

## DIABETES - A CARDIOVASCULAR DISEASE

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The situation is alarming in developing countries as glycaemia and diabetes are rising, driven both by population growth and ageing and by increasing age-specific prevalences.<sup>1</sup> The changing associations of metabolic risk factors with macroeconomic variables indicate that there will be a global pandemic of hyperglycemia and diabetes mellitus, together with high blood pressure in low-income countries, unless effective lifestyle and pharmacological interventions are implemented.<sup>2</sup> Increasing prevalence of diabetes goes hand in hand with rising prevalence of obesity and physical inactivity in a society.<sup>3</sup> In Pakistan, the prevalence of diabetes has been documented as 12.14% in males and 9.83% in females in some parts. Overall total glucose intolerance (diabetes and IGT) was present in 16.68% males and 19.37% females. Central obesity, hypertension and positive family history were strongly associated with diabetes.<sup>4</sup> Peshawar Heart Study documented frequency of diabetes in healthy adults as 5.2% to 7.8% in different occupations.<sup>5,6</sup>

Epidemiological and pathological data documents diabetes as an independent and significant risk factor for coronary artery disease (CAD) in both males and females.<sup>7-9</sup> Diabetes deprive women most of their inherent protection against developing CAD.<sup>10</sup> CADs is the cause of death in more than 65% of persons with diabetes.<sup>11</sup> Diabetes has been documented as an independent risk factor for different forms of CAD. Patients with stress hyperglycemia, hyperinsulinemia and uncontrolled diabetes developed more mechanical and electrical complications claiming higher morbidity and mortality after a myocardial infarction.<sup>12-14</sup> Diabetic patients sustain a worse prognosis for survival and have more complications with thrombolytic therapy than patients without diabetes.<sup>15,16</sup> Though diabetic patients have same caliber coronary artery vessels compared to non-diabetics as documented on angiography, but vessel involvement is usually diffuse in diabetics.<sup>17,18</sup> Moreover, myocardial ischemia due to coronary atherosclerosis commonly occurs without symptoms in patients with diabetes.<sup>16</sup> As a result, multivessel coronary involvement often is present before ischemic symptoms occur and before treatment is instituted. A delayed recognition of various forms of CAD undoubtedly worsens the prognosis for survival for many diabetic patients.<sup>19</sup>

Besides being predisposed to development of accelerated coronary artery disease, patients with diabetes are unusually prone to diabetic cardiomyopathy leading to congestive heart failure.<sup>20,21</sup> Heart failure is a frequent and at times fatal complication of diabetes which is often forgotten.<sup>22</sup> This is due to enhanced myocardial dysfunction leading to accelerated heart failure. Diabetic patients develop diastolic dysfunction which is worse in uncontrolled diabetics.<sup>23,24</sup> Untreated, it leads to systolic dysfunction and reduction of ejection fraction which can be picked up earlier employing newer technology in echocardiography.<sup>25,26</sup> Several factors contribute to diabetic cardiomyopathy: severe diffuse coronary atherosclerosis, prolonged hypertension, chronic hyperglycemia, microvascular disease, glycosylation of myocardial proteins and autonomic neuropathy. Therapies that may prevent or mitigate diabetic cardiomyopathy include better glycemic control, optimal control of hypertension and prevention of atherosclerosis with cholesterol-lowering therapy.<sup>27</sup>

An increased likelihood of sudden cardiac death and unrecognized myocardial infarctions in patients with diabetes has been documented in prospective studies.<sup>16,19</sup> More so, acute ischemic syndromes, peripheral arterial disease, and advanced CAD complications are seen more commonly in patients with diabetes than in those without.<sup>16</sup> As typical cardiac symptoms often are masked in patients with diabetes, diagnosis of myocardial infarction may be missed or delayed. Effective strategies for earlier detection of clinical CAD could reduce morbidity and mortality in patients with diabetes.

How does hyperglycemia induce atherosclerosis has been the focus of recent research. Hyperglycemia in patients with the metabolic syndrome appears to accelerate atherogenesis, possibly by enhanced formation of glycosylated proteins and advanced glycation products and/or by increasing endothelial dysfunction.<sup>28,29</sup> These direct consequences of hyperglycemia probably contribute to the microvascular disease underlying nephropathy and retinopathy, and they may promote macrovascular disease as well. Recent prospective studies confirm that all of the major cardiovascular risk factors-cigarette smoking, hypertension, and high serum cholesterol-act as independent contributors to CAD in patients with diabetes.<sup>4-8</sup>

Studies confirm a positive association between insulin resistance and hypertension.<sup>30,31</sup> Hypertension in itself is a multifactorial disorder and the mechanical connections between insulin resistance and hypertension are largely academic, however evidence for a causal link is growing.<sup>32</sup> When hypertension coexists with overt diabetes, which it commonly does, the risk for CAD and nephropathy, is doubly increased. It is interesting to observe that most patients with diabetes do not have elevated serum LDL cholesterol. However these patients have high enough levels to support the development of atherosclerosis. A role for LDL in hyperglycemic patients became apparent in landmark clinical trials, eg, the Scandinavian Simvastatin Survival Study (4S), the Cholesterol and Recurrent Events (CARE) trial, and the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID).<sup>33-35</sup> In all of these trials, aggressive LDL-lowering therapy reduced recurrent CHD events in patients with diabetes.

Aggressive comprehensive medical intervention in patients with established CAD may confer the following benefits: it extends overall survival, improves quality of life, decreases the need for intervention procedures - such as angioplasty and coronary artery bypass graft surgery and reduces the incidence of subsequent myocardial infarction.<sup>36</sup> In many patients with CAD, aggressive risk reduction with medical therapy will delay or eliminate the need for revascularization procedures. Secondary prevention entails treatment of risk factors in patients with established CAD. Though the number of patients with diabetes included in clinical trials has been limited, the available results suggest that these patients respond to secondary prevention interventions at least as well as those without diabetes.<sup>7,8,33-5</sup> Therefore, general guidelines for noninvasive, medical management in secondary prevention can be applied to diabetic patients with clinical CAD.<sup>37</sup>

It is imperative that other risk-reduction strategies shall be given equal importance as compared to that given to glucose control in patients with diabetes. Patients with type 2 diabetes should increase physical activity and eliminate excess body weight. Antiplatelet agents have become almost a norm in patients with CAD, and their use can be extended to patients with diabetes who have established CAD.  $\beta$ -Blockers have been shown to reduce cardiovascular mortality after myocardial infarction. They may be particularly effective in patients with diabetes, who are at risk for symptomatic ischemic episodes secondary to increased sympathetic activity.<sup>37</sup>  $\beta$ -Blockers are often mentioned as being contraindicated for patients with diabetes because of their blocking of hypoglycemic symptoms. Though physicians should be aware of this potential hazard, this shall not preclude use of  $\beta$ -blockers when CAD patients have diabetes. Angiotensin-converting enzyme inhibitors (ACEI) and Angiotensin Receptor Blockers (ARBs) are widely prescribed in the post-myocardial infarction period to favorably influence myocardial

remodeling and fibrosis, and they should be continued indefinitely in all patients with reduced left ventricular ejection fraction or symptomatic heart failure.<sup>38</sup>

Comprehensive risk assessment of diabetic patients must take into account major risk factors of CAD like cigarette smoking, elevated blood pressure, abnormal serum lipids and lipoproteins and hyperglycemia and predisposing risk factors like excess body weight and abdominal obesity, physical inactivity and family history of CAD. Identification of risk factors shall include a thorough medical history, careful physical examination, and appropriate laboratory measurements.<sup>37</sup> Risk factors like obesity, physical inactivity, and family history of premature CAD must be evaluated. Identification of predisposing risk factors may provide insight into the causation of major risk factors. Careful assessment of the status of the predisposing risk factor sets the stage for therapeutic intervention to control risk factors.<sup>2,3,10,37</sup>

Diabetes may be labelled as a cardiovascular ailment and it has a dominant role in causation of various presentations of CAD. It conspires with other risk factors and amplifies their role. Presence of diabetes determines worse outcome for patients afflicted with acute coronary syndrome. Diabetes lowers the threshold for the treatment of other risk factors and reduces the ideal goals for blood pressure and cholesterol. Diabetes plays an important role in selection of interventional strategy for obstructive coronary artery disease patient. The outcomes after intervention in diabetics are worse than non-diabetics and demand a more meticulous control of hyperglycemia and associated risk factors.

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