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Review

Microvascular complications in diabetes: A growing concern for cardiologists

Angelo Avogaro *, Gian Paolo Fadini

Department Medicine, Section of Diabetes and Metabolic Diseases, University of Padova, Italy

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ABSTRACT

Randomized, cross-sectional, and prospective studies have demonstrated that microvascular complications in patients with diabetes are not only the cause of blindness, renal failure and non-traumatic amputations, but also powerful predictors of cardiovascular complications. Beside the metabolic theory, the pathophysiology of diabetic microvascular complications is determined by the interaction among several factors, including epigenetic modifications and the reduced release of progenitor cells by the bone marrow, that contribute simultaneously to damage and impaired vascular protection against hyperglycemia. Identifying and preventing microvascular complications has the significant potential to reduce major adverse cardiovascular events. For these reasons, there may no longer be a rational to consider microangiopathy and macroangiopathy as entirely separate entities, but they should most likely be viewed as a continuum of the widespread vascular damage determined by diabetes mellitus.

1. Introduction

Microvascular complications (MICRO) are highly prevalent in patients with diabetes: 38% of the patients with type 2 diabetes (T2D) present any stage of chronic kidney disease (CKD) [1], almost 30% have retinopathy (DR) [2], and >30% have peripheral neuropathy (PN) [3]. While the onset and the progression of macrovascular disease (MACRO) are determined by the combined negative effects of several risk factors, MICRO are mostly determined by hyperglycemia, but significant roles are also provided by high blood pressure and hyperlipidemia [4]. MICRO can lead to visual impairment, advanced CKD, and amputations; cardiologists tend to underappreciate the clinical significance of MICRO in people with diabetes, while they focus the attention mostly on MACRO, without linking the two conditions. The perception that the clinical importance of MACRO outweighs that of MICRO is wrongly dictated by the design of typical cardiovascular outcome trials (CVOTs), wherein the primary end-point is composed by the composite of cardiovascular death, non-fatal acute myocardial infarction, and non-fatal stroke (3-point MACE). MICRO is almost exclusively included as secondary outcomes, mostly as renal end-points, frequently ignoring retinal complications, and completely neglecting neuropathy [5]. While this standard has been generated by guidance for industries issued by the U.S. Food and Drug Administration (FDA), it is important to underline that MICRO should be considered in the overall assessment of treatment efficacy.

Contrary to cardiologists, after the results of the Diabetes Control and Complication Trial (DCCT) and the United Kingdom Diabetes Prospective Study (UKPDS) on the role of a good metabolic control on MICRO [6,7], diabetologists mostly emphasized the MICRO and deflated the MACRO. Thus, cardiologists and diabetologists perceive the two entities as separate, and not tightly linked, as it should be. An additional relevant point is that MICRO are perceived as existing only in selected organs such eyes, kidneys, and nerves. Rather, functional and structural microvascular alterations have been recognized also in other organs such as the heart [8] where they can be viewed as an early event of more widespread derangement of coronary circulation (Fig. 1). Noteworthy, there is an ample variation in the individual propensity to develop MICRO: some patients with chronic metabolic decompensation never develop either CKD or DR, while others display serious complications despite an optimal metabolic control. In the DCCT, duration of diabetes and HbA1c explained only about 11% of the variation in the risk of DR [9]. This may be probably ascribed to the existence of a genetic predisposition: relatives of patients with diabetes and DR have approximately a 2- to 4-fold risk of developing DR compared with relatives of patients with diabetes but without DR. Heritability has been estimated to be almost 30% for DR and 52% for proliferative DR [10]. Also CKD runs in families: the 25-year cumulative incidence of CKD was 25% in diabetic siblings of probands without CKD, the risk was 43% and 58% in siblings of probands with diabetic nephropathy (DN) or end stage renal disease (ESRD) [11]. Thus, consistent data suggest a heritability

* Corresponding author at: Dipartimento di Medicina, Via Giustiniani 2, 35128 Padova, Italy.
E-mail address: angelo.avogaro@unipd.it (A. Avogaro).

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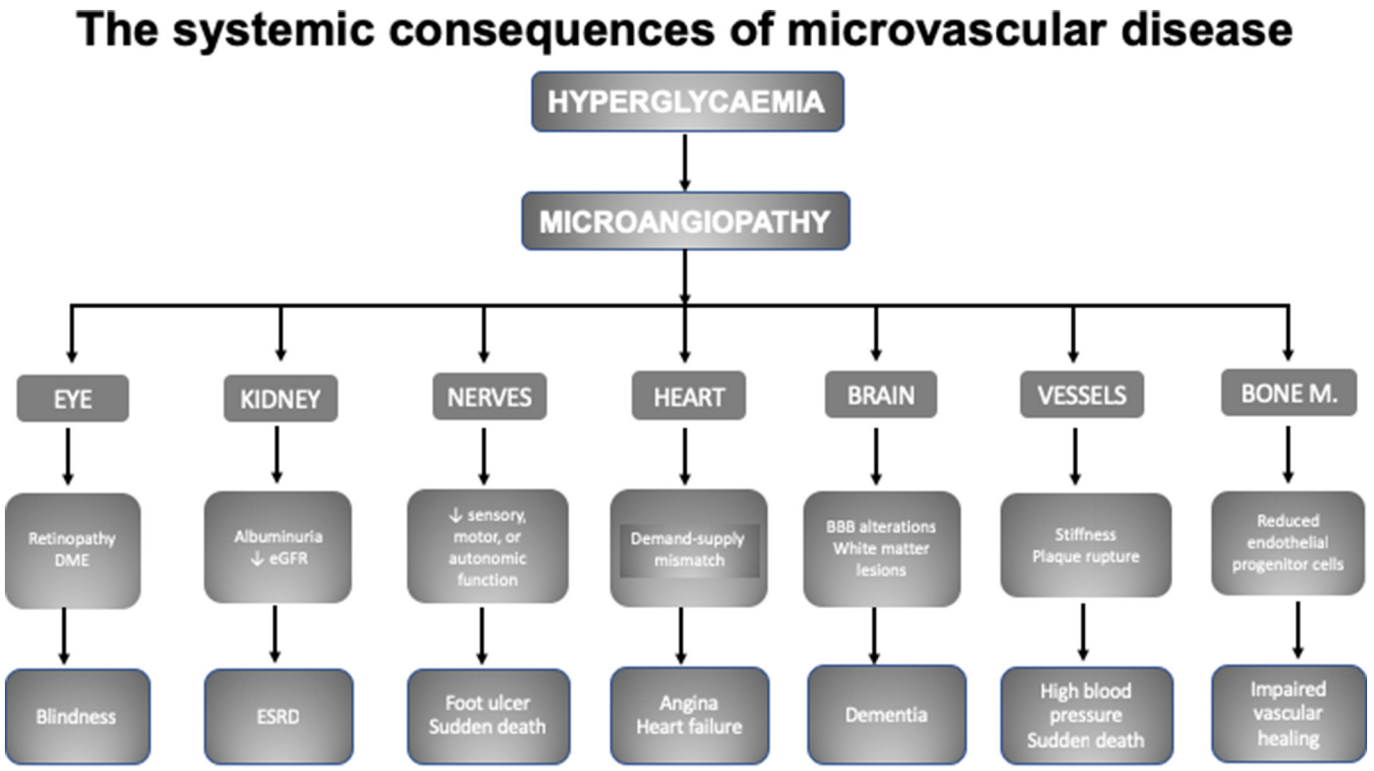

Fig. 1. The widespread consequence of microvascular disease. DME: Diabetic Macular Edema; eGFR: estimated glomerular filtration rate; BBB: blood brain barrier; ESRD: end-stage renal disease.

of microangiopathy: for more in depth knowledge on this issue we refer the readers to dedicated reviews [12,13].

We believe that MICRO should be considered as a continuum of cardiovascular disease (CVD) in patients with diabetes, and their clinical and prognostic impact on CVD thoroughly appreciated also by cardiologists. This concept is underscored by the findings that having MICRO increases by 18% the risk of a composite endpoint of cardiovascular death or heart failure hospitalization [14], and that having one or three MICRO increase the risk from 32% as compared to none to 99%, respectively [15].

2. Pathophysiology of microangiopathy: old and novel insights

In the recent years, several mechanisms have been identified to explain the pathogenesis of MICRO in patients with diabetes (Supplement Fig. 1). Unfortunately, in this article only selected mechanisms have been taken into account, since a comprehensive review of the pathways promoting the development of diabetic complications is beyond the scope of the manuscript. Among these the so called "metabolic hypothesis", clarified by Brownlee and coworkers, who showed that high glucose concentrations lead to a maladaptive production of reactive oxygen species (ROS) within endothelial cells [16]. The metabolic theory foresees an increased aldose reductase substrate conversion, Increased intracellular formation of the advanced glycation end-products methylglyoxal, activation of protein kinase C β, δ, and θ, increased protein modification by O-acetylglucoseamine, an increased production of reactive oxygen species (ROS), and decreased concentration of anti-oxidant enzyme such as Decreased Nuclear Erythroid–Related Factor 2 (Nrf2).

Low grade inflammation is a major factor leading to atherosclerosis: this condition, mediated by the nod-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, leads to increased levels of citokines, and, subsequently, to cell death known as pyroptosis [17]: interestingly, this pathway may also represent the common denominator between metabolic alterations and premature ageing [18].

Epigenetic mechanisms, a set of reactions which regulate the activity of DNA without changes in the nucleotide sequence, such as DNA methylation, histone modifications, and the expression of microRNAs can influence gene expression, and contribute to the onset of MICRO. Hyperglycemia increases trimethyl-histone H4 lysine 20 (H4K20me3) at retinal superoxide dismutase (sod)2, while reversal of hyperglycemia failed to prevent these alterations, suggesting that epigenetic changes not only are causative of DR but they may also explain the so called metabolic memory [19,20], a condition in which changes in microcirculation due to hyperglycemia are relatively reversible if an early and adequate control of blood glucose is achieved [21]. The epigenetic regulation of oxidative stress in endothelial cells has been further clarified by Paneni and Cosentino, who showed effects of hyperglycemia through the activation of p66shc, a mitochondrial adaptor protein, that is epigenetically regulated by the promoter CpG hypomethylation: this effect maintains protein kinase (PKC) βII upregulation thus leading to glucose-induced ROS production and detrimental "metabolic memory" [22–24]. Epigenetic modifications were also shown in several genes coding for proteins mediating antioxidant [25,26], and pro-oxidant effects in the retina [27], and kidney [28–33].

The renin-angiotensin system (RAAS) has been implicated in the pathogenesis of MICRO: the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin type-1 receptor blockers (ARB), and their combination may delay both the onset and the progression of CKD and DR [34,35]. The endoplasmic reticulum stress (ERS) induced by misfolded proteins, and intracellular calcium perturbations, may play a role in the pathogenesis of MICRO [36]: unresolved ERS initiates signaling that promotes apoptosis. The break of this process protects from DN, improves permeability in the retina, and ameliorate peripheral DN. Finally, diabetes compromises mechanisms of tissue repair. Our group have found that reduced number of circulating endothelial progenitor cells (EPC) is associated with MICRO [37]. Low $CD34^{+}$ EPC count correlate with the progression of CKD, DR, and PN even after correction for age, HbA1c, and duration of the disease [38]. It was experimentally shown that autonomic neuropathy and loss of the circadian

rhythm leads to impair release of EPCs, to their blunted functionality, and to DR [39]. However, the reduced circulating EPC levels is mostly related to the presence of a so called "diabetic mobilopathy", the incompetence of the bone marrow (BM) of patients with diabetes to efficiently respond to ischemic stimuli [40]. Different causes have been hypothesized to explain this condition, but an important role may be played by resident macrophages in the BM. It has also been described a specific MICRO of the BM [41], which could further explain the low EPC count: since low EPC also strongly associated with major adverse cardiovascular events, this regenerative defect may represent the link between MICRO and MACRO in patients with diabetes [42]. As it can be appreciated, a consistent amount of detrimental mechanisms explain the pathogenesis of MICRO in patients with diabetes. Notably, most of these mechanisms damage not only the endothelial cells in the microcirculation, but also the endothelial layer in the macrocirculation: therefore the glucose-mediated endothelial dysfunction may be indeed represent the link between MICRO and MACRO in patients with diabetes.

3. Retinopathy, macular edema and cardiovascular disease

Retinopathy is a common complication of diabetes: its onset and progression are closely related to plasma glucose. A 1% increase in HbA1c is associated with >30% increase in retinopathy risk, with >20% in its progression, and with almost 15% increase in blindness [43]. Recently, the concept of DR as a MICRO has evolved into the concept of neurovascular unit composed by several cellular phenotypes, including endothelial cells, pericytes, glial cells, microglia and neurons: diabetes impairs all these components [44]. Diabetic macular edema (DME) is another sight-threatening complication of diabetes, and represents an accumulation of fluid within the central portion of the retina, which arises as a consequence of failure of the blood-retinal barrier (BRB). Diffuse edema is caused by extensive capillary leakage, whereas localized edema is caused by focal leakage from grouped microaneurysms [45]. DME is classified as a distinct entity from DR because it can occur in isolation without other signs of microangiopathy in the retina. DME is often associated with hard exudates and causes blurring and distortion of central vision. The Wisconsin Epidemiologic Study of Diabetic Retinopathy found that 20% of patients with type 1 diabetes and 25% of those with type 2 diabetes will develop DME after 10 years of follow-up [46].

The 2019 Standards in Medical Care in Diabetes [47] state that adults with type 1 diabetes should have a comprehensive eye examination within 5 years after the onset of diabetes while patients with type 2 diabetes should have a comprehensive eye examination at the time of the diabetes diagnosis. If there is no evidence of retinopathy, a follow-up examination should be performed every 1–2 years. In the presence of DME and/or severe non-proliferative diabetic retinopathy patients must be immediately referred to an ophthalmologist.

Randomized controlled trials, cohort studies, retrospective studies, and meta-analyses show that the presence of any retinopathy, and particularly proliferative retinopathy and DME confer an increased risk of all-cause mortality, coronary heart disease (CHD) (Fig. 2), hospitalization for heart failure (hHF), stroke, and lower limb amputation both in type 1 and type 2 diabetes (Supplemental Table S1). The pathophysiological link between DR and CHD has been a matter of debate. On the one side, pathologic angiogenesis plays an important role in the development of retinopathy, while defective vascularization is a key factor in CHD. This dichotomous behaviour has been identified as the diabetic paradox [48]. DR may be simply a marker of a widespread continuum of the vascular disease induced by the diabetic state [49], or a representation of the same pathologic processes taking place in the cardiovascular system. Kampschulte and colleagues, using ex vivo micro-CT scans, demonstrated that pathological sprouting pattern, similar to that observed in the retina, can also be observed in vasa vasorum of small animal models of atherosclerosis [50]. Pathologic angiogenesis also associates with inflammation and increased permeability, equivalent to those observed in DME [51]. In general, MICRO is associated with coronary plaque progression with a subsequent compromised structural integrity of microvascular endothelium, which may explain both a broad spectrum of coronary syndromes and HF [52], and the leakage responsible for intraplaque haemorrhage in coronary plaques [53]. Thus, we should emphasize the importance of the retina as a mirror of a more widespread MICRO, and highlight the concept that MICRO is not confined only in the retina but it is frequently present within the cardiovascular system.

3.1. Neuropathy and cardiovascular disease

Diabetic neuropathy may occur in proximal or distal nerve fibers as mononeuritis or may affect the somatic or autonomic nervous system. Distal symmetric polyneuropathy affects up to one third of persons with type 1 or type 2 diabetes [54]. Decreased sensation confers a predisposition to painless foot ulcers and subsequent amputations. The lifetime risk of a foot lesion, including an ulcer or gangrene, is 15 to 25%. A neuropathic foot ulcer per se increases the odd of having CHD by >3-fold [55]. Particularly in patients with long diabetes duration, autonomic neuropathy (AN), when it involves the cardiac function, independently predicts risk of CV death and AMI. The ADA guidelines state that a screening for diabetic neuropathy should be performed at diagnosis in patients with type 2 diabetes, and 5 years after the diagnosis of type 1

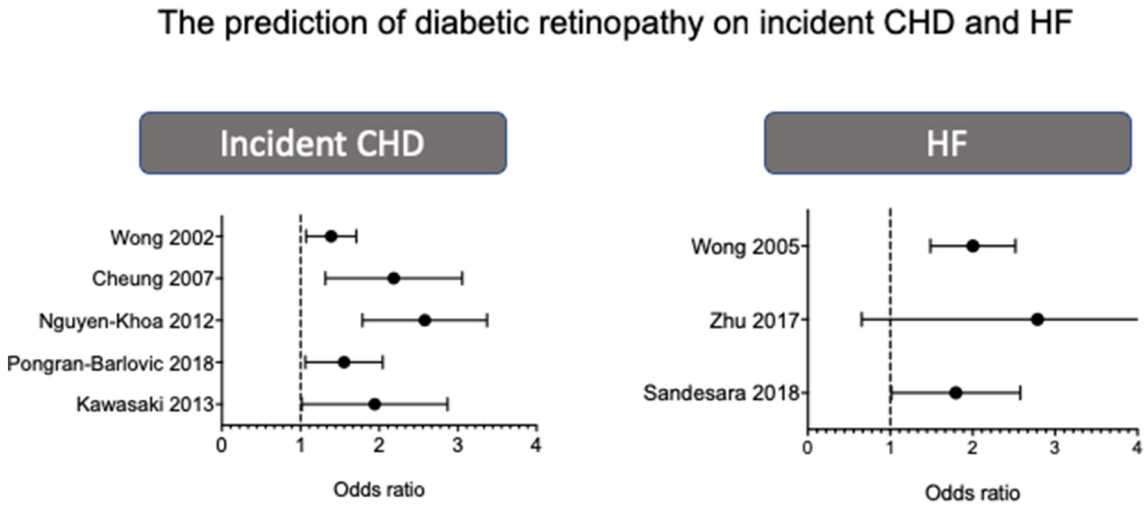

Fig. 2. The prediction of diabetic retinopathy on incident CHD (left panel) and HF (right panel) in cohort studies.

diabetes, and at least annually thereafter [47]. Most importantly, symptoms and signs of autonomic neuropathy (AN) should be assessed in patients with MICRO. As shown in Supplemental Table S2, when considering publications reporting outcomes, alterations of several measures of autonomic functions, such as orthostatic hypotension, heart rare response (HRR) to adenosine, RR interval, heart rate variability were all linked to substantial increased mortality, AMI, and HF.

The presence of AN disrupts the so called sympatho-vagal balance, and predisposes to arrhythmias and sudden cardiac death [56]. To understand the mechanisms responsible for this condition, we assessed the mechanisms of exercise-induced left ventricular (LV) dysfunction in asymptomatic patients with type 1 diabetes in the absence of hypertensive or coronary artery disease [57]. Myocardial iodine-123 metaiodobenzylguanidine (MIBG) uptake, a method to assess adrenergic cardiac innervation, was significantly blunted in patients with diabetes, with a strong linear correlation between left ventricular ejection fraction (LVEF) at peak handgrip and myocardial MIBG uptake normalized for LV mass. These findings have been confirmed by others [58]: interestingly, in patients with diabetes and with HF showed lower cardiac sympathetic activity than HF patients not having diabetes or than patients with diabetes and with a similar degree of autonomic dysfunction not having HF [59]. The underlying alteration of β-adrenoceptor (β-AR) signaling in AN is a major factor for cardiac dysfunction in patients with diabetes: this has been confirmed in animal studies showing a reduction of left ventricular β-AR, and a parallel Gs (guanine nucleotide binding protein stimulatory) reduction [60]. The clinical importance of these alterations is magnified in response to insulin-induced hypoglycemia, during which various degrees of heart block are observed, mediated through a maladaptive sympatho-adrenal activation of β1 adrenergic receptors [61]. Overall, it is clinically relevant to rule out or confirm the presence of AN since this condition may aggravate the clinical outlook of patients with diabetes. Unfortunately, beside a good metabolic control, there is no specific treatment for this complication nor robust results from the CVOTs that suggest that the innovative antidiabetic drugs could modify the natural history of neuropathy.

3.2. Diabetic kidney disease and cardiovascular disease

Diabetic kidney disease is a heterogeneous condition, such that in patients with diabetes, various kidney diseases may coexist. The National Kidney Foundation Work Group for Diabetes affirmed that the presence of retinopathy in patients with a urinary albumin/creatinine ratio (UACR) >300 mg/g strongly suggests a classic DN, while a reduced estimated glomerular filtration rate (eGFR) and albuminuria 30–300 mg/g creatinine may suggest nondiabetic CKD [62,63]. The concerted and negative actions of both hyperglycemia and inflammation alter the fenestrated glomerular endothelium, leading to the loss of glomerular permeability and selectivity, followed by glomerular cell apoptosis and a concomitant triggering of abnormal angiogenesis [64]. Maladaptive expression of angiogenetic factors, mainly vascular endothelial growth factor (VEGF), causes further albuminuria. In classic DN, mesangial expansion, glomerular basement membrane thickening, and podocyte loss are observed: the latter being the best predictor of albuminuria and progression [65]. A crowd of RCT, observational, and retrospective studies [66,67] have definitively confirmed that both DN and CKD substantially increased the risk for CVD (Table S3). An additional validation of both the existence of a cardio-renal syndrome, and the importance of the kidney protection as a major drive of CV protection comes from the 12 available CVOTs: in these trials it appears that a positive primary outcome may be associated to a positive renal outcome (Fig. 3).

A reduced eGFR as an indicator of reduced function increased the odd ratio for CV risk from 1.5 for a eGFR of 60–89 to an odd ratio of 10–50 for eGFR <15 [68].

There are several explanations linking CKD to adverse cardiovascular outcomes, including dyslipidemia, anemia, calcium/phosphate abnormalities, chronic inflammation, sodium overload, and uremic toxins [69]. Nonetheless, the precise link between albuminuria and CVD has not been entirely clarified: therefore, it is unclear whether protein loss in the urine is causative of vascular damage or simply a marker of it. Some hypothesis have been proposed such as: 1. endothelial dysfunction as common ground between CKD and CVD [70]; 2. reduced levels of heparan sulfate, which exerts anti-thrombogenic effects and decreases vessel permeability in the glycocalyx [71]; 3. Low grade inflammation being the common soil of CKD and CVD [72]. Whatever the mechanism(s), two important facts remain: first albuminuria is a powerful risk factor for MACE not only in patients with diabetes but also in non-diabetic individuals: a ACR > 30 mg/g confers a 41% higher risk of hHF, and a ACR >300 mg/g an 88% higher risk [73]. Second, the relationship between albuminuria and CV disease extends below traditional lower-limit thresholds of albuminuria: in the Framingham Offspring Study without prevalent CV, hypertension, diabetes, or kidney disease, an albuminuria as low as 5.3 mg/g in men and 10.8 mg/g in women discriminated between incident CHD, HF, peripheral vascular disease, or death [74]. For these reasons, the 2019 ADA recommendations state that, at least once a year, urinary albumin and eGFR in both patients with type 1 and type 2 diabetes.

3.3. The case for treating microvascular complications

Both the 2019 Medical Care Guidelines and the 2018 Consensus Report by the ADA and the EASD [47,75] endorse specific therapeutic approaches that should be followed not only by diabetologists but also by cardiologists, in patients with diabetes especially if they share patients either with CVD or HF and MICRO. These approaches derived both from the old efficacy trials (treat to target) and by the recent CVOTs (treat to benefit). Needless to say that glucose control must be optimized to reduce the risk or slow the progression of MICRO. However, it is important not only to reduce glucose but how this is reduced: for patients with type 2 diabetes and CKD, we should consider the use of a sodium-glucose cotransporter 2 (SGLT2) inhibitor or glucagon-like peptide-1 receptor agonist (GLP-1RA) that have been shown to significantly reduce the risk of CKD and CVD or both [76]. These drugs should be prescribed according to renal function, and specific contraindications. However, it should be bear in mind that the use of GLP-1RA yielded conflicting results in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), where the drug increased the risk for retinopathy by 76% [77]. Yet, this relationship has not been replicated [78]. Further studies will be necessary in order to precisely identify the role of both SGLT2 inhibitors and GLP-1RA on all the components of the retinal neurovascular unit. The control of blood pressure with RAAS inhibitor

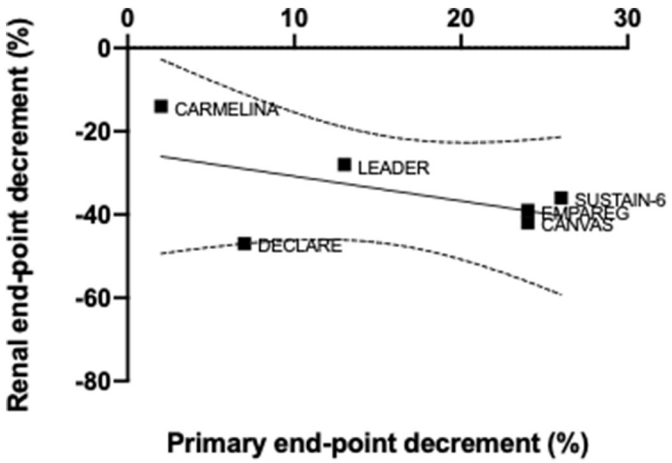

Fig. 3. Correlation between the percentage decrement in the risk of primary end-point and the percentage decrement in renal end-point.

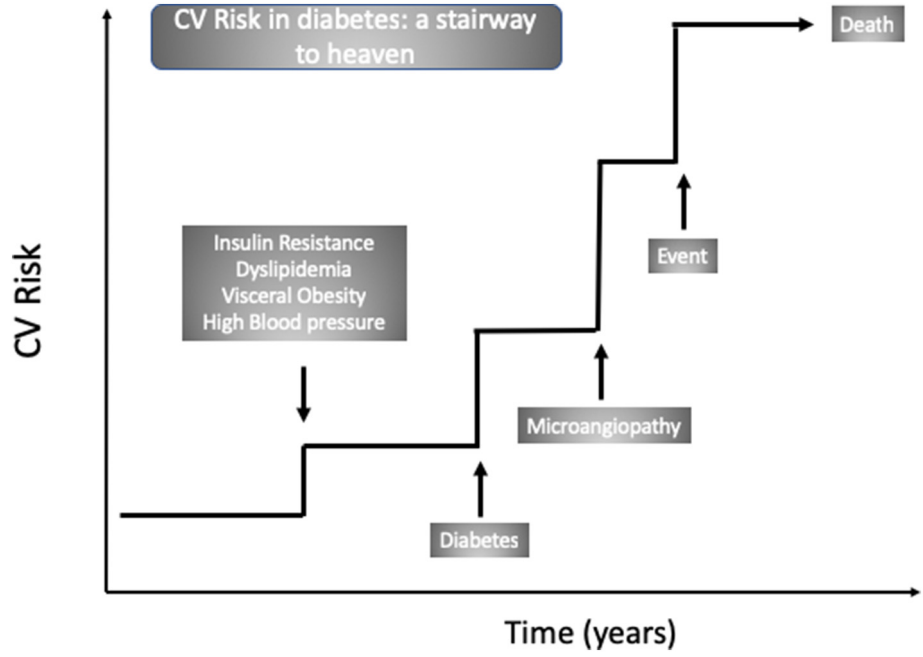

Fig. 4. The additive effect of traditional risk factor for CV disease, diabetes, microvascular complication, and events in the natural history of vascular disease in patients with diabetes.

and of blood lipids is equally important also for DR and DN. In the presence of ongoing CVD, the coexistence of retinopathy is not a contraindication for the use of aspirin therapy. There have been some concerns on the use of GLP-1RA in the presence of HF and DR, as well as the use of dipeptidyl peptidase (DPP-4) inhibitors in the presence of HF. Indeed the use of saxagliptin [79] and liraglutide [80] as antidiabetic drugs should not be supported in patients with advanced HF, as semaglutide in the presence of severe diabetic retinopathy [77], although the relationship between GLP-1RA and retinopathy has been thoroughly questioned [81].

4. Conclusions

Glucose control in patients with diabetes is not less important than lipid and blood pressure control because hyperglycemia is the single most important risk factor for MICRO: once MICRO boosts the risk of CVD and HF, not only in patients with diabetes, but also in the general population, and much more if several MICRO of them co-exist (Fig. 4). For these reasons, MICRO should represent a concern for cardiologists who should search and treat these conditions as it is exactly equally important for the diabetologist to search and recognize the importance of macrovascular complications.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.02.030.

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Conflicts of interests

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Authors' contribution

Data collection and analysis: AA and GPF. Manuscript writing: AA and GPF. All authors approved the final version of the manuscript.

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