Cardiovascular Disease in Women With Diabetes Mellitus: a Review

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Objective. **To analyze cardiovascular disease (CVD) along wit it's contributing risk factors in women with diabetes mellitus (DM) and from this, to recommend prevention strategies.**

Methods. **A review of pertinent studies serves as the basis for the analysis and recommendations of prevention strategies in this group.**

Results. **Women with (DM) show a higher morbidity and mortality from CVD. The presence of DM confers these individuals the same risk of having a coronary event as present in a non-diabetic person who has suffered a previous myocardial infarction. Arterial hypertension, a characteristic dyslipidaemia (hypertrigliceridemia, low level of high density lipoprotein cholesterol and elevated low density lipoprotein cholesterol), obesity, microalbuminuria, platelet hyperaggregability and endothelial dysfunction converge conferring the women with DM a higher susceptibility to atherosclerosis. Recommendations include: lifestyle intervention weight reduction, increase in physical activity and smoking cessation. Women with DM should target to lower the LDL-C to a level below 100 mg/dl, the blood pressure level to below 130/80 mm Hg and triglycerides to less than 150 mg/dl. The goal is to raise HDL-C to a level over 45 mg/dl and reduce hemoglobin A1c (HbA1c) levels to below seven (7%) percent. Women with DM should use aspirin on a daily basis, unless contraindicated. These actions may lead to the reduction of the burden of CVD in women with DM.**

Conclusion. **This article summarizes the recent salient features of CVD in women with DM with emphasis on preventive measures as well as on the understanding of prevailing guidelines established under the principles of evidence based medicine.**

Key words: Diabetes mellitus,Women with diabetes mellitus,Cardiovascular disease in women, Cardiovascular risk factors in diabetic women

Cardiovascular disease (CVD) is the leading cause of death among women, but particularly in those with diabetes mellitus (DM). Women with DM show a higher mortality,morbidity and they also have a worse prognosis. The disease appears at an earlier age and carries greater morbidity in these individuals. Studies in diabetic women have shown a higher mortality after an acute coronary event as compared to males (1). Women with DM lose the protective effect from CVD conferred by the premenopausal years. DM accelerates the clinical course of atherosclerosis and increases both cardiovascular mortality and morbidity. Eight out of ten persons with DM die of CVD. Ischemic heart disease is the leading cause of death in both the United States and in its non-contiguous land areas including Puerto Rico, the U.S. Virgin Islands and Guam. Although CVD in the US general population has decreased by approximately one-third from 1980 to 1998, mortality has increased in the diabetic population by more than one-third over the same period (2). In a recent study, Haffner et al. (3) compared diabetic subjects without prior CVD and nondiabetic subjects with established CVD. Rates of myocardial infarction (MI) were 18.8% for nondiabetic persons with previous MI and 20.2% for diabetic patients without previous MI, similar after adjusting for age, sex and other cardiovascular risk factors. A similar increase in CVD mortality in both groups was found, which prompted the National Cholesterol Education Panel (NCEP) III to confer DM a long-term coronary heart disease risk level equivalent to that observed among patients without DM but who have had a previous myocardial infarction (4) .

Several risk factors contribute to the higher prevalence of CVD among women with DM. These factors include arterial hypertension (HTN), a characteristic dyslipidaemia, obesity, microalbuminuria, platelet hyperaggregability and endothelial dysfunction.

This review will comment on the risk factors that make the women with DM more vulnerable to CVD. It will also address the current recommendations on risk reduction strategies of CVD in women with DM.

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Hypertension. Hypertension (HTN) is a major risk factor for CVD morbidity and mortality. It affects up to seventy percent (70%) of persons with DM. HTN increases the risk of CVD two to three fold and contributes to the renal complications seen in diabetes. There is overwhelming evidence that hypertension control is associated with a significant reduction in total mortality and morbidity. Hypertension is twice as frequent in patients with DM. Sixty percent (60%) of patients with DM over the age of sixty (60) are hypertensive (5).

According to the National Health and Nutrition Examination Survey (NHANES) series (6), conducted by the National Center for Health Statistics, HTN prevalence for the women of different ethnic groups has increased between 1988 and 2000 (Non-Hispanic whites from 25.1% to 30.2%; Non-Hispanic black from 28.6% to 35.8% and Mexican American from 16.5% to 20.7%). Women, as compared to men, have the highest rates of HTN and the greatest increase in HTN prevalence. Awareness, treatment and control rates of hypertension remained unchanged throughout this period (7). According to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), although awareness of hypertension during the same period has increased, the percentage of persons with controlled HTN has not increased at the same rate. According to the NHANES findings, the percentage of control among all with HTN has increased from 24.6% in 1988 to 31.0% in 2000, but women tended to have the lowest rates of control (8).

The United Kingdom Prospective Diabetes Study (UKPDS), including 516 women, showed a significant reduction on mortality and cardiovascular events with tight control of HTN. This beneficial effect was independent of the therapeutic intervention with the beta-blocker atenolol or the ACE inhibitor captopril. (9) When all macrovascular diseases were combined (myocardial infarction, sudden death, stroke and peripheral vascular disease) there was a 34% risk reduction in the group assigned to tight blood pressure control compared with the group assigned to less tight control. UKPDS failed to show a statistically significant risk reduction in myocardial infarction related to blood sugar control.

The Captopril Prevention Project (CAPPP) (10) trial included over ten thousand patients with diastolic hypertension randomized to receive captopril, a thiazide diuretic or a beta-blocker. There were better overall outcomes and a risk reduction of CVD in the diabetic subjects assigned to captopril.

The JNC 7 (8) recommendations on blood pressure levels in subjects with DM are based on several studies including patients with either systolic and diastolic hypertension or isolated systolic hypertension: the UKPDS (11), the Systolic Hypertension in the Elderly Program (SHEP) Study (12), the Hypertension Optimal Treatment (HOT) (13) trial and the Systolic Hypertension in Europe (Sys-Eur) (14) trial findings. The JNC 7 recommends that blood pressure should be lowered to < 130/80 mm/Hg if no microalbuminuria is present. In subjects with microalbuminuria, the target should be < 120/80. Most subjects will require using a combination of multiple antihypertensive medications to reach goals. The current recommendation of the American Diabetes Association is that patients with DM should be treated to a systolic blood pressure of less than 130 mmHg and a diastolic blood pressure of less than 80 mmHg (15).

Microalbuminuria. Diabetic subjects with or without HTN develop microalbuminuria before they develop any clinical evidence of CVD (16). Microalbuminuria (MA) represents a urinary albumin excretion of 30 to 300 milligrams in a 24 hours collection period. MA is part of the Dysmetabolic Syndrome, which is associated to atherosclerosis. In the sub-analysis of the Heart Outcomes Prevention Evaluation (MICRO-HOPE) (17) Study, 3577 subjects with DM were analyzed to study the relationship between MA and cardiovascular and renal outcomes. The macrovascular composite primary outcome of myocardial infarction, stroke, or death from cardiovascular disease was reduced by 25% in patients with MA treated with ramipril compared to those on placebo. Total mortality and the need for revascularization were also reduced. This finding, similar to the findings of the Heart Outcomes Prevention Evaluation (HOPE) Study, occurred in spite of a modest reduction in HTN (3/2 mm Hg).

MA is a CVD risk factor and provisions should be taken to reduce the amount of MA. Prospective randomized well-designed studies (DCCT, UKPDS and Kumamoto) have shown that intensive blood glucose control reduces the incidence of MA. It is widely known that subjects with DM reaching Hemoglobin A1c levels equal or below 7.1% have shown a reduction in the rate of microvascular complications of DM such as Nephropathy. Tight control of HTN has also shown a reduction in microalbuminuria.

Dyslipidaemias. Subjects with diabetes, women included, have an alteration in lipoprotein metabolism, which leads to a characteristic dyslipidaemia: elevated levels of triglycerides (hypertriglyceridemia) and a decrease in the level of high-density lipoprotein cholesterol (HDL-C). The metabolic alteration defect consists of a delayed clearance of chylomicrons after meals, leading to an accumulation of triglycerides (TGS) in the blood stream. There is also a reduction of uptake of cholesterol by the low-density cholesterol (LDL-C) receptors, which leads

to a reduction in HDL-C and the formation of a denser, smaller particle of LDL-C. Small, dense cholesterol particles are more prone to be oxidized. Lower HDL-C levels, small dense LDL-C and hypertriglyceridemia are all associated to the development of CVD in diabetic subjects.

Women characteristically have higher levels of HDL-C. Estrogen up-regulates the LDL-C receptors, lowering LDL cholesterol levels in the blood. Pre-menopausal non-diabetic women have less prevalence of CVD than men. Women with diabetes (both pre and post-menopausal) have lower clearance of post-prandial TGS levels (18), higher levels of TGS after meals and more prevalence of CVD.

Hypertriglyceridemia. In women, several studies have linked elevated levels of TGS with increased risk of cardiovascular disease. A meta analysis of the population based Lipid Research Clinic (LRC) Follow-up Study, the Study of Women in Göteburg (GW), the Stockholm Prospective Study (SPS), the Framingham Heart Study (FHS) and the Cardiovascular Epidemiology Study (CES) showed a thirty-seven percent (37%) increased risk of CVD in women, which was independent of HDL-C levels. (19) Women with type 2 DM have a high risk of CVD. This may be secondary by reduced clearance of chylomicron remnants and associated postprandial hyper-triglyceridemia. Hypertriglyceridemia can be modified by blood sugar control and or the use of fibrates. The Helsinki Heart Study (20) showed a reduction of relative risk of 78% in CVD with the use of gemfibrozil in males and the Diabetes Atherosclerosis Intervention Study (DAIS) (21) showed a reduction of relative risk of 40% with the use of fenofibrate.

Hypercholesterolemia. Primary prevention studies in women with LDL-C elevation have demonstrated a reduction in CVD and mortality. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group concluded that Pravastatin therapy reduced mortality from coronary heart disease, overall mortality and cardiovascular events in patients with a history of myocardial infarction or unstable angina that had a broad range of initial cholesterol levels. Although the effect of treatment did not differ by sex, the power of the study cannot determine with reliability the effect in the small group of women with diabetes. The Scandinavian Simvastatin Survival Study (4S) (22) concluded that simvastatin therapy reduced mortality from coronary heart disease, overall mortality and cardiovascular events in patients with a history of myocardial infarction or unstable angina and elevated cholesterol levels. This study showed a 34% risk reduction in cardiovascular events in the group treated with simvastatin. The Sub-study of the Scandinavian Simvastatin Survival Study (4S) (23) of women with DM showed a reduction in coronary heart disease, overall mortality and cardiovascular mortality which was greater than in the non-diabetics. The risk reduction was of 55% in diabetics against a 32% risk reduction in non-diabetics. There were a total of 202 women in this study. The Cholesterol and Recurrent Events Trial (CARE) Study showed a greater relative effect of treatment in reduction of risk in coronary events in women with diabetes (24). The Heart Protection Study (HPS) (25), including 5963 subjects with DM, also demonstrated a reduction in risk of about 25% for cardiovascular events with the use of forty (40) milligrams of Simvastatin daily. The benefit in the latter study was independent of the presence of coronary disease, sex, the degree of blood glucose control or normal initial levels of cholesterol.

Aggressive lipid lowering therapy in women with DM should reduce CVD. The goal is to reduce LDL-C to < 100 mg/dl, reduce hypertriglyceridemia to less than 150 mg/dl and raise HDL-C to > 40 mg/dl. Statins are the best drugs for LDL-C reduction. The HPS findings show that simvastatin has a beneficial effect in reducing CVD even when baseline LDL-C values are not elevated beyond 100 mg/dl. HDL-C can be raised with physical activity, statins or niacin. The American Diabetes Association recommends aggressive therapy for diabetic dyslipidemia for reduction in CVD and agree with targets mentioned at the beginning of this paragraph. Patients with DM not reaching the targets with lifestyle modifications require pharmacological therapy (26).

Smoking. Smoking increases the risk of CVD. Smoking cessation reduces the risk of CVD. This intervention and that of maintaining physical activity are the lifestyle modifications that will have the highest impact in the reduction of CVD (27). Subjects with DM should be advised not to smoke and, if currently smoking, cessation of that practice should be pursued.

Obesity. Obesity is an independent risk factor for CVD mortality. An increase in body weight of one (1) Body Mass Index (BMI) unit (kg/m^2) was related to a 4% to 5% increase in CVD mortality in the Finnish Heart Study. An association between obesity and the risk of death from CHD was confirmed by this study of 8373 Finnish women aged 30-59 years, followed for 15 years. A substantial part of the risk was mediated through the link between body weight and blood pressure (28).

Obesity is also directly associated with the development of insulin resistance, hyperglycemia and diabetes. Having diabetes equals having CVD. The National Cholesterol Education Program Adult Treatment Panel III [NCEP ATP III] guidelines of 2001 consider DM as a coronary heart disease risk equivalent. (29) The link between diabetes and rising body weight has also been evident in the

NHANES study series. In the Nurses' Health Study, a direct association between baseline body weight and the latter development of diabetes was also found. (30)

Not all obesities have the same clinical connotations. Visceral or central obesity is more strongly related to CVD. Visceral fatty cells release pro-inflammatory substances such as interleukin-6 (I-16); tumor necrosis factor alpha (TNF-α) and plasminogen activating factor inhibitor (PAI-1), which predisposes to atherosclerosis. The visceral fatty cells presents the liver with an excessive burden of free fatty acids, which leads to overproduction of triglycerides and to a reciprocal decrease of high density lipoproteins (HDL).

The NCEP ATP III Panel (4) defined the Metabolic Syndrome in women as the presence of three or more of the following conditions: central obesity with a waist circumference greater than 35 inches, glucose intolerance, blood pressure over 130/85 mm Hg, high triglycerides (over 150 mg/dL) or low HDL-C (< 50 mg/dL) The Metabolic Syndrome is a prevalent risk factor for the development of CVD.

Hormonal replacement therapy. The long-term effects of hormonal replacement therapy (HRT) in women with or without DM do not confer cardiovascular protection. (31) The major factor for halting the Prempro arm of the Women Health Initiative (WHI) Study in July 2002 was the finding of an increased risk of cardiovascular events in this group. (32) In the HERS trial, in older postmenopausal women with established CVD, the use of HRT was associated with an increase in the risk of CVD events during the first year of use (33).

Aspirin. Aspirin has been used in primary and secondary prevention studies of CVD. The Early Treatment Diabetic retinopathy Study (ETDRS) (34) and the Hypertension Optimal Treatment (HOT) Trial (13) both included women. In both studies aspirin significantly reduced cardiovascular events and myocardial infarctions. The use of aspirin as a prevention strategy for CVD in women with DM is recommended.

Conclusions

CVD is the leading cause of death in women with diabetes. Women with DM are at a high risk for CVD. Several risk factors combine to make this group more vulnerable to CVD. Risk factors include HTN, microalbuminuria, obesity, smoking and dyslipidaemia. Since several of these risk factors are modifiable, women with DM should be encouraged to follow preventive strategies. Lifestyle intervention to lower the risk of CVD is of utmost importance. Women with DM should target the lowering of LDL-C to a level below 100 mg/dl, the blood pressure level to below 130/80 mm Hg and triglycerides to less than 150 mg/dl. Smoking cessation is recommended. The goal is to raise HDL-C to a level over 45 mg/dl. Women with DM should use aspirin on a daily basis, unless contraindicated. The modification of the identified risk factors is attainable through lifestyle interventions and the use of medications. This may lead to the reduction of the burden of CVD in women with DM.

The American Heart Association (AHA) recently published a scientific statement titled Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women. (35) Included among the AHA recommendations are to consistently encourage women not to smoke and accumulate a minimum of 30 minutes of moderate intensity physical activity most, but preferably all, days of the week. AHA recommends maintaining the waist circumference less than 35 inches. Women with DM are considered high-risk individuals for CVD and should use aspirin unless contraindicated, achieve a near normal HbA1c (< 7%), achieve optimal blood pressure of less than 120/80 mm Hg and optimal levels of lipids and lipoproteins (LDL-C < 100 mg/dL, HDL-C > 50 mg/dL, triglycerides < 150 mg/dL)

This review has summarized multiple studies that included women with DM and CVD that have provided scientific evidence for deriving guidelines for prevention and management of cardiovascular disease in women with diabetes.

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