

Special Article – Diabetes

Co-Morbid Presentations and Coronary Heart Disease Risks with Type 1 Diabetes Mellitus

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This paper features putative risk factors and concomitant sequelae in the coexistence or co-morbidity of type 1 diabetes and coronary heart disease. Type 1 diabetes mellitus is associated with an increased risk of developing coronary heart disease. The coexistence of Type 1 diabetes and Coronary Heart Disease (CHD) impact deleteriously on patients presenting both ailments. Diabetes mellitus incidence persists at an accelerating rate, and has become an expansively prevalent and exorbitant in costs regarding chronic diseases.

Keywords: Co-Morbidity; Macro vascular disease; Prevalence; Etiopathogenesis; Complications

Introduction

Coronary Heart Disease (CHD) is one of the major complications of Type 1 diabetes whose etiopathogenesis still confounds both researchers and clinicians. CHD contributes a higher morbidity and mortality among diabetic persons with an earlier inception than in the non-diabetic population. Prospective population-based studies of the incidence and risk factors of CHD in patients diagnosed for early-onset Type 1 diabetes have elevated risk of cardiovascular aberrations and accelerated mortality in contradistinction to the non-diabetic/general population. Type 1 diabetes need to be carried out in populations with different CHD risk and incidence of Type 1 diabetes. To achieve adequate prevention, management and treatment, it is pertinent that veritable measures in the understanding of CHD as related to Type 1 diabetes mellitus are put in place. In conclusion, diabetes patients presenting with coronary heart disease have lower quality of life in comparison to non-diabetic patients as related to clinic pathological, physical and psychosocial parameters [1-4].

A plethora of studies depict that Type 1 diabetes mellitus patients present with augmented risk for diverse cardiovascular disorders, such as coronary heart disease, cardiomyopathy, congestive heart failure, peripheral artery disease, stroke and other cerebrovascular challenges. Cardiovascular sequelae are the salient aetiologies in diabetes-associated morbidity and mortality. In Type 1 diabetic persons, the coexistence of diabetes duration and prognosis, glycaemic control and the treatment drugs available to achieve control, hypertension, lipid profile and other risk presentations are liable to confound the impact of Type 1 diabetes mellitus and the risk of coronary heart disease. Coronary Heart Disease (CHD) connotes a clinical entity embracing numerous clinical syndromes indicative of damaging effects of coronary atherosclerosis. The clinical and/or epidemiological relationship between Type 1 diabetes and CHD still confounds both researchers and clinicians alike. Most of the mortality of diabetic patients in comparison to the general population [1-3] is attributed to macro vascular disease [4]. The manifestation of macro vascular lesions as ischemic heart disease or peripheral artery disease is the main reason for increased mortality in diabetic patients [5]. All vascular diseases (both micro- and macro-vascular entities) account

for most of all deaths manifested as ischemic heart disease in diabetic patients [6].

Several data are suggestive that by the fifth decade of life, circa thirty-three percent of Type 1 diabetes patients die from atherosclerotic lesions, which present more excruciating and expansive impact in Type 1 diabetic patients of both sexes. CHD also manifests as cardiac perturbations, such as silent myocardial infarction. This paper will be limited to macro vascular lesions. Epidemiological investigations have attempted the identification of several attributes of individuals and environmental factors [7], which probably augments the mortality of the clinical entities, which constitute CHD [8].

Coronary Heart Disease (CHD) constitutes a long-term complication of Type 1 diabetes, and is a major concern for the patients, their families and healthcare providers. For the essence of this study, CHD will be presented as CVD and other macro vascular events, even though; they may represent disparate path physiological pathways. Although, the increased premature heart disease risk in Type 1 diabetes has been realized for a while, the underlying etiopathogenesis has not been properly elucidated. Hyperglycemia is the culprit, a priori, that is accountable for the increased risk. Evidence and risk management are oftentimes extrapolated from experience in Type II diabetes and the general population. The drawback is that the underlying path physiology, natural history and demographics as well as the greater life expectancy in young Type 1 diabetes differ from Type II diabetes and the concerned population [9]. There is an extant inextricable linkage between diabetes and cardiovascular that is one of the most prevalent etiological contributors of morbidity and mortality in the diabetic population. Risk factors in diabetes, such as unwholesome diet, physical inactivity, dyslipidemia, hypertension and obesity are ubiquitous in diabetic patients with resultant cardiac perturbations. Thus, it is pertinent to target coronary heart disease risk factors in diabetic patients to mitigate the long-run sequence of the diseases.

Parameters of Type 1 diabetes associated with CHD

CHD comprises numerous clinical syndromes involving myocardial ischemia with an association of profound coronary

atherosclerosis [8]. Coronary atherosclerosis has frequently been described as coronary heart disease [10] and as ischemic heart disease [11], per se. Also, invasive studies of a select group of subjects by means of echocardiograms or exercise radionuclide ventriculograms in conjunction with coronary angiography or exercise thallium studies were suggestive of abnormal ventricular function without the manifestation of CHD [12], characterizing asymptomatic CHD. It has been shown that diabetes constitutes a major risk factor for atherosclerotic disease. An association has been shown between diabetes and a cluster of coronary risk factors in comparison to the general population [13]. The coronary risk factors have similar prognostic significance, though the overall risk of CHD in the diabetic population is higher than among non-diabetic people [14]. One of these is the elevated triglyceride levels, which constitute an independent risk factor in diabetic patients [15].

There are geographical differences [2,3,16] in the prevalence of CHD among cohorts of diabetes [17], and as depicted in the incidence of the general population [18]. It is suggestive that diabetes is not primarily causative of the accelerated development of atherosclerotic lesions. The presence of Impaired Glucose Tolerance (IGT) among people who do not have diabetes may constitute an increased risk of cardiovascular lesions [19]. There is a high prevalence of IGT especially among adolescents with CHD [20]. Coronary risk factors and hyperinsulinemia tend to cluster in subjects with IGT.

Diabetic females are reported to have an increased risk of macrovascular lesions in comparison with their male counterparts [21], which, however, diminishes relatively with age [22]. The susceptibility of the diabetic arterial wall to pathogenic factors, hormonal and metabolic perturbations in association with other risk factors may predispose to atherogenesis [5]. The control of cardiovascular risk factors in diabetic subjects is more important than in the general population due to the several complications involved. Practically, preventive measures and control including multivariate risk assessment would depend on medical, lifestyle or individual attributes and environmental factors [3], which could enhance the reduction of CHD in diabetic persons. Generally, Type 1 and Type II diabetic subjects including persons with IGT are considered susceptible to higher mortality if ischemic heart disease is manifested [13]. This review will be particularly limited to Type 1 diabetes with some specific generalizations to other types of diabetes. Complications may not be specific to Type 1 diabetes but may also be related to other types of diabetes.

Etiopathogenesis

Notwithstanding the determined risk of Cardio Vascular Disease (CVD) in Type 1 diabetes, the pathophysiology linking cardiovascular events, CVD risk factors, and Type 1 diabetes remains incomprehensible. Management strategies for CVD mitigation have been extrapolated expansively from Type II diabetes irrespective of the more extended duration involved in Type 1 diabetes than in Type II diabetes, and the particular differentiations in the presenting pathophysiology. In addition, there is an extensive metamorphosis in Type 1 diabetes phenotype necessitating rigorous diabetes management as the standard of care tending to increased life span. It is pertinent to note that the current understanding of cardiovascular aberrations emanate from erstwhile periods of diminished intensive

glycemic control. Current expansive and intensive glycemic control is inextricably linked with significant risk of weight gain that may become profound during the prevailing preponderance of obesity epidemic. Much interest is to comprehend more of the debilitating impacts of glycemia, the prevalence and characteristics of Type 1 diabetes, lipid derangements, the prognostic features of albuminuria and renal impairment or insufficiency, neurological perturbation as well as the functionality of blood pressure in cardiovascular disease. Obesity-linked metabolic perturbations, such as the pro-inflammatory condition may alter the risk of CVD in Type 1 diabetes; the impact may differ from what is observable in Type II diabetes, though [23] the peculiarity of Type 1 diabetes may be due to the genesis of antibodies, which perturb the heart [24].

Gross anatomic and histologic revelations

Diabetic persons manifest greater atherosclerotic lesions than the general population of similar age and sex [25]. Experimental investigations on the morphology of extramural or epicardial coronary arteries have been mainly on Type II rather than on Type 1 diabetic subjects. These studies have concentrated on gross anatomical considerations or few histological examinations of the coronary arteries. Only few comparisons were made with non-diabetic controls. Intramural coronary arteries have been examined extensively in Type II and not in Type 1 diabetic subjects. A detailed quantitative examination of the coronary arteries in a group of Type 1 diabetic patients was performed and the results compared to those of controls [26]. The study showed that Type 1 diabetes presents increased epicardial coronary atherogenesis than controls of similar age and sex. The accelerated coronary atherogenesis in diabetes in contrast to controls does not imply the manifestation of coronary heart lesions in later life because of the early inception of diabetes [27]. Thoracic pain is not as intense and frequent in diabetes as in the absence of diabetes of similar age and sex who have been electrocardiographically detected as having acute myocardial infarction [28].

Pathologic manifestations of cardiovascular lesions in diabetes involve intimal proliferation, wall thickening and perivascular fibrosis [29], thickened capillary basement membrane [30] including micro aneurysms [31]. Diabetic mortality due to heart failure devoid of marked constriction of either the coronary arteries or intramural vessels was shown at autopsy to have great accumulation of PAS-positive material in the area of the left ventricular interstitium as well as marked interstitial fibrosis. Inasmuch as the arterial wall is especially susceptible to pathogenetic factors in diabetes, hormonal and metabolic perturbations undergo diverse interactions with antidiabetic drugs, such as exogenous insulin and lipoprotein disorders as associated risk factors in the initiation and promotion of atherogenesis [5].

Insulin

Hyperinsulinemia has been suggested to be a significant independent risk factor for CHD via the review of prospective population studies [13]. Insulin augmentation in the development of atheromatous lesions of the arterial wall has been observed experimentally [32]. Increased concentrations of unbound insulin resulting from inadequate insulin treatment were detected in several Type 1 diabetics subjects [33,34]. Excluding intraperitoneal

administration, the problem in insulin medication is the resultant abundant insulin-flow to peripheral tissues. The resultant effect is hepatic hypoinsulinemia with concomitant peripheral hyperinsulinemia [5]. This is in contradistinction to the normal physiological conditions where insulin secreted by the pancreas is mainly acted on by the hepatic system. There is an extant association of hyperinsulinemia with arterial disease other than with myocardial ischemia as observed in elevated levels of insulin in myocardial infarction, angiographically identified coronary artery atherosclerosis [20], cerebrovascular [35] and peripheral vascular [36] lesions. The association of insulin with atherogenesis may be due to its indirect effect on the arterial wall or interactive effects(s) with lipids and lipoproteins [37].

Etiopathologically, primary diabetes with insulin deficiency [34] and secondary hyperlipoproteinemia are in abundance in neglected and inappropriately controlled Type 1 diabetes. This is due to the decreased lipoprotein lipase activity because of the lack of unbound insulin resulting in impaired removal of triglycerides. There is a marked decreased HDL level and moderately to highly elevated levels of VLDL and chylomicrons. Marked lipemia/“chylomicronemia syndromes” result if chronic insulin deficiency interacts with on-going processual hypertriglyceridemia in Type 1 diabetic patients on inappropriately high insulin administration, hyperinsulinemia will culminate in secondary hyperlipoproteinemia. This is due to increased hepatic synthesis of VLDL in the presence of hyperinsulinemia that is characteristically manifested in Type 1 hyperlipoproteinemia with mild to moderate increase of triglycerides, and diminished effect on cholesterol fractions [5]. Even though, speculations are rife as to the true etiopathogenesis in the perturbation of plasma lipoprotein levels in Type 1 diabetes, it is suggestive that accelerated HDL production manifests during normal or augmented lipoprotein lipase activity and high levels of triglyceride bearing circulating lipoproteins [38].

A study provided a risk estimation model to predict Silent Myocardial Ischemia (SMI) in Type 1 diabetes. The model merely included insulin resistance and active smoking as major SMI predictors [39]. Insulin resistance induces an imbalance in glucose metabolism that causes chronic hyperglycemia, triggering oxidative stress and precipitates an inflammatory response culminating in cell degeneration. Insulin resistance is liable to perturb systemic lipid metabolism resulting in dyslipidemia development and consequently the lipid triad: (a) elevated concentration of plasma triglycerides; (b) decreased concentrations of HDL; and (c) the presence of small dense LDL. This triad in combination with endothelial dysfunction induced by aberrant insulin signaling enhances atherosclerotic plaque formation. Insulin resistance in the myocardium generates metabolic cardiac alterations via three disparate mechanisms: (a) alteration in signal transduction, (b) dysfunctional regulation of substrate metabolism, and (c) impaired substrate transport to the myocardium with expansive progression of cardiovascular disease [40].

Lipids and glycemic control

Numerous factors may be involved in the differential concentrations of lipoprotein sub fractions in Type 1 diabetes. The extent of glycemic control has an influence in the concentrations of lipoproteins in early-onset Type 1 diabetes [41], and differences in the concentration of lipids have been detected in microalbuminuric

diabetes with poor glycemic control in comparison with concentrations observed in diabetic patients with normal concentration of albumin and good glycemic control [42].

In Type 1 diabetes patients, HDL cholesterol, total cholesterol and total glycerides maintain normal limits during controlled blood sugar. Good glycemic control present in Type 1 diabetes decreases LDL and VLDL to normal concentrations with tendency to elevate HDL in excess of the normal ranges. Poor metabolic control significantly predicts CHD events in patients having late-onset Type 1 diabetes, solely without other risk factors [43].

Coagulation factors

Many views have been given as to the effect of perturbations of the coagulation system as risk determinants in CHD in Type 1 diabetes [44]. Platelet adhesiveness was found to be increased in diabetes in pregnancy in the presence or absence of vascular lesions with concomitant increased sensitivity to aggregating agents. In the general population, fibrinogen concentrations are predictive of heart lesions [45] with a higher increase in diabetes, though [44]. In another study, it was shown that there is an acceleration of vascular disease due to enhanced thromboxane production by platelets, marked decrease in the production of prostaglandin 12 (prostacyclin) glycosylated collagen-promoted platelet aggregations and decrease in the life span of platelets in diabetes [46]. Atherothrombotic complications are the major etiological agents of mortality in diabetic persons. Premature atherosclerosis, elevated platelet activity and coagulation factor activation combined with hypo fibrinolysis are contributory to augmented cardiovascular risk in diabetes. Blood clot generation is the ultimate step in the atherothrombotic trajectory, and the framework of the fibrin network has functionality in a determined predisposition to cardiovascular disease. Thus, newfangled antithrombotic procedures and high potent agents or drug combinations could provide expansive clinical advantages in diabetic patients than in the general population [47].

The increased post-synthetic chemical modification of low-density lipoproteins

It is well established that there is an increase in the glycosylation of Low Density Lipoproteins (LDL) in diabetes, but inadequate evidence as regards the oxidation of LDL necessitates further investigation. In this regard, the contribution of increased oxidation of LDL to marked atherogenesis in diabetes becomes pertinent. Chemical modification of post-synthesized LDL by increased oxidation and/or glycosylation may precipitate endothelial cell injury in the presence or absence of acceleration of foam cell formation due to monocyte-macrophage action in the intima of the artery. Available data do not make provision for adequate proof that lipid peroxidation is associated with the initiation or enhancement of uncomplicated human diabetes. Increased glycosylation of LDL is depicted from diabetes inception, and is more atherogenic in contradistinction to pronounce to heightened oxidation [48].

Factors associated with CHD in the general population and in Type 1 diabetes

Epidemiologically, numerous risk factors for CHD development in the general population have been identified as family history, advanced age, male sex, IGT, hypercholesterolemia, hypertension,

smoking, lack of physical activity and obesity. None of the conventional cardiovascular risk factors, such as cigarette smoking, serum cholesterol or blood pressure, disparately or synergistically definitely explicates or elucidates the excess or abundant risk of ischemic heart lesions in diabetes [30]. The greater the number of coronary risk factors, the higher the susceptibility or predisposition to CHD, irrespective of the presence or absence of diabetes. No absolute or overwhelming correlation is extant between risk factors and CHD incidence. Other associated risk factors include family history and IGT [31]. There is not available at this time any long-term population-based prospective study regarding the risk and determinants of CHD in Type 1 diabetic patients.

A double increased risk of cardiovascular events and mortality is extant in patients with manifested IGT; however, evidence is not available of inextricable linkage between asymptomatic hyperglycemia and the risk in the development of cardiovascular disease [49]. In patients with coronary heart disease, such as Myocardial Infarction (MI) and angina, there is an increased prevalence of IGT [50]. Coronary heart disease is more prevalent in diabetes with a doubling mortality effect than in the general population [51]. The incidence of CHD is greater amongst diabetic subjects than the general population [52]. There is no clear evidence that hyperglycemia constitutes a risk factor in Type 1 diabetes.

Mortality resulting from CHD is greater in male persons than in female persons; this discrepancy diminishes with increasing age at about the fifth decade of life. The reason for this phenomenon is not pellucid. A study showing higher HDL-C levels in Type 1 diabetes in comparison to non-diabetic adults revealed that differences are greater in male than in female subjects [53].

It has been observed that the female survival advantage as regards cardiovascular disease in the general population is not evident among diabetic women [54]. Another study indicated that a probable existence of human female survival advantage observed in the general population might be evident in Type II but not in Type 1 [55]. Further studies are necessary to elucidate this observation. In diabetic females, there is a greater risk of vascular complications than in male subjects resulting in a two-fold increase of higher mortality [56], increase in the prevalence of congestive heart failure and increase in morbidity due to CHD [21]. This susceptibility of female subjects to CHD may indicate that diabetes selects or is selective of one or several of the risk factors inextricably linked in atherogenesis and/or develops a marked aspect of a vascular lesion more susceptible in female than in male persons. Type 1 diabetes confers a greater risk in incident CHD in women than in men due to the probability that at any provided glycemic control, women present a worse risk factor profile than men. In addition, diabetic women may be sub-optimally treated in comparison to men concerning lipid and blood pressure targets and trends as well as the impact of diabetes duration in explicating cardiovascular disease risk disparities between the sexes [57]. The protective effect of the status of pre-menopause is diminished in diabetes [58].

Risk factors for CHD in Type 1 diabetes

Lipids and associated factors: There have been implications of elevated serum lipid and lipoprotein levels as etiological agents in premature incidence of CHD in diabetic patients [55]. Low levels of

HDL cholesterol in NIDDM patients superimposed on atherosclerotic macro vascular disease have been reported [59]. Similarity exists in these findings and those conducted with non-diabetic atherosclerotic patients, which showed an inverse correlation between HDL and CHD incidence [60]. The measurements of plasma and lipoprotein cholesterol and triglycerides, glucose and hemoglobin A_{1c} (HBA_{1c}) concentrations were performed in 106 patients and 36 normal volunteers having age similarities and sex distribution. The analysis was based on the extent of metabolic control by 24h glycosuria and HBA_{1c} levels. The results showed that there exists no significant difference between normal volunteers and Type 1 diabetic subjects in good and fair control. On the other hand, Type 1 diabetic subjects of both sexes who had poor control had a marked decrease in HDL cholesterol level, and high concentrations of all lipoproteins and lipids [61]. A group of researchers reviewed case histories of Type 1 diabetic patients and revealed an excessive frequency of cardiovascular mortality and MI [62]. It was found that the excess risk was not adequately quantified, and lack of clear association with poor metabolic control of hyperglycemia as well as perhaps absence of explanation due to conventional cardiovascular risk factors. The lowering of HDL cholesterol levels was not consistently observed in diabetic patients than in normal subjects. The description of anomalies of the coagulation system in diabetic CHD eluded the researchers. Anomalies of path physiologic consequences were observed in some younger patients in the absence of macro vascular disease; however, their relative significance to excess cardiovascular morbidity and mortality remains confounding.

Blood pressure and associated factors: An assessment of cardiovascular risk factors inter alia blood pressure, lipoprotein concentrations including diet was performed involving 149 diabetic adolescents and 45 non-diabetic siblings. They presented with Type 1 diabetes at least for two years, and were attending the Children's Hospital of Pittsburgh Diabetes Clinic. There was mild perturbation of cardiovascular risk profiles as regards diabetic persons in comparison to normal siblings for both sexes. The derangements included higher systolic and diastolic blood pressures and higher HDL₃ cholesterol levels [63].

Elevated total cholesterol levels were observed in the diabetic girls in adolescence in contrast to the usual decrease observed in normal adolescents including the normal siblings studied. In contrast to the boys, the diabetic girls exhibited a mean pulse rate of 12bpm higher than that of the normal female siblings. With the analytical use of multiple linear regression, glycemic control (worse in diabetic girls), diet, or physical activity could not explain any of the detected measurements of blood pressure or lipoprotein [63]. It was, therefore, suggestive that there was a relative perturbation of the cardiovascular risk profile of diabetic girls in comparison to diabetic boys. Trends and targets have been clearly explicated in the general population regarding high blood pressure [64] that can be extrapolated to Type 1 diabetes.

Proteinuria and associated factors: A retrospective study of the risk of premature CHD and its determinants using a cohort of 292 Type 1 diabetic subjects was performed [49]. Irrespective of the observation that Type 1 diabetes had profoundly high risk of premature CHD, mortality occurred within the third decade. Beyond the third decade, the CHD-related mortality rate increased

geometrically, especially in both sexes of those patients with nephritic complications. About the fifth decade, the cumulative CHD-related rate was 30-40%. This showed a higher rate than that of normal persons in the Framingham Study, i.e. 8% for male subjects and 4% for female subjects [65].

A similar pattern was observed in angina and acute MI as was evident in asymptomatic CHD revealed by stress test giving the resultant combined prevalence rate as 33% for survivors of the age range 45-59 years [65]. It was suggested that this pattern of Type 1 diabetes and its nephritic complications tend to modify the natural history of atherosclerosis and are not contributory to atherosclerotic inception, even though, they severely accelerate the progression of minor atherosclerotic lesions to profound proportions as evident in CHD.

Type 1 diabetic persons showing the development of proteinuria may face premature mortality while those without this complication may comparatively have a normal life. The frequent excessive mortality in proteinuric diabetic patients results from cardiovascular and renal diseases with no definite explanations. An assessment of risk factors for vascular diseases was performed in 22 Type 1 diabetic patients with proteinuria but not renal failure [66]. They were matched for sex, age, diabetes duration and glycalated hemoglobin values with an equal number and normal urinary albumin excretion rates. The accumulation or aggregation of risk factors for macro vascular disease in Type 1 diabetes with a complication of proteinuria assisted in the explanation of the increased prevalence of ischemic cardiovascular and peripheral vascular lesions observed in the study. Another study investigated the incidence of CHD and its associations with blood pressure, serum cholesterol and smoking in a cohort of young Type 1 diabetic individuals at the inception of clinical nephropathy [67]. It was found that Type 1 diabetic subjects with clinical nephropathy have a much higher increased incidence of CHD in contrast to those without nephropathy. The characteristic measures of those who developed CHD were elevated blood pressure and serum cholesterol concentrations.

Evidence is increasing that susceptibility to proteinuria seems to be a marker for an elevated increase in vascular permeability contributory to an enhanced predisposition of diabetic persons to arterial disease [68]. Microalbuminuria is an early marker of renal damage in Type 1 diabetes with or without CHD. There is a significant predictive functionality of baseline albuminuria of CHD pathogenesis in Type 1 diabetes [69]. In addition, sex-specific risk factors, such as fasting triglycerides or HDL cholesterol, systolic blood pressure and WHR were determined to be pertinent in CHD development. It is important to elucidate the atherogenic mechanisms in diabetes, screening guidelines, the clinic epidemiological resultant impact of diabetes and heart disease, with the underlying premise to regard diabetes a cardiovascular equivalent in the exploration and recommendations for cardiac screening and testing for asymptomatic diabetes [70].

Discussion

The ubiquitous conditions in coexistence with Type 1 diabetes mellitus, such as dyslipidaemia and hypertension are veritable risk factors for coronary heart disease and other cardiovascular disorders,

with diabetes posing as an independent risk. The efficacy in the control of individual cardiovascular risk factors in the prevention or mitigation of coronary heart disease in Type 1 diabetic subjects is tenable. Cardiovascular disease persists as a leading cause of death worldwide. In the general population, the determinants of CHD are important for the prevention, management and treatment of morbidity and/or premature mortality in diabetic patients. A study indicated that CHD does not constitute a precise and appropriate monitor of the severity of atherosclerosis, and that CHD risk factors are erroneously assumed etiologic agents of atherosclerosis by inapplicable extrapolation [8]. The study cited the misuse and profound diagnostic error of CHD, errors in the determination of the prevalence of risk factors, the use of young minority sufferers who do not represent the CHD population, inclusion-bias of Familial Hypercholesterolemia (FH) in clinical studies, and the inability of multivariate statistical analyses to adequately differentiate between the effects of the mutual relationships, influence of genetics and age-dependent hypercholesterolemia, hypertension, diabetes and obesity as the confounding variables detected in many research papers [8,71].

A lot is needed for the comprehension of interrelationships between diabetes and heart disease with regard to incidence, prevalence, analytical effects of age and diabetes duration including other cardiovascular manifestations in Type 1 diabetes. In addition, prospective studies of the role of risk factors inter alia HDL-cholesterol and its sub-fractions, coagulation factors and glycemic control seem pertinent. It has been recognized that accelerated atherogenesis and premature cardiovascular mortality constitute complications of diabetes. It has been suggested that by epidemiologists that an excess risk of macro vascular disease exists in Type 1 diabetes.

Not only diabetic subjects in good metabolic control may present with relatively normal levels of lipids and lipoproteins but also those in fair metabolic control. The evident correlation between HBA_{1c} and lipids including lipoproteins in the plasma is suggestive that the concentrations of the latter are indicative of metabolic regulation in young Type 1 diabetic individuals [61]. Cardiovascular disease represents the major cause of excess and premature mortality in diabetes in comparison to the general population. This excess mortality, especially in industrialized countries may be attributable to increased prevalence of vascular disease [72-74]. The protective effect of the status of pre-menopause is diminished in diabetes including the presence of a few select complications, for instance, diabetic nephropathy [50] as detected in Type II diabetes [72].

Diabetes duration, economic and clinical features [1] are important factors in the development of several complications. A cohort of diabetic patients is invariably a survivor population, however, the effect of mortality associated with diabetes antecedent to age 35 may not be relatively large enough, and may be characteristic of Type 1 diabetes. Even though, the reasons the reasons for the excess cardiovascular mortality in diabetes remain elusive at present, there is accumulative evidence that proteinuria may constitute a marker for a broad-based increase in vascular permeability and adverse contributory factor to arterial disease [68]. Diabetic nephropathy and proteinuria form a linkage with atherogenic predilection of plasma lipids [42], elevated arterial pressure [50,64] and abnormal hemostatic factors [75] which may be contributory factors to atherogenesis, even

at the inception of microalbuminuria [76].

However, many patients do not present with CHD irrespective of long duration of persistent proteinuria and renal failure [77]. It may mean, therefore, that diabetes and diabetic nephropathy influence the progression of atherogenesis and not in its initiation. In corollary, countries with low risk of CHD seldom have diabetic patients with renal lesions presenting with CHD [78]. Practically, efforts in the reduction of excessive cardiovascular mortality in Type 1 diabetes should consider proteinuric patients who may be the beneficiary-recipients of intensive management care using lipid modifying and anti-hypertensive agents [66]. There have been no trials or innocuous drugs for specific treatment of these manifestations.

Diabetic patients with cardiovascular lesions usually present with adverse lipid and lipoprotein profiles in established nephropathy [79] and incipient diabetic nephropathy [42]. The association of atherosclerotic lesions in the diabetic patient necessitates the incorporation of diverse risk factors in general management and care. Macro vascular disease is not necessarily a concomitant feature of diabetes. The manifestation of atherogenesis in diabetes can be obviated by inter alia primary prevention traits of cholesterol reduction, glycemic control, nutritional counseling and exercise. For monitoring purposes, the application of the fructose-amine test in the assessment of adequate diabetes control may be beneficial to ensure appropriate and veritable stabilization and prognosis of the diabetic patient [64,80,81].

The manifestation of cardiovascular disease in type 1 diabetes expansively debilitates quality of life and expectancy. Hyperglycaemia resulting in oxidative stress plays a fundamental role as a path physiological factor of both micro- and macro-vascular sequelae. It is observed that in Type 1 diabetes, the manifestation of coronary calcifications is inextricably linked to coronary artery disease. Type 1 diabetic patients are susceptible to elevated risk of latent or patent risk of cardiovascular mortality risk of coronary heart disease [82]. Patients diagnosed as early-onset Type 1 diabetes present greater risk of cardiovascular disease and accelerated mortality in comparison to the general population.

Conclusion

Cardiovascular disease is a potential deranging long-term Type 1 diabetes complication. Type 1 diabetes increases the risk of cardiovascular deterioration. The risk of these complications can be substantially mitigated by controlling blood sugar through less intake and preventing hyperglycemia. Type 1 diabetes presents greater risk in the development of cardiovascular perturbations, such as atherosclerosis, coronary heart disease, heart attack, high blood pressure and peripheral artery disease. It is pertinent to control blood sugar to obviate hyperglycemia, and to monitor the blood pressure of Type 1 diabetes patients. Type 1 diabetes patients are ten times more at risk to develop cardiovascular disease than the non-diabetic population. Diabetes may be inextricably-linked with high LDL as bad cholesterol and low HDL as good cholesterol levels which could be controlled by proper nutrition to boost the HDL levels.

Respectively, Type 1 diabetic nephropathy and neuropathy precipitate blood pressure culminating in heart attack and restricted blood flow and diverse cardiovascular perturbations. Coronary heart

disease presents as plaque, such as cholesterol, lipids and triglycerides resulting in atherosclerosis. Proper Type 1 diabetes self-management, healthy life-style choices, controlled blood sugar levels, exercise adequate insulin administration, low-dosage aspirin therapy in advanced age to control coagulation factors; whereby healthy blood sugar levels are liable to mitigate cardiovascular deteriorations, such as coronary heart disease. With persistent increasing prevalence of diabetes, its inextricable linkage with coronary heart disease, adequate treatment and control of diabetes and associated coronary heart disease risk factors must be the focus to harness or curb the accelerating prevalence and progression of type 1 diabetes and coronary heart disease. Proper measures are necessary in the treatment and control of these inextricably linked disorders as both the prevalence and socioeconomic costs have reached astronomical proportions, which contribute to the burden in Society and disrupting sustainable development in human resources.

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