Epidemiology And Biological Mechanisms Of Cardiovascular Disease And Diabetes

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ABSTRACT
The risk of CVDs in T2DM patients in LMICs is higher than in developed nations. It is essential to make an evaluation of the current situation of CVDs among people with T2DM. These CVDs are easily preventable through intervention especially in T2DM patients and this should be done in a comprehensive manner. The following targets and principles should be considered: individual targets of HbA1c for patients, a rigorous control of cardiovascular risk factors such as blood pressure and lipids, and incorporation of newer anti-diabetic, lipid-lowering and anti-hypertensive agents. It is, therefore, crucial to design a stepped-wedge approach that bundles a patient-level intervention, lifestyle, and pharmacological interventions to reduce the risk of CVD in LMIC T2DM populations. When selecting medications for T2DM patients with cardiovascular conditions, several key considerations must be made: When selecting medications for T2DM patients with cardiovascular conditions, several key considerations must be made: It should be noted that the choice of anti-diabetic drugs should take into consideration cardiovascular safety. SGLT2 inhibitors and GLP-1 agonists are newer agents for managing diabetes and have been found to have cardiorenal benefits. The choice of lipid-lowering should be targeted to lower LDL cholesterol and triglycerides as effectively as possible. If the intensity of statin is high; it is considered first-line therapy, and other optional medication includes ezetimibe and PCSK9 inhibitors. To maintain the best pressure level that is suitable for an individual, and as a result control hypertension, the use of antihypertensive drugs is necessary. This makes ACE inhibitors or ARBs the preferred first-line antihypertensive agents because of their cardiovascular benefits. For the purpose of secondary prevention in individuals who have experienced a cardiovascular event, the antiplatelet drug aspirin in a dosage of between 75 to 150 milligrams per day should be administered. This is to minimize the probability of such difficulties re-emerging by influencing platelet activity. In general, adequate blood pressure management and antiplatelet aggregation therapy are key interventions with specific antiplatelet medication needs in this setting.

Introduction

Diabetes mellitus (DM) remains one of the most prevalent health issues with a significant increase in its incidence over the past decades globally. Based on the estimates provided by the International Diabetes Federation, such statistics will not decrease in the future, and according to the forecast for 2035, 9.7% of the world's population or 591 million people will suffer from any form of diabetes. Diabetes cases in the world have increased sharply over the last 30 years. It has continued to rise a lot due to type 2 diabetes more than type 1, so the new cases are coming from lifestyle and obesity rather than autoimmunity. In summary, diabetes particularly type 2 has risen sharply in the recent past and has become a major global health crisis. The forecasted medical opinion about this type of diabetes is that it will persist throughout the years, reaching nearly 10% of the global increase and nearly 600 million total cases by 2035 if current trends are maintained [1].

The medical system and the individual are both burdened financially because of the increased prevalence of DM. Mean DM costs $2108 per patient per year in the Western world, nearly twice as costly as non-diabetic people. Diabetes mellitus (DM) has a very severe economic burden arising from both direct costs, which comprise medical expenses and the other costs due to lost productivity due to conditions associated with DM. Most of the costs attributed to DM are usually weighted on vascular complications that involve both the small and the large blood vessels. Some of these vascular diseases include peripheral neuropathy, nephropathy, retinopathy, hypertension, myocardial infarction, and atherosclerotic cardiovascular disease. The care needed to manage these complications is very demanding and consuming and results in reduced productivity among patients thus posing significant costs [2, 3].

Among the diseases, DM and CVDs share a very strong link. Another interesting fact is that CVDs have been identified as the biggest killer among diabetic patients. According to American statistics, cardiovascular death risk and probability of heart attack and myocardial infarction increases by 1.8 % in adults with diabetes aged 18 years and above compared to those without diabetes. The risk for CVD-related death is higher for men and women with diabetes, today in developed countries. If we are to focus on the mortality rates, research proves that the total probability of dying from CVDs is one to three times more for male diabetics and two to five times more for female diabetics than for male and female non-diabetic controlsDiabetes increases the risk of cardiovascular diseases in patients and up to 80% of diabetics die from cardiovascular diseases. This shows that cardiovascular diseases related to diabetes necessitate regular check-ups and treatment before the diseases escalate to dangerous levels or critical stages. Evaluating and monitoring cardiovascular disease risks and timely intervention are critical for diabetic patients to avoid developing more severe stages or die prematurely. [4].

T2DM is prevalent and comes with high-risk factors for MCDs such as ischemic heart disease, heart failure, stroke, CAD, and PAD. These cardiovascular diseases are strongly associated with T2DM as atherosclerosis, hypertension, and vascular inflammation, which are well known to be comorbid with diabetes. Some strategies can help prevent cardiovascular complications in people with T2DM, such as controlling blood sugar, blood pressure, and cholesterol [5]. T2DM poses a high risk of CVD in the patients, thus complicating the disease outcome. T2DM is characterized by insulin deficiency and the presence of elevated blood sugar for an extended period. In addition, although not present in all patients, lipid metabolism is also typically disrupted in T2DM patients. This is because insulin resistance is the first abnormality observed in an individual with T2DM, even before the onset of hyperglycemia. This resistance and the consequential Metabolic dysfunction stimulate the development and progression of CVDs in the T2DM group [6]. T2DM is a major independent risk factor for the occurrence of CVD events and other complications. One of the most potential pathways through which T2DM and CVD are related is insulin resistance, which is the inability of cells to respond efficiently to insulin. The effects of insulin resistance are manifold which precipitates other metabolic derangements. To begin with, it causes accumulation of high and unrelenting levels of circulating blood glucose which is detrimental to blood vessels. The challenging issue is that both big vessels, such as arteries, and small vessels, such as capillaries, are involved, and the disease affects various organs and systems. Secondly, there is deposit of lipids in some tissues such as heart muscles. This leads to increased fat deposition in the heart muscle and consequently brings about changes in the physical structure of the heart muscle, whereby stiffness and scarring are enhanced. It also specifically suppresses the function of insulin receptors in the heart muscle cells, thus affecting the energy utilization of the muscle. Lastly, to treat T2DM some drugs have been known to worsen CVD risk objectively. Medications that help to reduce the level of glucose in the blood may cause blood sugar levels to fall to dangerously low levels and cause hypoglycemia. This promotes counter-regulatory mechanisms that are are deleterious to the cardiovascular system. Therefore, the primary lesion of T2DM in insulin resistance produces hyperglycemia, increased lipid levels and hypoglycemia due to drugs used. All three intermediaries have leading structural, metabolic, and functional effects on CVD, blood vessels, and tissues such as the heart. Subsequently managing these upstream risk factors can help reduce the disproportionate CVD risk prevalence among T2DM patients [7]. In general, CVD linked to diabetes is a significant cause of death and disability among T2DM patients.

Diabetes mellitus is an alarming and prevalent disease that affects a large number of people globally and has substantial expenses. Substantial control and management of DM is necessary since several patients with DM are likely to acquire cardiovascular problems. While there are many linkages between DM and CVDs it is a problem that can no longer be solved separately. Among the strong

predictors of cardiovascular disease, obesity, hypertension and dyslipidemia are some of the most common conditions that are often observed in diabetic patients, especially those with type 2 diabetes mellitus. In addition to these traditional risks that are associated with diabetes, high sugar levels cause blood vessels and nerves to be damaged, and therefore, diabetics are predisposed towards CVD.
To sum up, additive traditional CV risks in diabetic patients increased by high levels of hyperglycemia directly damaging blood vessels, CVD rates are significantly increased. It is therefore important to note that while management of DM itself is crucial, management of cardiovascular risk factors associated with DM is equally important in order to enhance prognosis outcomes.
Introducing the risk factor triad of obesity, hypertension and dyslipidemia of type 2 diabetics and their cardiovascular implications. The following are the straight-forward ways through which DM fuels CVD risk including: increased oxidative stress, increased platelet aggregation, blood vessel irregularities, and nerve dysfunction. Therefore, atherosclerosis not only aggravates conventional risk factors but also experiences direct injury by high blood sugar. [8,9], Type 2 DM, in particular, increases the absolute risk of first and recurrent major CV events in the form of myocardial infarction, revascularisations, stroke and heart failure. Since DM is closely associated with CVD, goals for managing diabetics should therefore focus on achieving the greatest reduction in CV events among these patients. This article focuses on the potential relationships between DM and CVD on pathological level. It also summarise the present day approach towards managing diabetes and other related CV risks. Although there have been many advances in the understanding of this disease and its effects on the cardiovascular system, there is still much more that needs to be done in eradicating the disease and treating the heart. As a result, the focus should be to devise better interventions that also decrease both the acute and chronic CV risk in diabetic individuals. Hence, the future management of diabetes must aim at the reduction of both hyperglycemia and CV risk in a patient. While today's choices do have some effectiveness, there are probably soon to be much superior forms of treatment for the complex interaction of these two significant disease processes.

This study was done in the Department of Medicine, Jawaharlal Nehru Medical College, Bhagalpur, India

Epidemiology

Analysis of many cross-sectional surveys and cohorts in different parts of the world, shows that CVD happens 2-3 times more often in T2DM patients than in other patients. Nevertheless, the global trend in the incidence of CVD in patients with T2DM has been decreasing over time for all ages and both sexes. A systematic quantitative synthesis of previous CVD prevalence studies for T2DM patients conducted in 2019 also revealed that in 2007-2017, the prevalence of CVD among T2DM patients was 14.3%-46.9% up to 2016. This reiterates that T2DM patients exhibit a higher CVD risk as opposed to non-diabetic individuals; however, evidence implies that the CVD risk associated with T2DM is diminishing across the years. This positive trend suggests that T2DM patients benefited from enhanced quality of prevention and management geared at reducing risks of CVD. However, future research with a larger sample still has to be conducted to confirm or refute the current tendency of decreasing CVD-T2DM prevalence. A cross-sectional study done across thirteen countries in 2019 revealed average CVD was at 34.8% among T2DM patients. However, the results were not consistent across the countries – the lowest density of Facebook users was 18% in Saudi Arabia and the highest was 56.5% in Israel. In conclusion, because the CVD risk is heightened among T2DM patients, recent statistics demonstrate that the incidence of CVD attributable to T2DM appears to be gradually declining, implying stricter and better CVD control and management in these patients. While more such population-based studies can provide more evidence for this, the evidence suggests that it may be reducing the incidence of CVD-T2DM worldwide.
There is an evidence that some cardiovascular diseases such as peripheral artery disease, myocardial infarction, stroke, and heart failure in patients with T2DM have had a mild decreasing trend in Spain.

Despite the measures taken, cardiovascular disease remains common in this population, with a prevalence ranging from 7% to 41% of patients with type 2 diabetes. This shows that cardiovascular diseases are still a significant health risk for such patients, while the consistent decline in some of the diseases suggests a positive trend. In Spain, 6-11% of treated patients with type 2 diabetes and cardiovascular disease die while hospitalized. Thus, although there has been a small sign of a decline in the rate of some cardiovascular disorders in the recent past for these patients, they remain a significant percent of the population. Subsequent attempts to enhance cardiovascular health understands the type 2 diabetes population in Spain are still highly required. In conclusion, cardiovascular diseases remain a major modality of type 2 diabetes complication in the country and even though there is a general tendency of decline in some of these diseases such as stroke and heart attack. Hypertension and heart diseases are still major concerns among this population and maintaining cardiovascular health should not be overlooked [10].

The increased use of medications, lifestyle changes, and better medical control of type 2 diabetes mellitus observed in studies from South Korea, Sweden, and Ethiopia corroborate this finding that cardiovascular disease rates have decreased among patients with type 2 diabetes mellitus. However, one South Korean study was different, and it showed that though there was a reduction in cardiovascular disease occurrence from 2006-2015 among this population, the risk of heart failure had risen within the same period. This underlines the importance of continuing tracking of trends and prognostic factors for different forms of cardiovascular disease in patients with diabetes [11], It has thus been observed that T2DM patients have a higher chance of developing HF than other groups of patients. Namely, the study showed that patients with T2DM > 10 years had a higher HF risk, than Diabetic patients with a history of hypertension. The study was able to prove that there exists an association between the duration of T2DM diagnosis and the probability of developing HF in the future. This made it possible to establish that for every additional five years that the patient had since their initial T2DM diagnosis, their risk of developing HF had shot up by 17%. Thus, based on the results of this study, it is possible to conclude that long-duration T2DM patients, especially those with comorbidity of hypertension, would be at an increased risk of getting HF with each passing year after diagnosis [12].

Several cross-sectional, population-based surveys of patients with T2DM from high-income countries – including Sweden, the United States, Canada, and the United Kingdom – show an annual decline of 3-5 % in the CVD rates since early 1990s. Although the disparities in CVD incidence and mortality between T2DM patients and the general population of non-diabetic adults have been narrowing, they remain considerable. Though, internet usage has grown in general, daily Internet usage is not the same across segments. However, few data are available on the current status of CVD incidence rate among T2DM consumers particularly in the middle and low income countries. Many canonical epidemiologic works offering data on temporal changes in the CVD risk in T2DM patients originate from LMICs. While these countries have evidenced a progressive decline in CVD in the recent decades, further studies on trends across income states globally are required [13]. Evaluating incidence can contribute to reducing opportunities for the development of negative outcomes and increasing the survival rate among T2DM groups at risk globally. In addition, other researches assessing the rates of CVD events in T2DM patients worldwide can help to determine priorities in resources for early detection and prevention. Contingent strategies based on the findings from higher-income states may help other countries to address income difference. Implementing standardized CVD monitoring and rigorously developing comprehensive epidemiological models of the risks for T2DM groups can contribute to the increased preventability of complications globally.

Clinical Presentations of Diabetes Mellitus

Diabetes that is current today comes in several types and the most prevalent is the type 2 diabetes mellitus. Type 2 diabetes on the other hand is more common in adults and is sometimes diagnosed after the age of twenty years. Type 2 diabetes is characterized by two key precursors: insulin

resistance, which is a failure of the tissues to respond effectively to insulin; and insulin deficiency, which is the failure of the beta cells in the pancreas to produce sufficient insulin. Insulin resistance is a condition whereby the recipient body tissues fail to respond adequately to the effects of insulin. Finally, the pancreas is unable to produce enough insulin to cope with this overwhelming demand. As the body responds to high demands, insulin production also tries to rise to the occasion but again it cannot. So, elevated blood sugar levels occur, and this is when type 2 diabetes begins. The perturbed relationship between insulin sensitivity and demand, as well as the insulin output and hyperglycemia, define the key aetiology of type 2 diabetes, which has become the most prevalent form of diabetes globally.

The onset of type 2 diabetes in some people is as a result of several factors, as pointed out below. Cigarette smoking, lack of exercise, and poor diet cause insulin resistance in those with an inherited tendency to the condition. Also, age is a factor that tends to decline the efficiency of the pancreas to produce enough insulin for the body. Thus the ageing process by itself can slowly and over time damage the capacity to secrete insulin and turn the individual into a type 2 diabetic if this capacity falls below a certain level while other risk factors aren't present. This process of decline in insulin secretion changes with age at different rates and thus acknowledges the roles played by genetic factors. Therefore, the more insulin secretory capacity declines, the higher the chances of type 2 diabetes development in individuals, including when one's genes promote a rapid pancreatic deterioration even in cases of moderate-insulin resistance. In a nutshell, factors such as lifestyle, genetic makeup, and aging contribute to decreasing insulin secretion in different ways, which culminates in diabetes in vulnerable individuals.

The two are, for example, abnormally high blood pressure, high cholesterol levels and increased tendency for blood clotting. These conditions are grouped together under the label called metabolic syndrome. Metabolic syndrome patients have increased chances of heart disease since each component condition is associated with a cardiovascular risk. Thirdly, those with mets are at a higher risk of getting type 2 diabetes later in their lifetime.

It is quite important to point out that the diagnostic criteria for type 2 diabetes have changed several times during the recent years. Fasting plasma glucose, which was formerly defined as having an upper limit of normal of 140mg/dL, is now diagnosed at 126mg/dL. Likewise, the acceptable levels of fasting plasma glucose that was once diagnosed as normal has gradually lowered – the current upper limit is 110 mg/dL while before it was 115mg/dL. For instance, prediabetes has changed its characterization from a category with FPG of 110-125 mg/dL [14].

There has been an evolution in the definition of the disease, which implies diabetes can be diagnosed at lower fasting plasma glucose levels than years ago. To sum up, diabetes is diagnosed when fasting plasma glucose is equal to, or higher than, 7.0 mmol/L, without requiring a follow-up test called an oral glucose tolerance test. In conclusion, it can be noted that the plasma glucose values used for diagnosing diabetes and prediabetes have been gradually reduced over time due to the discoveries and enhancements of medical science. This will ensure that patients are diagnosed and treated early enough, considering the consequences of uncontrolled high blood sugar levels for a prolonged period. But it also implies that some who did not meet previous diagnostic criteria can be newly diagnosed as diabetics under the current criteria .

Furthermore, the classification of types of diabetes has been done based upon the diagnostic criteria changes. Historically known as insulin-dependent diabetes mellitus, this disease is currently categorized as type 1. In the same way, non-insulin-dependent diabetes mellitus is known as type 2 diabetes.

Type 1 diabetes is the autoimmune disease that seizes and destroys the beta cells of the pancreas responsible for producing insulin and usually develops during childhood or adolescence. That is why type 1 diabetes is also referred to as juvenile diabetes. Type 1 diabetes involves the complete absence of insulin and, therefore, poses direct threats of acute complications such as diabetic ketoacidosis unless patients maintain proper glycemic control. Long-term complications of type 1 diabetes encompass cardiovascular diseases and microvascular disorders in the kidney, retina and nerves [16]. Type 2 diabetes is more common than type 1, and millions of people are diagnosed with the disease. It includes insulin insensitivity and a relative decline in insulin levels over time. Similar to type 1, type 2 diabetes is an independent risk factor for macrovascular diseases, most notably cardiovascular disease over the long term [17]. Therefore, even though type 2 diabetes accounts for most diagnoses, both types of diabetes increase cardiovascular risk.

Thus, to control both short-term risks associated with acute fluctuations in blood sugar levels as well as chronic complications of diabetes affecting blood vessels, individuals with either type 1 or type 2 diabetes need coordinated care. Potential complications include skin breakdown, infections, and poor wound healing, which can be lessened if blood sugar is closely monitored and well-managed. There are also other aspects of a person's daily living such as diet, physical activity, obesity, and smoking as well as other risk factors. If necessary, simple prescriptions like insulin, injectable forms, or oral drugs to regulate glycemic control as well as other cardiovascular risks such as high blood pressure or high cholesterol can be used.

Risk factors

Obesity

According to dietary guidelines, obesity is having a weight exceeding the optimal for a particular height and sex in addition to fat tissue necessary for physiological functions, and it is a global health epidemic associated with chronic diseases. According to WHO, there are more men suffering from obesity today than women in the entire global society. Obesity has been linked to various ailments including hypertension, diabetes, hyperlipidemia, rheumatoid arthritis, sleep apnea, and cardiovascular and cerebrovascular disorders.

Overweight and obesity are two of the most chronic and rising major non-communicable diseases that have increasingly affected the global population in the past few decades. For instance, the descriptive survey of the data from the U.S National NHANES established that the obesity rate within the United States region rose from 22.9% to 30.5% within the years 1988-1994 and 1999-2000 respectively. Consequently, the prevalence of being overweight was also on the increase, having increased from 55.9% to 64.5% within the same period.

This rapid increase in obesity and being overweight is plausible to be associated with some of the current trends in the developed world's lifestyle. As a result, obesity has turned into a genuine illness threatening epidemic affecting people and making them more prone to chronic disease. In addition, it is evident that males are more vulnerable to obesity than females.

Summarizing the information presented above, it is possible to conclude that obesity and being overweight have risen steeply over the past few decades for many countries. Probably, the Australia-specific increased prevalence of overweight status is owing to the modern life features such as physical inactivity and easy availability of energy dense foods. Thus, it is for this reason that obesity has emerged as a global concern with capacity to compromise the health of any individual to other chronic diseases. This epidemic also appears to be affecting men more than women, and the results are devastating [18].

Diabetes and insulin resistance are closely associated with a high body mass index. Several biochemical mediators of insulin resistance, as well as markers of inflammation and coagulation, are upregulated in obesity; these include glycerol, free fatty acids, TNF-α, and interleukins, leptin, fibrinogen, plasminogen activator inhibitor-1, resistin, and angiotensin. These biomolecules as we

have seen incite inflammation and interfere with normal insulin signal transduction. Diabetes involves insulin resistance to glucose and impaired function of the insulin-producing pancreatic beta cells. These two defects are seen in severe forms of the disease and they coexist. The next reason is obesity which is a leading cause of diabetes since it modifies the ability of insulin to bring down blood sugar by reducing the uptake of insulin in fat, liver and muscles. This insulin resistance due to obesity is considered a strong trigger of diabetes particularly among the genetically vulnerable population group. With a continuously emerging global obesity, characterized by unhealthy dieting, high in energy, and low in energy expenditure, the incidence of a form of diabetes in obese persons due to insulin resistance has escalated. This form of obesity-related diabetes can develop relatively quickly when the insulin resistance crosses a certain point that the diminishing beta cells cannot cover for. Understanding the societal factors of obesity gives a clue on how to diminish the increasing prevalence of this type of diabetes in the obese population [19]. Therefore, from inflammation and hormonal disruption, obesity leads to insulin resistance, pressure on the pancreatic beta cells, and, finally, diabetes.

Hypertension

This is because hypertension is a very common complication of diabetes with a staggering 75% of diabetics experiencing high blood pressure at some point in their lives. In more detail, patients with T2DM are characterized by a 60% increased probability of a concurrent hypertension. Hypertension is a condition that is prevalent all over the world with many individuals being affected at any age. If for instance a patient has both a hypertension and diabetes then the patient will be susceptible to complications in both the small and large vessels in the body.

Microvascular diseases are diseases involving small blood vessels, such as those supplying organs like the kidneys or eyes. This microvascular damage results from harm of small blood vessels, which causes macrovascular diseases that include heart attacks, strokes among others. In other words, the vascular chaos seen in the rogue diabetes type and hypertension influence wellbeing significantly.

All in all, diabetes and hypertension are two disorders that frequently coincide with each other and, in both conditions, vascular involvement occurs in the microcirculation that may deteriorate to actual problems in larger vessels. Such vascular complications are detrimental to health if the diabetes and hypertension are poorly managed. Therefore, controlling hyperglycemia and hypertension in patients with both conditions becomes important in order to prevent progression of microvascular complications to severe macrovascular complications including renal failure, myocardial infarction as well as stroke. [20].

Having hypertension as a comorbid condition puts a person with diabetes at risk for developing diabetic nephropathy whether they have type 1 or type 2 diabetes. Among type 1 diabetes patients, high blood pressure is identified on average three years prior to the diagnosis of diabetes, and diabetic kidney disease is already present on the time of diabetes diagnosis. Pre-hypertension or hypertension can be seen in type 2 diabetes before the onset of hyperglycemia. Both the conditions increase the risk of developing diabetic nephropathy, with each of the condition doubling the risks.

Kinds cells release cytokine and growth factors due to hyperglycemia. It also causes changes in the structure of the kidney and in the glomeruli since the glomerular wall becomes more permeable and the deposition of collagen increases. These changes lead to microalbuminuria and activation of the RAAS, as well as other changes. RAAS plays important role in controlling the blood pressure and managing the body fluids. Abnormalities in this system cause hypertension and renal involvement in diabetes.

Therefore, hyperglycemia and hypertension are factors that worsen the situation by advancing the development of kidney diseases in diabetes. Ketones derived from high blood sugar levels stimulate

functioning of kidney cells, mechanical modifications such as breaking of the glomerular basement membrane and chemical changes including activation of the renin angiotensin aldosterone system. However, high blood pressure continues to cause harm further. All these mechanisms work together to contribute to the progression of diabetic nephropathy. It is known that patients with diabetes should keep their blood sugar levels and blood pressure levels as low as possible in order not only to delay the development of kidney disease but also to manage the disease [21].

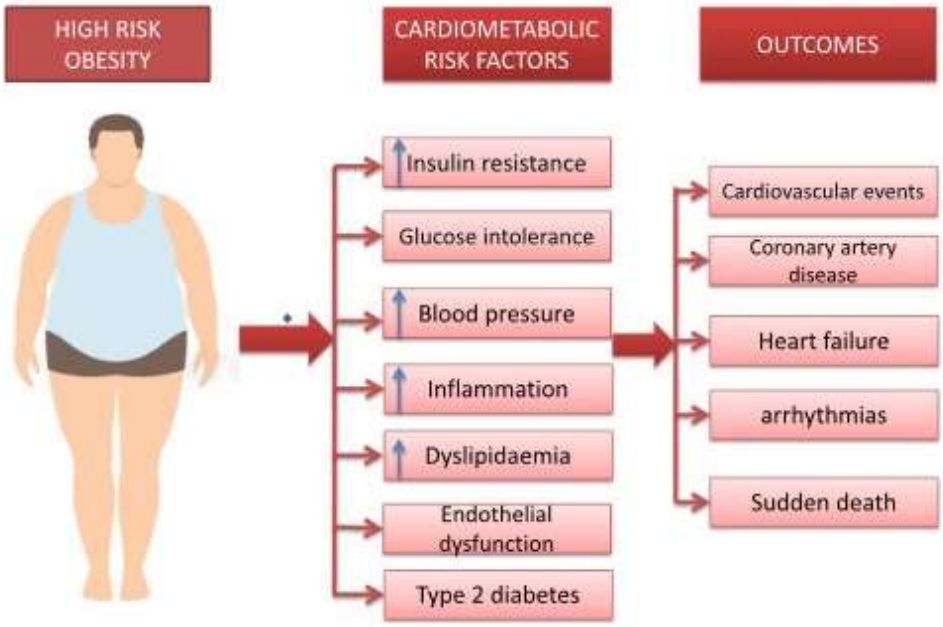

Fig 1: Relationships among high-risk obesity, intermediate cardiometabolic risk factors, and cardiovascular outcomes (obesity phenotypes, diabetes, and cardiovascular illnesses)

Dyslipidemia

An elevated rate of dyslipidemia which is an abnormal blood lipid pattern is one complication that patients with diabetes often exhibit. Diabetic dyslipidemia is manifest by increased plasma triglyceride concentration, increased LDL cholesterol (so-called “bad” cholesterol), and decreased concentration of HDL cholesterol (referred to as “good” cholesterol). In particular, elevated LDL particle number (LDL-P) or apolipoprotein B (ApoB) is typical of diabetic dyslipidemia. However, the type of LDL particles that is implicated in diabetic dyslipidemia is more atherogenic – meaning it increases the risks of plaque in the arteries – and therefore this places diabetics at higher risk of developing vascular complications such as nephropathy [22]. The diabetic condition is normally characterized unwholesome blood lipid profile containing high triglycerides, raised LDL cholesterol, low HDL cholesterol, and raised LDL particle concentration contributing to the increased risk of vascular diseases affecting organs like kidneys. Control of dyslipidemia is well recommended to lessen the impact of diabetes on patients.

Insulin resistance, as depicted in Fig. 2 [23], The pathogenesis of the development of abnormal blood lipid levels (dyslipidemia) in diabetic patients is mainly associated with peripheral insulin resistance. Finally, if tissues become insulin resistant, there will be a rise in the concentration of FFA in the blood as a result of the increased mobilization of fat in the body. These fatty acids are further retained in the liver, hepatic cells produce more of triglycerides, and add to the problem of obesity. Diabetic patients are also characterized by increased apolipoprotein B and have a higher proportion of atherogenic small dense LDL particles. In diabetes to cut down the cardiovascular risk the lipid management has come out as an important part of the current therapies.

These changes in the liver lead to an enhanced production of triglyceride-rich VLDL particles by converting the excess glucose into triglycerides. This exchange occurs through the action of an enzyme known as cholesterol ester transfer protein allowing the triglyceride rich VLDL to get rid of triglycerides by exchanging them with cholesterol esters in particles of both the HDL and LDL. This leads to the cholesterol enrichment in the particles of the high-density lipoprotein and low-density lipoprotein. In conclusion, this discussion has shown that insulin resistance is the primary factor that results in lipid disorders in diabetic patients, which warrants the use of lipid-lowering agents in managing diabetes to reduce the incidence of CVD [24]. When triglyceride-rich LDL particles are catabolized through lipoprotein lipase and hepatic lipase, the product plays a role in the formation of small dense LDL particles. The elevated level of lipids in the blood is called dyslipidemia and association with cardiovascular diseases has been established. Specifically, the action of these lipases on triglyceride-rich LDL produces atherogenic remnants as a result. They also help in generating more atherogenic small dense LDL particles or LDL particles, in the later stages. By this route, it promotes the elevated risk of cardiovascular disease through dyslipidemia.

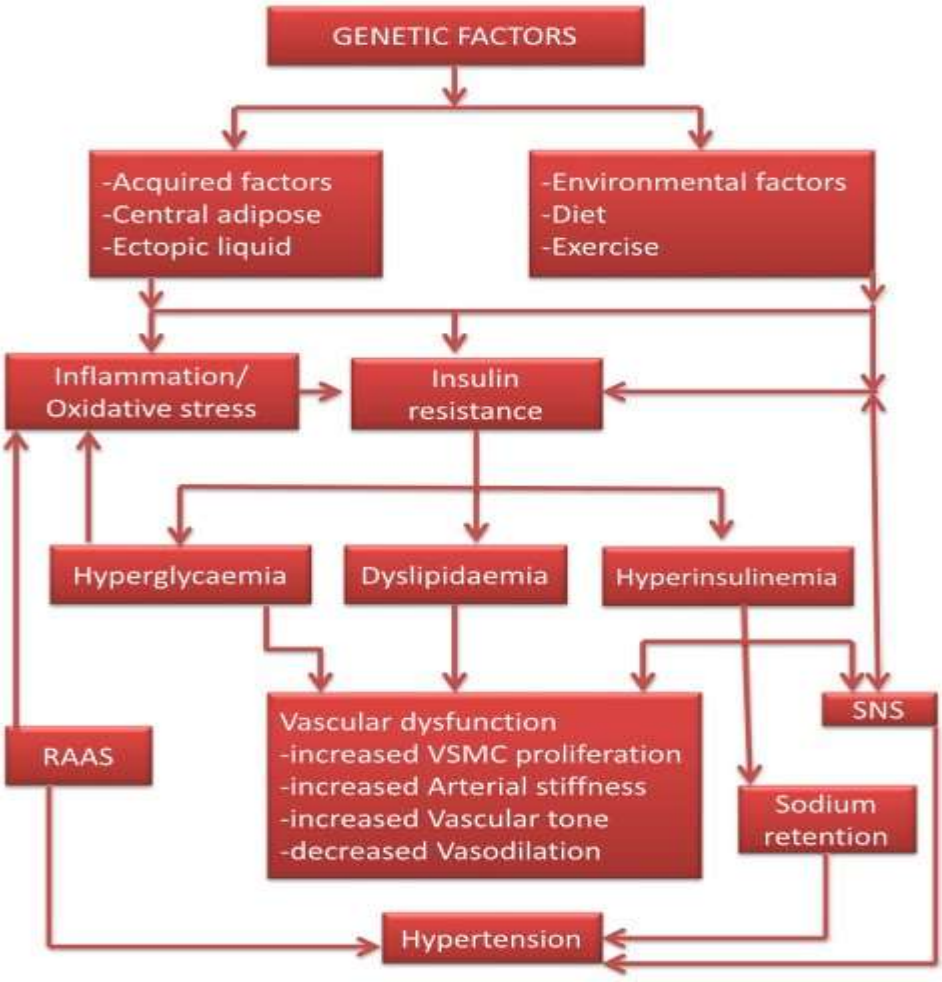

Fig 2: An overview of the pathophysiologic pathways that lead to hypertension in people with diabetes mellitus (VSMC, vascular smooth muscle cell)

Cardiomyopathy

Cardiomyopathy can occur as a direct result of diabetes mellitus. Fig. 4 depicts the pathophysiological processes involved in diabetic cardiomyopathy. The left ventricle of the heart exhibits structural and functional alterations because of diabetes cardiomyopathy. In comparison to non-diabetics, the diabetic patient has an enlarged left ventricular mass. It is possible to hypothesize that the increased

production of cytokines from adipocytes that have hypertrophic effects on cardiac cells, such as resistin and leptin, is what causes the increased heart mass in diabetics. In several previous researches, it has been highlighted that diabetic patients have slightly diminished diastolic heart function compared to patients with no diabetes. Systolic function means the efficiency of cardiac contraction while diastolic function is the efficiency of the heart at resting and refilling with blood between contractions. The causes of diastolic dysfunction in diabetics are not evident, but diabetic heart disease is likely associated with progressive remodeling of the cardiac myocytes due to sustained exposure to high glucose concentration. More work needs to be done to determine if there is a causal relationship between diabetes and diastolic dysfunction [25-27]. The mechanisms of diabetes cardiac system failure. One suggested explanation for this is the higher triglyceride content in cardiomyocytes as a result of diabetics' enhanced triglyceride production.

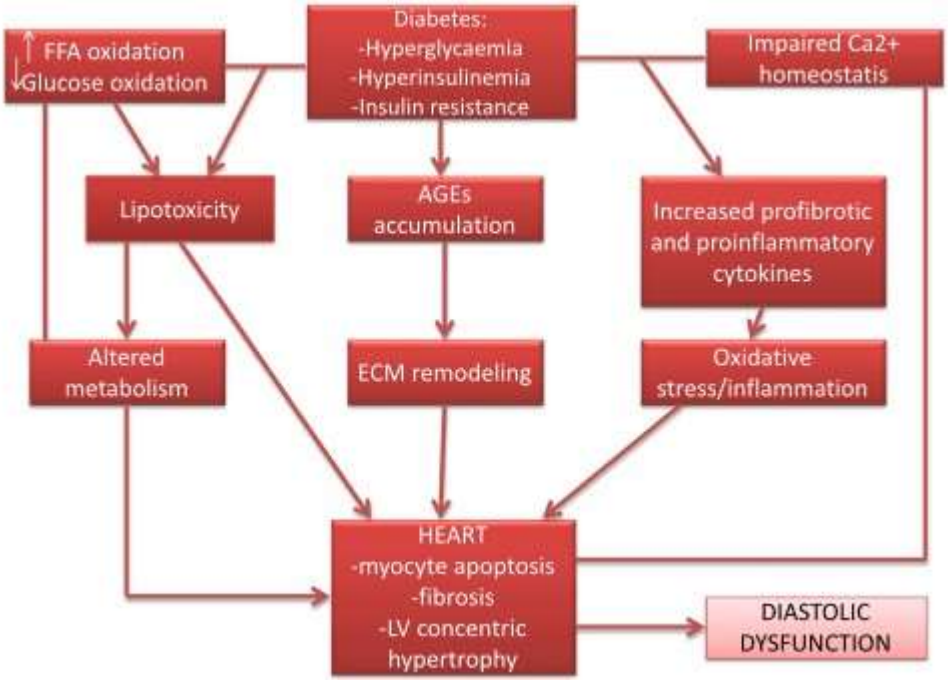

Fig 3: Diabetic cardiomyopathy's pathophysiological mechanisms

Genetic polymorphism

Cardiovascular disease (CVD) and diabetes mellitus (DM) have a genetic aspect in a multi-locus model throughout the whole human genome. These large-scale genetic investigations, including cohort studies and GWAS, have defined the most prevalent genetic markers linked to the risk of developing these diseases [28]. At present more than 30 genomic loci have been confidently associated with CVD risk. Perhaps surprisingly, at least 83 of these have been linked to DM at genome-wide significance. Despite the dissimilarities in genetic background, there is some extent of overlap, wherein some of the variants are associated with both CVD and DM [29]. Future investigations of the particular genes or the mechanisms that underlie such pathways should be revealed. However, the present data make it quite evident that the genetic bagenese disorders is profoundly polymorphic. Each demands analysis of the genome on a massive scale to unravel inheritability within the population base.

Individualized glycemic management in T2DM and CVD patients

Information provided indicates that elevated and low blood glucose levels contribute to higher CVD risks among persons. In the review of the 102 prospective trials by Roongsritong et al . It found that low fasting blood glucose level below 7 mmol/L also increases risk of CHD. This shows that CVD

risk is not just high in individuals with poor glycemic control but also in those who have tight glycemic control.

Abnormal glucose metabolism includes IGT and Hb A1c > 5.7% which are associated with increased CVD risk in addition to diabetes, which is defined as FPG ≥ 7.0 mmol/L and/or 2-h PG ≥ 11.1 mmol/L. This is true for both the primary prevention population without prior atherosclerotic CVD and for the secondary prevention population with a history of atherosclerotic CVD. In such groups, elevated levels of blood glucose increase the risk of CVD and all-cause mortality.

Altogether, these studies suggest that blood sugar levels and their regulation modulate CVD risk at all stages of glycemic control. It may be more to the point to set individual glycemic targets for patients with type 2 diabetes because general glycemic targets may not adequately address CVD risk. More studies are required to address knowledge gaps with regard to the most effective, person-centered approaches to intervene to decrease CVD events among patients with T2DM.

All in all, one should ensure that their blood glucose level remains within a desirable level so as to reduce CVD incidence and mortality among those with type 2 diabetes or glucose metabolism disorders. There is a need to abandon a “cook and spice” model of glycemic control, which implies that it is impossible to have a single approach that would work for each and every patient. Thus, it is crucial to focus on the tailoring strategy, tailored to an individual’s CVD risk factors and comorbidities to identify safe HbA1c targets and anti-hyperglycemic therapy. Hitting set targets for individualised glycaemic control can help prevent chronic cardiovascular effects. Further research on other intervention types for type 2 diabetes to ward off CVD should be conducted to support the notion of personalized treatment regimens.

Glycemic targets

Current HbA1c targets proposed by key diabetes and cardiovascular disease management associations include AHA, ADA, ESC, and ESC/EASD, which are set at 7% for most patients with diabetes. This level is linked to relative protection against the risk of microvascular complications as well as cardiovascular disease. More or less stringent HbA1c targets may be suitable for certain patient groups: More or less stringent HbA1c targets may be suitable for certain patient groups: A stringer target of 6.5% may be suitable for late diagnosed, very old patients, patients with no prior history of cardiovascular diseases. This is in concordance with the directives of the ESC, ADA, and AHA. In children, adolescents, patients with T2DM in the early stage, and those without histories of cardiovascular diseases, achieving an HbA1c level of 6.5% seems reasonable if hypoglycemia is not frequently encountered. In pregnant patients, hence the targets of 6% may be excellent if they can be achieved without posing the risk of problematic hypoglycemia. For patients over the age of sixty, those with severe complications or different diseases, or those who have been diagnosed with type 2 diabetes for many years, the target should not be as strict and should be set at 8% or higher. In totality, it asserts that even though 7% is globally recommended, caution should be observed when using targets while addressing the condition, with the proviso based on the risks/benefits analysis of every patient. Lower intensity goals can be relevant for patients with the more advanced stage of the disease or who have numerous other diseases. [31].

Antidiabetic treatment choice

Newer drugs for diabetes have cropped up revealing that SGLT2 inhibitors and GLP-1 receptor agonists lessen cardiovascular disorders and heart failure in diabetics without altering baseline HbA1c. Every case of diabetes includes factors like appropriate glycemic targets and the choice of glucose-lowering medications [32]. As part of the diabetes treatment plan, medical providers have to consider the cardiovascular health of the patient; they have to always consider the patient’s wishes and the

patient's prescription record. The goals include further improving the cardiovascular profile while at the same time ensuring acceptable levels of glycemic control with specific medications and life changes.

Metformin

This post aims at discussing whether routine use of metformin as the initial pharmacological management of patients diagnosed with new T2DM will reduce CVD. Although there are some data suggesting that the early start of metformin treatment in T2DM patients without history of CVD reduces the risk of CVD incidence as primary prevention, however, there are no enough data for the use of metformin only for secondary prevention in T2DM patients with known CVD. There is little proven benefit of metformin in cardiovascular health as only a single small randomised controlled trial of metformin shows that it reduces cardiovascular risk in patients with coronary artery disease. The third trial with 36 participants showed that Metformin enhanced the heart performance of the HF patients with reduced ejection fraction [33].

Altogether, it can be stated that there are very few studies addressing the use of metformin for the prevention of CVD in the patients with newly diagnosed T2DM, but the evidence that has been found seems rather encouraging. However, further research including more RCTs with increased number of participants, greater sample size and a higher number of events, is required to determine whether metformin when prescribed after a diagnosis of T2DM has any primary preventive effect for CVD in those without evidence of CVD. However, there is at present a deficiency of high-quality evidence to support commencing metformin for secondary CVD prevention in T2DM patients with CVD. Future research regarding the impact of metformin in T2DM populations with and without CVD is needed to elucidate a potential cardioprotective effect of metformin in newly diagnosed type 2 diabetes.

Nevertheless, metformin has been postulated to have further benefits apart from CVD prevention. Among these are the prevention of T2DM development in overweight individuals, avoidance of worsening diabetes and cancer, avoidance of weight gain and hypoglycemia in diabetes, and prolongation of pregnancy to avoid preterm preeclampsia in pregnant women. Thus, based on these additional gains, treatment with metformin may be appropriate for T2DM patients without CVD for primary prevention purposes, as well as for T2DM patients with CVD, although there is no data on the effectiveness of metformin for secondary prevention of CVD [34]. This is to enhance the benefits of metformin, especially its possible cardiovascular protective roles in patients with the established disease and to await further information.

Sodium-glucose cotransporter 2 inhibitors

The efficacy of SGLT2 inhibitor drugs on major adverse cardiovascular events (MACE) in patients with type 2 diabetes and established cardiovascular disease was looked into on three trials, a meta-analysis. The review showed that SGLT2 inhibitors achieved a statistically significant of 11% in reducing the entire danger of MACE among the high-risk population. The drugs were also demonstrated to have an impact on the severity of other forms of cardiac arrhythmias such as atrial fibrillation and atrial flutter reducing the likely progression of these conditions. In addition to cardiovascular protective impacts, SGLT2 inhibitors showed renal improvement as well. It also reduced the risk of death from cardiovascular causes or hospitalization due to heart failure by a third. Furthermore, they reduced the progression of diabetic nephropathy by 45% among patients with diabetes. In conclusion, this meta-analysis provided evidence of moderate to high quality that SGLT2 inhibitor drugs are associated with significant benefits for A CVD risk T2DM patients. The drugs were found useful in preventing serious cardiac events, lowering the rates of hospitalization due to heart failure, and delaying the decline of renal functions in these sensitive patients. The studies reveal that SGLT2 inhibitors have multiple benefits for organ protection in high-risk diabetes patients [35, 36].

Some of the SGLT2 inhibitors available in the current market are empagliflozin, canaglifozin , dapaglifozin , ertuglifozin, tofoglifozin, luseoglifozin and ipraglifozin. Randomized controlled trials conducted on patients in Asia Pacific, Middle East and North America have confirmed that these drugs have the ability to reduce cardiovascular events in most patients [37]. In particular, the SGLT2 inhibitors, including canagliflozin, dapaglifozin, ertuglifozin, have been shown to have an effect in reducing the overall risk of heart failure events in patients with HFrEF and HFpEF. Emerging evidence suggests increased safety and efficacy of empagliflozin for the management of HFrEF phenotype. Based on current evidence and RWE studies in diverse population, empagliflozin, canaglifozin, dapaglifozin, and ertuglifozin have been shown to have less risk of CV and HF in patient with HFrEF, HFpEF, and in broader patient population [38]. Such studies reveal the cardiovascular as well as heart failure advantages that emanates from these glucose-reducing drugs.

Conclusion

The current goals for glycemia, lipid profile, and hypertension in T2DM patients should have plans for the prevention of CVD as per guidelines. Regarding the cases of death, it has been observed that even though death rates from CVDs have reduced in T2DM populations, the incidence and mortality with CVDs remain high. Some of the CVDs associated with T2DM can be prevented by modifications in lifestyle and the use of anti-hyperglycemic medications. Unlike broad measures, precision medicine keen on the patient now guides the management of T2DM-related CVD. Current and specific management of T2DM in patients with CVD include glp-1 agonists, sglT2 inhibitors, and medications for hypertension and dyslipidemia. Altogether, patient-tailored management strategies employing the best available T2DM drugs in patients with previous CVD are less aggressive than the prior standardized treatments aimed at decreasing the risk and mortality of CVD. This approach has now become major-oriented in T2DM-related CVD prevention and management as compared to earlier more general approaches. Priorities include achieving the use of patient-specific therapy that includes lifestyle modification and integration of new antidiabetic, antihypertensive, and lipid-lowering drugs.

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