

# Cardiovascular Risk Factors in Type 2 Diabetes Mellitus

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## ABSTRACT

Diabetes is expanding in pandemic proportions worldwide. Escalation in prevalence of diabetes appears to be more pronounced in developing countries, particularly in India. Presently more than 30 million people are affected by diabetes in India. These numbers are expected to increase to 80.9 million by year 2032. In addition the emergence of the cardiovascular disease epidemic in India has added to the economic and health burden of the nation. Various epidemiological studies have consistently reported high prevalence rates of diabetes and CAD among migrant Indians compared to the native population. The risk for CAD among diabetic subjects is greater by a factor of 2 to 4 compared to non-diabetic subjects.

Diabetes is expanding in pandemic proportions worldwide. Escalation in prevalence of diabetes appears to be more pronounced in developing countries, particularly in India. Presently more than 30 million people are affected by diabetes in India. These numbers are expected to increase to 80.9 million by year 2032. In addition the emergence of the cardiovascular disease epidemic in India has added to the economic and health burden of the nation. Various epidemiological studies have consistently reported high prevalence rates of diabetes and CAD among migrant Indians compared to the native population. The risk for CAD among diabetic subjects is greater by a factor of 2 to 4 compared to non-diabetic subjects.

Type 2 diabetes is associated with a marked increase in both cardiovascular risk and disease. This risk is multifactorial including from a practical point of view, bad companions like; hyperglycemia, hypertension, dyslipidemia, obesity, and smoking. The prothrombotic state can also be added.

In clinical setting the approach to cardiovascular risk is the only way to achieve a control of all these factors and a subsequent reduction of cardiovascular, morbidity and mortality. The approach means the following steps:

1. The identification and evaluation of each risk factor.
2. The evaluation of global cardiovascular risk.
3. The evaluation of global cardiovascular risks and the intervention for each risk factor

The implementation of approach to cardiovascular risk in type 2 diabetes is a huge task for practitioners implying a high effort. But this is worth doing because the significant benefits have been demonstrated. All manifestations of macrovascular disease, coronary heart disease, cerebrovascular disease and peripheral

vascular disease are significantly more common in diabetic patients than in non-diabetic subjects. The risk for cardiovascular disease (CVD) events is relatively higher among female type 2 diabetic patients than among male type 2 diabetic patients and it is largely independent of age.

One of the paradoxes of CVD in type 2 diabetic is that macrovascular disease starts even before the diagnosis of frank hyperglycemia, a sharp contrast to microvascular complications, which are mainly depending on glycemic control.

### PATHOLOGY OF CARDIAC INVOLVEMENT IN DIABETES

The central metabolic dysfunction in the diabetic heart is the decrease in the rate of glucose and lactate oxidation secondary to a decrease in mitochondrial pyruvate oxidation. Levels of FFA (free fatty acid) and fatty acid esters are elevated.

The interaction between lipids and glucose is in the glucose fatty acid cycle. There is a competition for respiration between substrates: glucose and fatty acids. Increased glucose provision leads on to glucose oxidation and glycogen and lipid storage and inhibition of fatty acid oxidation, and vice versa. Long term exposure of beta cells to FA (fatty acid) impairs the insulin secretory response to sugar.

Ischemia induces increased anaerobic glycolysis and reduced pyruvate oxidation. Ischemia is followed by lactate production and glycogen breakdown. These lead on to contractile dysfunction. Elevated insulin levels induce elevated PAI-1 (Plasminogen activator inhibitor-1) antigen, which is thrombogenic.

Elevated blood glucose levels increase glucose uptake into cells. The excess glucose is metabolized via sorbitol pathway.

Diacylglycerol synthesis is increased which produces activation of protein kinase C (PKC). This increases endothelial permeability. Hyperglycemia increases the production of specific proteins, endothelin, collagen IV, fibronectin and adhesion molecules. This leads to atherosclerosis.

Hyperglycemia promotes non-enzymatic glycosylation of proteins. Initially a reversible formation of “Amadori product” occurs. Later irreversible advanced glycosylation end-products (AGE) form. These are associated with atherosclerosis and elevated cytokines.

## CARDIOVASCULAR RISK FACTORS

- A. Dyslipidemia
- B. Hypertension
- C. Microalbuminuria
- D. Obesity
- E. Oxidative stress
- F. Lifestyle and other cardiovascular risk factors
- G. The prothrombotic syndrome
- H. Hyperhomocysteinemia
- I. Cardiac autonomic neuropathy.

### Diabetic Dyslipidemia

Main metabolic abnormalities in Type 2 diabetes are hyperglycemia, insulin resistance, increased hepatic glucose production and impaired secretion of insulin by the pancreatic beta cells.

#### Lipid Abnormalities

Hypertriglyceridemia (increased VLDL-TG and VLDL-apoB concentration)

Decreased HDL-cholesterol concentration

Decreased HDL-2 and HDL-2/HDL-3 ratio

Elevation of free fatty acids in fasting and postprandial situation.

LDL phenotype B (small and dense LDL particles)

Decreased lipoprotein-lipase activity

Prolonged postprandial lipemia

Increased  $L_p(a)$  in the presence of diabetic nephropathy.

This cluster of lipid abnormalities, also known as diabetic dyslipidemia is thought to play a central role in the macrovascular complication.

Lipid metabolism in diabetes is modulated by a series of factors among which the degree of glycemic control and the presence of insulin resistance are two most prominent players.

The effect of insulin resistance on lipid metabolism in type 2 diabetes includes:

1. Lack of activity of lipoprotein lipase which explains the increased post-prandial lipemia characteristic of these patients; this is associated with decreased exogenous and endogenous triglyceride clearance and low plasma levels of HDL-cholesterol.
2. Increased hepatic lipase activity which follows the production of small, dense LDL particles.

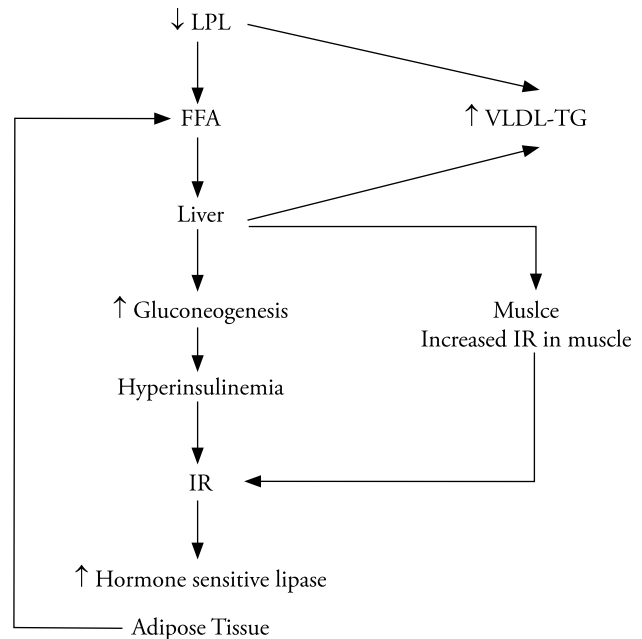


Fig. 1: Free fatty acid metabolism and insulin resistance, LPL—Lipoprotein lipase, VLDL-TG—very low-density lipoprotein triglyceride, FFA - Free fatty acids, IR—Insulin resistance

3. Increased lipolysis with an elevated flux of FFA to the liver and increased triglyceride and apo-B secretion.

This increase in FFA has important consequences i.e. hypertriglyceridaemia, hyperglycemia (due to less peripheral utilization and increased hepatic production) and hyperinsulinaemia and insulin resistance.

### Hypertension in Type 2 Diabetes Mellitus

Hypertension is one of the most common morbid associations in type 2 DM, with an average estimated prevalence of 40%. Hypertension is an independent risk factor associated with type 2 DM. It has been estimated that the prevalence of hypertension in diabetes is about 2-5 times higher than in non-diabetic population, though varying in Type 1 and in Type 2 DM. In Type 1 DM the prevalence of hypertension is mostly related to renal disease and increases after microalbuminuria is detected. In Type 2 microalbuminuric patients the prevalence of high blood pressure (HBP) is 70% and might be higher if current criteria for the definition of higher blood pressure are applied. In Type 2 DM the prevalence of hypertension shows wide interethnic variations, being higher in Afro-Americans and Mexican-American but not in Pima Indians. Most important is hypertension which precedes Type 2 DM, and may be present at a very early degree of glucose intolerance ( $\leq 20 - 40\%$  in IGT) in any age group. In fact, a high prevalence of BP has been detected in newly diagnosed Type 2 diabetics or very shortly after the clinical diagnosis was made. Thus in the United Kingdom prospective study (UKPDS23) 32% of men and 45% women with recently diagnosed type 2 diabetes were already hypertensive. The coexistence of arterial hypertension and type 2 DM in an individual patient conveys a three-fold increased risk of CV mortality as compared to non-diabetic persons across all blood pressure levels as reported in the MRFIT study. Further more the UKPDS 23 (Turner et al, 1998) reported a hazard ratio of 1.72 for coronary heart disease in type

2 diabetics with arterial hypertension particularly in those with systolic blood pressure over 142 mm Hg.

The WHO multinational study demonstrated that in 4740 diabetics (over 80% of the type 2) the appearance of hypertension and proteinuria increased the CV risk five-folds in men and women when compared with normotensive normoalbuminuric diabetics. Moreover, recently available evidence points out that the hypertensive type 2 diabetics with higher systolic blood pressure (SBP) have an increased risk for cardiovascular heart disease (CHD) and that even single high BP value may be predictive. Arterial hypertension in type 2 DM adds a very strong risk for stroke when compared to normotensive diabetics and non-diabetics, this added risk being independent of others such as obesity or dyslipidemia. As shown by a study in Finland including diabetic patients, established that HBP was also a strong predictor of non-traumatic limb amputation. Several studies have also shown that both diabetes and hypertension are strong risk factors for renal disease in either type of diabetes as well as for retinopathy. The UKPDS 38 demonstrated that the tight control of HBP is as important as the meticulous glycemic control in reducing total mortality; any death related to diabetes and other diabetes-related events. Abundant available clinical and epidemiological evidence indicated that the coexistence of hypertension and diabetes significantly increased the risk of nephropathy and retinopathy in those patients.

#### ***Pathogenesis of Hypertension in Type 2 DM***

The aetiology/pathogenesis of hypertension in diabetes is multifactorial but somehow different in type 1 and type 2 DM. Most cases of hypertension in Type 2 DM are of the so-called "essential" type and secondary hypertension is not as common.

#### ***Renal Disease***

Nephropathic hypertension is however, a most important cause. The incidence of diabetic nephropathy in type 2 DM has been reported to be slightly less or equal (20-30%) than in type 1 DM (30-40%) when variables such as age and BMI are controlled. The natural history of diabetic renal disease is less well characterized in type 2 DM than in type 1 DM. However, it has been reported that renal hypertrophy and hyperfiltration, typical of the earliest stages of renal disease in type 1 DM; may also be found in newly diagnosed type 2 DM and it can be equally reversible by appropriate glycemic control. Available data show that microalbuminuria has a strong predictive value in type 2 DM for progression to overt diabetic nephropathy. In the light of current clinical and epidemiological evidence it must be stressed that the role of the diabetic nephropathy should not be underestimated, as it is a most important aetiology of arterial hypertension in type 2 DM.

#### ***CV Risk Assessment***

The evaluation of CV risk in every newly (and established) patient with Type 2 DM demands an exhaustive medical history and clinical examination at baseline and at every follow-up visit. A Type 2 diabetic patient whether hypertensive or not is more than just a hyperglycemic individual. Detailed protocols for clinical practice are available from the European Consensus for the management of Type 2 DM and the ADA clinical recommendations. Emphasis is made on the measurement of BP

both in supine, sitting and standing positions since in a number (25%) of Type 2 patients, some degree of misleading autonomic dysfunction may be present after 10 or more years from diagnosis. It is not uncommon to find the combination of systolic hypertension in the supine position with orthostatic hypotension. It is important to remember that BP readings usually change over time and that of course "White coat" arterial hypertension may be present, requiring reconfirmation of the readings obtained at the office under well controlled conditions in the ambulatory setting. Continuous 24 hours BP monitoring may be required before or during treatment. Not uncommonly BP recordings during the night in diabetic patients show abnormal patterns with no evidence of a nocturnal BP fall (non-dippers). This latter phenomenon is often found in hypertensive diabetics and more so in those with microalbuminuria and established renal disease. This finding is important since the mean 24 hours BP increased by a factor of four or more in microalbuminuric diabetic patients compared to normoalbuminuric and may be interpreted as marker of progression to clinical diabetic renal disease.

#### ***Microalbuminuria***

About one-third of diabetic patients develop diabetic nephropathy during their life. The presence of a level of proteinuria above 0.3g/24 hour (>300mg / 24 hours) indicates the diagnosis of diabetic nephropathy. Eventhough in the initial stage renal function is usually normal; the natural history of diabetic nephropathy foresees a progressive decline of functionality toward end-stage renal disease. Clinical diabetic nephropathy is usually preceded in years by a condition of a slight increase in urinary excretion of albumin below the threshold for overt proteinuria, called "microalbuminuria".

Microalbuminuria is defined as urinary albumin excretion rate (UAER) in the range of 20-200 µg /min (30-300 mg/24 hours).

The appearance of microalbuminuria is consequent to an increased leakage of albumin through the basement membrane of the glomeruli. Two mechanisms can lead to this increased leakage. The first one is an increased intraglomerular capillary pressure that is typical in diabetes mellitus and that is also present in hypertension. Furthermore, a hyperglycemic condition can produce a loss of negative charges on the basement membrane of the glomeruli with the consequence of an increased capillary permeability to negatively charged proteins such as albumin.

Originally microalbuminuria was only considered as an early predictor of risk for development of diabetic nephropathy, in fact up to 80% of diabetic patients with microalbuminuria, if not adequately treated, show a progression towards macroalbuminuria.

More recently several studies have indicated that microalbuminuria is an independent risk factor for cardiovascular morbidity and mortality in diabetes.

#### ***Epidemiology of Microalbuminuria and Cardiovascular Disease***

In the past two decades, different investigators have demonstrated the correlation between microalbuminuria and excess mortality in type 2 diabetes, mainly for cardiovascular disease.

Jarrett and colleagues demonstrated, that subjects with AER (albumin excretion rate) greater than 30 µg/min had an increased risk of early death (all causes but chiefly cardiovascular); moreover albumin excretion rate (AER) resulted independent of age, sex, diabetes duration and blood pressure values, as risk factors for mortality.

A larger retrospective study of 232 type 2 diabetics, from Mogensen et al, confirmed the importance of microalbuminuria as a predictive factor for premature mortality. In this study mortality risk was found to be correlated with the increasing level of urinary albumin excretion (UAC). A UAC of 15 µg/ml corresponded to an increased risk of 37% with respect to the normal controls and a UAC comprised between 30-140 µg/ml to a risk of 148%.

Schmitz and Vaeth retrospectively investigated the role of microalbuminuria and other risk factors (age, sex, age at diagnosis diabetes duration, blood pressure, fasting plasma glucose, weight, serum creatinine, retinopathy), treatment in the prediction of increased mortality in a Danish population of 503 subjects with diabetes mellitus. They showed that UAC above the limit of 40 µg/ml was an independent risk factor as far as age, serum creatinine and duration of diabetes.

On the basis of these three retrospective studies that showed a clear correlation between AER and an increased risk for cardiovascular disease, it was concluded that microalbuminuria was an independent risk factor for CVD mortality.

#### ***Pathogenetic Mechanisms for the Associations of Microalbuminuria to Cardiovascular Disease***

##### **1. Endothelial dysfunction and haemostasis disturbances**

The increase of AER could be associated to a generalized dysfunction of the endothelium. Different plasma markers of endothelium function or of endothelium damage have been identified: von Willebrand factor (vWF), endothelin-1, angiotensin converting enzyme, adhesion molecules such as ICAM-1 or VCAM-1 and e-selectin. Endothelial cells of the glomerular capillary barrier are involved in glomerular function and particularly in the filtration of proteins; the loss of albumin, typical of microalbuminuria, consequently may be due to glomerular endothelial damage. Bruno et al, using the plasma fibrinogen levels as a marker of enhanced coagulation, showed the presence of a pro-thrombotic status related to microalbuminuria. Gabazza et al also demonstrated an enhanced activation of the clotting system in Type 2 diabetic patients as a consequence of an altered anticoagulant activity.

##### **2. Lipid abnormalities**

##### **3. Blood pressure levels**

##### **4. Insulin resistance and hyperinsulinaemia**

##### **5. Hyperhomocysteinemia**

##### **6. Chronic inflammation**

#### **Obesity**

Obesity and type 2 diabetes mellitus frequently occur together. They are closely linked by commonality of aetiology and pathogenesis (genetics, insulin resistance and lifestyle), clinical and therapeutic features. Both of these chronic diseases are

major causes of morbidity and mortality from atherogenic macrovascular disease and they are independent factors for coronary heart disease, resulting also in increased economic costs. Their complex connection support the term “diabesity” proposed by Satrap and Finer.

Obesity is the strongest risk factor for the development of type 2 diabetes mellitus. Together with overweight with abdominal fat distribution, they play the major etiological role in about 80-90% cases and represent a major obstacle to the successful long term management of the disease. The risk for developing diabetes rises steadily once BMI exceeds 24kg/m<sup>2</sup>. Weight gain after the age of 21 significantly increases the risk of developing diabetes. Considering BMI at age 18, a 20Kg weight gain increases the risk for diabetes 15-fold. Women with a BMI 24-25 Kg/m<sup>2</sup> have a five-fold increased risk for developing type 2 diabetes and a BMI>35Kg/m<sup>2</sup> increases the risk 93-fold. On this basis, obesity could be considered the most important problem in type 2 diabetes care worldwide.

The risk of developing type 2 diabetes and cardiovascular disease is highly associated with abdominal (visceral) fat distribution. The clinical marker of visceral fat deposition is waist circumference. It has been found to be a strong predictor of diabetes. Obesity is involved in determining the cardiovascular risk both as an independent factor and as part of the metabolic X Syndrome (Reaven), where it is highly associated with hypertension, dyslipidemia, increased prothrombotic status and endothelial dysfunction. The combination of insulin resistance and hyperinsulinemia is considered to be the main pathophysiological link of this association. The presence of Type 2 diabetes mellitus completes the feature and multiplies the cardiovascular risk by adding a significant burden through specific metabolic and haemorrhological disturbances.

#### ***Cardiovascular Risk in Obese Type 2 Diabetes Patients***

The key feature which links visceral obesity, type 2 diabetes mellitus and cardiovascular risk status is considered to be insulin resistance and hyperinsulinaemia, developed in the first phase.

#### ***Insulin Resistance/Hyperinsulinaemia***

Insulin resistance has a double determination, genetic and acquired. Both factors interact determining a post-insulin receptor mechanism mainly at skeletal muscle level. The fat deposits at this level have an important role in this mechanism. Genetic anomalies refer to insulin receptors or intracellular signaling glycogen synthesis, hexokinase II, Glut- 4 glucose transporter and Glut-2. Their expression is under acquired factors such as hypercaloric diets rich in fat, poor in fibers and antioxidants and low physical activity.

Visceral adipocytes have a high secretory activity, acting like an endocrine organ: it secretes free fatty acids, leptin, lipoprotein lipase, angiotensinogen, TNF-α (tumour necrosis factor-α) and SR (soluble receptors), PAI – 1 (plasminogen activator inhibitor- 1), IGF-1 (insulin-like growth factor-1), IL-6 (interleukin), Apo E, prostaglandins, steroids, adiponectin, adipophilin, tissue factor and resistin. Visceral fat depots determine a high basal and catecholamine-induced lipolytic activity. As a result, an increased flow of free fatty acids is directed towards periphery, acting;

1. Directly on the liver to interfere with glucose handling, insulin clearance and increasing lipoprotein synthesis.
2. On skeletal muscle where FFA (free fatty acid) is preferentially oxidized, leading to the development of insulin resistance. Hyperinsulinemia, developed as compensation, maintains normoglycemia in the first phase, but induces a cascade of metabolic, haemodynamic and haemorrhological disturbances.

#### ***Lipid Disorders and Oxidative Stress***

Changes in plasma lipoproteins are influenced by insulin resistance, hyperinsulinaemia and altered sex steroids and glucocorticoid levels, seen in visceral obesity. Both qualitative and quantitative changes occur.

- Quantitative alterations
  - Hypertriglyceridemia (VLDL and LDL increase)
  - Post-prandial hyperlipidaemia
  - Decrease of HDL-2 (reduced lipoprotein lipase activity)
  - Increased ApoB concentration
- Qualitative alterations
  - Increased triglyceride-rich lipoproteins
  - High percentage of small and dense HDL particles, with low cholesterol removal capacity.

#### ***Haemodynamic Effect***

Hyperinsulinaemia and visceral obesity are considered independent risk factors for hypertension. The mechanisms involved refer to: higher sodium and water retention, enhanced sympathetic nervous system activity, increased sodium-pump activity in skeletal muscles, and arterial wall hypertrophy (IGF-1 induced).

#### ***Haemorrhological Effect***

IR/hyperinsulinaemia is associated with the inhibition of fibrinolysis and hypercoagulability, with impact on cardiovascular and macrovascular disease. These haemorrhological alterations consist of elevation of:

1. Plasminogen activator inhibitor (PAI-1) leading to fibrinolysis inhibition.
2. Plasminogen activator tissue antigen (tPA)
3. Fibrinogen
4. von Willebrand factor (vWF)
5. Factor VII
6. High blood viscosity and erythrocyte aggregability.

#### ***Atherogenic Effects***

Endogenous hyperinsulinaemia is involved in atherogenesis by

1. Stimulating mitosis and DNA synthesis in endothelium and smooth muscle cells
2. Increasing PAI-1 (plasminogen activator inhibitor-1)
3. Increasing intracellular cholesterol
4. Inducing foam cells
5. Increasing procoagulation factors

The insulin effects are mediated through IGF-1 receptors.

#### ***Endothelial Dysfunction***

Is one of the major factors involved both in the progression of atheroma plaque and in its instability, favoring the development of intravascular thrombosis.

#### ***Metabolic X Syndrome***

The concept of the metabolic syndrome X introduced by Reaven, recently called "dysmetabolic syndrome" (Valantine), includes the association of the following features:

- Insulin resistance/hyperinsulinaemia, recognized as the etiopathogenic element.
- Glucose intolerance or Type-2 diabetes mellitus
- Hypertriglyceridemia
- Post-prandial hyperlipidaemia
- Low HDL-cholesterol
- Hypertension
- Abdominal obesity
- Hyperuricaemia
- Sedentary lifestyle
- Low fibrinolysis activity through PAI-1 increased plasma level
- Prothrombotic tendency
- High level of small and dense LDL particles
- Endothelial dysfunction
- Microalbuminuria
- Hyperleptinemia
- Low chronic inflammation state (raised interleukin-6 and C-reactive protein)
- Non-alcoholic fatty liver disease.

This cluster of the above mentioned anomalies substantially increase the risk of coronary heart disease in affected persons. The cardiovascular risk related to metabolic syndrome consists of the high and early probability of developing atherosclerotic pathology and is a result of the specific action of each component, amplified by their association.

In accordance to the WHO proposal, the diagnosis of the metabolic syndrome in persons with type 2 diabetes is confirmed if two of the following criteria are fulfilled:

- Hypertension (systolic BP > 160mm Hg and DBP > 90mm Hg) or antihypertensive treatment.
- Dyslipidaemia, defined as triglyceride  $\geq$  1.7 mmol (150 mg%) and/or HDL cholesterol <0.9 mmol/l (35 mg/dl) in men and < 1.0 mmol/l (38mg/dl) in women.
- Obesity
- Microalbuminuria (urinary albumin excretion rate AER)  $\geq$  20  $\mu$ g/min.

In person without diabetes a positive diagnosis requires the presence of insulin resistance defined as the highest quartile of the HOMA IR index.

According to the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults-Adult-Treatment Panel III (ATP III), the metabolic syndrome is diagnosed if three of the following five criteria are fulfilled:

- Abdominal obesity, defined as waist circumference > 102 cm (>40 inch) in men and > 88cm (>35 inch) in women.
- Triglyceride  $\geq$  150 mg/dl (1.7 mmol/l)
- HDL-cholesterol < 40 mg/dl in men and < 50mg/dl in women
- Blood pressure  $\geq$  130/  $\geq$ 85mm Hg
- Fasting glucose  $\geq$  110mg/dl

In men, waist circumferences of 94-102cm (37-39 in) can be associated with increased metabolic risk.

### **Metabolically Obese, Normal Weight (MONW)**

MONW concept refers to the presence of insulin resistance/ hyperinsulinaemia, subsequently metabolic disorders and high cardiovascular risk, in non-obese individuals.

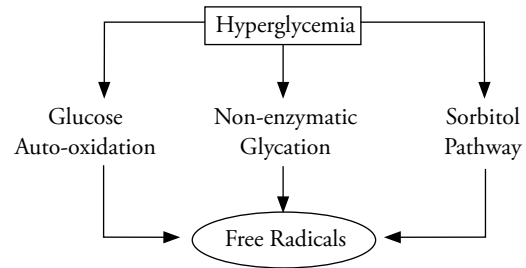
MONW individuals' characteristics are; BMI=20-27Kg/m<sup>2</sup>, moderate weight gain (2-10 Kg of adipose mass) in adult life, central fat distribution and enlarged fat cells, physical inactivity and low level of fitness, high prevalence in general population and high risk of developing Type 2 diabetes, dyslipidemia, hypertension and cardiovascular disease.

Other potential factors related to MONW individual might be low birth-weight and genetic predisposition. The therapeutic consequence is that optimizing the life-style significantly reduces the entire cluster of metabolic and haemostatic abnormalities.

### **Oxidative Stress**

Accelerated atherosclerotic vascular disease is the leading cause of mortality in patients with diabetes mellitus. Endothelium-derived nitric oxide (NO) is a potent endogenous nitro vasodilator and plays a major role in modulation of vascular tone. Selective impairment of endothelium-dependent relaxation has been demonstrated in aortas of both non-diabetic animals exposed to elevated concentrations of glucose in vitro and insulin-dependent diabetes animals. The impaired NO release in experimentally induced diabetes may be prevented by a number of antioxidants. It has been hypothesized that oxygen-derived free radicals (OFR) generated during both glucose auto-oxidation and formation of advanced glycosylation end-products may interfere with NO action and attenuate its vasodilator activity. The oxidative injury may also be increased in diabetes mellitus because of weakened defense due to reduced endogenous antioxidants (vitamin E, reduced glutathione EGSH). A defective endothelium-dependent vascular relaxation has been found in animal models of hypertension and in hypertensive patients. An imbalance due to reduced production of NO or increased production of free radicals, mainly superoxide anion, may facilitate the development of an arterial functional spasm.

Type 2 diabetes is associated with an excessive incidence of cardiovascular disease and a reduction in life-expectancy of 5-10 years. This is mainly due to a clustering of established risk factors such as hypertension, hyperlipidaemia, smoking and activation of thrombosis and hyperglycemia, a typical feature of diabetes, also an important contributing factor.



**Fig. 2 :** Glucose can produce free radicals through glucose auto-oxidation, non-enzymatic glycation and sorbitol pathway activation.

### **Lifestyle and Other Cardiovascular Risk in Type 2 Diabetes**

Numerous population studies, as well as ecological data and observational studies, provide evidence for environmental and lifestyle influences affecting the development of type 2 diabetes. These environmental and lifestyle factors include:

- Diet (Increased caloric intake, carbohydrates and fat intake).
- Alcohol consumption
- Obesity
- Thinness at birth
- Socioeconomic status (lower income, education and social class)
- Urbanization (stress)
- Acculturation to western lifestyles
- Interactions between genetic and environmental factors

### **Prothrombotic Syndrome in Type 2 Diabetes**

High plasma levels of fibrinogen, clotting factor VII, PAI-1 (plasminogen activator inhibitor-1) as well as of endothelial-derived von Willebrand factor are increased in patients with type 2 diabetes and are considered to be predictive for the thrombotic complications of atherosclerosis. Circumstantial evidence suggests that a peculiar association of stimuli including hyperinsulinism and the release into the portal circulation of excess free fatty acids and of proinflammatory cytokines, originating in the enlarged visceral adipose tissue, would enhance the synthesis of liver-derived homeostatic balance. It should be mentioned that association of cardiovascular disease with clotting factors and antifibrinolytic potential elevations illustrates correlations not causality. The above-mentioned changes of hemostatic variables are therefore relevant only in context with hyperreactive platelets and endothelial lesions or dysfunction. Correction of overweight and the improved metabolic control would however diminish the pathologically increased plasma levels of prothrombotic haemostatic variables and in association with an efficient antiplatelet therapy (clopidogrel) may reduce the thrombotic tendency.

### **Hyperhomocysteinemia**

Hyperhomocysteinemia has been associated with the development of cardiovascular disease; mainly premature atherosclerosis and thromboembolic disorders. Experimental results indicate an involvement of hyperhomocysteinemia in endothelial

dysfunction, lipid peroxidation, impaired synthesis of nitric oxide and reduced expression of thrombomodulin.

Genetic defects leading to deficiencies of cystathionine-beta synthase and methylenetetrahydrofolate reductase are responsible of increased plasma homocysteine in homozygotes.

Increased plasma homocysteine have been recorded in both type 1 and type 2 diabetic subjects. Experimental evidence suggests that advanced glycation end-products may act synergistically with homocysteine in the development of endothelial dysfunction. In general, diabetic patients with associated hyperhomocysteinemia showed higher levels of serum creatinine, and in type 2 diabetic subjects, multiple regression analysis has depicted albumin excretion rate as the parameter with strongest independent association with elevated plasma homocysteine. Patients with nephropathy and hyperhomocysteinemia were older and showed a more advanced stage of renal disease.

### Cardiac Autonomic Neuropathy

Is it a cardiovascular risk factor in Type 2 diabetes?

The autonomic nervous system, through the sympathetic and parasympathetic pathways, supplies and influences every organ in the body. It closely integrates vital processes such as heart rate, blood pressure, and myocardial contractility and as a consequence plays a pivotal role in the regulation of the cardiovascular system.

Cardiac autonomic neuropathy (CAN) represents a serious complication as it carries an approximately five-fold risk of mortality in patients with diabetes just as in those with chronic liver disease. The high mortality rate may be related to silent myocardial infarction, cardiac arrhythmias, cardiovascular and cardiorespiratory instability and to other causes not explained yet. Resting tachycardia due to parasympathetic damage may represent one of the earliest signs. Typical findings referring to autonomic dysfunction may include exercise intolerance, orthostatic hypotension and cardiac dysfunction during rest or exercise. Severe autonomic neuropathy may be responsible for spontaneous respiratory arrest and unexplained sudden death which is not rare among diabetic patients. A relationship between the presence and/or severity of CAN (cardiac autonomic neuropathy) and corrected QT interval prolongation is well documented.

The natural history of neuropathy is governed by the degree of glycaemic control. The unfavorable impact of long term poor glycemic control on the development and progression of CAN is now generally well accepted.

### CONCLUSIONS

Type 2 diabetes mellitus is a chronic insidious process contributing to an overwhelming amount of morbidity and mortality, much of which is related or attributed to cardiovascular disease. Cardiovascular disease is two to fourfold more common in patients with diabetes than without. This difference in prevalence of CVD in diabetes is associated with various cardiovascular risk factors such as dyslipidemia, hypertension, obesity, microalbuminuria, oxidative stress, hyperhomocysteinemia, prothrombotic state and possibly cardiac autonomic neuropathy. Environmental risk factors such as smoking, socioeconomic status, diet, alcohol

consumption, urbanization, and decreased physical activity also account for increased morbidity and mortality in type 2 diabetes mellitus. The evaluation of cardiovascular risks and intervention for each risk factor is huge task for physicians implying a high effort but this is worth doing because significant benefits have been demonstrated.

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