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Review

Old and Novel Predictors for Cardiovascular Risk in Diabetic Foot Syndrome—A Narrative Review

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Abstract: Diabetic foot syndrome (DFS) is a complication associated with diabetes that has a strong negative impact, both medically and socio-economically. Recent epidemiological data show that one in six patients with diabetes will develop an ulcer in their lifetime. Vascular complications associated with diabetic foot have multiple prognostic implications in addition to limiting functional status and leading to decreased quality of life for these patients. We searched the electronic databases of PubMed, MEDLINE and EMBASE for studies that evaluated the role of DFS as a cardiovascular risk factor through the pathophysiological mechanisms involved, in particular the inflammatory ones and the associated metabolic changes. In the era of evidence-based medicine, the management of these cases in multidisciplinary teams of "cardio-diabetologists" prevents the occurrence of long-term disabling complications and has prognostic value for cardiovascular morbidity and mortality among diabetic patients. Identifying artificial-intelligence-based cardiovascular risk prediction models or conducting extensive clinical trials on gene therapy or potential therapeutic targets promoted by in vitro studies represent future research directions with a modulating role on the risk of morbidity and mortality in patients with DFS.

Keywords: diabetic foot syndrome; diabetes mellitus; cardiovascular risk

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1. Diabetes Mellitus and the Cardiovascular Continuum

Diabetes mellitus (DM) is one of the main medical challenges of the century, with multiple prognostic values representing a real cardiovascular risk factor responsible for increasing morbidity and mortality alike [1]. From 1550 BCE to the present day, advances in technology and the discovery of new therapeutic molecules have reduced the risk of potentially fatal complications leading to a reduced quality of life [2,3]. The widespread introduction of bariatric surgery, microbiome analysis as well as the deepening of pathophysiological mechanisms on the study of bile secretion and adipose tissue in terms of their effects on metabolism are some of the research directions in the field in recent years [4–6].

Epidemiological studies in recent years confirm the increasing prevalence of DM, especially in underdeveloped or developing countries, with the number of cases expected to double by 2045 [7,8]. From an economic point of view, the burden corresponds to more

than 12% of the health systems budget, with most of the expenditure associated with the management of complications [9].

The psychological impact associated with the presence of diabetic foot syndrome (DFS) and its cardiovascular implications is negative from a psycho-emotional point of view [10]. Family support and understanding of the course of the disease are social factors that contribute to increased quality of life by improving adherence to treatment, combating depression and anxiety and maintaining a positive status regarding the outcome of the disease [11–13].

This article aims to review the latest information from the literature on the role of DFS as a cardiovascular risk factor through the pathophysiological mechanisms involved, in particular the inflammatory ones and the associated metabolic changes.

2. Materials and Methods

We searched the electronic databases of PubMed, MEDLINE and EMBASE for studies that evaluated the impact of DM and DFS on the cardiovascular risk, with the aim of conducting a review of recent literature on the impact of DFS on the cardiovascular system, from pathophysiological mechanisms to the role of cardiovascular risk factors associated with DM or DFS as well as new biomarkers with potential therapeutic and prognostic value.

The words or phrases we used for searching were "diabetes mellitus" or "diabetic foot syndrome" plus one of the following (in various associations): "cardiovascular risk", "cardiovascular mortality, "cardiovascular prognosis", "cardiovascular risk factors", "cardiovascular biomarkers" and "cardio-diabetology". Observational studies, including prospective or retrospective cohort studies, RCTs, meta-analyses, guidelines and case reports related to our topic were included. We also searched manually the reference sections of the identified articles for additional publications. We excluded studies or case reports that referred exclusively to DM without including data on the diagnosis, management or prognostic role of DFS. Two independent reviewers selected studies by analyzing the title and abstract.

3. Past, Present and Future in Assessing the Cardiovascular Risk

The prevalence of type 2 DM increases with age, being predominantly found in patients over 60 years old. Thus, in the case of type 1 DM, women are associated with poor glycemic control compared to men, while in men the proportion of comorbidities is higher with age, as they are frequently hypertensive and refractory to commonly used medication [14,15]. Type 2 DM is more common in male patients, usually younger and with a lower body mass index than women [16–18]. Gender-associated hormones play an essential role in modulating both the risk of onset and progression of diabetes by modulating the pathophysiological phenomena involved in glucose homeostasis or insulin secretion and action [16,19].

DM is associated with long-term multi-organ damage [20], but of all the potential complications, heart disease has the most pronounced impact, affecting about 30% of diabetic patients and being responsible for half of all deaths [21–23]. A systematic review that included more than 4 million patients with diabetes between 2007–2017 classified the most common cardiovascular entities encountered in diabetic patients, the most common being chronic coronary syndrome (29.1%), heart failure (14.9%) and stroke (7.6%) [21].

DM doubles the risk of a myocardial infarction or stroke [18]. However, a number of gender differences are reported in the literature, with diabetic women having a 40% higher risk of coronary heart disease than diabetic men [24–26]. Patients with DM frequently associate hypertriglyceridemia and low serum HDL cholesterol [27–29].

With advancing age, the association between diabetes and cardiovascular disease decreases, which is partly explained by the reduced cardiovascular risk of young people compared to the elderly [30–34]. Age modulates the associated cardiovascular risk of diabetic patients [35], with the risk of death found to be twice as high in patients diagnosed under the age of 40 compared to those over the age of 80 [36]. Sattar et al. [36] analyzed the

Swedish National Diabetes Registry and observed that the survival of patients diagnosed with diabetes over 80 years of age is similar to that of those without diabetes.

Clinical studies presented in the literature conclude that diabetes mellitus eliminates (at least partially) the protective effect of hormones for women in terms of risk of cardiovascular morbidity and mortality [18,20,37–39]. The presence of diabetes leads to a 4-fold increase in the risk of an acute cardiovascular event and an 8-fold increase in the need for vascular intervention compared to patients with associated cardiovascular disease without DM [40,41]. Diabetic women are also associated with an up to 58% risk of a fatal acute coronary event ($p < 0.001$) [42].

Patients with type 1 DM have a 5.1-fold and 3.4-fold higher associated risk for women and men of developing heart failure. This is compared to type 2, where the reported differences are minor and the associated risk is almost twice as high in both sexes, albeit higher for the female gender [43–46].

Diabetes mellitus is a risk factor for developing peripheral artery disease, regardless of gender, with an associated risk approximately twice as high [47,48]. Duration of diabetes mellitus, carbohydrate profile parameter values and insulin resistance markers contribute to the increasing prevalence of peripheral artery disease in this category of patients [49,50].

Glycated hemoglobin values also modulate the weight distribution of atherosclerotic lesions in the lower vascular axis [51–53]. The association between DM and PAD increases the risk of an acute vascular event leading to limb loss, the amputation rate being directly proportional to glycated hemoglobin levels [54–57]. Diabetes mellitus is associated with male gender and older age as predisposing factors for infra-geniculate atherosclerotic involvement [58]. Diabetic patients show more frequent damage to the arteries than non-diabetics [59]. Young diabetic men are more frequently diagnosed with severe atherosclerotic lesions, especially in the proximal arteries [58,60].

Shatnawi et al. [49] have demonstrated that patients with glycosylated hemoglobin above 7.5% more frequently have atherosclerotic lesions in the superficial femoral artery, popliteal artery, anterior tibial artery, posterior tibial artery and peroneal artery. Femuropopliteal segment involvement occurs more frequently in patients with glycosylated hemoglobin values below 7.5%, while exceeding this limit correlates more frequently with crural segment involvement [49]. The severity and distribution of atherosclerotic processes at the crural level negatively impacts the functional status and, therefore, the quality of life of diabetic patients with peripheral arterial disease and is associated with a reduced life expectancy in the medium-term in the case of advanced lesions [53,59,61–63].

The risk of death secondary to an acute cardiovascular event is also higher among women with DM compared to men (with a women-to-men ratio of relative risk of 1.13) [42]. Glycosylated hemoglobin values influence the risk of mortality and the risk of developing an acute coronary event [64], with a U-shaped relationship between these two entities in which low values of glycosylated hemoglobin (6.1–6.6%) and high values (10–11.2%) are associated with a high risk of death [65]. Patients with average values around 7.5% have the lowest associated cardiovascular risk [66,67]. Furthermore, each 1% increase in glycosylated hemoglobin increases the risk of acute macrovascular event [68] by 38% and 4% in the case of microvascular damage, while also increasing the risk of death by approximately 40% ($p < 0.001$) [69,70]. In another similar clinical study, focusing on the impact of glycosylated hemoglobin on cardiovascular risk, Arnold et al. [68] demonstrated that there is a J-type relationship between the two aforementioned parameters in which the risk of death from any cause decreases with each increase in glycosylated hemoglobin to values below 7.5% and increases directly proportional to the value in patients with glycosylated hemoglobin values above 7.5%.

In addition to glycosylated hemoglobin, serum blood glucose levels also modulate the risk of death. Djupsjö et al. [71] analyzed a cohort of approximately 619,000 patients with no history of diabetes and, analyzing blood glucose at admission, concluded that hypoglycemia or hyperglycemia are associated with twice the rate of death compared to

normoglycemic patients, the risk being higher in hypoglycemic patients (odds ratio of 2.58 versus 1.69).

4. Diabetic Foot Syndrome

Diabetic foot (DF) is one of the most serious complications of diabetes with negative prognostic implications [10,72,73], being defined by the World Health Organization as ulceration of the distal leg of the ankle, including the ankle, associated with neuropathy and varying degrees of ischemia and infection [74]. DFS is defined as ulceration of the foot associated with neuropathy, ischemia and intermittent infections of any type [75,76]. Diabetic foot can be classified from a pathophysiological and clinical point of view into several forms: ischemic diabetic foot, neuropathic ischemic foot and infected diabetic foot [77]. For diabetic patients, leg ulceration is the main cause of lower limb amputation. DM is also responsible for the majority of non-traumatic amputations, 85% of which are predisposed by foot ulceration [78–80]. The occurrence of ulcers in diabetic patients is accompanied by a high rate of morbidity and mortality, and also represents an economic and social burden through its implications for functional status and quality of life [81].

The prevalence of DF is about 6%, with recent epidemiological studies estimating the occurrence of an ulcer in at least 1 in 6 diabetic patients during their lifetime [82]. Men have a higher risk of developing DF compared to women [83–86]. The recurrence rate of diabetic foot after healing is 30% [83,87]. Based on these data and taking into account the high costs associated with medication and hospitalization, it has become necessary to develop primary or secondary prevention strategies to decrease mortality and acute vascular events in this category of patients [88]. The risk of developing diabetic foot is assessed using nomograms based on the main independent risk factors associated with it such as age, glycosylated hemoglobin, low density lipoprotein cholesterol, total cholesterol, smoking and alcohol consumption [80,89,90]. Several risk scores have been developed for diabetic patients prone to ulcers, which have both preventive and therapeutic roles [91,92].

Diabetic peripheral neuropathy is the main promoter of ulceration in diabetic patients, leading to autonomic, motor or sensory alterations [93]. The increased cardiovascular risk of these patients results from the cumulative effect of associated neuropathy and peripheral arterial disease [94,95]. The pathophysiological mechanisms involved are diverse, involving a variety of factors such as foot deformities, abnormal foot pressures, limited joint mobility, external trauma, peripheral arterial disease or edema (Figure 1) [96].

Sensory neuropathy may cause minor, repeated insults secondary to increased pressure or improperly felt mechanical and thermal stimuli [97]. Peripheral arterial disease causes a number of pathophysiological changes, both microvascular and macrovascular, which do not allow ulcers to heal. Clinical studies have shown that identifying an ankle–brachial index of less than 0.90 correlates with a 1.25-fold increased risk of developing an ulcer in diabetic patients compared to a similar cohort of patients without peripheral vascular disease. Sleep apnea syndrome and nocturnal hypoxia are two risk factors associated with the development of diabetic peripheral neuropathy, the associated risk of these patients being 4 times higher [98–100]. The apnea–hypopnea index can be used as a marker for the presence of diabetic microvascular complications [101,102].

Diabetic foot may be a marker of cardiovascular risk. The increased cardiovascular risk—and, therefore, the risk of complications and death in patients with diabetic foot—can be explained by biochemical alterations of the lipid and carbohydrate profile represented by hypercholesterolemia, the association of a serum LDL cholesterol level above 130 mg/dL, hypertriglyceridemia and microalbuminuria or even proteinuria [96].

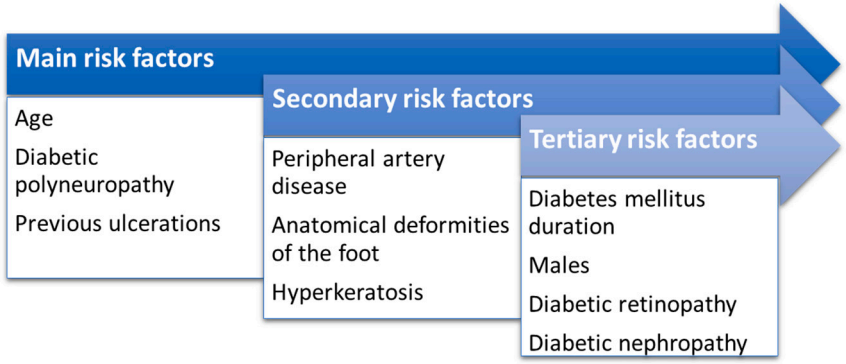

Figure 1. Risk factors for DFS (adapted from [103]).

Pinto et al. [104] analyzed the impact of the association of DFS with cardiovascular risk and demonstrated that patients with diabetic foot are associated with more cardiovascular risk factors and have a higher prevalence of cardiovascular pathologies with a negative prognostic role or subclinical impairment. In the same study, follow-up over a 5-year period showed an increased risk of an acute vascular event, the main factors associated with cardiovascular morbidity being duration of diabetes, age, glycosylated hemoglobin value and association of DFS. Diabetic foot may also be considered a marker of cerebrovascular risk through the clinical picture marked by numerous associated cardiovascular risk factors [105].

Imaging assessment of patients with DFS provides details with therapeutic value for the diabetologist and surgeon alike by identifying associated osteitis or neuroarthropathy or by providing for assessment of the arteries prior to angioplasty [106]. The methods used are varied, from bone X-rays to computed tomography (CT) or nuclear magnetic resonance (MRI) evaluation, vascular ultrasonography (US), radionuclide imaging examination or positron emission tomography (PET) [107]. One of the main challenges is to differentiate infectious radiological changes from those associated with neuroarthropathy [108].

MRI is the gold-standard imaging method for the detection of osteomyelitis [109]. A meta-analysis by Kapoor et al. [110] revealed that of all the previously mentioned imaging methods, MRI is the only one with a sensitivity and specificity of over 90%.

Bone X-rays can be used in the initial screening of DM patients, but the sensitivity is low. In the early stages, radiographic evaluation does not identify osteomyelitis [111]. Its most common applications are in the identification of Charcot osteoarthropathy or the detection of calcification of the posterior dorsal artery in Mönckeberg's sclerosis [112–114]. DFS-associated infections are easily diagnosed with CT and MRI by highlighting small intraosseous abscesses or sinus tracts [115]. Radionuclide imaging is often associated with imaging techniques that identify morphological aspects, thus providing superior accuracy. Single-Photon Emission Computed Tomography can be used both as a screening test and to assess labeled leukocyte imaging location and activity [116,117].

US has multiple implications in the assessment of patients with DFS, being used both in risk stratification of patients with DM and for arterial mapping, assessment of arterial vascular lesions or identification of calcifications [118,119]. US is also involved in the diagnosis and management of patients with DF ulcers. The results of three prospective randomized clinical trials have been reported in the literature demonstrating additional reduction in ulcer area and faster complete healing compared to sham treatment [120–122].

The management of patients with DFS is complex, involving both glycemic control, control of cardiovascular risk factors, administration of analgesic medication, revascularization and surgical treatment [123]. The surgical treatment of these patients is complex and includes various types of interventions such as debridement, Achilles tendon lengthening (reduces the risk of recurrence of ulcers [124,125]) and vascular surgery. Foote et al. [126] recently highlighted that this minimally invasive technique is associated with a faster re-

covery compared to the classical conservative management represented by immobilization, while improvements in radiological aspects are also targeted.

Superficial ulcers can be treated conservatively, but bone or tendon involvement requires surgical reconstruction sometimes associated with revascularization methods to prevent osteomyelitis [127]. Data from the literature emphasize two basic principles in the surgical management of patients with DFS: revascularization of lesions (endovascular or bypass techniques) and management of associated infections [128].

Microvascular myocutaneous or fasciocutaneous tissue transfer, local flaps, small free microvascular flaps or arterialized venous flaps are surgical techniques used to prevent the occurrence of amputations accompanied by a high rate of morbidity and mortality, functional decline and decreased quality of life [128]. Hutting et al. [129] discusses an alternative to the classical management of ulcers in patients with DFS by surgical resection and filling of dead spaces with various biocomposites such as gentamicin-loaded calcium sulphate–hydroxyapatite which resulted in ulcer healing without recurrence in 66% of cases. The use of a gentamicin-loaded calcium sulphate–hydroxyapatite biocomposite is not covered by good practice guidelines, but the promising results of published cases already justify the development of advanced clinical trials to assess the feasibility of this therapeutic method [111].

5. Discussions

5.1. Cardio-Diabetology: The Role of Biomarkers and Inflammatory Molecules

Pathophysiological analysis of the adipovascular axis revealed the determinant role of inflammatory markers such as IL-6 and resistin in modulating cardiovascular risk in diabetic patients [96]. Patients with DF syndrome associate metabolic disorders that modulate the associated cardiovascular risk. Hyperglycemia causes axonal and microvascular injury over time. In addition, in diabetic patients, hypertriglyceridemia is a known independent risk factor for amputations [75,130].

Clinical studies in the field associate low serum levels of adiponectin and high levels of IL-6 with the development and progression of inflammatory mechanisms involved in the pathogenesis of diabetic ulcers. In diabetic patients, microalbuminuria correlates with serum IL-6 and adipocytokine levels, thus playing a dual role as a contributor to the progression of insulin resistance and the production of inflammatory cytokines [96]. Besides adiposity, oxidative stress, mitochondrial dysfunction, activation of the polyol pathway or accumulation of pro-inflammatory and advanced glycation end-products are pathophysiological mechanisms underlying the cardiovascular damage associated with DF syndrome [131–134].

Hyperglycemia affects ischemic preconditioning, being associated with elevated serum catecholamines, the presence of a no-reflow phenomenon, increased oxidative stress, prothrombotic status and inflammation (Figure 2) [135,136]. Hyperglycemia also leads to endothelial dysfunction, with activation of various metabolic pathways mediated by protein kinase C resulting in excessive production of reactive oxygen species [75]. Miric et al. [137] have shown that serum xanthine oxidase activity is an independent predictor for the occurrence of diabetic peripheral neuropathy, thus contributing to the development of DF syndrome. The administration of vitamin D for 12 weeks is accompanied by an improvement in carbohydrate metabolism, which also contributes to the healing process of diabetic ulcers [138]. Silent myocardial ischemia is common among diabetic patients, the presence of diabetic peripheral neuropathy being a risk factor associated with it; it has a screening role to detect patients at risk of developing an acute cardiovascular event [139].

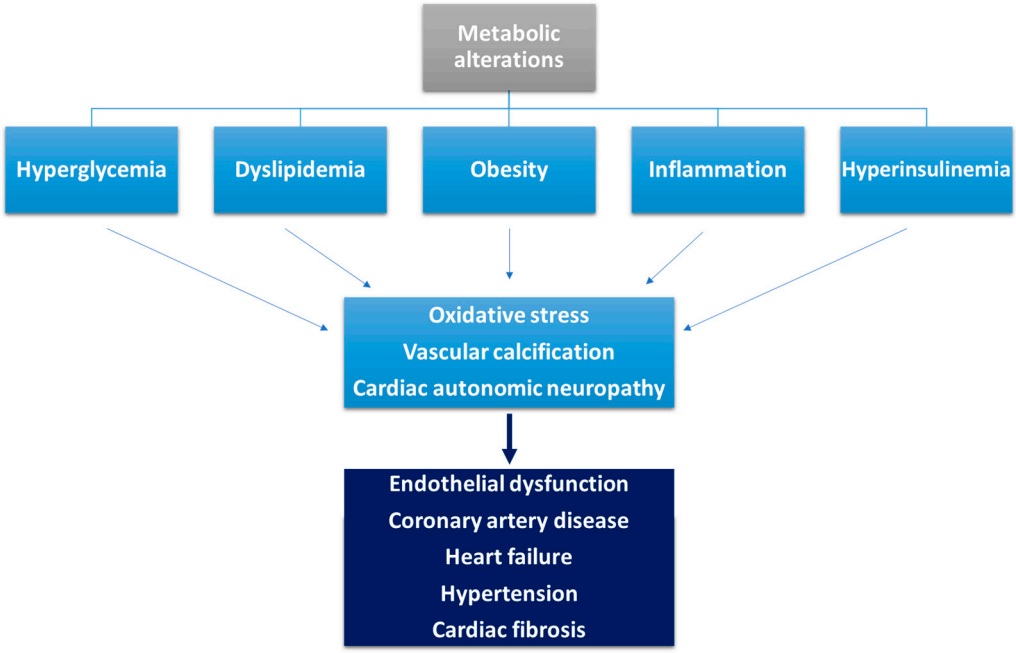

Figure 2. Pathophysiological mechanisms involved in the occurrence of cardiovascular disease in diabetic patients (adapted from [135]).

In addition to IL-6, other cytokines that modulate inflammatory processes have been identified such as leptin, tumor necrosis factor-α, plasminogen activator inhibitor, uric acid or oxidized low-density lipoproteins [103,140–142]. Afshinnia et al. [142] identified several lipid determinants with a role in the development and progression of diabetic neuropathy such as acylcarnitines, free fatty acids, phosphatidylcholines, and lysophosphatidylcholines, the presence of which can be identified up to 10 years earlier in a high titer. Some of these lipid compounds are also responsible for the development of cardiac autonomic dysfunction in patients with type 2 DM [143] and insulin resistance [144].

The identification of a serum cystatin C level above 0.735 mg/L is a potential biomarker for the identification of diabetes-associated complications and is correlated with the occurrence of DF and tissue loss in patients with type 2 DM [145].

In patients with type 2 diabetes, elevated homocysteine levels are associated with the presence of heart failure with a low ejection fraction and are an independent risk factor for all-cause mortality [44]. The connection between cardiac autonomic neuropathy and subclinical inflammation, with multiple prognostic implications on associated cardiovascular risk and morbidity, was examined in diabetic patients, with differential results depending on the type of molecule involved [146–148]. Heart rate variability is dependent on altered sympathetic and parasympathetic tone in young patients with DM, correlating with glycated hemoglobin values [149,150].

While IL-18 and soluble E-selectin are associated with reduced vagal activity, adiponectin can be used as a marker of decreased sympathetic activity [151]. Adiponectin has a dual, titer-dependent role, being both a cardioprotective hormone with an anti-inflammatory role and a marker of high cardiovascular risk through its association with an assessment of the risk of death [152,153]. Adiponectin also prevents cardiac remodeling after myocardial infarction and inhibits the action of the sympathetic nervous system on this pathophysiological process, also having a potential therapeutic role in these patients [154]. Zhu et al. [155] demonstrated that elevated serum adiponectin levels are an independent predictor of atrial fibrillation in women and men under 65 years old.

Peripheral somatic neuropathy contributes to the development of medial arterial calcification [156]. In diabetic patients, it plays a role in activating the receptor activator of nuclear factor kappa B ligand/osteoprotegerin signaling pathway that modulates the pathophysiological processes involved in the calcification of smooth muscle cells in the coronary arteries and peripheral limbs [130]. Advanced glycation end-products also contribute to the production of vascular calcification and, thus, to the progression of atherosclerotic lesions in diabetic patients [157,158].

Serum B-type natriuretic peptide levels correlate with the risk of onset and progression of diabetic neuropathy, but further clinical research is needed to unravel any pathophysiological implications. Data in the literature to date attest to the role of this cardiovascular biomarker in identifying and assessing the extent of neuropathic damage in diabetic patients. Based on the role of BNP to assess the presence of systolic and diastolic dysfunction as well as to assess the prognosis of patients with heart failure, the identification of a connection with DFS is of great clinical importance, as it can also assess the cardiovascular risk of patients without previously known cardiac pathology [159–161]. Yan et al. [162] demonstrated that serum BNP levels were higher in patients with type 2 DM and diabetic neuropathy compared to a cohort without microvascular damage ($p = 0.001$), while positively correlating with systolic blood pressure, serum creatinine, prevalence of diabetic ulcers ($p = 0.039$) and vibration perception threshold values ($p = 0.021$). Identification of a BNP value above 15.18 pg/mL has a sensitivity of 78.7% and a specificity of 48.2% in assessing the presence of diabetic neuropathy.

A recently published meta-analysis by Ramzi et al. [163] highlights that the presence of a serum N-terminal prohormone brain natriuretic peptide (NT-proBNP) level above 225 pg/mL correlates with a high risk of death from any cause among diabetic patients, while serum levels above 100 pg/mL are predictive of the occurrence of acute cardiovascular events. This biomarker, along with IL-6 and resistin, correlates with the presence of left ventricular dysfunction and left ventricular hypertrophy and can thus be used as non-invasive biomarkers for assessing cardiovascular risk in patients with DM [164].

5.2. Diabetic Foot Syndrome and Diabetic Cardiomyopathy

The identification among diabetic patients of a multitude of cardiovascular risk factors such as smoking, hypertension and dyslipidemia ($p < 0.05$ for each one) with both short- and long-term prognostic value led to the investigation of echocardiographic parameters associated with increased cardiovascular risk [165]. LV systolic dysfunction is initially assessed by reduced longitudinal function, at which stage the ejection fraction is maintained within normal limits by radial and circumferential compensation. Literature data attest to improvement of echocardiographic strain parameters in subclinical systolic dysfunction secondary to treatment of hypertension and obesity in patients with diabetes mellitus [166].

Most patients with DFS also have associated diabetic cardiomyopathy, defined as the presence of systolic dysfunction or at least moderate diastolic dysfunction, independent of the presentation of LV modulation in the absence of chronic ischemic heart disease, hypertension, valvular heart disease or congenital heart disease [167].

Diabetes mellitus induces a number of phenotypic changes assessed by LV mass and LV systolic or diastolic function (Figure 3). Patients with DFS need multimodal imaging evaluation with the aim of early identification of myocardial damage and identification of determinants associated with heart failure [167–173]. Myocardial fibrosis, microcirculatory damage, metabolic disorders and disorders of cardiac innervation are the pathophysiological mechanisms underlying the development of diabetic cardiomyopathy in patients with DFS.

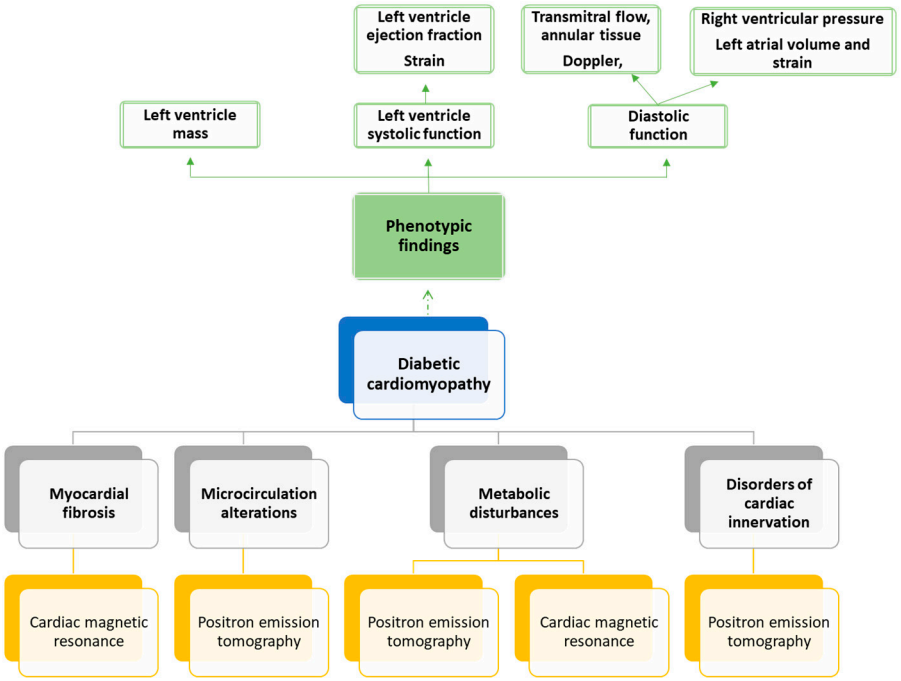

Figure 3. Diabetic cardiomyopathy phenotypic findings and multimodal imaging assessment (adapted from [167]).

Clinical studies in the literature emphasize the role of renin–angiotensin–aldosterone system dysfunction, oxidative stress, pro-inflammatory status or endothelial dysfunction in the development of systolic and diastolic dysfunction in patients with DFS [174,175]. Concentric LV hypertrophy in patients with DFS is a common finding secondary to associated lipotoxicity which results in excess lipid accumulation in cardiomyocytes and thus systolic dysfunction [176–180].

Demirtas et al. [165] investigated for the first time the change in echocardiographic parameters (ejection fraction, strain parameters) secondary to DF treatment [181]. These investigators analyzed two groups of patients, the first with 54 patients with diabetic foot and the second with 22 patients without diabetic foot, demonstrating that LV dimensions were larger and LV ejection fraction smaller in the group of patients with diabetic foot ($p < 0.05$). Dynamic assessment of echocardiographic parameters 3 months after the start of diabetic treatment showed a statistically significant improvement in strain parameters of systolic function ($p < 0.001$), but without an increase in ejection fraction ($p = 0.747$). A significant proportion of patients with DFS associate heart failure with preserved left ventricle ejection fraction (LVEF), so that the identification in these patients of concentric hypertrophy as well as increased relative wall thickness suggests subclinical involvement [182]. The results of the Irbesartan in Heart Failure With Preserved Ejection Fraction (I-PRESERVE) trial published in 2018 targeted a number of echocardiographic changes in patients with DM such as increased LV size and mass and increased filling pressures (assessed using the E/e′ ratio) in the presence of normal systolic function and mitral annular systolic velocity (similar to patients without DM) [183–185].

Modern echocardiographic assessment techniques such as speckle tracking reveal alterations in systolic strain that are considered preclinical changes of diabetic cardiomyopathy [167]. In some patients only changes in longitudinal systolic function compensated by an increase in radial systolic function have been identified, while the majority of cases associate a dysfunction involving both types of alterations [186–188]. Approximately one fourth of patients with DM are associated with a decrease in global longitudinal strain (GLS) of more than 18%, which has a negative prognostic value [189]. Patients with diabetic cardiomyopathy are frequently associated with diastolic dysfunction manifested by abnormal

mitral flow (E velocity), abnormal annular tissue Doppler (e′) and a reduction in total and positive left atrial strain independent of functional status; thus, it acts as a predictive factor associated with subclinical impairment with prognostic value in assessing the development of future complications such as DFS [190–192]. Tadic et al. [193] recently demonstrated that, in patients with DM, glycated hemoglobin, LV mass index and mitral E/e′ ratio correlate independently with peak oxygen uptake. Insulin resistance is correlated with diastolic dysfunction [194], and the identification of an E/e′ ratio above 15 plays an independent role in the development of heart failure and increases the risk of death in patients with diabetic cardiomyopathy independently of the presence of hypertension, chronic ischemic heart disease or changes in other echocardiographic parameters [167]. Ernande et al. [189] analyzed a cohort of 114 asymptomatic diabetic patients without known coronary artery disease and demonstrated the presence of diastolic dysfunction in 47% of them (with age, hypertension and hemodynamic parameters as predictors)—a higher percentage than the change in systolic function assessed by a decrease in LV GLS, which was present in 32% of cases.

In addition to echocardiography, other imaging investigations with prognostic value in patients with DFS have been identified, such as cardiac magnetic resonance (CMR) and positron emission tomography (PET) which are used in the identification of cardiac fibrosis, microcirculatory disorders, associated metabolic disorders or disorders of cardiac innervation [167] (Figure 3).

In patients with chronic diabetic ulcers, the percentage of patients with cardiovascular damage is very high even in the absence of hypertension or known heart disease [195], which justifies the use of echocardiography as a screening method for assessing cardiac involvement in patients with diabetic ulcers [196,197]. Patients with DFS have a pro-inflammatory status which leads to insulin resistance and endothelial dysfunction, pathophysiological processes underlying the cardiovascular continuum. The inflammatory cytokine titer is extremely high and is a pathophysiological substrate associated with the development of silent myocardial ischemia or cardiac arrhythmias [165,198–201].

A recently published meta-analysis highlights the high risk of patients with DFS developing an acute cardiovascular event or even death [202]. The association of hypertension, male gender, smoking or peripheral arterial disease with DFS negatively modulates the prognosis of these patients.

6. Future Directions

DFS per se is a cardiovascular risk factor with multiple therapeutic and prognostic implications alike, requiring multidisciplinary, integrative management [203,204].

6.1. The Role of Artificial Intelligence in Assessing CVD Risk in DM

The applications of artificial intelligence in the medical field are becoming more and more extensive, being able nowadays to generate various models of cardiovascular risk assessment with both therapeutic and prognostic roles [205,206]. Imaging assessment of the ulcerative lesion is essential in order to identify an associated infection [207] and to provide accurate epidemiological data on the prevalence of DM [208]. Clinical studies in the literature have demonstrated that diabetic foot infections act as a cardiovascular marker based on a directly proportional correlation between the severity of infection and atherosclerotic lesions [75,209].

Machine Learning (ML) and Deep Learning (DL) algorithms have various applications in cardiology and diabetology [210,211], having both diagnostic and prognostic roles by identifying predictors associated with cardiovascular risk [212–214]. Technologies using artificial intelligence are based on the analysis of complex databases, and current data on diabetes-related cardiovascular risk assessment show non-linear connections between input predictors and the obtained risk. The advantage of using the aforementioned algorithms is obtaining intrinsic relationships between several predictors used simultaneously [215–217]. To date, several algorithms have been developed to assess associated

cardiovascular risk [218–220], one such example being the one proposed by Jamthikar et al. [221] which, using carotid vascular Doppler assessment and the presence of traditional cardiovascular risk factors, can assess associated cardiovascular risk with superior accuracy to traditional methods of calculation. Based on the socio-economic importance of the complications associated with DFS, artificial intelligence algorithms have been developed to screen diabetic patients to identify risk factors for the development of ulcers using different optical sensors [222–225].

6.2. Predictive Risk Models for CVD Events in DM

The development of cardiovascular risk prediction models in diabetic patients is an extremely valuable clinical tool in the daily practice of cardio-diabetology [226]. Most risk prediction models to date are based on data from the Framingham Heart Study, in which diabetes is included as a risk factor [227,228]. This prediction model can be used among diabetic patients due to the underestimation of the associated cardiovascular risk, which has required the development of new prediction tools for this population [226,229]. The United Kingdom Prospective Diabetes Study and the ADVANCE study [230–232] identified a number of predictors which were demographic (age), associated with DM (time since diagnosis, glycosylated hemoglobin value) or derived from major cardiovascular risk factors.

Similarly, Mu et al. [233] developed an algorithm to predict the risk of an acute fatal or non-fatal cardiovascular event (especially acute myocardial infarction or stroke) in the next 10 years in patients with type 2 diabetes. Thus, the QRESEARCH risk estimator version 3 is superior to the Framingham risk score by using a much larger number of clinical–paraclinical parameters and has a much higher predictability among diabetic patients [234,235]. Based on the observation that approximately 50% of patients with cardiovascular disease do not associate with traditional cardiovascular risk factors, some clinical prediction models integrate biomarkers, comorbidities, polygenic-based scores [236,237] or metabolomic patterns [238–240].

Although various such prediction models have been developed, methodological issues, high risk of bias and lack of clinical validation studies are some of the main drawbacks identified that reinforce the need for extensive clinical research on large cohorts of patients before introduction into clinical practice [241].

6.3. Novel Therapeutic Targets

Advances in technology have enabled advanced clinical research, and various signaling pathways are currently being investigated for future use in the development of targeted therapeutic molecules [180]. P38 kinases are considered valuable and promising therapeutic targets in preventing the onset or progression of diabetic cardiomyopathy based on p38-MAPK-generated inhibition that resulted in improved inflammatory status and systolic function in previous animal studies of diabetic mice [242]. The use of phosphodiesterase type 5 inhibitors may prevent hyperglycemia-induced changes in cardiomyocyte gene expression, thereby counteracting the increased cyclic adenosine 5-monophosphate-responsive element modulator [243].

Modulation of nuclear factor erythroid 2-related factor 2 activity is associated with decreased inflammation and lipid accumulation or prevention of the development of fibrosis secondary to DM, thus representing a potential therapeutic target in patients with diabetic cardiomyopathy [244]. The use of exosomes developed from heat shock protein 20 has been shown in animal studies to modulate the secretory activity of cardiomyocytes [245]. microRNAs and the correction of intestinal dysbiosis interfere with the pathophysiological processes of diabetic cardiomyopathy [246]. In a previous clinical study, Katare et al. [247] demonstrated that anti-miR1 induces survival signals in cardiac progenitor cells or cardiomyocytes subjected to permanent hyperglycemic status.

Gene therapy is a very promising future research direction in relation to DM and DFS. To date, pre-clinical research with murine leukemia virus-1 (PIM-1) via cardiotropic

serotype-9 adeno-associated virus (AAV) which increased PIM-1 expression and cardiac phosphoinositide 3-kinase using AAV6 has demonstrated in vitro prevention of cardiac apoptosis, fibrosis or development of heart failure and increased LV systolic function in diabetic mice [176,178,247].

The Charcot DF is frequently encountered in patients with DM, being one of the most disabling and severe complications [248]. The pathophysiology is complex and multifactorial, involving numerous signaling pathways and molecules that mediate diverse, interconnected processes that over time result in osteolysis and ultimately bone destruction [249,250]. One such example is the receptor activator of the NF-κB ligand receptor activator of NF-κB osteoprotegerin (RANKL-RANK-OPG) pathway which modulates inflammatory processes, its overexpression and activation being accompanied by increased osteoclast activity and osteolysis [251]. Taking into account the role of this signaling pathway in bone remodeling in patients with DFS, several therapeutic agents have been developed to act at different levels of the signaling pathway with the aim of halting the disabling progression of Charcot DF [251]. One such example is the administration of anti-RANKL monoclonal antibodies such as Denosumab, which—although it has, so far, been studied in small groups of patients—has encouraging results that justify further research in larger groups of patients [252,252–254].

In terms of wound healing, previous clinical and animal studies have demonstrated that ulcer-associated pro-inflammatory status, lack of ischemia correction and lesion maturation are therapeutic targets associated with improved wound healing in patients with DFS [255]. The neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio are two easily measurable, reproducible inflammatory biomarkers with prognostic value in both the onset and progression of DFS. Among patients with DF-associated infections, elevated values of these biomarkers correlate with the occurrence of osteomyelitis, the need for amputation or septic complications [256,257].

7. Conclusions

Diabetes mellitus, one of the epidemics of the modern world, has multiple clinical, therapeutic and prognostic implications. Given the increased prevalence of DF syndrome and its disabling complications, multidisciplinary team assessment of these patients is required. DF can be considered a true marker of associated cardiovascular risk, which is supported by the pathophysiological mechanisms involved and the connection with the processes involved in the development of cardiac pathologies. The development of models to predict or assess cardiovascular risk using artificial intelligence in this category of patients is an extremely promising research direction.

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