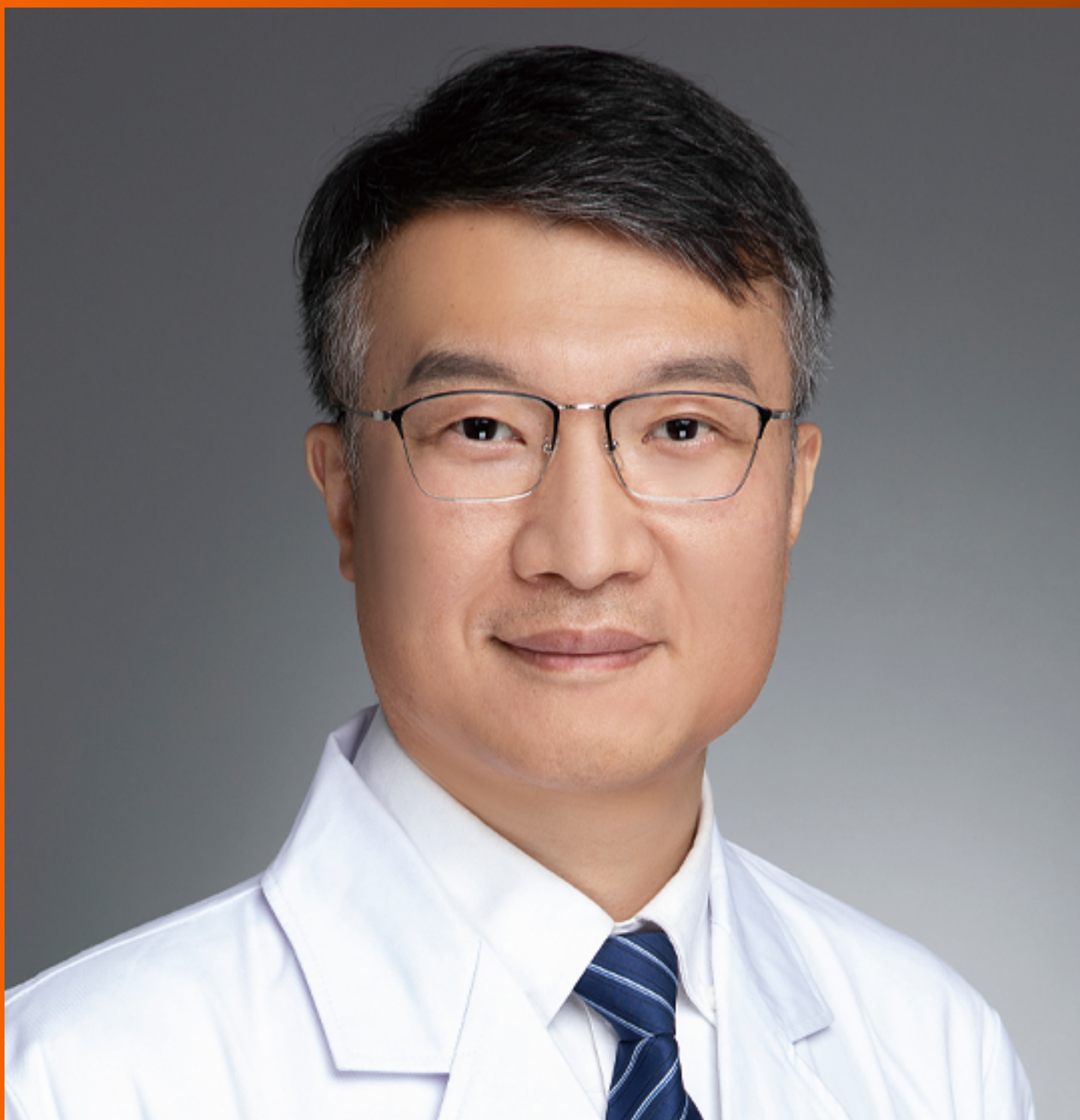


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The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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Diabetic patients with chronic kidney disease: Non-invasive assessment of cardiovascular risk

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Abstract

The prevalence and burden of diabetes mellitus and chronic kidney disease on global health and socioeconomic development is already heavy and still rising. Diabetes mellitus by itself is linked to adverse cardiovascular events, and the presence of concomitant chronic kidney disease further amplifies cardiovascular risk. The culmination of traditional (male gender, smoking, advanced age, obesity, arterial hypertension and dyslipidemia) and non-traditional risk factors (anemia, inflammation, proteinuria, volume overload, mineral metabolism abnormalities, oxidative stress, *etc.*) contributes to advanced atherosclerosis and increased cardiovascular risk. To decrease the morbidity and mortality of these patients due to cardiovascular causes, timely and efficient cardiovascular risk assessment is of huge importance. Cardiovascular risk assessment can be based on laboratory parameters, imaging techniques, arterial stiffness parameters, ankle-brachial index and 24 h blood pressure measurements. Newer methods include epigenetic markers, soluble adhesion molecules, cytokines and markers of oxidative stress. In this review, the authors present several non-invasive methods of cardiovascular risk assessment in patients with diabetes mellitus and chronic kidney disease.

Key Words: Diabetes mellitus; Diabetes complications; Chronic kidney disease; Atherogenesis; Atherosclerosis; Cardiovascular risk

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Core Tip: The culmination of traditional and non-traditional atherosclerosis risk factors in patients with diabetes mellitus and chronic kidney disease leads to fulminant and advanced atherosclerosis, consequently resulting in cardiovascular morbidity and mortality. Non-invasive cardiovascular risk assessment should therefore be performed in all these patients and can be based on standard laboratory parameters, cytokines and markers of oxidative stress, 24 h blood pressure measurements, ankle-brachial index, arterial stiffness parameters, imaging techniques and epigenetic markers. In this review article, we present different methods of non-invasive cardiovascular risk assessment in patients with diabetes mellitus and chronic kidney disease.

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INTRODUCTION

The burden of diabetes mellitus (DM) on global public health and socioeconomic development is heavy and is escalating. The International Diabetes Foundation has stated that in 2017, 451 million people worldwide have lived with DM and that this number would soar in the next couple of years and decades[1].

DM is the number one cause of chronic kidney disease (CKD) worldwide and is inherently linked with increased mortality mostly due to cardiovascular causes[2]. CKD is another major public concern with rising prevalence, which is now estimated at 9.1%[3]. In 2017, CKD resulted in 1.2 million deaths and was the 12th leading cause of death globally. Additionally, 7.6% of all cardiovascular deaths were due to CKD[4].

Cardiovascular disease in patients with DM and CKD is attributed to advanced and fulminant atherosclerosis, due to the presence and interplay of traditional [male gender, smoking, advanced age, obesity, arterial hypertension (AH), dyslipidemia] and non-traditional, CKD-specific risk factors (anemia, inflammation, proteinuria, volume overload, mineral metabolism abnormalities, oxidative stress, etc.)[5].

Due to the increased rate of cardiovascular events, prompt and timely cardiovascular risk assessment is crucial in reducing the morbidity and mortality of these patients[6]. In this review article, the authors present non-invasive methods of assessing cardiovascular risk in patients with DM and CKD (Figure 1).

STANDARD LABORATORY PARAMETERS

Estimated glomerular filtration rate

The diagnosis of CKD is based on functional and structural changes of the kidneys, with the former assessed by estimating or measuring the glomerular filtration rate (GFR) and albuminuria/proteinuria and the latter by using different imaging techniques and/or kidney biopsy. Multiple creatinine and/or cystatin C based equations are only an assessment of kidney function and have several limitations, but the alternative (measurements of GFR) is usually not available in routine clinical practice[7].

Reduced estimated GFR is an important marker of cardiovascular risk. Go *et al*[8] performed a study in which they estimated the longitudinal GFR among 1120295 adults in whom serum creatinine had been measured between 1996-2000 and who had not undergone dialysis or kidney transplantation. Of the included patients, 9.6% had concomitant DM. They found an independent, graded increase in cardiovascular deaths, events and hospitalization rates in those with reduced estimated GFR. The authors postulated that the relationship between reduced GFR and cardiovascular disease is partly due to the presence of several traditional atherosclerosis risk factors and partly due to the presence of several CKD-specific risk factors, such as increased levels of inflammation markers, hyperhomocysteinemia, abnormal apolipoprotein levels, enhanced coagulability, anemia, left ventricular hypertrophy (LVH), increased

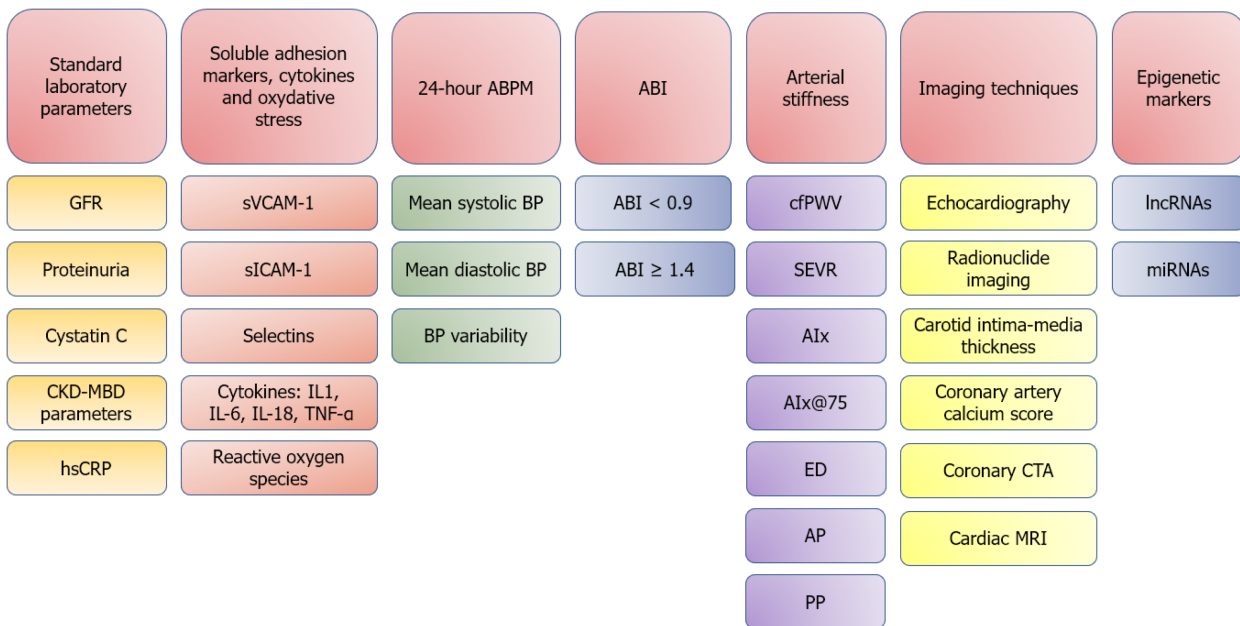


Figure 1 Non-invasive assessment of cardiovascular risk in patients with diabetes mellitus and chronic kidney disease. GFR: Glomerular filtration rate; CKD-MBD: Chronic kidney disease mineral bone disorder; hsCRP: High sensitivity C-reactive protein; sVCAM-1: Soluble vascular cell adhesion molecule-1; sICAM-1: Soluble intercellular adhesion molecule-1; IL-1: Interleukin-1; IL-6: Interleukin-6; IL-18: Interleukin-18; TNF-α: Tumor necrosis factor-α; ABPM: Ambulatory blood pressure measurements; BP: Blood pressure; ABI: Ankle-brachial index; cfPWV: Carotid-femoral pulse wave velocity; SEVR: Subendocardial viability ratio; AIx: Augmentation index; AIx@75: AIx adjusted for heart rate 75/min; ED: Ejection duration; AP: Augmentation pressure; PP: Pulse pressure; CTA: Computed tomography angiography; MRI: Magnetic resonance imaging; lncRNAs: Long non-coding ribonucleic acids; miRNAs: Micro-ribonucleic acids.

endothelial dysfunction, increased arterial stiffness and augmented arterial calcifications.

In a study by Wu *et al*[9], the authors found that reduced estimated GFR was an important hallmark of diabetic retinopathy, which is commonly associated with advanced diabetic nephropathy and increased cardiovascular risk as well. In a 1-year cross-sectional study by Babaliche *et al*[10], the authors found that reduced GFR in type 2 DM patients was significantly associated with a higher incidence of microvascular complications, such as diabetic neuropathy, retinopathy and nephropathy.

DM exerts its negative effects on kidney function through negative glomerular hemodynamic effects, especially through glomerular hyperfiltration, which is defined as an estimated GFR more than two standard deviations above the mean estimated GFR of healthy individuals. In a study performed on healthy, middle-aged individuals by Dupuis *et al*[11], the authors found that glomerular hyperfiltration is independently associated with higher cardiovascular risk, similar to the risk observed in patients with CKD stage 3A. Similar findings have been observed in several studies on patients with type 1 and type 2 DM, with and without previous cardiovascular disease[12-14]. Glomerular hyperfiltration was also associated with an increased incidence of coronary artery calcification and LVH, both important cardiovascular risk markers[15].

Proteinuria

Proteinuria (defined as urine protein excretion greater than 300 mg over 24 h) and moderately increased albuminuria (defined as urinary albumin excretion of 30-300 mg over 24 h) are usually signs of renal injury and can often be detected earlier than any tangible fall in GFR[16]. Both are strong and independent predictors of increased risk for all-cause and cardiovascular mortality in patients with and without DM. Additionally, both are risk factors for faster CKD progression as well and are therefore included in the KDIGO (kidney disease: Improving global outcomes) CKD staging system[16].

In a post-hoc analysis of the Reduction in Endpoint in Non-insulin dependent DM with the angiotensin II antagonist losartan trial, the authors found that proteinuria of 3 g or more per day was associated with a renal endpoint of doubling of creatinine or end-stage renal disease (ESRD) in 85% of patients and with a cardiovascular endpoint (defined as the composite of myocardial infarction, stroke, first hospitalization for heart failure or unstable angina, coronary or peripheral revascularization or cardiovascular death) in 44% of patients. In the same study, moderately increased

albuminuria was associated with an increased likelihood of kidney disease progression and cardiovascular risk as well, even after adjusting for estimated GFR and comorbidities[17].

The Strong Heart Study showed that patients with type 2 DM and proteinuria had worse left ventricular function and impaired diastolic left ventricular filling compared with patients without proteinuria[18]. According to studies, diabetic patients with proteinuria are at increased risk for peripheral artery disease (PAD)[19] and incident stroke as well[20].

In a Heart Outcome Prevention Evaluation (HOPE) substudy, a linear relationship between moderately increased albuminuria and cardiovascular events, especially in patients aged 55 years or more with previous cardiovascular disease or DM, was proven. In the same study, a higher incidence of systolic and diastolic dysfunction was found in patients with moderately increased albuminuria[21]. A study of 308 patients showed that patients with angiographic evidence of coronary artery disease (CAD) had higher urinary albumin levels than disease-free individuals and that urinary albumin excretion increased progressively with CAD severity[22].

All the above-stated studies confirm the fact that the detection and early recognition of moderately increased albuminuria and proteinuria is crucial in managing cardiovascular risk and the rate of CKD progression[23,24].

The exact pathophysiologic pathways that would explain the mechanism behind increased cardiovascular risk and proteinuria are still not known. It is postulated that the proteins that leak through damaged glomerular capillary endothelium cause tubulointerstitial injury and inflammation and subsequently lead to parenchymal damage, renal fibrosis and progressive decline in renal function[25]. The steno hypothesis suggests that urinary protein excretion signals a subclinical renal disease and systemic endothelial dysfunction and systemic inflammation[26]. Additionally, several thrombogenic factors, for example, von Willebrand factor, fibrinogen, cell adhesion molecules and tissue plasminogen activator have also been connected with proteinuria. It has been suggested that high platelet adhesiveness and erythrocyte aggregation demonstrated in diabetic patients with proteinuria could indicate increased thrombosis risk. Insulin resistance has been proven in patients with proteinuria, implying the role of hyperinsulinism in explaining the increased cardiovascular risk in these patients[26].

Cystatin C

Serum cystatin C is a low-molecular-weight, non-glycosylated protein from the family of cysteine protease inhibitors that closely approximates what could be considered an ideal marker of renal function because it is freely filtered by the glomerulus, reabsorbed and degraded completely by proximal tubule and is not secreted by the tubules. It is more sensitive than usual endogenous markers (serum creatinine and urea) used in kidney function assessment, especially in the early stages of CKD[27]. However, cystatin C can also be used as a cardiovascular risk marker having important prognostic implications in patients with different degrees of CKD[28].

According to a cross-sectional epidemiological study by Cepeda *et al*[29], elevated cystatin C was associated with an increased presence of several cardiovascular risk factors, such as DM, AH and CKD, along with higher levels of C-reactive protein (CRP), homocysteine and fibrinogen. Correa *et al*[30] performed a study on 4965 individuals after acute coronary syndrome in which they found a higher likelihood of adverse cardiovascular events in those with increased cystatin C, opening up a potential new role of cystatin C in risk stratification. Madero *et al*[31] performed an arterial stiffness study on 2468 individuals (24% diabetic) and found an association between cystatin C and increased arterial stiffness, especially in older patients. In two mortality studies, elevated cystatin C levels were associated with increased all-cause mortality, even in patients with normal renal function[32,33].

It has been suggested that cystatin C exerts its function through inhibition of lysosomal cathepsins, which leads to a reduction in atherosclerotic plaque degradation and increased risk of cardiovascular events[34].

Calcium, phosphate, parathyroid hormone, fibroblast growth factor-23 and vitamin D homeostasis

CKD mineral and bone disorder (CKD-MBD) refers to the clinical syndrome of laboratory abnormalities, bone disease and extraskeletal calcification, including the arterial system. Among the earliest manifestations of CKD-MBD are vitamin D deficiency, disordered calcium and phosphate homeostasis, elevated levels of parathyroid hormone and fibroblast growth factor-23 (FGF-23). These alterations lead

to an increased risk of ESRD, cardiovascular disease and mortality[35]. The amount of evidence is especially strong for elevated serum phosphate and FGF-23, both of which have direct negative cardiovascular effects through promoting LVH and consequent left ventricular dysfunction[36,37]. Several cross-sectional studies have demonstrated that vitamin D deficiency also increases the risk of developing AH, heart failure and sudden cardiac death, all through downregulation of the renin-angiotensin-aldosterone system, impaired insulin sensitivity, direct effects on the heart and vasculature and through worsened glycemic control[38,39].

The difference in CKD-MBD according to diabetes status has also been noticed. In a large descriptive study of patients with CKD stages 2-4, participants with DM had higher levels of serum phosphate, parathyroid hormone and FGF-23 and lower levels of vitamin D compared to patients without DM. Moreover, the elements of CKD-MBD evolved earlier in the course of CKD in diabetic patients, partly explaining the higher cardiovascular risk in diabetic CKD patients. An inverse relationship between the level of proteinuria and vitamin D was also observed, further confirming the importance of surveillance of mineral metabolism in diabetic CKD patients[40].

High-sensitivity CRP

Chronic, low-grade inflammation plays a grand role in the initiation and progression of atherothrombosis, metabolic disorders, AH, DM and renal disease[41]. High-sensitivity CRP (hsCRP) is an established inflammatory biomarker and is one of the most widely used markers associated with risk of cardiovascular events[42]. In the study by Ridker *et al*[43], 27939 presumed healthy American women were followed up for a mean of 8 years for incident myocardial infarction, ischemic stroke, coronary revascularization or death from cardiovascular causes. The authors found that cardiovascular events were more common in those with higher hsCRP levels, independent of traditional atherosclerosis risk factors. In the Cardiovascular Health Study, nearly 6000 subjects were followed up for 3-4 years, and their inflammatory markers were measured before and after completed follow-up. The results of the study showed that those with higher baseline hsCRP values were more likely to develop DM in the follow-up period[44]. An association has also been found between higher values of glycated hemoglobin and hsCRP, suggesting the role of systemic inflammation in diminished insulin sensitivity and suboptimal glycemic control[45].

Interestingly, studies have not shown uniform results regarding the role of hsCRP as a marker of cardiovascular risk in diabetic patients. In a pooled analysis of 25797 patients from four different United Kingdom prospective cohort studies, hsCRP was linked to increased risk of cardiovascular events and mortality only in patients without DM[46]. Similar results were found in the Jager *et al*[47] study and in the Strong Heart Study as well[48]. In the Diabetes Heart Study, hsCRP was analyzed in 846 type 2 DM patients who had follow-ups for a mean period of 7.3 years. On the contrary to other studies, baseline hsCRP was a strong predictor of mortality in this group of patients[49].

Elevated hsCRP has been found to be an important marker of acute kidney injury, subclinical kidney injury, incident CKD and CKD progression[50,51]. Sinha *et al*[52] found that higher baseline hsCRP is associated with incident diabetic nephropathy. In a study by Jalal *et al*[53] in which 3166 elderly subjects were included (18% diabetics), high hsCRP was associated with a higher likelihood of major adverse cardiovascular events. In a meta-analysis by Li *et al*[54] on CKD and ESRD patients, hsCRP was associated with a significantly higher risk of cardiovascular morbidity and mortality. Besides being an important biomarker of cardiovascular risk, a change in hsCRP can be a sign of changed renal and consequently cardiovascular risk profile. Liu *et al*[55] found that a reduction in hsCRP favored kidney outcomes in patients with impaired glucose metabolism or DM, showing that serial measurements of hsCRP can be indicative of change in systemic inflammation and atherogenesis.

SOLUBLE ADHESION MOLECULES, CYTOKINES AND OXIDATIVE STRESS

Inflammation underlies all stages of atherosclerotic plaque formation, even in the early stages where inflammatory cells adhere and infiltrate the subendothelium. The two most important adhesion molecules that play a major role in atherosclerosis are vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1). Selectins are another group of adhesion molecules and are found on leukocytes, endothelial cells and thrombocytes[56]. Cell adhesion molecules and

selectins can be broken off into the circulation and can be measured in the serum. Soluble adhesion molecules have shown potential as biomarkers of cardiovascular risk [57].

Increased levels of soluble VCAM-1 (sVCAM-1) and soluble ICAM-1 (sICAM-1) have been found in diabetics with increased stages of CKD [57,58]. In a study by Bavbek *et al* [56], increased serum levels of selectins were associated with microvascular complications of DM, including proteinuria and decreased estimated GFR. Becker *et al* [59] demonstrated increased 10-year cardiovascular mortality in diabetic patients with increased sICAM-1 levels, independent of other known traditional cardiovascular risks. Both sICAM-1 and sVCAM-1 were higher in elderly patients with type 2 DM with cerebrovascular and cardiovascular disease [60,61].

Another important component of the inflammatory process in atherosclerosis are cytokines and their receptors. Interleukin (IL)-2 receptor has been associated with increased carotid intima-media thickness (IMT) and advanced atherosclerosis in hemodialysis patients [62]. Population-based studies have shown that inflammatory cytokines are strong predictors of the development of DM and are also important in the development of micro- and macrovascular complications in diabetic patients [63]. IL-1, IL-6, IL-18 and tumor necrosis factor- α enhance the expression of ICAM-1, VCAM-1 and selectins, affect the dynamics of the mesangial matrix, lead to glomerular basal membrane thickening, alter glomerular hemodynamics and lead to renal toxicity [64,65]. Cytokines can also lead to dysregulation between antioxidative mechanisms and the formation of reactive oxygen species, such as superoxide anions, hydrogen peroxide and hydroxyl radicals. Ineffective antioxidant capacity or excess reactive oxygen species is implicated in the development and progression of renal and cardiovascular disease through several pathophysiologic mechanisms, including through direct tissue toxicity and promotion of further inflammation [66-68].

TWENTY-FOUR HOUR AMBULATORY BLOOD PRESSURE MEASUREMENTS

In patients with AH, multiple blood pressure measurements during longer periods of time [for example 24 h ambulatory blood pressure measurements (ABPM)] are more likely to predict cardiovascular risk and are therefore superior to those obtained in the doctor's office for estimating the risk of future cardiovascular morbidity and mortality [69].

In a population-based prospective study on 1700 Danish people by Hansen *et al* [70], the authors found that 24 h ABPM was an important prognostic tool in assessing subjects' cardiovascular risks and that isolated ambulatory systolic hypertension as well as blunted decrease in blood pressure during the night were both prognostically unfavorable. The percentage of DM was higher in the sustained high blood pressure group (4.3%) compared to the isolated ambulatory hypertension group (2.8%), isolated office hypertension group (1.3%) and normotensive group (1.2%).

In a cohort study by Grezzana *et al* [71] that included 569 hypertensive patients, the 24 h ABPM showed a predictive result for new cases of atrial fibrillation and a combination of cardiovascular outcomes, mortality and hospital admissions. In a study by Iqbal *et al* [72] in which 1187 individuals were included, significant associations were found between cerebrovascular events and absent nocturnal drop in blood pressure ($\leq 10\%$), between high day time diastolic blood pressure, PAD and morning surge $\geq 20/15$ mmHg and between cardiac arrhythmias, high day time and nighttime diastolic blood pressure.

In patients with and without DM, 24 h ABPM is superior to office recordings in terms of recognizing masked and white coat hypertension [73]. A lack of nocturnal dip in blood pressure is suggestive of autonomic neuropathy and is commonly observed in diabetic patients and can very commonly be a sign of concomitant obstructive sleep apnea, which is a known cardiovascular risk factor [74]. In a study by Eguchi [75] performed on patients with type 2 DM, 24 h systolic blood pressure was significantly correlated with silent cerebral infarcts and LVH, even more so than the values of glycosylated hemoglobin, indicating that perhaps uncontrolled hypertension is the main cause of accelerated atherosclerosis and increased cardiovascular risk in this population.

Like DM, CKD is also associated with a distinctive blood pressure profile, resulting in undiagnosed hypertension, which is a major factor in a continuing decline in kidney function. Manios *et al* [76] demonstrated that short-term blood pressure variability is more pronounced in CKD patients, rendering office measurements obsolete and

imprecise in this population. Similar studies have confirmed these findings and additionally showed a larger presence of non-dippers and patients with masked hypertension in the CKD group as well[77]. Decreased diurnal blood pressure variation is independently associated with a faster decline in kidney function[78] and with increased cardiovascular mortality in CKD patients[79]. In the prospective African American study of kidney disease and hypertension cohort study of 617 CKD patients, Gabbai *et al*[80] demonstrated that 24 h systolic blood pressure predicted both kidney and cardiovascular outcomes. Wang *et al*[81] studied a large ($n = 1219$) cohort of diabetic and non-diabetic CKD patients and found that blood pressure load and ABPM levels were independently correlated with left ventricle mass index, estimated GFR and proteinuria in all groups of CKD patients. Besides CKD stages 2-4, studies have shown an adverse cardiovascular profile in ESRD patients with elevated 24 h systolic blood pressure and a non-dipping ABPM profile as well[82-84].

ANKLE-BRACHIAL INDEX

PAD is usually diagnosed by ankle-brachial index (ABI) < 0.9 and can be considered a clinical model for atherosclerosis. It is the result of structural and functional vessel wall aberrations, resulting in limb ischemia and changes in pulse wave propagation, ultimately impacting the myocardium as well[85]. PAD is an independent risk factor for stroke, myocardial infarction and cardiovascular death, and the risk is even more apparent in diabetic patients[86]. In a study by Li *et al*[87] that was performed on 1647 patients with type 2 DM, low ABI (≤ 0.9) was independently associated with a high risk of all-cause and cardiovascular mortality. In a retrospective study by Alves-Cabrata *et al*[88] in which 34689 patients with type 2 DM were included, the authors found that even ABI in the lower normal range (0.91-1.00) was associated with significantly increased risk for nephropathy, retinopathy, acute myocardial infarction and mortality. In the same study, high ABI (> 1.3) was a marker of increased medial calcinosis and was associated with cardiovascular complications, most likely due to increased arterial stiffness, directly leading to increased cardiac workload, left ventricular hypertrophy, myocardial fibrosis, ischemia and arrhythmias[89].

CKD patients are especially prone to complications of atherosclerosis, PAD, calcifications of arterial walls and increased arterial stiffness[90]. According to the Cardiovascular Health Study, in which 4.513 community-living subjects aged 65 years or more were enrolled (15.3% diabetics), CKD was associated with both high (> 1.4) and low (< 0.9) extremes of ABI, which was explained by advanced atherosclerosis and increased vessel wall calcifications in this subgroup[90]. The prevalence of medial calcinosis has been shown to be even higher in patients on hemodialysis[91]. The results of the prospective NEFRONA study, in which 2445 CKD and 559 non-CKD subjects were included, showed higher prevalence of PAD in CKD patients and a rising prevalence of ABI > 1.4 in advanced stages of CKD. DM was the only factor predicting both pathological values of ABI in all CKD stages[92].

Both high and low ABI measurements play a role in assessing cardiovascular risk and renal outcome. According to a study by Chen *et al*[93] in which 436 CKD patients were enrolled (36.9% with DM type 2), reduced ABI (< 0.9) was associated with a more rapid decline in renal function and with a higher incidence of cardiovascular events. Similar association was found between renal function, cardiovascular events and high ABI[94]. In a study on 52 hemodialysis patients by Bevc *et al*[95], survival analysis showed higher risk for cardiovascular death in patients with ABI > 1.4 . It appears that the systemic nature of atherosclerosis is only partly responsible for these effects of changed ABI and that increased arterial stiffness and consequent hemodynamic changes play an integral role as well[96].

ARTERIAL STIFFNESS PARAMETERS

Increased arterial stiffness is recognized as a surrogate endpoint for cardiovascular disease and is the result of several structural alterations in the arterial walls, leading to reduced distensibility and decreased buffering capacity of arteries to pulsatile cardiac ejection[97].

Applanation tonometry is a non-invasive, easily reproducible technique often used for measuring arterial stiffness. It enables us to perform pulse wave analysis on the radial artery, giving us information on indirect parameters of central arterial stiffness and blood supply to the endocardium of the heart[98]. It also allows us to measure

carotid-femoral pulse wave velocity (cfPWV) on the carotid and femoral arteries, which is the most precise way to non-invasively determine central arterial stiffness [99]. All the applanation tonometry-derived arterial stiffness parameters are presented in Table 1.

Increased arterial stiffness is a well-known risk factor for major cardiovascular events. Weber *et al* [100] performed a prospective study on 465 male patients undergoing coronary angiography and found that augmentation pressure, augmentation index (AIx), and AIx@75 (AIx adjusted for heart rate 75/min) were strong predictors of obstructive CAD. Prskalo *et al* [101] performed a study on 160 patients with CAD undergoing elective coronary angiography and found that increased values of PWV and AIx were associated with a more advanced CAD, a higher likelihood of in-stent restenosis and left main CAD. An association between PAD and increased arterial stiffness has also been described [96]. A prospective Rotterdam study involving 2835 volunteers aged 55 years or more reported that subjects with higher values of cfPWV had a higher risk of coronary and cerebrovascular events [102]. A population Hoorn study included 261 healthy subjects and 358 patients with prediabetes or diabetes and found that the latter group had significantly higher values of cfPWV and AIx, indicating increased arterial stiffness in patients with impaired glucose metabolism [103]. In a 2015 meta-analysis by Prentner *et al* [104], increased arterial stiffness (in most studies determined with cfPWV and AIx) correlated with higher mortality and a more advanced target organ damage (nephropathy, neuropathy and retinopathy) in diabetic patients. Laugesen *et al* [105] demonstrated that female patients with DM have the lowest values of subendocardial viability ratio (SEVR) compared to men with and without DM, indicating impaired subendocardial perfusion and endothelial dysfunction in this population.

Briet *et al* [106] performed a study on 95 patients with CKD (GFR measured with ⁵¹Cr-EDTA clearance; 11% diabetics) and 121 hypertensive patients without CKD (GFR estimated with the use of Modification Diet in Renal Disease equation; 5% diabetics). They found that patients with CKD presented with increased arterial stiffness, determined by higher values of cfPWV. They explained their findings by the higher presence of DM and other traditional and non-traditional atherosclerosis risk factors in the CKD group. According to Sedaghat *et al* [107], the correlation between CKD and arterial stiffness is reciprocal, suggesting that besides being the result of CKD, increased arterial stiffness can lead to a faster CKD progression as well. A similar finding was found in a study by Fountoulakis *et al* [108], which was performed on diabetic patients with CKD. Proteinuria has also been linked to higher cfPWV and reduced SEVR and ejection duration [109,110].

Di Micco *et al* [111] performed a prospective, 3-year study involving 212 patients with CKD stages 3 and 4. During the study period, 34 patients died, 29 of them due to cardiovascular causes. Patients with lower SEVR had higher mortality. Post-mortem evaluation showed a higher degree of coronary artery calcification and a larger myocardial mass in patients with previously lower values of SEVR. Ekart *et al* [112] performed a study on non-dialysis CKD patients (27% diabetics) and found that SEVR < 130% predicted fatal and non-fatal cardiovascular events.

In a study by Kimoto *et al* [113], the authors found that the degree of CKD-associated increase in arterial stiffness varies among arterial regions in type 2 DM and is predominantly increased in the aorta. This has clinical implications because aortic stiffness is a strong and independent predictor of cardiovascular death, as shown in ESRD, DM, hypertensive and elderly patients.

IMAGING TECHNIQUES

Echocardiography

Structural and functional changes of the heart muscle are pivotal in understanding the increased cardiovascular risk in patients with DM and CKD. Both entities are related to macrovascular and microvascular pathology, resulting in increased myocardial fibrosis and subsequently in systolic and diastolic dysfunction [114,115]. It appears as though these changes are even more pronounced in the uremic milieu and are most likely intensified through myocardial calcifications in CKD patients [116]. Several studies have shown an independent association between DM, LVH and reduced systolic function of the left ventricle, both of which are commonly linked to an increased likelihood of sudden cardiac death, mostly due to arrhythmias [114,117,118]. LVH is especially common in CKD patients as it is linked to common comorbidities in these patients (AH, DM) and to CKD-specific factors, for example, volume overload,

Table 1 Arterial stiffness parameters and their definitions[98,99]

| Arterial stiffness parameter | Definition |
|------------------------------|--|
| cfPWV (m/s) | Pulse wave distance between two measuring sites (carotid and femoral artery) divided by pulse transit time (measured by electrocardiographic monitoring) |
| PP (mmHg) | Difference between systolic and diastolic pressure |
| AP (mmHg) | Difference between systolic and inflection pressure |
| AIx (%) | AP divided by PP |
| AIx@75 (%) | AIx adjusted for heart rate at 75 beats per minute |
| ED (ms) | Duration of left ventricular systolic ejection |
| EDI (%) | The ratio of the duration of systolic ejection to the total duration of the heart cycle |
| SEVR (%) | The diastolic area under the curve divided by the systolic area under the curve, derived from the pulse wave curve |

cfPWV: Carotid-femoral pulse wave velocity; PP: Pulse pressure; AP: Augmentation pressure; AIx: Augmentation index; AIx@75: AIx adjusted for heart rate 75/min; ED: Ejection duration; EDI: Ejection duration index; SEVR: Subendocardial viability ratio.

hyperphosphatemia and elevated levels of FGF-23. The clinical significance of LVH is prognostically unfavorable and is linked to increased cardiovascular mortality in patients with different degrees of CKD, including those on hemodialysis[119,120]. An additional strength of echocardiography is shown in a study by Di Cori *et al*[121], in which the authors found important subclinical dysfunction in asymptomatic type 1 DM patients aged under 40 years by using strain, strain rate and integrated backscatter. A similar finding was demonstrated in a study by Ha *et al*[122], in which the authors presented the importance of tissue Doppler indexes for unmasking subclinical myocardial ischemia. The prevalence of diastolic dysfunction, left atrial fibrosis and left atrial enlargement is also higher in patients with DM and CKD. All of the mentioned changes are a reflection of structural myocardial disease and are markers of increased cardiovascular risk as well[123].

Radionuclide imaging

Regadenoson-stress single-photon emission computed tomography (SPECT) is particularly appealing for cardiovascular risk assessment in asymptomatic diabetic patients [124]. The cause of concern in this population is silent myocardial ischemia and the data on the prevalence of this condition have been disparate. In the prospective detection of ischemia in asymptomatic diabetics study, which included asymptomatic patients with type 2 DM, a 22% prevalence of any perfusion defect or left ventricle dysfunction by SPECT was detected, and in 6% of patients, a moderate to large myocardial ischemia was found[125]. In a more recent analysis of 1354 asymptomatic patients (302 without DM) a lower prevalence of myocardial ischemia was found (7.2%). An important finding of the study was a much higher prevalence of silent ischemia observed in diabetic patients (12.5% *vs* 5.6%)[126]. The Basel asymptomatic high-risk diabetes outcome trial prospectively recruited 400 asymptomatic patients with type 2 DM. In the study, nearly a quarter of asymptomatic patients had silent myocardial ischemia, which was associated with a worse outcome and a higher likelihood of major adverse cardiovascular events[127]. The yield of SPECT can be further improved by choosing patients with higher basal cardiovascular risk, especially patients with certain other comorbidities, such as CKD. According to studies, abnormal SPECT is a good indicator of future acute coronary events and cardiovascular disease in diabetic and non-diabetic CKD patients[128]. Conversely, a normal SPECT is associated with a fairly good cardiovascular outcome in CKD patients, but it should be noted that due to accelerated coronary atherosclerosis in patients with CKD stages 4 and 5, a normal SPECT testing is still linked to higher cardiovascular risk compared to patients with better renal function[129]. In these patients, continuous follow-up is pivotal in preventing major adverse cardiovascular events[130].

Carotid intima-media thickness

Carotid IMT is an ultrasound-based, non-invasive measurement of atherosclerosis burden. It is used to investigate the determinants and consequents of atherosclerosis

and has been used as a surrogate end-point and a therapeutic target in some clinical trials as well[131,132].

Several clinical studies have demonstrated the association between the presence of atherosclerotic plaques in the carotid arteries, increased carotid IMT and atherosclerosis in other vascular territories[133]. Bots *et al*[134] have shown that patients with an increased carotid IMT have a higher likelihood of having advanced atherosclerotic plaques in the abdominal aorta. In a study by Ogata *et al*[135], a significant correlation between left main coronary atherosclerosis (determined by intravascular coronary ultrasound) and increased carotid IMT was observed. A positive association was also found for patients with symptomatic CAD, cerebrovascular disease and patients with PAD[136]. A descriptive, cross-sectional study was performed by Gómez-Marcos *et al* [137] in which they found an increased carotid IMT in patients with DM compared to patients without DM, and the difference was even greater in patients with advanced age. Signs of carotid damage were found in 23% of patients with DM. In a study by Matsagoura *et al*[138] that included patients with type 2 DM, an increased carotid IMT was observed in patients with moderately increased albuminuria or proteinuria compared to patients without proteinuria.

Kota *et al*[139] demonstrated a higher risk for ischemic stroke in type 2 DM patients with increased thickness of carotid intima-media. Sunil Kumar *et al*[140] performed a study on 30 patients with ESRD in which they found increased carotid IMT in these patients. They found the measurements to be an easy, non-invasive, easily-reproducible and cost-effective investigation in assessing cardiovascular risk in patients with chronic kidney failure. According to a study by Ekart *et al*[141], carotid IMT correlated with higher blood pressure in hemodialysis patients. In a study by Lawal *et al*[142], carotid IMT correlated with many cardiovascular risk factors among CKD patients, serving as a potential surrogate marker for cardiovascular disease in these patients. Roumeliotis *et al*[143] performed a study on 142 diabetic patients with different stages of CKD. Patients with increased carotid IMT had higher all-cause and cardiovascular mortality and had a higher degree of atherosclerosis in other vascular territories, further confirming the important role of carotid IMT measurements in recognizing patients with higher cardiovascular risk.

Coronary artery calcium score

High coronary artery calcium (CAC) score is associated with advanced atherosclerosis and with a 4-10-fold increase in the incidence of cardiovascular disease, independent of other risk factors[144]. Diabetic patients harbor larger amounts of CAC than non-diabetic patients of similar age[145]. Additionally, asymptomatic diabetic patients have a similar CAC than non-diabetic patients with known CAD[146]. In the coronary artery calcification in type 1 diabetes study, 656 adult patients with type 1 DM had higher CAC compared to 764 age- and sex-matched individuals without DM, with no differences between genders. Extensive vascular calcifications were registered even in younger patients with type 1 DM (17-28-years-old)[147]. The extent of CAC has also shown an important positive association with SPECT-registered myocardial ischemia, cardiovascular events and mortality[148,149]. Anand *et al*[150] followed 392 patients with type 2 DM and found that CAC progression was among the best predictors of increased cardiovascular risk.

Patients with CKD exhibit a higher prevalence of vascular calcification than the general population. In a 10-year prospective study on 137 CKD patients, the authors found that severe CAC was an important predictor of cardiovascular mortality[151]. Krajnc *et al*[152] compared CAC score between patients on hemodialysis and diabetic patients without renal involvement and found higher CAC score in the hemodialysis group, with the difference between both groups especially evident in the very high risk CAC score category. Besides being an adverse prognostic sign, higher CAC has been associated with faster progression of CKD to ESRD[153]. According to a study by Cano-Megias *et al*[154], the synergistic effect of DM and CKD leads to an even higher CAC score, increased inflammation and higher mortality compared to patients without DM, showing the importance of higher CAC in cardiovascular risk assessment of diabetic CKD patients.

Coronary computed tomography angiography

Coronary computed tomography angiography (CTA) is a non-invasive imaging modality that provides a detailed and comprehensive evaluation of the presence and the extent of CAD. According to a study by de Araújo Gonçalves *et al*[155], DM is an independent predictor of CAD and is associated with a more advanced CAD and a higher prevalence of atherosclerotic plaques in every anatomical subset of coronary arteries, all evaluated with the use of coronary CTA. An important obstructive CAD

was observed even in asymptomatic diabetic patients[156]. An additional important advantage of coronary CTA was found in a study by Madaj *et al*[157] in which they studied the presence of CAD in younger patients with type 1 and 2 DM. They found that coronary CTA detects CAD even in patients with a normal CAC score, which can be explained by a higher percentage of non-calcified plaques in younger patients with diabetes, rendering the CAC score less useful in this context. In diabetic CKD patients, coronary CTA is useful in determining the extent of CAD and atherosclerotic plaque characteristics; in CKD patients, a trend towards non-obstructive calcified plaques has been noticed[158]. There is, however, a reason for cautious use of coronary CTA in patients with advanced stages of CKD because of the risk of contrast-induced nephropathy[159].

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (CMRI) provides important prognostic information and aids in risk stratification in most cardiovascular diseases. It is a non-invasive imaging modality that can visualize myocardial scarring, myocardial steatosis and triglyceride content, interstitial fibrosis and interstitial myocardial edema. It is also useful in the evaluation of coronary arteries, valvular pathology, and in the differentiation of cardiomyopathies[160]. Diabetic patients are at risk of developing severe cardiomyopathy, partly due to CAD and partly due to metabolic derangements. The presence of late gadolinium hyperenhancement as a marker of prior myocardial infarction is associated with a 4-fold increased risk of a major adverse cardiovascular event and with a 7-fold increased risk of mortality[161]. Late gadolinium hyperenhancement was demonstrated in 4.3% of asymptomatic type 1 DM patients in the diabetes control and complications trial/epidemiology of diabetes interventions and complications trial[162] and 17% of asymptomatic diabetic older patients in a community-based study in Iceland[163].

T1 mapping is useful in assessing the amount of extracellular volume and interstitial fibrosis. Wong *et al*[164] demonstrated high short-term mortality in non-diabetic patients with increased extracellular volume. Some studies have shown increased extracellular volume and diastolic dysfunction in diabetic patients as well[165,166]. By using spectroscopy, myocardial lipid content can be assessed, which is an important pathophysiological step in understanding left ventricular dysfunction in diabetic patients[167]. Adenosine stress MRI test has excellent characteristics for the detection of obstructive CAD and microvascular dysfunction in patients with DM[168] and CKD patients as well[169]. Myocardial fibrosis is a hallmark of progressive CKD, uremic cardiomyopathy and is a crucial cause of increased cardiovascular risk in these patients[170]. Concerns relating to an association between gadolinium contrast agents and nephrogenic systemic fibrosis have led to the use of lower doses, lower risk gadolinium agents and even native CMRI in CKD patients, which is an important step forward in the wider use of CMRI in this subgroup of patients[171]. In the Graham-Brown *et al*[172] study on hemodialysis patients, a native CMRI was performed. The authors found an increase in myocardial fibrosis and interstitial edema, mostly in the septal region of the heart. By applying a similar methodology, Rutherford *et al*[170] showed that these findings were independent of patient's fluid status. In a study by Edwards *et al*[173] on CKD patients stages 2-4, a low dose gadolinium method was used. They found increased interstitial fibrosis and myocardial dysfunction in these patients, and the finding was not dependent on blood pressure. CMRI has a proven role in the understanding of uremic cardiomyopathy, ventricular dysfunction, myocardial fibrosis and cardiovascular risk assessment in patients with early and advanced CKD[171].

EPIGENETIC MARKERS

Epigenetics is the study of gene expression and involves phenotypic changes without changes in genotype. Several studies have confirmed that epigenetic regulations are crucial in the pathogenesis of atherosclerotic plaque formation, vessel wall inflammation and plaque rupture, in a cell-type and stage-specific manner[174,175]. Three epigenetic mechanisms are important in atherosclerosis: DNA methylation, post-translational modification of histones and the activity of non-coding ribonucleic acids (RNAs), most commonly long non-coding RNAs and micro RNAs (miR)[176]. The expression of non-coding RNAs can be measured in peripheral blood, urine and saliva using microarrays, indicating the potential of these markers as diagnostic tools and future therapeutic targets[177,178].

Several long non-coding RNAs are linked to LVH, myocardial infarction, heart failure and mortality[179]. Polymorphisms and increased expression of miR-124a, miR-375 and miR-146a are associated with obesity, insulin resistance and increased incidence of type 2 DM[180,181]. miR-27 exerts negative effects on adipogenesis and is associated with decreased incidence of DM[182]. In a study by Buraczynska *et al*[183], miR-196a2 has been linked to an increased likelihood of cardiovascular events in diabetic patients. miR-4513 is overly expressed in patients with metabolic syndrome and DM and is associated with major cardiovascular events, especially acute coronary syndrome[184]. Endothelial dysfunction is an important factor in CKD patients and according to a study by Kétszeri *et al*[178], miR-142-3p expression is linked to preventing endothelial dysfunction.

Non-coding RNAs are a marker of increased cardiovascular risk and can be employed to determine the risk of developing and/or progressing CKD in patients with DM. According to studies, several long non-coding RNAs (ERBB4-IR, MGC, ENSMUST00000147869) are centrally involved in the development and progression of CKD in patients with DM, either *via* direct pathogenic roles or as indirect mediators of different nephropathic and profibrotic pathways[185]. The upregulation of profibrotic miR-192 and miR-21 was confirmed to be linked to renal fibrosis, development and progression of CKD in diabetic patients[186]. Vice versa, reduced expression of anti-fibrotic miR-29 and miR-200 was also associated with more advanced kidney disease [187,188]. The downregulation of miR-30s, miR-124 and miR-93 has been shown to lead to increased podocyte injury and proteinuria[186]. In a study by Abdelsalam *et al* [189], miR-451 is a highly specific marker of CKD chronicity in patients with DM. In a study by Fourdinier *et al*[190], decreased serum levels of miR-126 and miR-223 were found in patients with advanced CKD with DM and were linked to increased mortality due to cardiovascular causes. It appears that the potential of non-coding RNAs is vast but currently of limited clinical importance due to high cost, limited availability and non-specificity of different molecules[176].

CONCLUSION

Due to the increasing burden of DM and CKD, the prevalence of the cardiovascular disease will continue to rise. To reduce morbidity, mortality and socioeconomic burden of these patients, immediate cardiovascular risk assessment is pivotal. Fulminant atherosclerosis, a hallmark of diabetic patients with CKD is a complex process, involving the interplay between traditional and non-traditional, CKD-specific risk factors, culminating in endothelial dysfunction, inflammation, plaque formation and ultimately target organ ischemia and damage. Due to the multifaceted process, it appears that a multimarker approach should be used to recognize patients with the highest risk for cardiovascular events. In the future, more attention should be given to the decrease in prevalence of DM and prevention of CKD development in diabetic patients.

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