessary. Predisposing risk factors are body weight and fat distribution in the body, physical activity and family history. Detection of clinical and sub clinical cardiovascular disease in diabetic patient. Evaluation of factor such as a stress testing for coronary heart disease, non-invasive evaluation of cardiac function, evaluation of autonomic dysfunction, detection of sub clinical cardio vascular disease and it treated by changing life style or by using insulin matrix.

Key words: Complications, Mechanism, Various systems play role in this mechanism, Management, insulate matrix.

INTRODUCTION

Diabetes Mellitus

Diabetes mellitus is a disorder in which the body is unable to metabolize carbohydrates properly. The disease is characterized by excessive amounts of sugar in the blood and urine; inadequate production and/or utilization of insulin; and by thirst, hunger and loss of weight (Rang et al., 1999).

Complications of Diabetes Mellitus

Diabetic complications are of two types, they are short term complication and long term complication. Short term complications are like diabetic ketoacidosis, hyperosmolar non ketotic coma and hypoglycemia (Charles et al., 2010; Goodman et al., 2006). Long term complications are like diabetic nephropathy, diabetic retinopathy, diabetic micro angiopathy, diabetic neuropathy, heart disease stroke and Arteriosclerosis. Prevalence of diabetes mellitus is much higher in Asian countries then European countries. One fourth to one half of patients with diabetes develop cardio vascular complication. An approximately 58.9% to 77.8% of all diabetics will develop evidence of cardio vascular complication. There are different types of cardio vascular complications in

in diabetics are Atherosclerotic chronic heart disease, diabetic cardiomyopathy, stroke and renal disease.

Mechanism Involved In Cardiovascular Complication

Increase of glucose

Glucose is the main cause for micro vascular complications of diabetes like retinopathy, nephropathy and neuropathy. The negative role of hyperglycemia on endothelial functions and pathological changes occurring in diabetes is well established. There are four major molecular signaling mechanisms activated by hyperglycemia in endothelial cells (Imenta et al., 1995). These include,

1. Activation of PKC
2. Increased hexosamine pathway flux
3. Increased advanced glycation end product formation and
4. Increased polyol pathway flux.

Most cardiovascular risk factors are affected directly by an acute increase of glycemia in individuals with diabetes and are modified in the postprandial phase. LDL oxidation in diabetes is related to metabolic control (Tsai et al., 1994) and it has been shown in type 2 diabetic patients that after meals, LDL oxidation increases (Tsai et al., 1994) and that this phenomenon is in strict relationship with the degree of hyperglycemia (Enkins et al., 1996). Endothelial function is altered early in diabetes. It has been demonstrated that in diabetic subjects, the vasodilating response to stimuli is diminished and that this anomaly is related to glycemic control (Diwadkar et al., 1999). In vivo studies have demonstrated that hyperglycemic spikes induce, in both diabetic and normal subjects, an endothelial dysfunction (Ceriello et al., 1999).

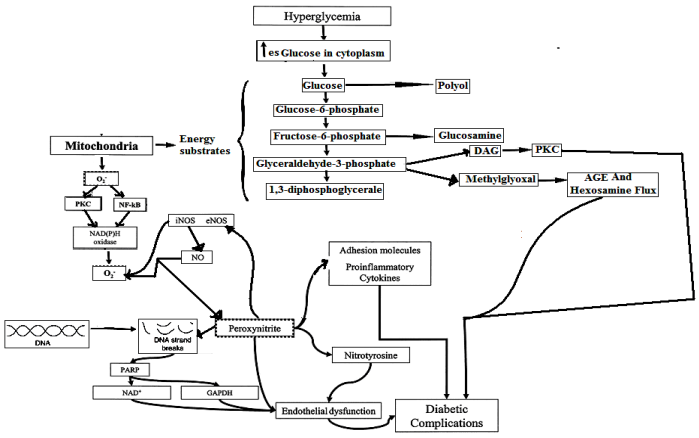

Fig 1.1: Described mechanism involved in cardio vascular complication.

This effect of hyperglycemia is probably linked with a reduced production/bioavailability of nitric oxide (NO), since hyperglycemia-induced endothelial dysfunction is counterbalanced by arginine (Jorgensen et al., 1998). Furthermore, it is very interesting that a rapid decrease of flow-mediated vasodilation has been shown in the postprandial phase in type 2 diabetic patients and that the decrease correlated inversely with the magnitude of postprandial hyperglycemia (Marfella et al., 1995). The possible role of hyperglycemia in the activation of blood coagulation has previously been reviewed (Kawano et al., 1999). It emerges that acute glycemic variations are matched with a series of alterations of coagulation that are likely to cause a thrombosis. This tendency is documented by studies demonstrating that when hyperglycemia is induced, a shortening of the fibrinogen half-life (Giugliano et al., 1997) and an increase in fibrinopeptide A (Shige et al., 1999; Ceriello et al., 1993), in fragments of prothrombin (Jones et al., 1979), in factor VII (Jones et al., 1985) and in platelet aggregation (Ceriello et al., 1989) can be found in both normal and diabetic subjects. These data indicate that during experimental hyperglycemia, the coagulation is activated. It is interesting that it already has been documented that in diabetic subjects, postprandial hyperglycemia causes an overproduction of thrombin (Ceriello et al., 1995). This phenomenon is strictly dependent on the glycemic levels reached (Ceriello et al., 1995). Adhesion molecules regulate the interaction between endothelium and leukocytes (Ceriello et al., 1988). They participate in the process of atherogenesis because their greater expression would imply an increase in the adhesion of leukocytes (monocytes in particular) to the endothelium (Sakamoto et al., 2000). It is well known that this is considered one of the early stages of the process leading to atheromatous lesion. Among the various proadhesive molecules, intracellular adhesion molecule (ICAM)-1 has received particular interest. Increase in the circulating form of this molecule has been demonstrated in subjects with vascular disease (Ceriello et al., 1996) and with diabetes, with or without vascular disease (Ruosladti et al., 1991; Lopes-Virella et al., 1992). These increases have been considered the indication of the activation of the atherogenic process. The soluble form of ICAM-1 is stored in the cells and can be quickly expressed outside them as a consequence of various stimuli. It has been demonstrated that acute hyperglycemia in both normal and diabetic subjects is a sufficient stimulus for the circulating level of ICAM-1 to increase, thus activating one of the first stages of the atherogenic process (Blann et al., 1994; Cominacini et al., 1995). The concept of atherosclerosis as an inflammatory disease even in diabetes is now well established (Ceriello et al., 1996). Studies support the evidence that an acute hyperglycemia during a hyperglycemic clamp (Ceriello et al., 1998) or in the postprandial state (Marfella et al., 2000) can increase the production of plasma interleukin- 6, tumor necrosis factor-α, and interleukin-18 which can causes various diabetic complication including cardio vascular disease.

Various systems play role in this mechanism

Renin angiotensin Aldosterone system

Aldosterone is a steroid hormone that is primarily produced in the zona glomerulosa, the outer layer of the adrenal cortex. Classical effects of aldosterone are to promote sodium retention and potassium loss by the kidney, although it exerts similar but lesser effects on the colon, sweat and salivary glands. The three principal factors that regulate aldosterone secretion are Ang II, ACTH and potassium. Changes in aldosterone secretion in response to changes in volume status or alteration in salt intake are

mediated primarily by Ang II. Most patients with type 2 diabetes have normal Ang II regulation of aldosterone and normal circulating level of this hormone (Sowers et al., 1995). However, in diabetic patients with dysautonomia, usually associated with long-standing diabetes, there may be impaired conversion of the precursor of renin, prorenin, to renin by the diabetic kidney (Sowers et al., 2001). Hypertension in diabetes is characterized by reduced nitric oxide (NO)-mediated vasorelaxation, reduced baroreflex sensitivity and enhanced sympathetic activity and abnormalities that are promoted by aldosterone (Sowers et al., 2001; Sacco et al., 2003; Rocha et al., 1999).

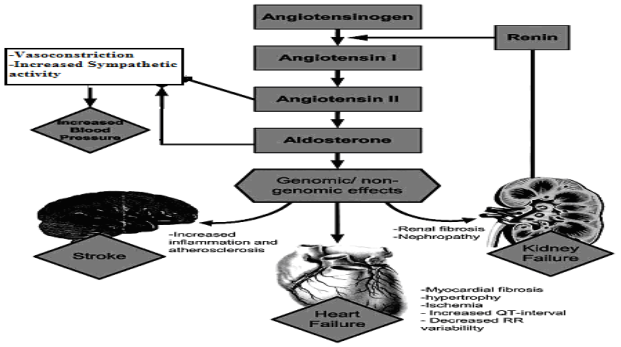

Fig 1.2: Described effects of aldosterone on the brain, heart and kidney.

Aldosterone appears to have effects on the brain, the heart, vasculature and kidneys that lead to elevated blood pressure. These changes include enhanced sympathetic nervous system activity, reduced vascular compliance and endothelial-derived vasorelaxation, increases in volume expansion, reduced serum potassium and increases in left ventricular mass and cardiac output (Duprez et al., 2000; The Lancet, 2000). Aldosterone antagonists have been shown to substantially reduce blood pressure in patients as well as in animal models with hypertension (Yee et al., 1998). Aldosterone antagonists also appear to have considerable potential in treating the diabetic patient with hypertension. There are data in the stroke-prone spontaneously hypertensive rats (SHRSP), suggesting that aldosterone antagonists may also reduce strokes.

Aldosterone and hypertension in diabetic patients

Hypertension in diabetes is characterized by reduced nitric oxide (NO)-mediated vasorelaxation, reduced baroreflex sensitivity and enhanced sympathetic activity and abnormalities that are promoted by aldosterone.

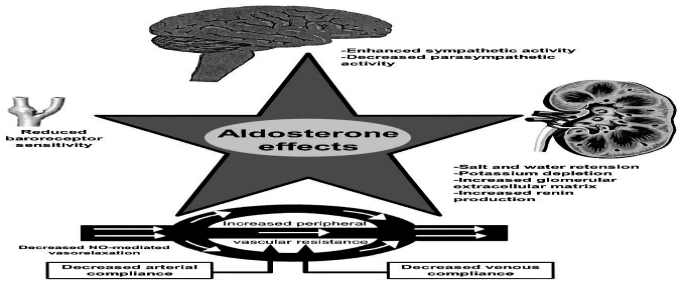

Fig 1.3: Described management of cardio vascular complication

Protein kinase c (pkc)

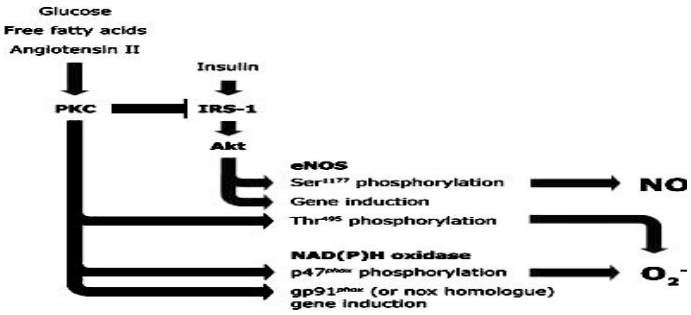

Fig 1.4: Described overview of PKC-dependent activation and induction of eNOS and vascular NAD(P)H oxidase (Farlane et al., 2003).

Glucose and free fatty acids stimulates PKC. PKC through IRS-1 stimulate phosphorylation and NAD(P)H oxidase (Griendling et al., 2000). Angiotensin II increases NAD(P)H oxidase gene expression. Vascular cells express several catalytic subunit isoforms, including nox2.The reactive oxygen species theory in the diabetic state, the generation of ROS is enhanced through the processes of glucose autoxidation, polyol pathway, prostanoid synthesis and protein glycation (Lassegue et al., 2003; Baynes et al., 1991). Hyperglycemia also attenuates anti-oxidative mechanisms (Giugliano et al., 1996). ROS formed in the diabetes associated autoxidation processes are superoxide anions, the hydroxyl radicals and hydrogen peroxides. ROS cause lipid peroxidation and damage proteins by chemical modifications through cross-linking and fragmentation. Therefore, oxidative stress has been considered to contribute to the pathological processes of diabetic complications (Lassegue et al., 2003; Giugliano et al., 1996).

The advanced glycation end-product theory

The glycation process, otherwise known as the Maillard reaction, is divided into three key stages: the early reactions resulting in the formation of base products, the rearrangements of these chemical groups and the final reactions forming the classical Maillard browning products or now known as AGEs (Wolff et al., 1991). The role of AGE in vascular disease was first identified by their ability to cross-link proteins of the vascular wall leading to the thickening of vessels and leakage from the vasculature (Baynes et al., 1991). Glycation of many structural and intracellular proteins occurs through covalent and cross-linking modifications by glucose, which may change protein conformation and permanently impair their functions (Singh et al., 2001; Bierhaus et al., 1998). AGEs can also alter cellular functions by binding to their receptors, such as the receptor for AGEs (RAGE) or other receptors, including the macrophage scavenger receptor, p60, p90 and galectin-3. RAGE is a trasmembrane protein that belongs to the immunoglobulin family. Upon binding to AGE-modified proteins; RAGE initiates multiple cascades of cellular signalling pathways, including p44/42 MAPK and PKCs, and further disrupts cellular homeostasis.

Age-rage and diabetic complications:

It is well established that other organ systems are strikingly susceptible to injury and dysfunction in chronic hyperglycemia. As discussed above, human diabetic kidneys display increased AGEs and increased expression of RAGE.

Although strictly an association, studies in animal models suggest that blockade of the receptor is beneficial in murine diabetes and nephropathy. Specifically, we have shown that RAGE blockade provides benefit in diabetes-associated nephropathy in db/db mice (Odetti et al., 1998).

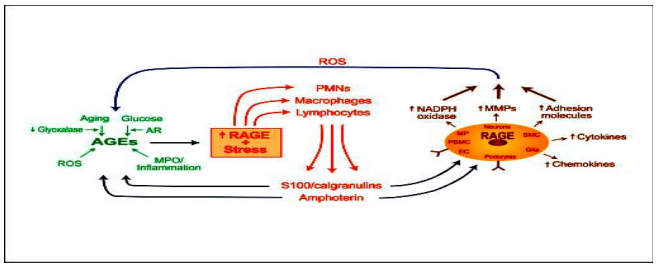

Fig 1.5: Described advanced glycation end product-receptor for advanced glycation end products (AGE-RAGE) and a vicious cycle of cellular perturbation and tissue injury: implications for diabetic complications.

In addition, the administration of stz triggered albuminuria and mesangial expansion in wildtype mice; these processes were significantly suppressed in diabetic homozygous RAGE null mice. Consistent with findings in human diabetes, in the mouse kidney in diabetes, podocytes were the principal RAGE-expressing cells. Intensive studies are underway to elucidate the precise link between AGE, RAGE, and podocytes in diabetic and, perhaps, other nephropathies, especially those characterized by heightened oxidative stress. In other studies, the role of RAGE blockade in the neuropathy of diabetes has been tested. Based on the hypothesis that the activation of NF-kB was a key and critical RAGE dependent contributing factor to the development of diabetic nephropathy, diabetes was induced with stz in transgenic mice in which the expression of β globin transgene was under control of an NF-kB dependent promoter. In the sciatic nerve, diabetes was associated with 20-fold increase in the induction of β-globin transcripts (which was reduced strikingly with intense insulin therapy to reduce hyperglycemia, and, thus, AGE generation). This was inhibited fully by pretreatment of the diabetic mice with sRAGE (Thornalley et al., 1998). To further dissect the role of RAGE, we rendered wild-type mice and homozygous RAGE null mice diabetic with stz. After 6 months, mice were killed. Although sciatic nerve demonstrated increased expression of IL-6 and activated NF-kB in the peripheral nerve of wild-type mice, there was no up-regulation of either IL-6 or NF-kB activation in RAGE null mice. The hot plate test was performed to test for thermonocieception after 3 months of stz diabetes. Treatment with sRAGE for 3 weeks completely restored pain perception and corrected the latency time. In RAGE null mice rendered diabetic with stz, compared to wild-type mice with diabetes, a significant protection against impaired thermonocieception was observed.

Metabolic syndrome and insulin resistance

Metabolic Syndrome is a collection of risk factors that substantially increase your chances of causing damage to your cardiovascular system, which can lead to a heart attack or stroke (Chisholm et al., 1997).Insulin Resistance is an underlying cause of Metabolic Syndrome and there are many influences that contribute to the presence of both these disorders in the body. In essence, our environment and lifestyles have evolved too rapidly for our bodies to keep pace (Muller et al., 1996). We are still genetically "wired" to thrive on the entrenched habits of our ancestors, who consumed different, nutrient-rich foods and a diet low in carbohydrates, as well as sustaining greater levels of movement and exercise (Dechenes et al., 1998; Humphriss et al., 1997).

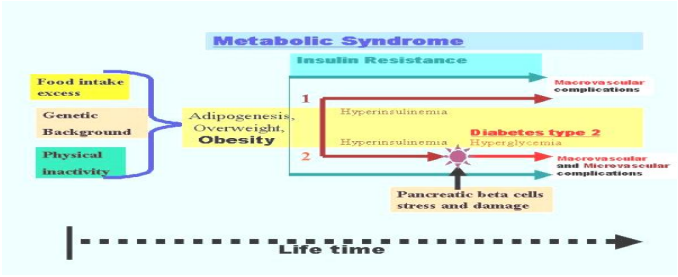

Fig 1.6: Describe the relationship between metabolic syndrome, insulin resistance, hyperinsulinemia and hyperglycemia.

Some people may also have a genetic predisposition to Insulin Resistance, while others develop the condition through high stress and unhealthy lifestyles (Hopkins et al., 1996). Over time, the above factors have damaged the complex ability of the body's cells to properly utilize insulin to convert glucose to energy. This process creates Insulin Resistance, which can cause Metabolic Syndrome.

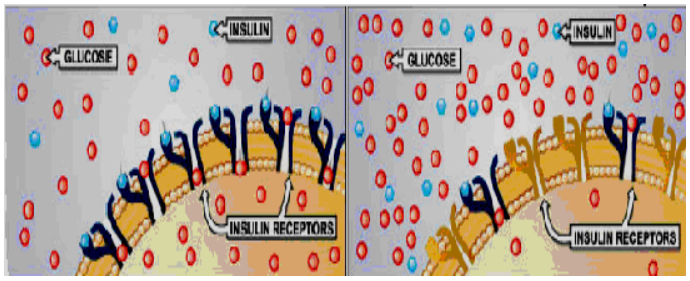

Fig 1.7: Describe normal cell and insulin resistant cell

The body draws its energy from a complex metabolic process whereby food is first converted into glucose in the bloodstream. The glucose then passes through the walls of your cells via insulin to be converted into essential energy. Insulin Resistance, however, desensitizes the cell wall to insulin, resulting in most of the glucose being unable to enter and be converted into energy. The unused glucose remains in the blood stream which carries it to the liver. Once there, it is converted into fat and distributed around the body via the blood stream. This process can lead to weight gain. Insulin Resistance also causes excess levels of insulin because the latter hormone is not being used properly. The resulting imbalance of glucose and insulin can lay the groundwork for Metabolic Syndrome as well as a variety of other disorders, including Pre- and Type 2 Diabetes, plus PCOS (Polycystic Ovarian Syndrome) - a leading cause of menstrual irregularity and female infertility.

Management of cardio vascular complication

Evidence from randomized controlled studies is lacking, the American Diabetes Association Consensus Development Conference on the Diagnosis of Coronary Heart Disease in People with Diabetes has recommended that patients with an established coronary heart disease (CHD) history or who have had a prior cardiac event warrant cardiac testing for risk stratification. Further, in patients without a prior history of an event or symptoms strongly suggesting CHD, testing for CHD is warranted in patients with the following.

1. Typical or atypical cardiac symptoms;
2. Resting electrocardiogram suggestive of ischemia or infarction;
3. Peripheral or carotid occlusive arterial disease;
4. Sedentary lifestyle, age 35 years, and plans to begin a vigorous exercise program (Wendt et al., 2003);
5. In addition to diabetes, two or more cardiac risk factors (total cholesterol 3240 mg/dl, LDL cholesterol 160 mg/dl, or HDL cholesterol <35 mg/dl; blood pressure >140/90 mmHg; smoking; family history or premature CHD; positive microalbuminuria test).

Cardiac testing might consist of exercise stress testing, stress perfusion imaging, stress echocardiography or catheterization. The type of testing and need for referral to a cardiologist depend on the severity of underlying or suspected coronary artery disease. At present, there is no single pharmaceutical drug that can reverse the symptoms of Metabolic Syndrome. We feel a complete system of elements is needed to treat a major factor in causing this condition, namely Insulin Resistance.

The Insulite Matrix

The Insulite matrix System is the first scientifically-formulated plan to address the underlying cause of Insulin Resistance and reverse its symptoms. The Insulite System supports your body's ability to balance glucose and insulin levels, thus helping you lose weight, which is crucial for reversing Insulin Resistance and Metabolic Syndrome.

1. Insulin Resistance can cause hyperinsulinemia, an excess of insulin in the blood stream and a symptom of Metabolic Syndrome. This latter condition may result in higher levels of LDL "bad" cholesterol that could damage the cardiovascular system and lead to a heart attack or stroke. Reversing Insulin Resistance is an important factor in heart disease prevention.
2. Insulin Resistance heightens the risk of Metabolic Syndrome sufferers becoming Pre-Diabetic which, if neglected, can lead to Type 2 Diabetes - an increased risk factor for Cardiovascular Disease. Insulin Resistance can also cause high blood pressure or hypertension, another risk factor for heart problems.
3. Type 2 Diabetes can only be managed for the rest of a Diabetic's life in the vast majority of cases and may require daily injections of insulin. Just by itself, Type 2 Diabetes is a seriously increased risk factor for blindness, kidney disease and the need for amputation.
4. Researchers have long known that people who are overweight and suffer from Type 2 Diabetes are at greater risk of developing Alzheimer's disease and other types of dementia.

Men with Metabolic Syndrome run a greater risk of developing prostate cancer. Because there is no single solution for Insulin Resistance and Metabolic Syndrome you might want to consider a multi-faceted approach. We feel that what's required to address the issues presented by these syndromes is a complete systematic approach, which includes nutraceuticals (vitamins, herbs and minerals that are disease specific), a realistic exercise program combined with nutritional guidance, advice on combating carbohydrate addiction and a support network that will help you change unhealthy lifestyle choices that could lead to weight loss (Farlane et al., 2003).

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