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Cardiovascular disease in diabetes

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Abstract. – OBJECTIVES: Obesity and type 2 diabetes (T2D) are major risk factors for cardiovascular disease (CVD), which is often fatal among diabetics. There has been a steady rise in obesity and in associated CVD in the last 2 decades. Despite improvements in clinical and treatment approaches, the prevalence of heart failure (HF) is rising with only minor extension in survival. Obesity and diabetes can potentially increase the risk of HF independent of coronary heart disease and hypertension. Aim of this paper was to systematically review literature in the last 10 years on the association of CVD with obesity and diabetes and to address the key clinical points relevant for diagnosis and risk factor assessment.

METHODS: Original research articles addressing molecular mechanisms, clinical articles and reviews published in the last 10 years in the area of diabetes and heart disease have been collected from different sources including PubMed, Scopus and other databases and critically compiled.

RESULTS: Insulin resistance, common to both T1D and T2D patients, is a major risk factor for cardiovascular events. Association of hyperglycemia with insulin resistance further increases the risk of CVD and heart failure. Even though obesity is an important risk factor for CVD, the risk is mediated mostly through insulin resistance but not body-mass index. The total risk of CVD in T2D patients cannot be explained by traditional risk factors alone and specific metabolic changes also significantly contribute to this.

CONCLUSIONS: The risk from the traditional cardiovascular risk factors for developing heart disease is further aggravated in diabetes. The treatment approach for diabetic patients to prevent cardiovascular complications should aim not only to control insulin resistance but should include lifestyle changes and early pharmacological intervention.

Key Words:

Diabetes, Obesity, Cardiomyopathy, Heart failure, Coronary artery disease, Cardiovascular disease, Atherosclerosis, Insulin resistance, Hyperglycemia, Heprinsulinemia.

Introduction

Approximately one third of mortalities in diabetic patients are due to cardiovascular diseases and, thus, making diabetes equivalent to coronary heart disease[1]. Incidence of diabetes and obesity is on steady rise and affects more than 371 million people worldwide and this number is expected to increase to half a billion by 2030. Complications of diabetes have deleterious effects on most body tissues leading to organ dysfunction and culminating in diabetes-related morbidity and death. There are mainly two kinds of diabetes, Type 1 diabetes mellitus (T1D) and Type 2 diabetes mellitus (T2D). T1D is immune-mediated diabetes and results from autoimmune destruction of the pancreatic β-cells and 5-10% of diabetic patients suffer from T1D. T1D patients are totally dependent on insulin administration and, thus, this condition was also in the past termed insulin dependent diabetes mellitus (IDDM). The diabetes epidemic is predominantly attributable to T2D as more than 90% of diabetic patients suffer from T2D. It is estimated that > 50% of diabetic patients die from a cardiovascular event – most likely coronary artery disease. Stroke, diabetic cardiomyopathy and peripheral vascular disease, atherosclerosis are other major causes of heart failure in these patients[2]. Patients with a combination of T1D and characteristics associated with T2D, such as adiposity and marked insulin resistance, are described to have "double diabetes mellitus"[3]. Double diabetes mellitus could have either an additive or synergistic effect on CHD risk.

Diabetes is a major risk factor for heart failure and according to the Framingham Heart Study the frequency of heart failure is twice in diabetic men compared to age-matched controls whereas this frequency is five times higher in diabetic women[4]. Several clinical studies indicated that heart failure among diabetic subjects can be as high as 19%-26% and that diabetes affects the heart in multiple ways including coronary artery disease (CAD), accelerated atherosclerosis and diabetic cardiomyopathy[5-7]. Diabetes impacts heart function in several ways and the underlying causes include chronic hyperglycemia, insulin resistance, disturbed lipid and

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glucose metabolism, microvascular disease, altered renin-angiotensin system (RAS), cardiac autonomic dysfunction and myocardial fibrosis[2,3,8]. Stroke appears to be the primary cardiovascular-related cause of death in T2D patients in China and Japan, whereas coronary artery disease (CAD) and peripheral vascular disease is considerably higher in T2D patients of Caucasian origin[9].

Methods

We performed literature search in Pubmed, Google Scholar and Embase databases for relevant studies on diabetes and cardiovascular disease and heart failure, published during the last two decades. We used type 2 diabetes, type 1 diabetes, coronary artery disease, cardiovascular disease, cardiomyopathy and heart failure and obesity as search terms. Only English language publications were selected and reviewed.

Effects of Chronic Hyperglycemia on Heart

Elevated oxidative stress by the production of reactive oxygen species (ROS) from mitochondria is one of the causes of myocardial damage (Figure 1) and this is aggravated in chronic hyperglycemia due to increased glucose metabolism[10]. Increased levels of superoxide produced by the mitochondrial respiratory chain reduce myocardial contractility and lead to myocyte fibrosis. Enhanced cellular DNA damage by ROS eventually leads to cardiomyocyte apoptosis and also activates poly-ADP ribose polymerase[11], which diverts glucose from glycolysis into alternative biochemical pathways that cause the production of advanced glycation end products (AGEs) which cause hyperglycemia induced cellular injury (Figure 1). There is also increased hexosamine pathway flux and activation of protein kinase C. The ability of AGEs to covalently crosslink intra and extracellular proteins is an important factor in diabetic complications as such crosslink in collagen and elastin can result in in-

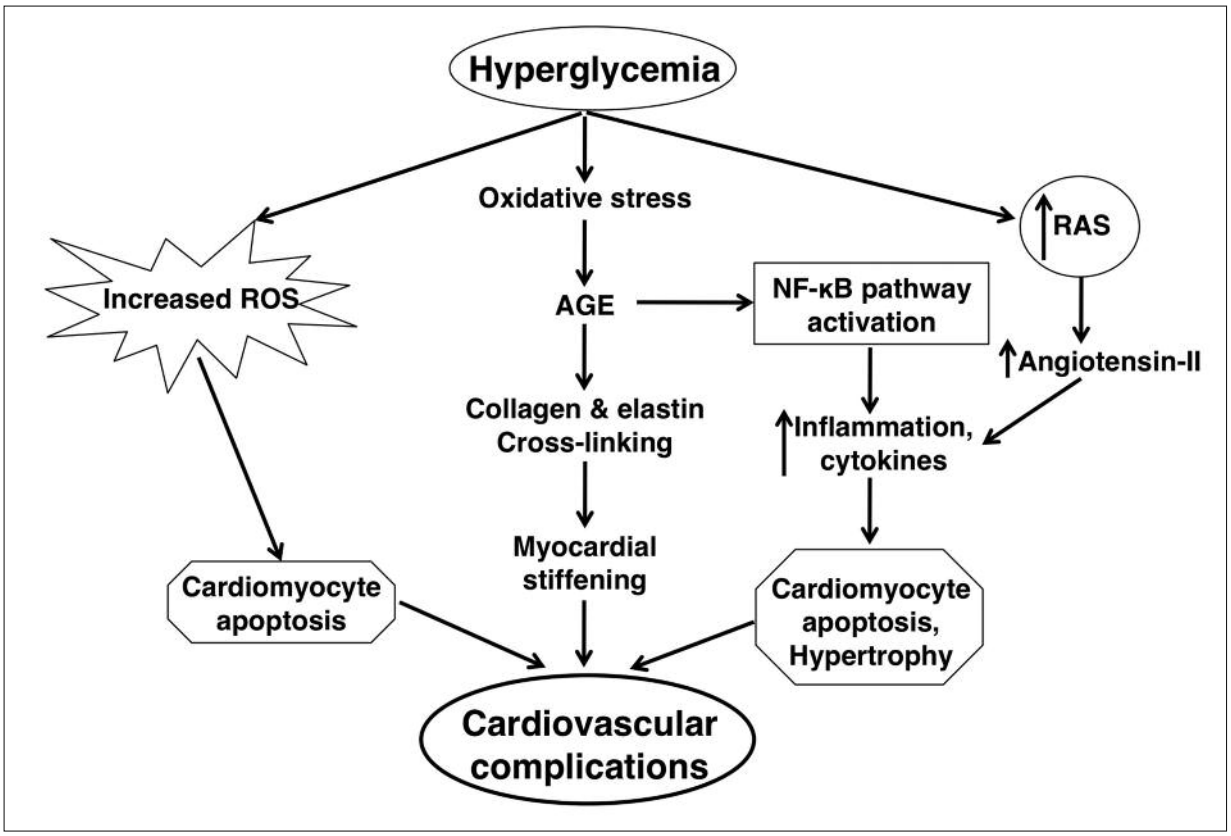

Figure 1. Schematic depicting the possible mechanisms by which hyperglycemia, the common denominator in both type 1 and type 2 diabetes, leads to cardiovascular complications. AGE: Advanced glycation end products; RAS: rennin-angiotensin system; ROS: reactive oxygen species; NF-κB: nuclear factor-κB.

creased myocardial stiffness and impaired cardiac relaxation both in animal models and in humans[10,12,13]. Besides, interaction of AGEs with their receptors and galectin-3 on myocardium results in activation of nuclear factor-kB (NF-kB), which in turn triggers several pathways that induce production of pro-inflammatory cytokines such as tumor necrosis factor- and cause myocardial damage[14,15]. On the other hand, increased diversion of glucose towards hexosamine pathway causes disruption of normal calcium flux in cardiomyocyte resulting in reduced myocardial performance and impaired diastolic relaxation[16]. Hyperglycemia and insulin resistance also increase thrombosis formation, platelet aggregation and plasma plasminogen activator inhibitor-1, which probably contributes to impaired fibrinolysis. Hyperglycemia in diabetic patients causes protein glycation and the generation of fibrin clots that are denser and less porous and resistant to fibrinolysis[17].

Hyperglycemia activates renin-angiotensin system in myocardial cells (Figure 1) and cardiomyocyte angiotensin-II levels increase several fold both in T1D and T2D patients[18]. Angiotensin-II is a vasoconstrictor molecule and is a key regulator of mean arterial blood pressure and vascular tone and, thus, is an important contributor to the development of diabetic vascular complications. Vascular complications in diabetic patients are two kinds –those affecting the macro-vasculature (e.g., aorta, femoral and coronary arteries) and those affecting micro-vasculature (e.g., capillaries of the eye, kidney and nerves). Macro-vascular complications contribute to the accelerated development of cardiovascular diseases leading to myocardial infarction and stroke[2]. Angiotensin-II signaling events in cardiomyocyte can lead to cell growth and cardiac hypertrophy[19] and these damaging effects can be further aggravated by oxidative stress, inflammation and aldosterone[20]. Cardiac dysfunction worsens by hypertension[21], which is seen in 30% T1D patients and almost twice as many T2D patients[22].

Hyperglycemia is directly proportional to HbA1c level, an important contributor to increased macrovascular risk. However, HbA1c measurements reflect only the average glycemic control over the preceding 3 months and not the cumulative total glucose exposure, which is more relevant in terms of long-term cardiovascular outcomes[23]. However, several clinical studies including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial and Veterans Affairs Diabetes Trial (VADT) that studied over 25,000 patients, have concluded that obesity, metabolic syndrome and insulin resistance are more important than HbA1c for the prediction of cardiovascular risk, especially for coronary heart disease[24-26]. These studies revealed that an aggressive approach to control HbA1c < 7.0%, had no significant impact on the incidence of cardiovascular events. In fact, increased mortality in the intensively treated group in the ACCORD study was attributed to an increased frequency of hypoglycemia. Intensive glycemic control in T2D patients may only lead to minor improvement in cardiovascular outcomes, and may even be harmful[27].

Disturbances in Lipid Metabolism in Diabetes and Their Effects on Heart Function

Effects on Myocardium

Exhausted and lowered cellular oxidation capacity in diabetes leads on to ectopic lipid deposition in non-adipose tissues such as skeletal muscle, liver and heart. Recent studies suggested that disturbed myocardial lipid metabolism causes cardiac steatosis and diabetic cardiomyopathy[28,29]. Patients with diabetes, obesity and impaired glucose tolerance have elevated plasma free fatty acids (FFA) with the resultant increase in cardiac FFA uptake, triglyceride accumulation and cardiac steatosis[28,30,31]. Excessive FFA entering into cardiomyocytes cannot be completely handled by the mitochondrial oxidative machinery and are channeled into non-oxidative pathways, such as ceramide synthesis, thereby, giving rise to toxic lipid intermediates, which cause lipotoxic cardiac injury. These lipid intermediates, when produced in high levels, can cause mitochondrial dysfunction, cellular damage, disrupt normal cellular signaling, apoptosis and ultimately to myocardial fibrosis and dysfunction[32,33]. Impaired myocardial energy production leads to disturbed mitochondrial calcium handling and reduced cardiac contractility cardiac dysfunction[34].

Abnormal lipid partitioning but not the disturbed insulin signaling is found to be responsible for the decreased tissue glucose uptake in T1D patients. Elevated lipolysis, secondary to the effects of insulinopaenia on adipocytes and hepa-

tocytes, leads to increased circulating FFA and intra-myocellular lipid[35,36]. In the DCCT-EDIC and EURODIAB studies, triglycerides and LDL cholesterol levels were positively related to the incidence of coronary events in the T1D patients[37].

While majority of T1D patients have normal levels of HDL cholesterol, a subgroup of T1D patients who develop premature CHD show a tendency for lower HDL cholesterol levels in association with elevated triglycerides and LDL cholesterol, similar to the atherogenic dyslipidemia, commonly seen in T2D patients[38]. Hepatic TG lipase is stimulated by insulin, thus, facilitating the cholesteryl ester transfer protein-mediated exchange of triglycerides for LDLs. This leads to lipoprotein particles with decreased HDL cholesterol content in individuals with central obesity, metabolic syndrome and T2D[39]. However, in T1D patients as exogenous insulin is delivered subcutaneously, portal vein insulin levels are low and the hepatic TG lipase is less active, which results in better maintenance of HDL cholesterol content of lipoprotein particles in these patients. Interestingly, a switch from subcutaneous to intraperitoneal route of insulin administration causes activation of hepatic TG lipase, and leads to lowered levels of HDL2 cholesterol and increased HDL3 cholesterol[40]. Thus, it is possible that in T1D, reduced hepatic insulin exposure and the subsequent beneficial lipid metabolism confers an atheroprotective phenotype. In line with this idea, it has been shown in a study of 44 T1D patients, pancreatic transplantation alters the lipid profile towards a more atherogenic phenotype with high levels of total cholesterol, LDL cholesterol and triglyceride but decreased HDL cholesterol level, reflecting increased hepatic insulin exposure[41]. In lean T1D patients, portal insulinopaenia can potentially exert cardioprotective effects by increasing HDL cholesterol levels and decreasing hepatic steatosis. However, in double diabetes mellitus patients, chronic hyperglycemia and abnormal lipid partitioning greatly aggravate atherothrombotic pathophysiology[3].

In T2D patients of different age groups, generally BMI and waist circumference are higher than T1D patients of similar age group and also plasma total triglyceride levels are high and HDL cholesterol levels are low[42,43]. A recent genome wide association study on 63,746 coronary heart disease (CHD) patients and 130,681 healthy controls suggested that lipid metabolism and inflammation are major players involved in the pathogenesis of CHD[44]. Atherosclerotic vascular disease, the major cause of death in diabetic patients, cannot be accounted for by the traditional cardiovascular risk factors alone and it has been proposed that FFA exert inflammatory effects in macrophages, and these inflammatory changes contribute to diabetes-accelerated atherosclerosis and other complications[45]. Inside the cells, fatty acids are activated by long-chain acyl-CoA synthetases (ACSLs) to acyl-CoAs, which are either incorporated into cellular lipids or used for β-oxidation. ACSL1 is induced several fold in monocytes and macrophages in type 1 diabetes, with the resultant increase in inflammatory mediators. Recently, it has been shown that myeloid-specific ACSL1 deletion blocks the inflammatory activation of macrophages and prevents atherosclerosis induced by diabetes[46].

Importance of Hyperinsulinemia and Insulin Resistance

Hyperinsulinemia and insulin resistance are hallmark abnormalities of T2DM and prediabetic states. Insulin is an anabolic hormone and has metabolic effects on various tissues including the liver, adipose tissue, and skeletal muscle. Insulin promotes glycogen synthesis and storage in liver and muscle, triglyceride synthesis and deposition in adipose tissue, and protein synthesis in different tissues. Insulin also enhances glucose utilization and oxidation. The normal cellular action of insulin is compromised under certain physiologic (pregnancy, adolescence) and pathologic (obesity, T2D, acute illness) conditions leading to the development of condition called insulin resistance. Compensatory mechanisms in the body try to overcome this by enhancing insulin secretion from pancreatic b-cells and this results in hyperinsulinemia. Chronic hyperinsulinemia further aggravates insulin resistance, and exerts significant metabolic stress on pancreatic b-cells ultimately leading to their dysfunction and death. Thus, hyperinsulinemia and insulin resistance together exert their detrimental effects on the body by the feed-forward vicious circle[47]. Insulin resistance leads to increase in circulating FFA, via accelerated adipocytes lipolysis. High level of plasma FFA further impair insulin action in peripheral tissues and insulin secretion by b-cells, the two main characteristics of T2D.

Hyperinsulinemia contributes to cardiomyocyte hypertrophy by various mechanisms (Figure 2). It has been shown that brain natriuretic peptide (BNP), which is released from ventricles and is a marker of cardiac hypertrophy and my-

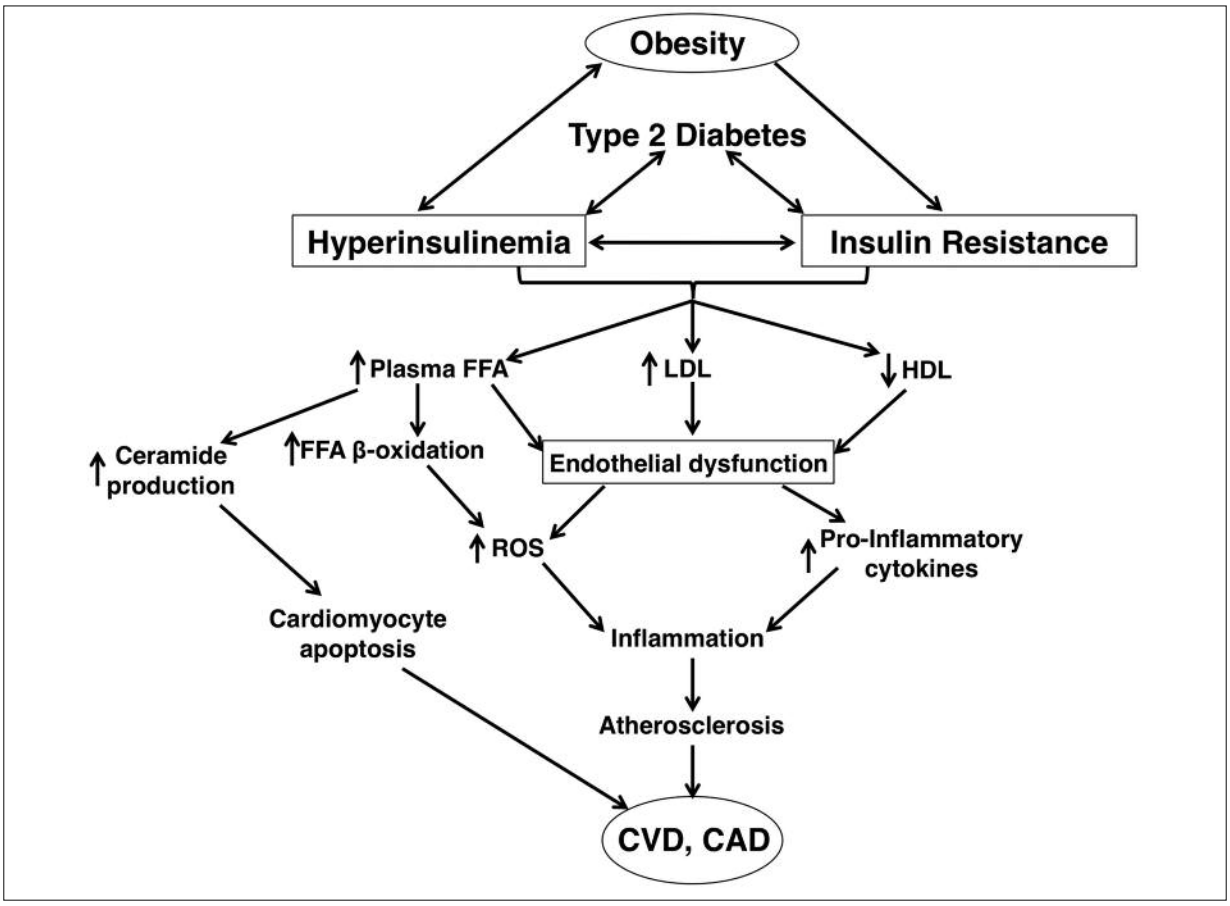

Figure 2. Mechanism of cardiovascular disease development due to type 2 diabetes and obesity associated complications of disturbed lipid metabolism, hyperinsulinemia and insulin resistance. FFA: Free fatty acids; HDL: high density lipoprotein; LDL: low density lipoprotein; ROS: reactive oxygen species, CAD: coronary artery disease; CVD: cardiovascular disease.

ocardial stretch, is increased in patients with heart failure. BNP expression is significantly higher in animal models of hyperinsulinemia and insulin resistance, which also display left ventricular hypertrophy and increased left ventricular weight[48]. Hyperinsulinemia-mediated genetic and epigenetic alterations result in the activation of various transcription factors that directly influence expression of intra- and extra-cellular proteins, which play important roles in cardiomyocyte hypertrophy and focal cardiac fibrosis in diabetes[49,50]. In conditions of hyperglycemia and insulin resistance, ROS and advanced glycation end products are increasingly produced and these further aggravate low-grade inflammation and contribute to an elevated cardiovascular disease risk (Figure 2).

T1D patients on insulin treatment also display insulin resistance and peripheral hyperinsulinemia and these are exaggerated in patients with double diabetes mellitus. Interestingly the increased risk of premature coronary disease in T1D patients is better predicted by markers of insulin resistance than HbA1c levels[3,51]. Insulin resistance is best measured by euglycemic hyperinsulinemic clamp and since this is a specialized procedure and not practical for routine clinical use, the whole-body estimated glucose disposal rate (eGDR) is used to measure insulin resistance in place of the clamp[52]. Thus, an elevated eGDR is an important predictor of both cardiovascular events and any macrovascular events. A high eGDR could also predict microvascular events as supported by the EURODIAB study on the incidence of retinopathy and nephropathy[53]. Insulin resistance is recognized as a feature of T1D as well, even in the absence of obesity and metabolic syndrome, even though the lowered insulin-mediated glucose uptake in T1D patients is likely due to abnormal lipid metabolism and elevated lipolysis, with consequently increased circulating FFA levels and intramyocellular lipid[35]. In T1D

patients, there is increased peripheral hyperinsulinemia and peripheral insulin resistance because of the subcutaneous insulin injections, which lead to the downregulation of insulin receptors and GLUT-4[54,55]. Besides, high levels of insulin can cause adverse cardiovascular effects, including sodium retention and vascular smooth muscle hypertrophy, and the associated vascular insulin resistance can lead to elevated blood pressure due to blunted insulin-mediated peripheral vasodilatation[56].

A recent meta-analysis indicated that insulin resistance as evaluated by HOMA index, could better predict CVD events in adults without diabetes[57]. The extent of coronary calcification in T1D patients could be predicted by insulin resistance independently of glycemia[51]. Insulin resistance is a central mechanism that connects different components of the metabolic syndrome, viz., hyperglycemia, obesity, low HDL cholesterol, high total triglyceride level and increased blood pressure[58]. Atherogenesis and plaque progression can be accelerated by insulin resistance via changes in classic CVD risk factors and downregulation of insulin signaling pathways[59]. There are ethnic differences in the susceptibility and incidence of insulin resistance and thus Asian American individuals with T2D are highly resistant to insulin even if they are not overtly obese as compared to Caucasians[60]. Also, T2D patients from southern Asian countries have greater abdominal fat mass as compared to white individuals despite similar total fat mass and are thus at much higher risk of CVD[61]. Insulin resistance in the liver and adipose tissue promotes the development of atherogenic dyslipidemia, generates a low-grade inflammatory state and enhances the release of inflammatory markers and it also affects blood pressure, endothelial cells and macrophages. Macrophage insulin resistance has modest effects on overall atherosclerotic lesion size[62]. Therefore, a combination of both hyperglycemia and insulin resistance mediate the detrimental effects that promote CVD risk in patients with T2D. Longer the duration of T2D, higher the risk for CAD-related adverse events by hyperglycemia.

Altered Cardiac Gene Expression in Diabetes Associated Heart Disease

It is widely accepted that several changes in gene expression pattern occur in CHD and related heart diseases associated with diabetes. Despite several large scale Genome Wide Association Studies (GWAS), genotyping based predictions for personal risk are not very successful, mostly because only a small proportion of risk can be accounted for by the known risk loci. Several GWAS studies have revealed that even though there can be a high number of significant loci, they account for about 6-10% risk. GWAS showed one important locus on chromosome 9p21, near *CDKN2A* and *CDKN2B* for coronary artery disease, *HDAC9*, an intergenic region at chromosome 6p21.1 for large vessel disease and *PITX2* and *ZFHX3* for cardioembolic stroke and atrial fibrillation[63]. Variants in five genes, viz., glucokinase, glucosese β and adrenoceptor 2A that lead to elevated glucose levels, identified by GWAS, were also found to be associated with CAD and myocardial infarction[64]. ROS and oxidative stress that result from hyperglycemia can lead to altered gene expression in myocardium. Thus ROS may lead to induction of pro-inflammatory gene expression and promote a proinflammatory state by elevating adhesion molecule expression[65]. Hyperglycaemia as such can cause epigenetic changes in the NFthway, responsible for the inflammatory changes[66]. Oxidative stress in diabetic subjects is also known to increase the AGEs, which induce myocardial damage by interacting and up-regulating AGE receptors and galectin-3, leading to the activation of NF-kB transcription factor, in turn triggering several pathways that induce production of pro-inflammatory cytokines[67]. It has been found that gene expression of brain natriuretic peptide (BNP), which is released from the ventricles in response to myocardial stretch and which is increased in patients with heart failure, to be significantly higher among animal models of hyperinsulinemia and insulin resistance. Because of this, BNP is now considered as a biomarker for subclinical ventricular diastolic dysfunction in patients with uncontrolled diabetes[67].

Preventive and Therapeutic Strategies

Primary approaches to prevent CVD risk in diabetics include changes in lifestyle, improving diabetic control, therapy to decrease lipid burden and management of coexistent hypertension, and management of heart failure. Regular exercise and healthy eating habits are important for the management of obesity and diabetes. It is well documented that exercise is associated with significant reduction in CVD in diabetic patients[68]. There is some evidence to show that tight glycemic control can improve stress-induced

ventricular dysfunction without CAD in diabetic patients[69]. Metformin, which improves peripheral insulin sensitivity and controls hyperglycemia upregulates cardiomyocyte autophagy that plays a role in the prevention of diabetic cardiomyopathy[70]. Statin treatment to patients with diabetes lowers lipid burden and vascular risk factors and has been shown to reduce cardiovascular events and mortality[71].

The ACCORD study showed that an aggressive approach for controlling glycemia intensively in T2D patients actually increased the mortality, even though the reason for this unexpected finding is not known[24]. A high percentage of intensively treated patients in this study were on insulin (77%) and/or thiazolidinedione (TZD) (91%) therapy and this group also had higher weight gain (3.5 kg vs 0.4 kg) as compared to patients who were received normal treatment. Considering that insulin sensitivity regulation is an integral component of normal metabolic physiology, the dogma that insulin resistance is "bad" as it is at the root of T2D, needs to be re-visited. The possibility that the insulin resistance in obesity-related T2D is more a defense mechanism than an unwanted detrimental effect, and overriding it by intensive therapeutic approach can potentially cause harm needs to be considered. For example, in response to even short term overfeeding, skeletal and cardiac muscle develop insulin resistance, which diverts the excess nutrients to adipose tissue for safe storage[72]. Therefore, induction of insulin resistance likely protects important tissues like heart from nutrient-induced dysfunction[73]. Thus, overriding insulin resistance in over-nourished T2D patients, by either intensive insulin therapy or other approaches, to enhance insulin sensitivity or both, may bypass a natural defense mechanism. Under these conditions, critical insulin-responsive tissues such as heart may no longer be protected from fuel surfeit toxicity as these intensive treatments promote excessive glucose entry in to tissue, thereby causing glucolipotoxicity in these hyperglycemic, dyslipidemic subjects, due to accumulation of intracellular nutrients (e.g. steatosis) and toxicity to mitochondria[74]. The complication of weight gain due to intensive glycemic control is also recognized in subsequent analyses of DCCT–EDIC subgroups as some patients in the trial who gained weight exhibited features of increased cardiovascular risk[75]. It is observed in this analysis that patients, whose BMI increased from 24 kg/m^2 to 31 kg/m^2, had much higher blood pressure, LDL cholesterol levels and a more atherogenic lipid profile than those with lesser weight gain. Thus the value of aggressive glycemic control in T1D patients is questionable, particularly if it is accompanied by marked weight gain and by accumulation of central fat stores[3].

Conclusions

Besides obesity and diabetes, several pathogenetic mechanisms appear to be operative in CVD, including increases in hemodynamic overload, apoptosis, ischemia-related dysfunction, ventricular remodeling, abnormal myocyte calcium cycling, abnormal extracellular matrix proliferation and genetic mutations. Biomarkers released from myocardium during the course of myocardial stretch are helpful in identifying the causative factors of CVD and in its prognosis and in choosing subsequent therapeutic measures, thereby improving the care of patients with heart failure. However, we still need vigorous, multifaceted preventive approaches for achieving significant reductions in the prevalence of heart failure and CVD. The main approach for reducing the risk of premature cardiovascular disease in diabetic patients should involve early identification of the potential risk factors, and choosing the necessary therapeutic regimen for their management. These treatment approaches include targeted lifestyle advice, advice to increased physical activity, healthy dietary regimen and early use of statins and antihypertensive drugs as primary prevention drugs. In high cardiovascular risk patients, particularly in those who show the complication of substantial weight gain due to intensive insulin treatment, relaxation of glycemic targets is necessary to facilitate management of their macrovascular risk.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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