DIABETIC RETINOPATHY: A TOOL FOR CARDIOVASCULAR RISK STRATIFICATION

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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. The pathophysiology of diabetic microvascular complications is determined by several factors including epigenetic modifications, and reduced release of circulating progenitor cells by the bone marrow. Identifying microvascular complications, in particular retinopathy, increases the ability to stratify patients in terms of cardiovascular risk. 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.

KEYWORDS: diabetes mellitus; diabetic retinopathy; coronary heart disease; heart failure

ДИАБЕТИЧЕСКАЯ РЕТИНОПАТИЯ: СРЕДСТВО ДЛЯ СТРАТИФИКАЦИИ СЕРДЕЧНО-СОСУДИСТОГО РИСКА

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Рандомизированные одномоментные и проспективные исследования показали, что микрососудистые осложнения у пациентов с сахарным диабетом не только вызывают слепоту, почечную недостаточность и нетравматические ампутации, но также служат мощным прогностическим фактором развития сердечно-сосудистых осложнений. Патофизиология микрососудистых осложнений сахарного диабета обусловлена несколькими факторами, включающими эпигенетические изменения и сниженный выход клеток-предшественниц из костного мозга в периферическую кровь. Выявление микрососудистых осложнений, особенно ретинопатии, повышает возможность стратифицировать пациентов относительно сердечно-сосудистого риска. Рассматривать микроангиопатию и макроангиопатию необходимо, скорее, не как отдельные нозологические формы, а как части непрерывного спектра генерализованного сосудистого поражения, обусловленного сахарным диабетом.

КЛЮЧЕВЫЕ СЛОВА: сахарный диабет; диабетическая ретинопатия; ишемическая болезнь сердца; сердечная недостаточность

Microvascular complications are highly prevalent in patients with diabetes: 22% have microalbuminuric, almost 5% have macroalbuminuria, and 17% have an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m2 (1); furthermore, 35% have any diabetic retinopathy (DR), 7% Proliferative retinopathy (PR), and 7% Diabetic Macular Edema (DME) (2); up to 50% have peripheral neuropathy (PN) (3). While macrovascular disease is determined by the combined effects of traditional risk factors such as high blood pressure, dyslipidemia, viscersal obesity, microvascular complications are mostly determined by hyperglycemia, although a significant roles by high blood pressure and hyperlipidemia (4) cannot be excluded. There is an ample variation in the individual propensity to develop microangiopathy: while some patients with poor metabolic control never develop either chronic kidney diasese (CKD) or DR, others present serious complications despite an optimal metabolic control. This discrepancy may be determined by the genetic background: heritability has been estimated to be almost 30% for DR and 52% for proliferative DR (5). Also CKD can be determined at least in part by genetic traits: the 25-year cumulative inci-

dence 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) (6). There is strong reason to believe that microangiopathy and macroangiopathy should be considered as a continuum of cardiovascular disease (CVD) in patients with diabetes, and their clinical and prognostic impact on cardiovascular disease (CVD) should be thoroughly appreciated in order to improve risk stratification.

EPIDEMIOLOGICAL EVIDENCES

The presence of microangiopathy (ocular, renal, or both) is a strong independent predictor for coronary heart disease (CHD) in both women and men with type 2 diabetes (7). In observational prospective studies the presence of DR appears to confer an additional risk beyond that determined by the CKD. In 2 independent cohorts of patients with type 1 diabetes, the absence of PR in those with stage 3b CKD is associated with a lower prevalence of CVD in patients with long duration of type 1 diabetes(8). In another

study, Yu-Hsuan Li and colleagues found that DR is an independent predictor for all-cause and CV mortality in hospitalized patients with type 2 diabetic with normoalbuminuria. Additionaly, the combined presence of DR with CKD shows the highest risks of all-cause and CV mortality (9). We have recently reviewed the predictive risk of DR on incident coronary heart disease, and found that that the presence of any retinopathy, and particularly proliferative retinopathy and DME confer an increased risk of all-cause mortality, CHD, hospitalization for heart failure (hHF), stroke, and lower limb amputation both in type 1 and type 2 diabetes(10). In an ample meta-analysis, Xie and colleagues have shown that, after a mean follow-up of 5.9 years, patients with DME or PDR were more likely to have incident CVD (IRR, 1.39; 95% CI, 1.16-1.67) and fatal CVD (IRR, 2.33; 95% CI, 1.49-3.67) compared with those without DME or PDR(11). The burden of microvascular disease is also a determinant of future CV risk: in patients with one, two, or three microvascular disease states versus none, the multivariable-adjusted HRs for the primary outcome were 1.32 (95% CI 1.16-1.50), 1.62 (1.42-1.85), and 1.99 (1.70-2.34), respectively (12). Microvascular complications may also determine the prognosis of patients affected with heart failure with preserved ejection fraction (HFpEF): microvascular complications were associated with more LV hypertrophy and a greater reduction in quality of life in HFpEF than HFrEF(13). Compared with participants with diabetes and without microvascular complications, the adjusted hazard ratio for the composite outcome of all-cause death or HF hospitalization was 1.35 (95% CI 1.04-1.76) for participants with diabetes and microvascular complications regardless of HF type.

The severity of DR can also identifies the severity of carotid vascular disease. We and others have found that patients with proliferative DR show significantly higher burden of carotid artery plaque compare to those with mild DR (14, 15).

These observations prompt the European Society of Cardiology and the European Association for the Study of Diabetes to include the assessment of microangiopathy in patients with prevalent cardiovascular disease (16). More recently, the American College of Cardiology included the presence of retinopathy among the risk enhancers in patients treated in primary prevention (17).

FUNCTIONAL VS. ANATOMICAL MICROANGIOPATHY: DO OUTCOMES DIFFER?

DR is considered a consequence of a structural disruption of the neurovascular unit (NVU), due to a long-term exposure to hyperglycemia. However, we should consider the occurrence of microvascular disease not only when anatomical alterations take place, but also in the presence of vascular dysfunction, i.e. the inability of the small vessels either to dilate or constrict physiologically in response to the prevailing stimuli. Evidences indicate that the risk of death and CV events sharply increases just in the presence of either anatomical or functional alteration of the microcirculation in the retina. A total of 10470 men and women without prior atherosclerotic CV events or HF in the ARIC Study (Atherosclerosis Risk in Communities) underwent retinal photography: subjects with wider retinal venules and narrower retinal arterioles had a higher risk of death and stroke in both sexes and incident coronary heart disease in women but not men

after adjustment (18). Again, Barthelmes and colleagues, using flicker-induced retinal arterial dilatation in patients with CAD, demonstrated a more pronounced impairment in this parameter in those with IHF, thus suggesting not only a decline of retinal arterial function in CAD patients, more pronounced in the presence of reduced left ventricular ejection fraction, but also a continuum of microvascular damage (19). Evidence exists that similar alterations are present in the coronary tree where the endothelium becomes dysfunctional, inducing microvascular alterations and a blunted coronary blood flow augmentation or vasoconstriction with frank reduction in blood flow (20). This functional alteration in the microcirculation within the heart, similar to that observed within the retina, greatly increase the risk for major adverse cardiovascular events (21). Based on these observations, we then must rethink the relationship between micro- and macrovascular complications. The classic view is that hyperglycemia leads to anatomical microvascular complications, which, in turn, greatly increase the risk determined by macrovascular complications. A new view is that the combined effects of traditional risk factors for CV disease plus hyperglycemia lead to functional microvascular disease, which, in turn, greatly increases the risk determined by macrovascular complications (Figure 1). Thus, the presence of anatomical alterations in the microvascular tree should be considered a later event in the continuum of the diabetic vascular disease (Figure 2).

MICROVASCULAR AND MACROVASCULAR DISEASE: WHICH COMMON LINK?

The pathophysiological link between DR and CHD has been a matter of debate. On 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 (22). DR may be simply a marker of a widespread continuum of the vascular disease induced by the diabetic state (23), or a representation of the same pathologic processes taking place in the cardiovascular system. Indeed, the two conditions share many common pathological processes such as the metabolic consequence of hyperglycemia, a pro-inflammatory state, alterations in epigenomics, and defective reparatory mechanisms (24, 25).

In our view, a potential pathophysiological link between micro-and macrovascular disease can be c onsidered a maladaptive angiogenesis.

Under normal conditions, there is a balance between the levels of angiogenic factors and antiangiogenic factors. In the presence of hypoxia, a proangiogenic imbalance in this process leads to abnormal growth of new blood vessels: this is the hallmark of PR where the maladaptive proliferation of new vessels in response to hypoxia, with the contribution of the Muller cells, interferes with light transmission (26).

During uncontrolled ocular angiogenesis, fragile and leaky vessels are formed: the consequence of this are haemorrhage, neurodegeneration, inflammation, and, eventually, blindness. Neovascularization and inflammation share a number of common mediators and signaling pathways such as the COX prostaglandin pathway, vascular endothelial growth factor (VEGF), and pro-inflammatory cytokines that may directly induce vessel formations (27). Within
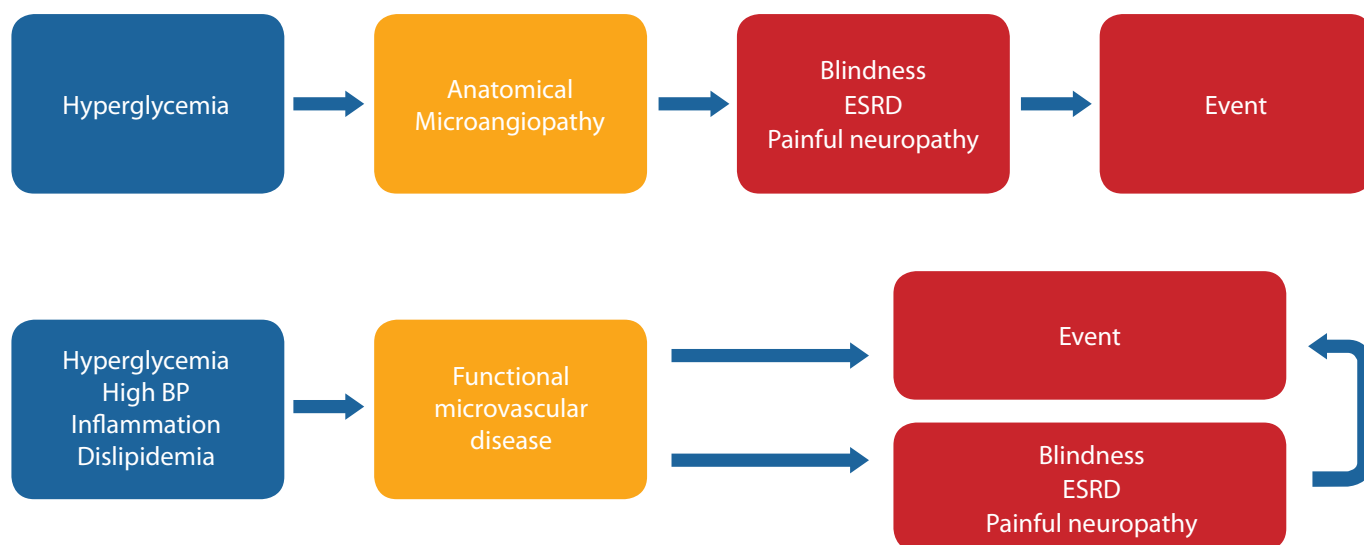
Figure 1. This figure illustrates a new paradigm of the relationship between microcomplications and events. The old paradigm states that chronic exposure to hyperglycemia leads to anatomical alterations of small vessels, and hence to the structural derangement of the target organ damage. The new paradigm (bottom) states that the small vessels exposed to multiple risk factors present functional alterations first that can leads to event before the structural alterations take place.
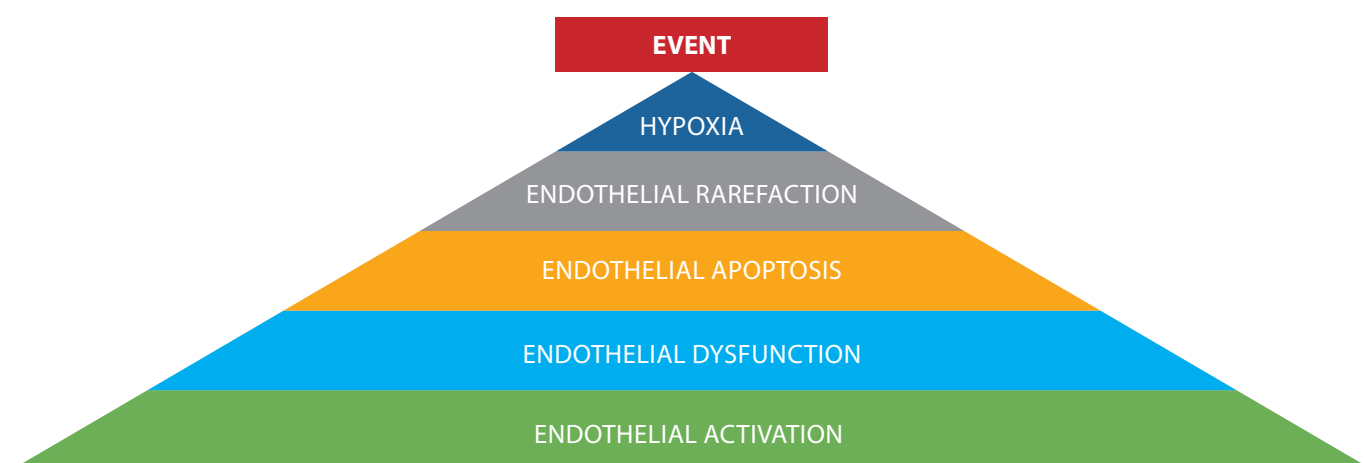

Figure 2. This figure illustrates the series of endothelial alterations that ultimately lead to event.

the atherosclerotic plaque in the vessel wall, as in the diabetic retina, a rarefaction of vessels within arterial wall has been observed (28), which leads to hypoxia. Sluimer et al. showed hypoxia in the center of advanced human carotid atherosclerotic plaques (29). Pimonidazole, a hypoxia marker, was co-localized with CD68 positive macrophages, HIF1-α and VEGF expression, suggesting the involvement of the HIF pathway and immunocompetent cells in the regulation of human plaque angiogenesis and lesion progression(30). Pathologic angiogenesis also associates with inflammation and increased permeability, equivalent to those observed in DME (31). Clinically, microvascular complications are 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 (20), and the leakage responsible for intraplaque haemorrhage in coronary plaques (32). Thus, we should emphasize the importance of the retina as a mirror of a more widespread cardiovascular disease, and

highlight the concept that these complications is not confined in the retina but they can be frequently present within the arterial tree.

DOES MALADAPTIVE REGULATION OF CIRCULATING PROGENITOR CELLS PLAY A ROLE?

Bone marrow releases pluripotent stem cells (HPSCs) in the adult human body: these cells either directly or indirectly participate in de novo post-natal vasculogenesis. A subset of these cells with markers of endothelial lineage, also called endothelial progenitor cells (EPC), have the potential to participate in new vessel formation and in the endothelial regeneration (33). Under basal conditions, EPC incorporate at low levels in the vascular endothelium layer. However, in the presence of tissue ischemia and consequent hypoxia, through the release of growth factors and cytokines, there is a powerful mobilization of EPC from the bone marrow, and their recruitment to sites of injury (33). Diabetes compro-

mises mechanisms of vascular repair: our group have found that reduced number of circulating endothelial progenitor cells (EPC) is associated with both macro-, and microvascular complications (34). Low CD34+ EPC count correlate with the progression of CKD, DR, and PN even after correction for age, HbA₁c, and duration of the disease (35). 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 (36). 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 microvascular disease of the BM (37), which could further explain the low EPC count (38). As it can be appreciated, a consistent amount of detrimental mechanisms explain the pathogenesis of microvascular complications in patients with diabetes. However, in the presence of PDR, we noticed that observed that the clonogenic expansion capacity of cultured EPCs in DR is significantly superior than that observed in patients with peripheral artery disease (39). Another study, in rodents, found that diabetes leads to a dramatic decrease in bone marrow innervation: this effect is associated with an increase in acellular capillaries in retinal vasculature isolated from diabetic animals compared with control (40). Once mobilized in the circulation, EPCs can home to areas of endothelial injury and ischemia, a process, this, regulated by the interaction of soluble or surface CXC-chemokines with their respective receptors on the EPC membrane. Interestingly, it has been reported that, within plaque, EPCs increases plaque size and decreases plaque stability in Apoe knock-out mice, an effect that could be partly by their angiogenic, as well proteolytic and proinflammatory properties of EPC (41). Therefore, it can be assumed that in the presence of both diabetes and hypoxia, despite reduced circulating levels, EPC within the retina and plaque may acquire a clonogenic potential leading to both PD and plaque instability. This set of data strengthen the hypothesis that tissue hypoxia and subsequent maladaptive revascularization taking place simultaneously in the retina and atherosclerotic plaque may represent the common denominator linking PR to CV events.

THE CASE FOR TREATING MICROVASCULAR COMPLICATIONS

Both the 2019 Medical Care Guidelines and the 2018 Consensus Report by the ADA and the EASD (42, 43) 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 glu-

cagon-like peptide-1 receptor agonist (GLP-1RA) that have been shown to significantly reduce the risk of CKD and CVD or both (44). 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% (45). Yet, this relationship has not been replicated (46). 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. In the presence of reduced glomerular filtration rate dipeptydil peptidase 4 inhibitors (DPP4i) may represent an alternative option to control plasma glucose expecially in the elderly population. The control of blood pressure with RAAS inhibitor 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 (47) and liraglutide (48) as antidiabetic drugs should not be supported in patients with advanced HF, as semaglutide in the presence of severe diabetic retinopathy (45), although the relationship between GLP-1RA and retinopathy has been thoroughly questioned (49).

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 micrvbascular complications: these boost the risk of CVD and HF, not only in patients with diabetes, but also in the general population, and much more if several microangiopathis of them co-exist (50). For these reasons, microvascular complications should be either confirmed or ruled out in patients with CV problems even if not affected by diabetes. Similar importance the the diabetologist should have for the presence of CVD once the presence of microvascular disease has been confirmed.

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