Introduction

Diabetes mellitus (DM) is a chronic metabolic disease widespread world which has provoked considerable worrisome for public health care. Despite the fact that there has been great progression in the treatment of diseases, prevalence and complications of DM is increasing and cardiovascular disease is the major cause of death in these patients. Many of diabetic patients with coronary artery disease (CAD) don't have any other classic risk factor for coronary disease and half of them have normal lipid profile, thus researchers in this field are looking for new risk factors to identify patients whom are prone to CAD **(Wild et al., 2004).**

Microalbuminuria (MAU) is a marker of endothelial dysfunction and vascular damage which could be a predictor for coronary artery atherosclerosis and early mortality in patients with DM type 2, independent of renal function **(Stehouwer et al., 2004).**

Many studies have shown positive relationship between increased MAU and CAD in diabetic patients, but there isn't a known specific cut off point for the level of MAU which may accompany with considerable increase in coronary artery stenosis. A few studies have suggested that the predictive level of MAU for vascular disease may be lower than threshold for diabetic nephropathy **(Zand Parsa et al., 2013).**

Atherosclerotic disease accounts for most of the excess mortality in patients with diabetes mellitus (DM).

Whereas much attention historically has focused on the prevention and treatment of micro vascular disease complications of diabetes (i.e., retinopathy, nephropathy,

and neuropathy), cardiovascular disease (CVD) remains the principal morbidity and driver of mortality in the setting of diabetes, most commonly in the form of coronary heart disease (CHD), but also in the incremental risk associated with diabetes for cerebrovascular disease, peripheral vascular disease, and heart failure. For these reasons, continual efforts toward mitigating the risk of CVD in diabetes remain a global public health imperative. Whereas older studies have suggested a diabetes-associated CVD risk similar to that observed among non diabetic patients with a prior myocardial infarction (MI) that is, a "coronary disease equivalent" ***(Donnelly et al., 2000).***

In the United Kingdom Prospective Diabetic Study (UKPDS), deaths from cardiovascular events were 70 times more common than deaths from micro vascular complications. Initial randomized trial showed that intensive glucose control (A1c<7%) decreases risk for a composite endpoint of all diabetes-related complications and significantly improved micro-vascular disease risk as well as significantly improved risk for MI and for all-cause mortality of obese patients. These observations have recently been extended by the publication of results derived from long-term post-trial follow-up, with an average duration of 10 years after completion of the trial reveal a significantly reduced risk for MI in those originally randomized to intensive control ***(Gerstein et al., 2008).***

Aim of the Essay

The aim of our essay was:

To investigate the correlation between both control of diabetes mellitus and microalbuminuria and the severity of coronary artery disease in diabetic patients.

Uncontrolled diabetes and coronary artery disease

Diabetes mellitus affects approximately 180 million people worldwide, and the number is expected to double by 2030, of those with diabetes, 90% have type 2 diabetes, approximately 80% of whom live in low- and middle-income countries. Future growth will be highest in developing regions such as Asia, Latin America and the Caribbean, and sub-Saharan Africa, where growth rates of diabetes are expected to be between 105% and 162%, compared with about 72% in the United States and 32% in Europe. In addition, most cases are and will remain within the 45- to 64-year-old age group in developing countries, whereas those older than 65 years are most affected in developed countries, **Figure (1).**

Rising rates of obesity, as well as an aging and urbanized population, likely link to the diabetes epidemic. Almost 90% of type 2 diabetes cases are related to obesity, and diabetes and its related complications are the costliest consequences of obesity. Mortality from diabetes is also increasing. About 1.1 million people died of diabetes in 2005, and that number is estimated to increase by 50% in 10 years ***(Gerstein et al., 2008)***.

Interestingly, Asian countries face a relatively larger burden of diabetes compared with the Europe and Central Asia or Latin America and Caribbean regions. For example, India and China have the largest numbers of diabetics 32 million and 21 million, respectively in the world. Indonesia, Pakistan, and Bangladesh are in the top 10 in terms of high absolute number of diabetics. Asian populations may have a higher risk for developing diabetes, even at a lower body mass index (BMI), because of a greater tendency toward visceral obesity. In addition, this population may experience

both under-nutrition (during the peri-natal period) and rapid weight gain (during childhood), a combination that increases the risk for insulin resistance (***Wild et al., 2004).***

In Egypt, it is estimated that; by the year 2025, the number of urban residents with diabetes will increase 3.2 times from approximately 2.28 million to 7.21 million and 13.3% of the population above 20 years of age will have diabetes.

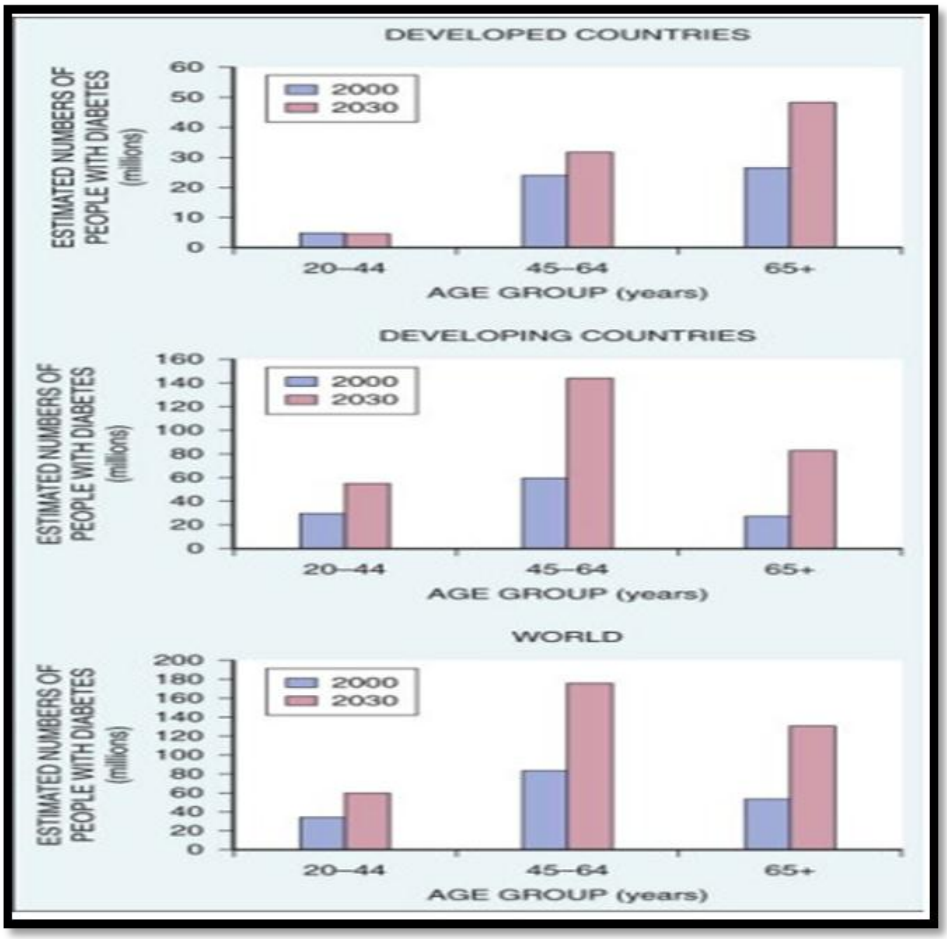

Fig. (1) : Estimated number of adults with diabetes in 2000 and projected for 2030 stratified by age group, with projections for the overall global population and by developed and developing country categories ***(Wild et al., 2004).***

Diagnostic criteria of diabetes:

Diabetes mellitus is a diseases characterized by insufficient production of insulin or by the failure to respond appropriately to insulin, resulting in hyperglycemia. The diagnostic criteria are summarized in Table (6). Importantly, new to the diagnostic criteria in 2010, HbA1c level ≥ 6.5% has been added. Diabetes is typically classified as type 2 diabetes, characterized by relative insulin deficiency with a backdrop of insulin resistance and representing >90% of all diabetes cases, or type 1 diabetes, characterized by absolute insulin deficiency ***(Alexander, 2014).***

Table (1): American Diabetes Association Diagnostic Criteria for Diabetes Mellitus

Fasting plasma glucose ≥ 7.0 mmol /liter (126 mg/dL) *
or
2-hour plasma glucose ≥ 11.1 mmol /liter (200 mg/dL) during standardized 75-g oral glucose tolerance test
or
Symptoms of hyperglycemia plus non-fasting plasma glucose ≥ 11.1 mmol/liter *
or
A1c ≥ 6.5% (200 mg/dL)

*should be confirmed by repeat testing on separate day (***Alexander, 2014).***

Influence of diabetes on cardiovascular disease:

Whereas much attention historically has focused on the prevention and treatment of micro-vascular disease complications of diabetes (i.e., retinopathy, nephropathy, and neuropathy), cardiovascular disease (CVD) remains the principal morbidity and driver of mortality in the setting of diabetes—most commonly in the form of coronary heart disease (CHD), but also in the incremental risk associated

with diabetes for cerebro-vascular disease, peripheral vascular disease, and heart failure. For these reasons, continual efforts toward mitigating the risk of CVD in diabetes remain a global public health imperative ***(Holman et al., 2008).***

Diabetes and Coronary heart disease:

Compared with non-diabetic individuals, patients with diabetes have a twofold to fourfold increased risk for development and dying of CHD as shown in **Figure(2).** Whereas older studies have suggested a diabetes-associated CVD risk similar to that observed among non-diabetic patients with a prior myocardial infarction (MI)—that is, a "coronary disease equivalent"—more recent observations from clinical trials including patients with diabetes suggest a substantially lower CHD risk, most likely reflecting the effectiveness of therapeutic interventions ***(Gerstein et al., 2008)***.

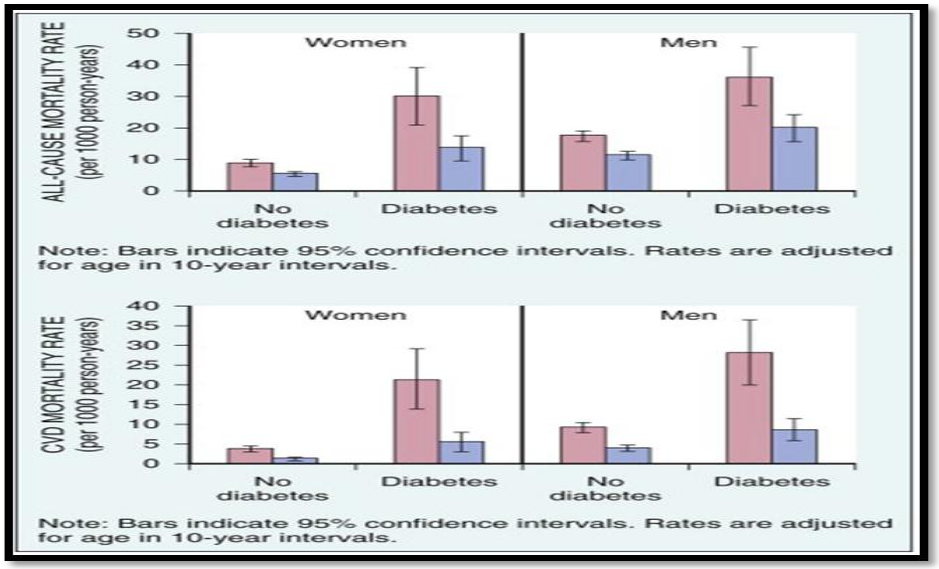

Fig. (2): Age-adjusted all-cause (top) and CVD (bottom) mortality rates among participants with and without diabetes mellitus by sex and time period. Pink bars represent earlier time period (1950 to 1975); blue bars represent later time period (1976 to 2001) ***(Gerstein et al., 2008).***

Diabetes is associated with an increased risk for MI; and across the spectrum of acute coronary syndrome (ACS) events, in which diabetes may affect more than one in three patients, patients with diabetes have worse CVD outcomes after ACS events **Figure (3)** ***(Wiviott et al., 2008)***

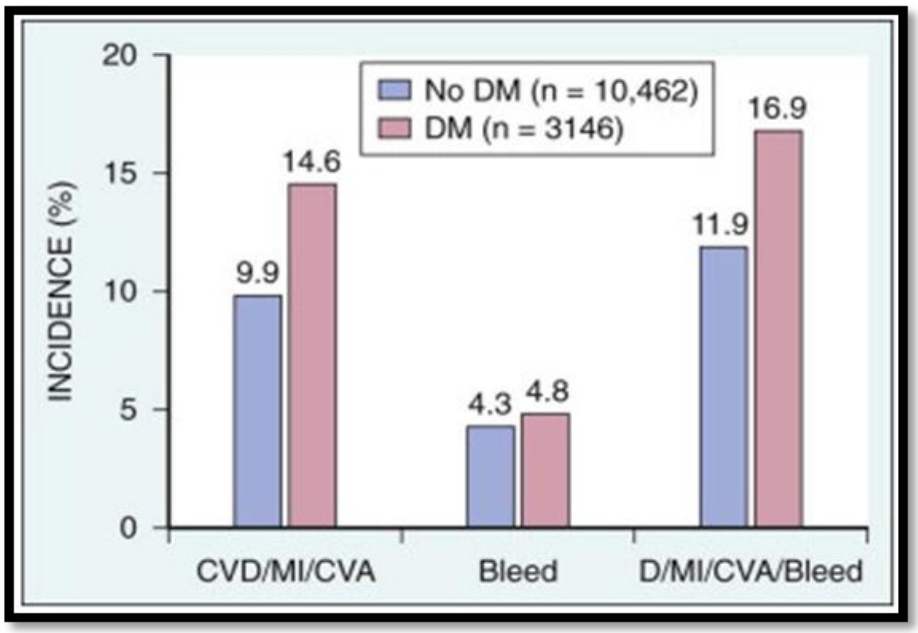

Fig. (3): Adverse clinical outcomes after acute coronary syndromes during more than 1 year of follow-up, according to diabetes status CVA = cerebro-vascular accident; CVD = cardiovascular disease; D = death; DM = diabetes mellitus; MI = myocardial infarction***(Wiviott et al., 2008)***.

Despite overall improvements in outcomes during the past several decades for patients with and without diabetes, the gradient of risk associated with diabetes persists **Figure** (4**) *(Pignone et al., 2010).***

Furthermore, the graded association of increased risk observed with diabetes in the setting of ACS events extends to glucose values in the range well below the diabetes threshold, whether it is analyzed by glucose values at the time of presentation or those observed throughout hospitalization, **Figure (5) *(Kosiborod et al., 2009).***

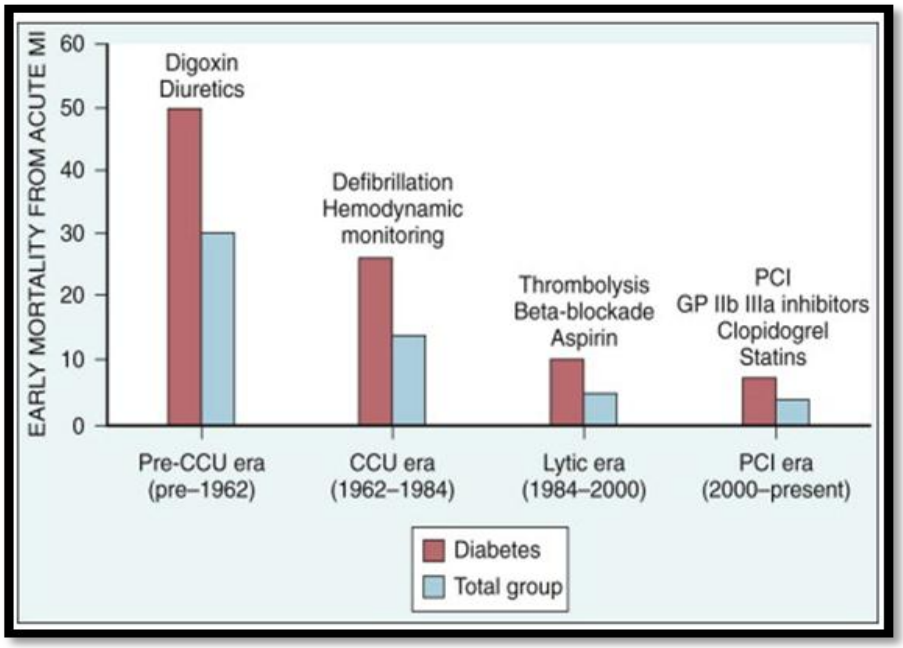

Fig. (4) : People with diabetes have an increased prevalence of atherosclerosis and coronary heart disease and experience higher morbidity and mortality after acute coronary syndrome and myocardial infarction than do people without diabetes.
CCU = coronary care unit; GP = glycoprotein; PCI = percutaneous coronary intervention ***(Kosiborod et al., 2009).***

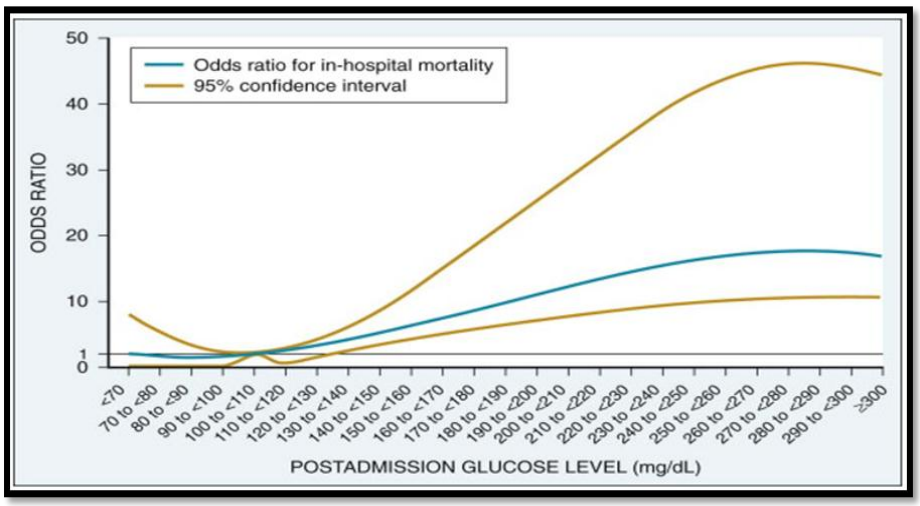

Fig. (5): Post-admission glucose levels and mortality in the entire patient cohort after multivariable adjustment (to convert glucose to millimoles per liter, multiply by (0.0555) ***(Kosiborod et al., 2009)***

Diabetes and peripheral arterial disease:

In addition to CHD, diabetes increases the risks of stroke and peripheral arterial disease. The diagnosis of diabetes portends a twofold increased stroke risk compared with non-diabetic individuals, with hyperglycemia affecting approximately one in three patients with acute stroke, associated with a twofold to sixfold increased risk for adverse clinical outcomes after stroke. Among patients with symptomatic peripheral arterial disease, diabetes prevalence ranges from 20% to 30% and accounts for approximately 50% of all lower extremity amputations (***Canavan et al., 2008).***

Diabetes and Heart Failure:

In the ambulatory setting, diabetes associates independently with a twofold to fivefold increased risk of heart failure (HF) compared with those without diabetes, comprising both systolic and diastolic HF, and diabetes patients have worse outcomes once HF has developed **(*Aguilar,2008).***

In addition, diabetes is associated with an increased HF risk in the setting of ACS events. The increased risk of HF observed in diabetes is multifactorial, caused by ischemic, metabolic, and functional myocardial perturbations **(*Saunders et al., 2008).***

Pathogenesis of Vascular Complications Of Diabetes:

Many complex mechanistic theories have been advanced with regard to diabetic atherosclerosis. These considerations have yielded an avid investigative field and have provided myriad potential therapeutic targets for which drug development programs are currently under way. Numerous mediators are emulated in the pathogenesis and the risk of CHD among patients with diabetes, **Table(2)**

Table (2): Mediators that implicated in Diabetic Vascular Disease *(**Orasanu and Plutzky, 2009**).*

Endothelium	↑ NF-κβ activat on ↓ Nitric oxide production ↓ Prostacyclin bioavailability ↑ Endothelin 1 activity ↑ Angiotensin II activity ↑ Cyclooxygenase 2 activity ↑ Thromboxane A_2 activity ↑ Reactive oxygen species ↑ Lipid peroxidatio products ↓ Endothelium-dependent relaxation ↑ RAGE expression
Vascular smooth muscle cells and vascular matrix	↑ Proliferation and mig ation into intima ↑ Increased matrix degradation Altered matrix components
Inflammation	↑ IL-1β, IL-6, CD36, MCP-1 ↑ ICAMs, VCAMs, and selectins ↑ Activity of protein kinase C ↑AGEs and AGE/RAGE interactions

AGEs = advanced glycation end products; ICAMs = intracellular adhesion molecules; IL = interleukin; MCP = monocyte chemoattractant protein; NF = nuclear factor; RAGE = receptor for advanced glycation end products; VCAMs = vascular cell adhesion molecule*(**Orasanu and Plutzky, 2009**).*

The pathobiologic attribution of hyperglycemia to CVD risk per se remains poorly understood; but given the clear associations between severity of hyperglycemia and CVD risk in both type 1 and type 2 diabetes (sharing hyperglycemia as the common pathophysiologic disturbance), hyperglycemia is likely to directly influence atherosclerosis development, progression, and instability.

The principal vascular perturbations linked to hyperglycemia include endothelial dysfunction, vascular effects of advanced glycation end products, adverse effects of circulating free fatty acids, and increased systemic inflammation. In addition, the pernicious effects of hypoglycemia complicating diabetes therapy, the sympathovagal imbalance due to diabetic autonomic neuropathy, and the vascular effects of constitutive exposure to excess insulin may further contribute to atherosclerotic risk ***(Orasanu and Plutzky, 2008).***

Endothelial dysfunction, a hallmark of diabetic vascular disease is associated with increased hypertension and adverse CVD outcomes. The myriad mechanisms contributing to endothelial dysfunction include abnormal nitric oxide biology, increased endothelin and angiotensin II, and reduced prostacyclin activity, all of which contribute to abnormal control of blood flow. In the setting of ACS events, no-reflow after percutaneous intervention reflecting acute endothelial dysfunction occurs more commonly in the presence of diabetes or hyperglycemia and may contribute to increased myocardial jeopardy, resulting in larger infarcts, increased arrhythmia, and worse systolic function **(*Rask-Madsen and King,2007).***

Abnormalities in lipid metabolism also contribute to the increased atherosclerotic risk associated with diabetes. Diabetic dyslipidemia is characterized by high triglyceride levels, low high-density lipoprotein (HDL) concentration, and increased atherogenic small dense low-density lipoprotein (LDL) particles, each of which is likely to contribute to the accelerated development and progression of atherosclerosis **(*Khera and McGuire,2005).***

Perturbations in the proteo-fibrinolytic system and platelet biology further compound the direct vascular effects of diabetes, yielding a constitutive prothrombotic milieu. These abnormalities include increased circulating tissue

factor, factor VII, von Willebrand factor, and plasminogen activator inhibitor 1, with decreased levels of anti-thrombin III and protein C. In addition, disturbances of platelet activation, aggregation, morphology, and life span further contribute to increased thrombotic potential, as well as to the acceleration of atherosclerosis ***(Mathewkutty and McGuire, 2009).***

Reduced membrane fluidity
Altered Ca^{2+} and Mg^{2+} homeostasis
Increased arachidonic acid metabolism
Increased thromboxane A_2 synthesis
Decreased nitric oxide and prostacyclin production
Decreased antioxidant levels
Increased expression of activation-dependent adhesion molecules (e.g., glycoprotein IIb/IIIa, P-selectin)
Increased platelet microparticle formation
Increased platelet turnover

Table (3): Perturbations of Platelet Structure and Function Associated with Diabetes ***(Mathewkutty and McGuire, 2009).***

Increased systemic inflammation portends an increased risk for diabetes and diabetic atherosclerotic diseaseand diabetes is associated with increased oxidative stress and the accumulation of advanced glycation end products ***(Libby and Plutzky,2007).***

For example, diabetes is associated with lipid-rich atherosclerotic plaque and increased inflammatory cell

infiltration, increased expression of tissue factor, and increased expression of the receptor for advanced glycation end products, yielding plaques with characteristics of higher risk in both coronary and carotid arteries (***Lindsey et al., 2009).***

Prevention of CHD and Its Complications in the Setting of Diabetes:

Life style modification:

Therapeutic lifestyle interventions remain the cornerstone of prevention of the atherosclerotic complications associated with diabetes; therapeutic targets are effective both for the prevention of type 2 diabetes and for the mitigation of atherosclerotic risk in the setting of diabetes. As recommended by the American Diabetes Association (ADA) and the American Heart Association (AHA), overarching therapeutic lifestyle targets include smoking abstinence, at least 150 minutes of moderate-intensity aerobic activity weekly, and medical nutrition therapy recommendations for weight control and dietary composition (**Standards of medical care in diabetes, 2010).**

Lipid Therapy:

Insulin resistance and type 2 diabetes are associated with a characteristic pattern of dyslipidemia. Each component of diabetic lipid abnormality independently associates with adverse cardiovascular outcomes, including increased small dense LDL particles, increased apolipoprotein B concentration, increased triglycerides, and decreased HDL cholesterol **(*Khera and McGuire,2005).***

Despite extensive research in modifying triglyceride and HDL cholesterol levels with a variety of pharmacologic agents, however, the net influence on CVD risk of these strategies remains uncertain, and the modification of LDL

cholesterol remains the cornerstone of therapeutic lipid intervention in patients with diabetes (***Pignone et al., 2010).***

(a) Statin Therapy:

Contemporary guidelines for the management of diabetic dyslipidemiafocus on the use of statin medications based on results from randomized clinical trials enrolling large numbers of patients with diabetes and supported by a recent meta-analysis yielding estimates of numbers needed to treat to prevent major adverse CVD complications in the setting of diabetes: 39 for primary prevention and 19 among patients with prevalent CVD ***(Kearney et al., 2008).***

Recommendations from many contemporary professional societies do not require elevation of LDL cholesterol as a requisite for the initiation of a statin; instead they use the aggregate risk assessment recommending statins for all patients with diabetes older than 40 years of age with one or more other CVD factors, or younger in the setting of prevalent CVD or clustering of CVD risk, endorsing the lower target of LDL <100 mg/dL or 35% to 40% reduction from baseline ***(Standards of medical care in diabetes, 2010).***

Once LDL cholesterol targets have been achieved through lifestyle modification and statin therapy, the principal secondary therapeutic lipid target for patients with diabetes who have persistent fasting triglyceride elevation >200 mg/dL is non–HDL cholesterol (i.e., total cholesterol − HDL cholesterol = non–HDL cholesterol). Therapeutic targets for this parameter are 30 mg/dL higher than the corresponding LDL cholesterol target for the individual patient ***(Pignoneetal., 2010).***

The preferred method to achieve the secondary non-HDL target is by intensification of statin monotherapy as tolerated, with the secondary option to add another lipid-