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VASCULAR BIOLOGY (RS ROSENSON, SECTION EDITOR)

Vascular Imaging in Diabetes

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Abstract Diabetes is a global epidemic affecting individuals of all socioeconomic backgrounds. Despite intensive efforts, morbidity and mortality secondary to the micro- and macrovascular complications remain unacceptably high. As a result, the use of imaging modalities to determine the underlying pathophysiology, early onset of complications, and disease progression has become an integral component of the management of such individuals. Echocardiography, stress echocardiography, and nuclear imaging have been the mainstay of noninvasive cardiovascular imaging tools to detect myocardial ischemia, but newer modalities such as cardiac MRI, cardiac CT, and PET imaging provide incremental information not available with standard imaging. While vascular imaging to detect cerebrovascular and peripheral arterial disease non-invasively has traditionally used ultrasound, CT- and MRI-based techniques are increasingly being employed. In this review, we will provide an outline of recent studies utilizing non-invasive imaging techniques to assist in disease diagnosis as well as monitoring disease progression. In addition, we will review the evidence for newer modalities such as MR spectroscopy, 3D intravascular ultrasound, and optical coherence tomography that provide exquisite detail of metabolic function and coronary anatomy not available with standard imaging, but that have not yet become mainstream.

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Introduction

Diabetes represents a global health crisis, with the number of adults diagnosed with this condition doubling over the past 30 years. Indeed, age-standardized fasting blood glucose levels have increased at a rate of 0.07 mmol/L per decade [1]. In 2008, it was estimated that 314–382 million adults worldwide had diabetes [1]. The International Federation for Diabetes projects that the prevalence of the disease will continue to rise over the next two decades, reaching 552 million by 2030 [2]. Like cardiovascular disease [3], this condition afflicts both affluent and developing countries, although geographic variances have been noted, with the highest rates in South Asia and Latin America and the lowest in sub-Saharan Africa. Whilst survival from the comorbidities of diabetes has improved in affluent nations, global mortality remains high, having increased by 20 % since 1990 [4].

While the pathophysiology of diabetes is complex, there are two major types of the disease. Type 1 diabetes is caused by the autoimmune destruction of the beta cells of the pancreas responsible for insulin production. Whilst diabetes has gained considerable attention as a result of afflicting children, the major burden occurs secondary to type 2 diabetes, as a result of a combination of deficiencies in insulin action, secretion, and endogenous release [5, 6]. Both forms are prone to the complications, which include both microvascular (nephropathy, retinopathy, and neuropathy) and macrovascular (cardiovascular, cerebrovascular, and peripheral vascular) disease.

Although advances in pharmacologic therapy and tight glycemic control have been shown to ameliorate microvascular complications, no therapy to date has demonstrated a reduction in macrovascular disease and improved secondary mortality outcomes [7, 8]. Indeed, diabetic patients with no prior history of coronary artery disease (CAD) are considered at high cardiovascular risk, similar to non-diabetic patients

with a history of myocardial infarction, the so-called "MI equivalent" [9]. Furthermore, there is a higher prevalence of cerebrovascular (CVD) and peripheral vascular (PVD) disease in diabetics [10]. PVD has a threefold greater prevalence in diabetic patients compared to the general population, and CVD is strongly associated with diabetes, with a 2.1–5.8 times greater relative risk of stroke [10]. Of concern is the fact that outcomes in diabetics with PVD are dependent on the presence of CAD, which occurs at a frequency of 2–4 times that of the general population [11].

Against this backdrop, it is increasingly clear that early detection and follow-up of therapeutic strategies to reduce the burden of micro- and macrovascular disease are of paramount importance. Non-invasive imaging is critical in the diagnosis and longitudinal evaluation of the complications of diabetes [12]. The clinician in 2014 has a variety of imaging modalities at his/her disposal to diagnose such complications and to offer insight into disease progression and remission [10]. These modalities include myocardial perfusion imaging, CT angiography, vascular ultrasound, MRI, and PET scanning. Various studies have demonstrated similar diagnostic capabilities in the diabetic as compared to the non-diabetic population [13]. In this review, we will summarize the major noninvasive modalities in the diagnosis and assessment of atherosclerotic and non-atherosclerotic disease secondary to diabetes and offer insight into novel modalities that may further assist in disease diagnosis, treatment, and prevention. Although there have been similar advances in invasive diagnostic and therapeutic cardiology, the details of these methodologies are beyond the scope of this review.

Cardiovascular Imaging

Detection of CAD

Numerous studies have demonstrated that diabetics with abnormal stress tests have an increased risk of cardiovascular death and non-fatal MI compared to diabetics with normal stress imaging. In addition, diabetics with a normal stress test have a higher CV risk than non-diabetics with a similar result, as there appears to be a residual CV risk that is not captured by a normal stress test [13]. It is of interest to note that the DIAD (Detection of Ischemia in Asymptomatic Diabetics) study demonstrated that silent myocardial ischemia was present in 22 % of asymptomatic diabetic patients [14].

Myocardial Perfusion Imaging (MPI)

Myocardial perfusion imaging is the most extensively studied stress modality in the diabetic population (Table 1) [26]. The sensitivity and specificity of MPI for CAD detection in the diabetic population has been validated and is similar to that of the general population (diabetics, sensitivity 86 %, specificity 56 %; non-diabetics, sensitivity 86 %, specificity 46 %) [15]. Giri et al. prospectively followed 929 (19.5 %) diabetics out of a cohort of 4,755 patients for 2.5 years. These patients had symptoms suggestive of CAD and were investigated with MPI. Diabetic patients, despite a higher revascularization rate, had a higher cardiac event rate (8.6 % vs. 4.5 %) as compared to non-diabetics. Abnormal MPI was an independent predictor of cardiac death and MI. Furthermore, the greater number of abnormal segments (fixed or ischemic) resulted in worse outcomes, suggesting that the burden of disease plays a key role in prognosis. In addition, a normal MPI portended the same cardiac prognosis regardless of diabetic status in the first 2 years, but diabetics had an increased rate of MI and cardiac death after this period [17]. MPI has also been studied in asymptomatic diabetic patients. Rajagopalan et al. investigated 1,427 asymptomatic diabetics without known CAD. Abnormal studies were present in 826 patients (58 %) and high-risk scans in 261 patients (18 %). Annual mortality rates were subdivided based on risk of the scan. Patients with high-risk studies had a mortality rate of 5.9 %; patients with intermediate risk, 5.0 %; and patients with low risk, 3.6 % ($p<0.001$ for differences among groups). Coronary catheterization was performed in 47 % of patients with a high-risk MPI, 61 % of whom had severe CAD (left main, triple-vessel, or proximal LAD disease) [16].

Despite evidence to suggest that asymptomatic diabetics with high-risk MPI have a worse prognosis, the 5-year follow up of the DIAD study did not demonstrate any clinical benefit in total mortality or cardiovascular outcomes. In this study, 1,123 asymptomatic diabetic patients were randomized to either MPI screening or no screening. The stress-testing group had a significant increase in number of patients referred to angiography but no change in major adverse cardiovascular and cerebrovascular events (MACCE). Both groups had a significant increase in primary medical prevention strategies such as use of statins and antihypertensive medications [27]. Patients enrolled in the DIAD study had repeat MPI 3 years after the initial evaluation, and 79 % of the patients with ischemia on their initial scan demonstrated resolution of ischemia on repeat imaging. During the intervening time, medical treatment was intensified, with greater utilization of ASA, statins, and ACE inhibitors. Therefore, the majority of asymptomatic diabetic patients had resolution of their ischemia with intensive medical therapy [28].

Computer Tomography (CT)

Coronary artery calcium (CAC) density, which can be assessed by coronary CT methodology, is an indicator of subclinical atherosclerosis that is directly proportional to the amount of coronary plaque. Previous studies have demonstrated that a CAC score of zero has a negative predictive value of 100 % in excluding significant CAD [29]. The 2010 Appropriate Use Criteria for Cardiac Computed Tomography

Table 1 Evidence-based indications for current imaging techniques. *There are a number of indications for the use of established techniques in the diagnosis and prognostication of cardiac disease in patients with diabetes. This table summarizes the evidence for clinical use of imaging techniques in this population*

Imaging Modality	Indications
Myocardial perfusion imaging (MPI)	Diagnosis: • Standard MPI features for diagnosis of CAD have equal sensitivity (86 %) in diabetics and non-diabetics. [15] • High-risk MPI features have good sensitivity (94 %) for subsequent angiographic diagnosis of CAD in asymptomatic diabetics. [16] Prognosis: • Normal MPI predicts low cardiac mortality in diabetics for at least 2 years, ruling out the need for angiography (as in non-diabetics). This predictive value declines after 2 years. [17]
Echocardiography	Diagnosis: • Dobutamine stress echocardiography has good sensitivity (81 %) and specificity (84 %) for diagnosis of CAD in diabetics comparable to non-diabetic population. [18] • Stress echo has good sensitivity (84 %) for asymptomatic CAD in diabetics. [19] • Transmitral Doppler and tissue Doppler imaging (TDI) can be used to detect a number of features of diabetic cardiomyopathy, including E/E' ratio, a predictor of clinical heart failure. [20] Prognosis: • Positive stress echo portends a 7-fold greater risk of MACCE compared to a normal study in diabetics. [21] • Stress echo findings can be used to risk stratify diabetics for MACCE for up to 7 years. [22•]
Cardiac magnetic resonance (CMR)	Diagnosis: • Myocardial perfusion reserve imaging with CMR has good sensitivity (88 %) and specificity (82 %) for diagnosis of CAD, and this is equivalent in diabetics and non-diabetics. [23••] • The presence of subendocardial late gadolinium enhancement is diagnostic for old silent myocardial infarction as in non-diabetics are diagnostic for old silent myocardial infarction in diabetics as in non-diabetics. [24] Prognosis: • Late gadolinium enhancement (LGE) is associated with a 3-fold increase in MACCE in diabetic patients without clinically apparent CAD, as with non-diabetics. [24]
Single-photon emission CT (SPECT)	Prognosis: • In diabetics with NYHA II/III heart failure and EF<35 %, ^{123}I-mIBG SPECT with a heart-mediastinum ratio (H:M) less than 1.6 predicts a 3-fold increase in 2-year mortality compared to H:M greater than 1.6. [25]

and the American College of Cardiology Foundation/American Heart Association guidelines suggest that testing asymptomatic diabetics over the age of 40 is reasonable (Class IIa, Level of Evidence B). There is some evidence that there is incremental prognostic value of CAC scoring over Framingham Risk Score alone [30]. In diabetics, mortality is consistently higher for any given CAC score as compared to non-diabetics, as demonstrated by a 44 % higher mortality for every increase in CAC score quartile. Interestingly, however, rates of mortality are similar when both groups do not have detectable CAC [31].

While coronary angiography provides information on the lumen of the coronary vessel, it cannot assess changes on the arterial wall due to positive arterial remodeling. Coronary CT angiography, however, can detect changes in the arterial wall as well as the lumen [32]. Although a CAC score of zero has a high negative predictive value of significant CAD, it was shown in one study that up to 5 % of diabetic patients with this score have significant stenosis when coronary CTA is performed. Furthermore, in the same study, 30.5 % of asymptomatic diabetic patients had significant CAD and 17.1 % had high-risk plaques as determined on CTA (positive remodeling and low attenuation) [33]. In a substudy of the CONFIRM (Coronary CT Angiography Evaluation For Clinical Outcomes) registry, 3,370 diabetic patients were evaluated with coronary CTA and compared to a non-diabetic cohort. Compared with matched non-diabetic controls, diabetic patients had greater prevalence and severity of CAD and had higher mortality at comparable levels of CAD [34].

The American Diabetic Association 2012 guidelines, however, do not recommend screening for asymptomatic CAD, as it does not improve outcomes as long as CAD risk factors are treated [35•].

Echocardiography

Stress echocardiography is another imaging technique that can be used to risk-stratify diabetic patients. Elhendy et al. demonstrated similar diagnostic accuracy of this modality in both diabetic and non-diabetic patients. The sensitivity and specificity as compared to invasive coronary angiography for detection of CAD was 81 % and 85 %, respectively, in the diabetic cohort. This was similar to the non-diabetic group (sensitivity 74 %; specificity 87 %) [18]. Stress echocardiography has been shown to identify asymptomatic CAD in diabetics. Fateh-Moghadam et al. followed 211 consecutive asymptomatic diabetic patients, all of whom had a stress echo. Over the course of follow-up (11+/−2 months), 39 patients suffered a MACCE, and 33 of these were identified in advance with a positive stress echo study. The decision to revascularize was made independent of the study results [19].

Stress echocardiography also provides prognostic information beyond exercise tolerance. In one study, 935 patients (131 diabetics) were investigated with a stress echo after a positive

exercise ECG stress test. Major event rates (MACCE) were nearly 7 times higher in the ischemic group with [21]. Results of the study indicated that, similarly to MPI, a normal stress echo indicated a good prognosis for the first 2 years after the study, although the event rate increased at 5 years [36]. Among diabetic patients who have limited exercise capacity, dobutamine stress echocardiography (DSE) has been shown to provide incremental predictive value over clinical parameters for risk stratification, with a "warranty period" that exists up to 7 years after normal DSE [22•].

The above-referenced studies utilized 2D imaging. New acquisition methods utilizing matrix-array transducers enable real-time 3D stress echocardiography. Visualization of the LV is achieved in multiple 2D views using biplane methodology, thus allowing for greater certainty in regional assessment of systolic function [37]. Furthermore, contrast perfusion imaging enables the assessment of coronary perfusion [38]. Regional changes in perfusion (hypoperfusion) precede the onset of regional wall motion abnormalities and may increase the sensitivity of CAD detection [39•]. Real-time and triggered imaging techniques have been utilized in which the timing of contrast returning in a vascular bed correlates with degree of CAD [40]. Despite promising early data, few large outcome studies have been performed, and the required expertise to perform data acquisition and analysis limits the applicability of these techniques. As such, they remain predominantly research tools.

Cardiac MRI (CMR)

Cardiac MRI (CMR) is a technology that is increasingly being used in the assessment of ischemia and infarction. Silent myocardial infarctions prevalent amongst diabetic patients can be detected using late gadolinium enhancement (LGE). Kwong et al. demonstrated that LGE by CMR was associated with a greater than threefold increase in MACCE in diabetic patients [24]. Diabetic patients have been shown to have increased myocardial edema and infarct size in the acute and chronic phases following acute coronary syndrome based on T1 and T2 sequences [41]. Myocardial perfusion MR imaging as a modality for detecting CAD has shown similar performance in diabetic patients, providing added information to clinical risk factors and resting wall motion abnormalities in high-risk patients [42]. In CE-MARC, the largest trial to date evaluating CMR for CAD assessment, Greenwood et al. studied 752 patients (96 diabetics) with suspected angina pectoris and at least one cardiovascular risk factor. All participants underwent CMR, SPECT, and coronary angiography. CMR evaluation consisted of rest and adenosine stress perfusion, cine imaging, LGE, and MR coronary angiography. CMR demonstrated sensitivity of 86.5 % (95 % CI, 81.8–90.1) and specificity of 83.4 % (79.5–86.7). This contrasts with sensitivity of 66.5 % (95 % CI, 60.4–72.1) and specificity of 82.6 % (78.5–82.8) for SPECT. The CE-MARC study underscores the role that CMR may play in the assessment of CAD [23••].

Positron Emission Tomography (PET)

Positron emission tomography (PET) is an imaging modality that uses positron-emitting radionuclides to produce images for assessment of cardiac perfusion and metabolism. Using a 70 % coronary stenosis angiographic cutoff, studies comparing the diagnostic accuracy of ^{32}Rb PET and ^{99m}Tc SPECT imaging for CAD assessment have reported 89 % and 79 % diagnostic accuracy for PET and SPECT, respectively, largely driven by a higher specificity for PET imaging [43]. Newer hybrid PET/CT scanners provide the opportunity to obtain both structural and functional information, allowing a true assessment of the burden of CAD. There is also the potential to image atherosclerotic disease activity, although whether this combined imaging modality is a cost-effective approach remains to be determined. To date, however, there are no published studies evaluating diagnostic accuracy in diabetic patients (Table 2) [43].

Diabetic Cardiomyopathy

Diabetic cardiomyopathy was first described by Rubler et al. over 40 years ago [49], yetmany unknowns regarding the pathophysiology and management of this condition still exist today. Diabetic cardiomyopathy is defined as cardiac dysfunction in the absence of CAD, valvular disease, or other causative factors. It frequently is associated with heart failure, with estimated 19–20 % prevalence in this population [50]. Although there is no diagnostic imaging technique that is pathognomonic for diabetic cardiomyopathy, among all of the imaging modalities, echocardiography and CMR have been studied the most [50].

Given its low cost, echocardiography is generally the initial diagnostic test for evaluation of diabetic cardiomyopathy. Structural heart disease associated with diastolic dysfunction and left ventricular hypertrophy can be easily detected. Furthermore, strain-rate imaging and speckle tracking have shown promise as early detectors of cardiac dysfunction prior to overt diastolic dysfunction [51]. In a recent study of 1,760 diabetic patients with tissue Doppler evidence of diastolic dysfunction (E/e'>15), 411 patients (23 %) met the criteria for diastolic dysfunction. The presence of diastolic dysfunction on echocardiography was an independent predictor of heart failure after adjusting for age, sex, body mass index, hypertension, and CAD. The cumulative probability of development of heart failure at 5 years was 36.9 % in the diabetic patients with diastolic dysfunction on echocardiography vs. 16.8 % for patients without these criteria. Furthermore, each

Table 2 Prospective novel imaging technique applications. *Novel imaging techniques include developments on current modalities or new clinical applications of basic science research tools. This table summarizes some of the prospective applications of these novel imaging techniques in patients with diabetes, either for the diagnosis of CAD or for providing prognostic information*

Imaging Modality	Indications
Coronary Artery Calcium Electron Beam Tomography (CAC EBT)	Prognosis: • Coronary Calcium Score (CCS) of 0 in diabetics predicts a mortality profile equal to non-diabetics, with no additional independent risk from having diabetes. [31] • Each increase in CCS level by predefined groupings (11–100, 101–400, 401–1,000 and >1,000) increases mortality in diabetics by 44 % (CI 20–80 %), and this increase is significantly greater than in non-diabetics. [31]
Contrast CT Coronary Angiography (CTA)	Diagnosis: • Coronary stenosis may be present in as many as 5 % of asymptomatic diabetics with CAC scores of 0. This stenosis is detectable by CTA. [33] Prognosis: • High-risk coronary plaques have radiographic features such as positive remodeling and low attenuation which portend a higher risk of plaque rupture. These features of plaque are detectable by CTA. [33]
Speckle Tracking Echocardiography (STE)	Diagnosis: • Reduced longitudinal strain (LS), a marker of myocardial dysfunction, can be detected by STE and can provide information about diastolic and systolic dysfunction prior to clinical symptom development. [44] • Elevated Post-systolic Shortening Index (PSI), a useful adjunct to LS change in the detection of diastolic dysfunction, can be detected by STE. [44]
Cardiac Magnetic Resonance (CMR)	Diagnosis: • T_1 relaxation time is useful to quantify diffuse interstitial myocardial fibrosis, the pathophysiological hallmark of diastolic dysfunction in diabetes. [45]
3D Carotid Ultrasound	Diagnosis: • Bilateral carotid plaque volume of ≤0.09 mL, measured by automated 3D ultrasound of the carotid bulbs, has a negative predictive value (NPV) of 93.3 % for the absence of significant CAD (angiographic score 2–3). [46]
Positron Emission Tomography (PET)	Diagnosis: • Fractional myocardial utilization of dietary fatty acids can be detected with ^{18}FTHA PET and is positively correlated with systolic dysfunction and increased myocardial oxidative metabolism, a marker of diabetic cardiomyopathy, in patients with impaired glucose tolerance (IGT). [47]
Optical Coherence Tomography (OCT)	Prognosis: • Thin-cap fibroatheromas (TFCA), the pathological lesions of ACS, are more prevalent in non-culprit lesions in diabetics than non-diabetics, which may portend greater risk of subsequent ACS after a first MI. The presence and number of TFCAs can be determined by OCT. [48]

additional unit increase (E/e') over 15 increased the likelihood of developing heart failure by 3 %. In addition, the cumulative probability of death at 5 years for diabetic patients with diastolic dysfunction on echocardiography was 30.8 %, compared with 12.1 % in diabetic patients without diastolic dysfunction [20]. Subclinical left ventricular dysfunction can be detected with the use of 2D speckle tracking to assess longitudinal function. Nakai et al. studied a group of 60 asymptomatic diabetic patients with normal ejection fraction and 25 control subjects, in which end-systolic longitudinal strain, radial strain, and circumferential strain were measured. Basal, middle, and apical longitudinal strain were lower in diabetic patients as compared with the control group. Basal radial strain and apical circumferential strain were lower in the diabetic cohort as well. The only independent variable associated with reduction of strain parameters was duration of diabetes [44].

Diabetic cardiomyopathy is associated with accelerated myocardial cellular apoptosis and necrosis, leading to interstitial fibrosis. These patients have normal ejection fraction but may have subclinical diastolic dysfunction, which can be detected through the use of sophisticated CMR techniques [45]. In CMR, gadolinium contrast may accumulate and have delayed washout times within regions of myocardial fibrosis. T1 mapping sequences can measure global contrast-enhanced T1 relaxation time to detect the extent of myocardial fibrosis, with a shorter global contrast-enhanced T1 time suggesting more fibrosis. In a study by Ng et al., 50 asymptomatic diabetic patients with normal ejection fraction underwent CMR assessment, which demonstrated a strong correlation between global contrast-enhanced myocardial T1 time and global longitudinal strain ($r=-0.73$, $p<0.001$). In fact, multivariate analysis demonstrated that global contrast-enhanced myocardial T1 time was the strongest independent factor of

global longitudinal strain. These results suggest that shorter contrast-enhanced myocardial T1 time is associated with impaired diastolic function in diabetic patients [45].

Patients with diabetic cardiomyopathy may also have right ventricular (RV) involvement, which can be clinically important, as the RV contributes substantially to overall myocardial contractility [52]. In a recent study, 78 type 2 diabetic patients were assessed with CMR and steady-state free precession sequences for ventricular dimensions. RV end-diastolic volume was reduced and RV systolic function was impaired in the diabetic cohort as compared to healthy controls, and RV diastolic parameters were impaired as well. The reduction in each of the RV parameters was strongly associated with its corresponding LV parameter ($p<0.001$). This study suggests that diabetic cardiomyopathy affects both the right and left ventricle, as demonstrated by adverse RV remodeling leading to impaired systolic and diastolic function [52].

Cardiac Autonomic Dysfunction

Activation of the sympathetic nervous system, as reflected by circulating levels of norepinephrine (NE), is a major predictor of survival in patients with heart failure [25]. Imaging of this system can be achieved with SPECT, which uses the norepinephrine analog meta-iodobenzylguanidine that is labeled with 123-iodine (^{123}I-mIBG). The kinetics of this analog is similar to NE, but it is not catabolized under the traditional pathway and therefore accumulates in the sympathetic nerve endings, allowing imaging of the cardiac sympathetic innervation [53•]. The most commonly measured parameter is the heart/mediastinum (H/M) ratio, with a value <1.6 considered to be abnormal. Autonomic dysfunction can be seen after cardiac transplantation, heart failure, myocardial infarction, and diabetes [53•]. Gerson et al. prospectively studied 343 diabetic patients with NYHA II or III heart failure and an ejection fraction <35 %, in whom ^{123}I-mIBG imaging was performed. The presence of a H/M ratio <1.6 was independently associated with an almost threefold greater 2-year rate of heart failure progression compared to those with a H/M ratio >1.6 [25]. Autonomic dysfunction in diabetics is also associated with diastolic dysfunction, as measured by ^{123}I-mIBG imaging and echocardiography [54]. Cardiovascular autonomic neuropathy in diabetics is associated with increased LV mass and concentric remodeling independent of traditional cardiac risk factors [55].

Metabolic Alterations

Positron emission tomography (PET) can be used to assess regional uptake of metabolic substrates. In diabetics, myocardial fatty acid utilization and myocardial fatty acid oxidation are increased, while myocardial glucose utilization is reduced [56]. Diastolic dysfunction in diabetics is associated with myocardial triglyceride content as measured by CMR and MR spectroscopy, and may represent an early marker of diabetic heart disease [57]. Labbé et al. recently demonstrated a significant increase in fractional myocardial dietary fatty acid uptake and an increase in myocardial oxidative index over the first 6 hours postprandial in overweight patients and those with impaired fasting glucose, and demonstrated an inverse relationship between myocardial fatty acid partitioning and ejection fraction. This study was the first to illustrate that excessive myocardial partitioning of dietary fatty acids is associated with left ventricular dysfunction and increased myocardial oxidative metabolism in pre-diabetic individuals [47]. There are also sex-related differences with regard to myocardial substrate metabolism. Myocardial blood flow and oxygen consumption are higher in diabetic women than in men. Additionally, fatty acid utilization and esterification are higher and percent of fatty acid oxidation is lower in diabetic women compared with men [58]. Despite significant interest, further development and standardization in this area is needed prior to routine clinical implementation.

Peripheral Vascular Disease (PVD)

Peripheral arterial disease: Diabetes is a leading cause of PVD, with a tendency to below-knee disease. The risk of developing PVD is 2.5–4 times greater in diabetic individuals than in the non-diabetic population [59]. Arteriography has been the gold standard for many years, given both its image resolution and the fact that it is the only modality to offer both diagnostic and therapeutic options [60]. Noninvasive assessment is crucial in evaluating diabetic patients who are at risk of or have symptoms of PVD. These studies provide critical information on the sites and severity of arterial stenosis as well as objective clinical data to help determine which interventional strategy, if any, is most appropriate [61]. The American Diabetes Association recommends vascular imaging for patients with significant symptoms of claudication and ankle-brachial index (ABI) screening for all diabetics over the age of 50 [35•]. Early identification of risk factors and aggressive treatment in diabetic patients has been shown to slow the progression of cardiovascular disease [62]. Screening for PVD should be performed using an ABI, which identifies those patients who require further investigations, usually with duplex ultrasound [61]. This approach allows direct visualization of the artery and identifies the anatomic site of obstruction, measuring the velocity of blood flow across it. This noninvasive method can demonstrate hemodynamic information in patients suspected of having significant PVD and can provide the information without the need for invasive arteriography. Furthermore, duplex ultrasound can help to guide selective arteriography when lesions are not fully appreciated or identified on anteroposterior arteriography [61].

Duplex ultrasound has been proven accurate in localizing and classifying aortoiliac occlusive disease. In one study, complete evaluation of the aortoiliac region was achieved in 91 % and correlated well with invasive angiography (exact agreement in 92 % of the segments). In cases of discrepancy (3 patients), intra-arterial pressure measurements demonstrated that the significance of these lesions was underestimated by angiography [63]. In addition, duplex ultrasound may be more sensitive than ABI in identifying stenosis in the superficial femoral artery (SFA) [64]. A systematic review demonstrated 88 % (80–98 %) sensitivity of duplex ultrasound and specificity of 96 % (89–99 %) [65].

Newer modalities such as magnetic resonance angiography (MRA) and computerized tomography angiography (CTA) are being increasingly employed as noninvasive alternatives for imaging in PVD. Imaging in diabetic patients can be more challenging given the preponderance of involvement of the distal vessels, and precise imaging of these vessels is critical in planning for endovascular procedures or bypass surgery [60]. Multi-detector CT scanners are able to acquire multiple slices per 360°-rotation at 1-mm or sub-mm thickness. Administration of contrast dye allows for differentiation of blood and soft tissue structures [66]. The data set can be reconstructed showing detailed sagittal and coronal views as well as three-dimensional shaded displays in striking color. There are certain limitations to this technology, as the images are reconstructions and are therefore subject to the potential of artifacts. This issue is most challenging when imaging calcified plaques within arterial structures, which is often the case in diabetic patients [60]. A systematic review demonstrated that the sensitivity of CTA to detect stenosis of >50 % or more was 91 % (89–99 %) and specificity was 91 % (83–93 %) [65].

MRA can be performed with or without contrast-enhanced techniques. Contrast-enhanced techniques have largely supplanted studies without contrast in patients with suitable renal function. Nephrogenic systemic fibrosis has limited the use of contrast-based techniques in diabetic patients with impaired renal function [60]. Techniques that are employed under these circumstances include time-of-flight angiography, steady-state free precession, arterial spin labeling, and half-Fourier fast spin-echo imaging, among others [67–69]. A recent meta-analysis of contrast-enhanced MRA for the detection of PVD in diabetics revealed a pooled sensitivity of 86 % and pooled specificity of 93 %, which is lower than the previously reported 95 % sensitivity and 97 % specificity in all patients with suspected PVD [59, 65].

Cerebrovascular Disease

Arterial stiffness: Arterial distensibility can be measured by pressure-related waveforms and pulse-wave velocity (PWV). Defined as the velocity at which a pulse wave travels through an arterial segment, arterial distensibility is an accepted measurement of arterial stiffness. Healthy vessels are compliant and have low PWV, resulting in reflected waves in the periphery returning to the central aorta during diastasis. As major vessels stiffen, this leads to a significant hemodynamic load [70]. PWV is related to the health of vascular function and has been shown to be a powerful independent predictor of mortality in diabetic patients. At any given blood pressure, PWV is greater in diabetics than in controls, and for each 1 m/s increase, there is an 8 % increase in all-cause and cardiovascular mortality [71]. White matter lesions (WMLs) are associated with risk of stroke. A recent study by Laugesen et al. examined well-controlled diabetic patients (avg. HbA1c 6.5 %, BP 127/79 mmHg, total cholesterol 4.3 mmol/L) and addressed the relationship between PWV and WML volume as assessed by MRI. Despite the well-controlled risk factors, PWV was higher in patients with diabetes as compared with controls. In addition, for every 1 m/s increase in PWV, there was a 32 % increase in WML volume (16–51 %; $p<0.001$). These findings suggest that PWV may represent a clinically significant parameter in the assessment of cerebrovascular disease risk in patients with diabetes [72].

Carotid intima-media thickness (CIMT) has been shown to be a surrogate marker for cardiovascular disease. Using B-mode ultrasound of carotid arteries, simple noninvasive assessment can be made of the arterial wall. CIMT provides incremental prognostic information regarding CHD risk prediction over and above traditional cardiac risk factors [73]. Carotid plaque occurs at sites of non-laminar turbulent flow, such as the carotid bulb. Combination of CIMT and plaque assessment has a higher diagnostic accuracy for predicting future CAD events than CIMT assessment alone [74]. Carotid plaque is a 3-dimensional structure, however, and can ideally be evaluated using automated 3D ultrasound acquisition. Johri et al. recently performed a feasibility study and demonstrated that 3D carotid ultrasound can be used to stratify patients who are at low risk of obstructive CAD. Furthermore, using predefined cutoffs, 3D carotid ultrasound was more sensitive (98 % vs. 93.9 %) and specific (66.7 % vs. 42.9 %) than 2D ultrasound in predicting the presence of obstructive CAD [46].

New Modalities

In many cardiac disease states, there is an alteration in substrate metabolism. These changes are now regarded as likely a cause rather than a result of cardiac disease. Magnetic resonance spectroscopy is a novel tool that can be utilized to characterize cardiac metabolism using carbon-13 (^{13}C) and phosphorus-31 (^{31}P) substrates. Hyperpolarization is a technique that increases signal availability for a given labeled substrate and allows powerful assessment of instantaneous substrate uptake and enzyme utilization [75]. It was recently

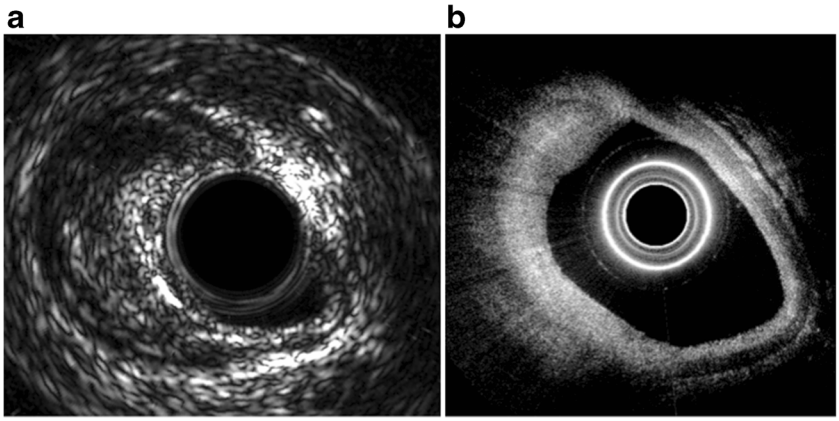

Fig. 1 **a** demonstrates intravascular ultrasound of the 1st diagonal artery of a patient with diabetes (cadaveric). **b** demonstrates optical coherence tomography of the same vessel. Note the different tissue characterization provided by the two techniques, with superior contrast, spatial resolution and near-field image quality provided by OCT. In contrast, intravascular ultrasound is able to image through blood and provides a more complete assessment of plaque volume due to its superior penetration through soft tissue

shown for the first time in an animal model that hyperpolarized (^{13}C) pyruvate is a feasible strategy to follow patients for cardiovascular disease progression and to establish diagnoses such as heart failure. Identification of metabolic stages and potential correlation with cardiomyopathy stage and etiology may help guide specific pharmacologic therapy [76]. Unfortunately, spatial resolution remains a limitation, and so the assessment of coronary plaque morphology and inflammatory response are unlikely with current technology.

Intravascular ultrasound (IVUS) is an imaging technique that uses a coronary catheter to assess the burden of CAD in a given coronary vessel. Newer strategies involve reconstructing a 3D image for analysis, which allows detailed characterization of the coronary plaque and quantifies arterial calcification. This assessment can be made in diabetic and non-diabetic patients and may provide insight into the severity of CAD [77]. Furthermore, IVUS evaluation in diabetics with CAD demonstrated a delayed coronary plaque volume regression when treated with a statin in comparison to non-diabetic patients [78].

Optical coherence tomography (OCT) is an intravascular imaging technique that provides greater spatial resolution and visualization of coronary plaque composition. Diabetics can have varied plaque characteristics, depending upon clinical status. In diabetic patients who present with an ACS, the plaque composition has a higher incidence of lipid-rich plaque, thin-capped fibroatheroma, macrophage infiltration, and thrombus compared to stable diabetic patients [48]. In addition, while both diabetics and non-diabetics who present with an ACS have a similar incidence of plaque rupture and thin-cap fibroatheroma in the culprit lesion, diabetics have more vulnerable plaques in non-culprit lesions. OCT provides unique insight into plaque composition and may be of help in the future in directing specific pharmacotherapy during an ACS (Fig. 1) [79].

Limitations of Review

There are many articles in the literature describing imaging techniques in diabetics. Given the limitations of this review, not all of the studies could be included. Additional vascular territories such as the kidney and skin have been studied but were not included in this review.

Conclusion

With an emphasis on the early detection and treatment of disease, vascular imaging in diabetes has gained significant relevance in patient management. What is not clear at this time is the incremental value of newer imaging techniques over older, better-validated imaging methods. It is also unclear whether the new methodologies will direct different therapeutic strategies. It remains speculative, for instance, whether metabolic imaging is able to demonstrate regional differences in substrate utilization in different vascular beds or whether 3D IVUS and OCT provide enough detailed information about plaque composition to direct specific therapeutic and treatment options. Further research is needed to better validate advances in CV imaging as well as to evaluate the outcomes of this strategy.

Compliance with Ethics Guidelines

Conflict of Interest Kevin Levitt, Lucas Vivas, and Kim A. Connelly declare that they have no conflict of interest. Brian K. Courtney is a director, inventor, shareholder, and CEO of Colibri Technologies.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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