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The importance of microvascular inflammation in ageing and age-related diseases: a position paper from the ESH working group on small arteries, section of microvascular inflammation

1   **The importance of microvascular inflammation in ageing and age-related diseases: a**

2   **position paper from the ESH working group on small arteries, section of microvascular**

3   **inflammation.**

4   Short title: microvascular inflammation in age-related diseases

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48   The present work has not been presented previously elsewhere.

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77

78   **Abstract**

79   Microcirculation is pervasive and orchestrates a profound regulatory cross-talk with the

80   surrounding tissue and organs. Similarly, it is one of the earliest biological systems targeted by

81   environmental stressors and consequently involved in the development and progression of ageing and

82   age-related disease. Microvascular dysfunction, if not targeted, leads to a steady derangement of the

83   phenotype, which cumulates comorbidities and eventually results in a non-rescuable, very high-

84   cardiovascular risk. Along the broad spectrum of pathologies, both shared and distinct molecular

85   pathways and pathophysiological alteration are involved in the disruption of microvascular

86   homeostasis, all pointing to microvascular inflammation as the putative primary culprit. This position

87   paper explores the presence and the detrimental contribution of microvascular inflammation across the

88   whole spectrum of chronic age-related diseases, which characterise the 21st-century healthcare

89   landscape. The manuscript aims to strongly affirm the centrality of microvascular inflammation by

90   recapitulating the current evidence and providing a clear synoptic view of the whole cardiometabolic

91   derangement. Indeed, there is an urgent need for further mechanistic exploration to identify clear, very

92   early or disease-specific molecular targets to provide an effective therapeutic strategy against the

93   otherwise unstoppable rising prevalence of age-related diseases.

94

95

96 **1. Introduction: microcirculation in cardiovascular disease**

97   Microcirculation is the network of terminal vessels of the systemic circulation comprising

98 arterioles, capillaries and venules less than 100 μm in diameter [1-3]. This network delivers oxygen and

99 other nutrients to tissues while removing carbon dioxide, cellular waste products and toxins [1].

100 Importantly, microcirculation also regulates fluid homeostasis, temperature control and inflammatory

101 response [1].

102   Contemporary evidence suggests that microcirculatory impairment may occur in adulthood and

103 further deteriorate across the lifespan. Ageing progressively decreases blood flow and vessel density,

104 ultimately reducing arterial compliance [1]. Beyond ageing, microcirculatory dysfunction (MD)

105 characterises a multitude of conditions, including diabetes mellitus (DM), hypercholesterolemia,

106 hypertension, peripheral arterial disease, chronic renal failure, menopause, obesity and chronic

107 inflammatory autoimmune disorders [4-8]. Multiple mechanisms may contribute to microcirculatory

108 impairment, including oxidative stress, enhanced leukocyte adhesion, activation of immune cells (both

109 innate and adaptive[9]), endothelial dysfunction, vasoconstriction, attenuated angiogenesis, increased

110 endothelial permeability, microcirculatory plugging and remodeling, lymphatic dysfunction as well as

111 impaired autoregulation [5,10-16].

112   MD may develop in multiple tissue beds as an underlying systemic process preceding clinical

113 symptoms long before their onset [17,18]. In this context, MD may reflect an early marker of vascular

114 disease and predispose to the development of atherosclerosis [5]. Accordingly, several minimally or

115 noninvasive techniques have been developed to provide useful MD biomarkers in different vascular

116 beds (summarized in **Table 1)** [19]. However, although circulating biomarkers, including increased

117 triglycerides, C-reactive protein (CRP), cystatin C, homocysteine, nitric oxide (NO), uric acid,

118 interleukin (IL)-6, N-terminal pro-b-type natriuretic peptide, cardiac troponin, thrombomodulin,

119 renalase, neuregulin-1, von Willebrand Factor, serotonin and asymmetric dimethylarginine, are

120 increased in patients with MD, their clinical use for this purpose is not yet validated [18,20-22].

121   MD is causally associated with the entire spectrum of ageing and age-related diseases, mainly

122   through pro-inflammatory mechanisms (**Figure 1**) [23] and may be the substrate for the further

123   development of numerous cardiovascular (CV) diseases, such as coronary artery disease and heart

124   failure with preserved ejection fraction (HFpEF). MD is also found in extra-cardiac tissues (*i.e.*, brain,

125   retina, and lungs) and clinically manifests as dementia, depression, anxiety, vision loss or pulmonary

126   hypertension [14]. In the same context, MD has been implicated in rheumatic (e.g., skin MD) and

127   oncologic diseases [24-32]. With respect to its prognostic value, MD is associated with an increased

128   risk of short- and long-term adverse CV outcomes [33,34]. Both peripheral and coronary MD has been

129   associated with adverse CV events and mortality [35-44]. Furthermore, MD has been linked with

130   progression to kidney failure [18]. Notably, cerebral small vessel disease features are strongly

131   associated with stroke, dementia- especially Alzheimer's disease (AD) and vascular dementias,

132   depression and all-cause mortality [45]. Uterine and placental MD predispose to the onset of

133   preeclampsia [46,47] and to early post-natal microvascular rarefaction and development of MD in

134   offspring [48,49]. Finally, testicular MD and penile skin MD are linked to endocrine disturbances and

135   the future development of hypertension and CV diseases [50,51]. Colletively, an integrative approach

136   to understanding MD is needed to implement effective early diagnosis and treatment strategies.

137

138   **2.   The link between inflammation and early microvascular ageing**

139   The microvasculature is pervasive, and its impairment influences every tissue in the human body

140   [52]. Consequently, vascular age is a reliable marker of biological age [53]. Microvascular ageing

141   reflects a point at which MD becomes persistent and further deteriorates over time. The onset of MD

142   marks a crucial point in the natural history of ageing.

143   We need to address lifestyle and environmental stressors to look at the earliest perpetrators of

144   microvascular damage. In addition to the genetic predisposition, each individual is constantly exposed

145   to various noxious *stimuli* that can induce MD. A sedentary lifestyle can increase vascular nicotinamide

146   adenine dinucleotide phosphate (NADPH)-derived reactive oxygen species (ROS) production that

147 affect the endothelial function [54]; similarly, exaggerated exercise training induces mitochondrial

148 dysfunction leading to MD [55]. Unhealthy dietary and eating patterns [56], as well as nutrient overload

149 [57], cause an imbalance in the oxygen supply/demand ratio, activating hypoxia-inducible factor 1α

150 (HIF-1α) and promoting impaired angiogenesis [58]. Additional environment determinants, including

151 environment pollutants, temperature, seasonal changes, circadian rhythm and infections have

152 demonstrated significant role in regulating microvascular inflammation and CV diseases [59-68]

153 The final effector through which all these stressors promote microvascular ageing [69-71] is the

154 immune-inflammatory response [60]. Ultimately, they create a low-grade pro-oxidant pro-

155 inflammatory environment [72] that leads to MD [73,74]. Inflammation disrupts microvascular function

156 by increasing ROS generation, reducing NO bioavailability, and leading to vascular wall

157 hyperpermeability and glycocalyx remodeling [75]. In the long term, this promotes the hyperactivation

158 of compensatory pathways such as endothelial and vascular smooth muscle cells (VSMCs)

159 proliferation, pathological angiogenesis [76-78]and, ultimately, permanent vessel wall remodeling. The

160 lymphatic vasculature also plays a role in this detrimental interplay. While it generally regulates dietary

161 lipid absorption and cholesterol efflux [79], it becomes dysfunctional when exposed to stressors, further

162 compromising local homeostasis. Lymphatic dysfunction results in reduced immune cell clearance,

163 increased insulin resistance [80] and reduced lymphangiogenic potential [79]. These maladaptive

164 changes, which are common in ageing and age-related diseases, ultimately prolong the inflammatory

165 response and microvascular remodelling [81]. The consequence of all these processes is that if the MD

166 is not rapidly targeted and reversed, its alterations become permanent, characterised by epigenetic cues

167 that are not easily targeted by current therapies [82] and predispose to more significant harm when a

168 subsequent exposition to risk factors [83] occurs, even several years ahead. This marks the point when

169 vascular age diverges from chronological age, and ageing diverges from his physiological trajectory.

170 An aged vasculature is characterised by a low-grade inflammatory state which originates directly

171 from the vessel and the surrounding environment (*i.e.* perivascular adipose tissue (PVAT) [84], neural

172 terminations [85], abnormal shear stress [86]), even after the removal of the *stimuli*. In this condition,

173 the vessel is not only the target of the damage exerted by the CV risk factors [87] but also becomes the

174   perpetrator by first-hand promoting the low-grade inflammatory response which characterizes chronic

175   time-dependent disease [72]. This, in turn, further dampen microvascular homeostatic control

176   mechanisms and aggravate MD [71]. This vicious cycle is characterised by a profound cross-talk

177   between non-immune and immune cells, which is often present in the context of CV disease, for

178   instance, in macrovascular atherosclerotic remodeling [88] and cardiac fibrosis [89]. However, a clear

179   understanding of this dialogue between distinct cell types is still an unmet need, especially in MD

180   setting.

181   This model accurately reflects cardiometabolic disease. First, environmental stressors significantly

182   influence the natural history of obesity, type 2 diabetes, arterial hypertension, and HFpEF [60]. Second,

183   they all present an early MD [38,90-92] and are characterised by accelerated microvascular ageing [58].

184   Third, these conditions are tightly connected [52]. Fourth, all of them are characterised by a persistent

185   systemic low-grade inflammation which further deteriorates the cardiometabolic homeostasis and that

186   it has in the microvascular bed one of its primary perpetrators [72,84,93].

187   Inflammageing [72,94] and immunometabolism [95] are thus fundamental integrated approaches

188   to explore the connections and the cross-talks between environment, metabolic disease, vascular health,

189   and CV risk. Although this conceptual framework is generally related to cardiometabolic disease, it

190   might be easily translated to other chronic and time-dependent conditions such as neurodegenerative

191   pathologies, autoimmune diseases, and cancer. As indirect evidence, epigenetic pan-deactivators of

192   vascular inflammation as the inhibitors of bromodomain and extraterminal domain (BET) proteins [96]

193   have recently been proposed for all these disease settings [97-103]. Similarly, anti-inflammatory drugs

194   are attracting substantial attention in the context of CV diseases [104]. But the link between

195   inflammation and microvascular ageing is multidirectional. As environmental stressors link

196   inflammation with microvascular ageing, inflammation also becomes the link between aged vasculature

197   and systemic metabolic diseases, which further promotes microvascular inflammation. The onset of this

198   vicious cycle is at the base of age-related diseases. It is clear that only by an accurate understanding of

199   the pathophysiologic and molecular mechanisms underpinning this connection we will be able to

200 develop therapeutic strategies to challenge the steadily increasing prevalence of chronic diseases

201 [105,106] (**Figure 2**).

202

203 *Statement: Environmental stressors predispose to unhealthy ageing and age-related disease by*

204 *promoting MD. If MD is not prevented or rapidly treated, the microvascular environment in turn*

205 *becomes the perpetrator of microvascular inflammation through detrimental cross-talk between non-*

206 *immune and immune elements, leading to the low-grade inflammatory response that characterises*

207 *unhealthy ageing and age-related disease.*

208

209 **3. Microvascular inflammation across the age-related diseases continuum**

210 *3.1. Physiological ageing*

211 Physiological ageing is a natural phenomenon driven by a variety of complex, and yet loosely

212 understood mechanisms that strongly interact with each other. In addition to these, initial emergence of

213 genomic instability, which includes dysregulated DNA damage repair pathways and telomere

214 shortening, other key mechanisms are involved. These include the stimulation of senescence and

215 impairment of autophagy at a cellular level and the consequential development of oxidative stress and

216 microvascular inflammation at the tissue level. Ultimately, these mechanisms contribute to the ageing-

217 related phenotype characterized by endothelial, vascular and consecutively tissue dysfunction (**Figure**

218 **3A**) [107,108]. Notably, these mechanisms are often bidirectional, ultimately establishing a vicious

219 cycle.

220 3.1.1. Senescence

221 Cellular senescence is a stress-induced, durable, cell cycle arrest of previously replication-

222 competent cells and is considered a central hallmark of ageing [109]. Senescence contributes to ageing

223 process through multiple mechanisms, among which the propagation of inflammation prevails.

224 Pertinent to this, it has been shown that senescent cells secrete a plethora of potent pro-inflammatory

225 factors termed the senescent-associated secretory phenotype (SASP), which drive an intense

226 inflammatory response [110,111]. SASP also contributes to the spread of inflammation and oxidative

227 stress from senescent to healthy non-senescent cells via paracrine fashion, which leads to a pro-

228 inflammatory and pro-oxidant phenotype at a microvascular level [107]. Consistent with its

229 inflammatory potential, several in vitro and preclinical data have documented the role of senescence in

230 promoting oxidative stress and endothelial dysfunction [112,113]. In healthy ageing humans, markers

231 of endothelial senescence have been correlated with significantly impaired endothelial function [114].

232   3.1.2.   Autophagy

233 Autophagy is a highly selective clearance pathway that degrades several defective cellular

234 components through lysosomal activation. Therefore it is tightly associated with the maintenance of

235 cellular and tissue homeostasis and, in the long term, longevity [115]. Altered autophagy has been

236 proposed as a prominent feature of physiological ageing, with increasing evidence suggesting an

237 impaired autophagic activity across ageing in different organisms [116]. In humans, it has been

238 demonstrated that the expression of autophagy-related genes (i.e. ATG5, BECN1) and the proteolytic

239 function of lysosomes decline with age [117]. Consequently, compromised autophagy leads to cellular

240 and vascular dysfunction and enhanced inflammation, as evidenced by the promotion of oxidative-

241 induced senescence, the production of endothelial reactive oxygen species (ROS) and the development

242 of endothelial dysfunction in both aged mice and human subjects [117-119]. In addition, autophagy has

243 been recognized as a significant inhibitor of inflammasome which is a potent mediator of microvascular

244 inflammation [120].

245   3.1.3.   Oxidative stress

246 Oxidative stress is a consequence of the imbalance between the production and detoxification of

247 reactive oxygen and nitrogen species (RONS) [121]. Ageing process is associated with reduced activity

248 of the antioxidant transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) [122]. Hence,

249 accumulation of oxidative damage by RONS produced by NADPH oxidases and mitochondria is

250 considered one of the core pathophysiologic pathways driving physiological ageing and age-associated

251 diseases [123]. Particularly in the context of ageing and age-related diseases, mitochondrial dysfunction

252 and mitochondria-derived ROS are key drivers of the inflammatory response leading to pathogenetic

253 processes [124,125]. The oxidative environment further stresses mitochondrial pathways, leading to the

254 detrimental escape of mitochondrial DNA from organelles and cells [126,127]. Mitochondrial-free

255 mitochondrial DNA and the pro-oxidant environment, in turn, transduce a pro-inflammatory signal

256 within and between cells, leading to the activation of multiple signaling pathways: NOD-like receptor

257 family pyrin domain containing 3 (NLRP3) inflammasome activation, DNA-sensing enzyme cyclic

258 GMP-AMP synthase stimulator of interferon genes (cGAS-STING) and toll-like receptor (TLR). It also

259 leads to induction of senescence and SASP production with consequent nuclear factor kappa-B (NF-

260 κB) activation, as well as hyperactivation of the pro-oxidant mediator p66Shc [82,125], consumption

261 of NAD+ and consequent mammalian silent information regulator 1 (Sirt1) dysregulation [52,128].

262 Furthermore, oxidative stress exerts a detrimental effect on endothelial function by quenching the

263 bioavailable, endothelium-derived NO and reducing both NO availability and endothelial NO synthase

264 (eNOS) expression. Therefore, oxidative stress is strongly linked to the development of endothelial and

265 microvascular dysfunction with ageing in humans [129,130].

266   3.1.4.   <u>Inflammation</u>

267   The inflammageing state, a sterile, subclinical, low-grade inflammation increasing with age and

268 promoting the development of age-associated diseases, has been well recognized in the elderly [72].

269 Indeed, in older adults are frequently reported persistently elevated circulating levels of SASP factors,

270 including IL-1β, IL-6 and tumour necrosis factor (TNF)-α [131-133]. In elderly, inflammageing is

271 largely considered an aftermath of immunosenescence, a significant immune system dysregulation

272 observed with ageing, which substantially propagates the inflammatory milieu and consists in overall

273 aberrant activation of innate and adaptive immune response [134]. In this context, microvascular

274 inflammation can be exacerbated by an age-associated inappropriate activation of TLRs and the NLRP3

275 inflammasome complex, both representing crucial activators of the innate immune inflammatory

276 response which leads to increased expression of NF-κB and the production of several proinflammatory

277 mediators [135-137]. Activation of the ROS-sensitive, proinflammatory effector NF-κB holds a central

278 role in the ageing-associated inflammatory response. Endothelial cells (ECs) from older humans

279 actively express NF-kB, which is directly implicated in endothelial dysfunction [132,138] as well as in

280 exacerbating inflammageing and oxidative stress, thus corroborating an intricate relationship between

281 senescence, oxidative stress and inflammation across ageing and extending the vicious cycle [139-141].

282 Finally, mammalian sirtuins represent another significant ageing-associated mechanism implicated in

283 microvascular inflammation. They are a family of nicotinamide adenine dinucleotide-dependent

284 deacetylases involved in several processes that regulate metabolic homeostasis and modulate the

285 benefits of calorie restriction and exercise. They control mitochondrial function, cell survival,

286 attenuation of inflammatory responses and circadian rhythm. Because of their contribution to many

287 protective pathways and their central involvement in longevity mechanisms, they have attracted

288 increasing attention as potential therapeutic targets [142]. In particular, Sirt1, a deacetylase implicated

289 in many critical physiological responses to altered energy metabolism and stress, has multiple anti-

290 inflammatory, anti-oxidant and anti-ageing properties [143-145]. Reduced expression of Sirt1 has been

291 observed in ECs and VSMCs obtained from older adults, associated with a senescent phenotype and

292 the development of endothelial dysfunction [125,146,147]. Furthermore, data has shown that

293 persistently reduced levels of Sirt1 lead to upregulation of NF-κB and NLRP3 inflammasome, hence

294 significantly amplifying the inflammatory response [145,148].

295

296 *Statement: In physiological ageing, stimulation of senescence, impairment of autophagy, and*

297 *increased oxidative stress lead to microvascular inflammation at the tissue level. This culminates in the*

298 *ageing-related phenotype characterized by MD and increased susceptibility to the onset of age-related*

299 *diseases.*

300

301 *3.2. Obesity*

302 Obesity, given its high and steadily increasing prevalence [105], probably represents the closest

303 human model to exploring the contribution of environmental stressors to microvascular inflammation

304 and accelerated ageing. Its relevance in the global landscape is sadly acknowledged: obesity ranks first

305   in terms of mortality related to metabolic diseases, with no trend towards reduction [149]. The impact

306   of obesity on MD starts very early: in patients with obesity, the slope of the media-to-lumen (M/L) ratio

307   plotted against age diverges from the healthy controls before the age of 20, being five times steeper

308   (**Figure 3B**) [125,150]. The increased nutrient supply ultimately overburdens the metabolic pathways,

309   promoting hypoxia with consequent HIF-1α activation [151]. The resultant pro-oxidant and pro-

310   inflammatory environment promotes the local low-grade inflammatory response, which eventually

311   turns systemic and characterises the generalized MD observed in obesity [91].

312   Although multiple pathways contribute to its clinical phenotype, obesity is characterised by a

313   prominent role of the PVAT. PVAT is a key member of the microvascular unit [91], with a brown-like

314   and anti-contractile phenotype in the healthy [152], which loses its thermogenic capacity and turns pro-

315   contractile in the condition of diseases such as obesity [153]. The deep cross-talk between PVAT and

316   the small vessels is directly responsible for both the inflammatory damage and response characterising

317   obesity [154]. PVAT phenotype shift leads to increased secretion of several adipokines and cytokines,

318   including chemerin, leptin, IL-6 and TNF-α [155]. While experimental studies in mice have reported

319   how leptin leads to MD by first targeting the hypothalamic microvasculature [156], *ex-vivo* observations

320   in humans have demonstrated how PVAT dysfunction, promoted by macrophage activation [157],

321   results in an increase in PVAT-derived cytokines secretion [84,93]. This fuels the vessel-specific

322   inflammatory response [93], induces endothelial dysfunction and further imbalance the homeostatic

323   response from the vasculature by increasing the expression of endothelin-1 (ET-1) and its receptor A

324   (ET_A). The altered ET_A/NO ratio upregulates c-Jun N-terminal kinase (JNK) signaling, increasing

325   NAPDH-derived and mitochondria-derived ROS [84]. The bidirectional cross-talk further aggravates

326   PVAT dysfunction, as the endothelium also secretes inflammatory cytokines and angiogenetic factors.

327   Indeed, to match the increased nutrient flow, PVAT develops a pro-angiogenetic phenotype trying to

328   compensate with an adequate oxygen supply. However, this neoangiogenetic process [76] ultimately

329   proves detrimental and further promotes an overt dysfunctional phenotype for both the PVAT and the

330   ECs. Recently, an elegant exploration in vivo has shown that, in high-fat diet mice, the ECs-specific

331   deletion of argonaute 1 (AGO1), a pivotal contributor to the ECs response to hypoxia, arrests impaired

332 angiogenesis and reverts the PVAT to a browning phenotype, rescuing the MD and the whole-body

333 metabolic homeostasis [158].

334 Finally, the overload of the metabolic processes leads to mitochondrial dysfunction in obesity,

335 which in turn promotes microvascular inflammatory response by increasing mitochondria-derived ROS

336 levels [125] and activating NLRP3 [159] and cGAS-STING pathways [160]. Evidence supports sirtuins

337 [125] (main elements in nutrient balance/imbalance signaling [161]) as crucial regulators of this

338 process. In ECs, lower levels of Sirt1 induce MD and are associated with an increase of pro-

339 inflammatory and pro-ageing factors p66shc [82] and Arginase II [150], an increase in mitochondria-

340 derived ROS, and a downregulation of several genes involved in the mitochondria electron transport

341 chain.

342 The documented MD confirms this experimental evidence in patients with obesity. An increased

343 vascular remodeling in visceral fat arteries [125], an impairment in finger microcirculation detected by

344 dynamic nailfold microcapillaroscopy [162], a thin sublingual microvasculature glycocalyx assessed by

345 sidestream darkfield imaging [163], an increased retinal arteriolar narrowing [164] and a decreased

346 retinal microvasculature response to flicker light [165] all characterise the microvascular damage found

347 in patients with obesity. Remarkably, bariatric surgery, the gold standard treatment for treating severe

348 obesity, showed a remarkable effect in terms of MD rescuing in patients with severe obesity, as shown

349 by an improvement in skin microcirculation [166] and in subcutaneous arteries reactivity, which appears

350 even more robust when including PVAT [167].

351

352 *Statement: Obesity-related microvascular inflammation is characterised by accelerated ageing*

353 *starting from adolescence/early adulthood, defined by a derangement in the PVAT phenotype, an*

354 *hyperactivation of inflammatory pathways (mainly TNF-α and IL-6), an impaired angiogenesis and a*

355 *early mitochondrial dysfunction.*

356

357 *3.3. Diabetes*

358   It is well recognized that low-grade inflammation plays an essential role in the pathogenesis of DM,

359   as well as in the development of diabetic microvascular complications. Studies have demonstrated that

360   inflammatory mediators, such as CRP, TNF-α, IL-6 and IL-18, have elevated expression in DM

361   [168,169]. Hyperglycemia acutely increases circulating cytokine levels through an oxidative

362   mechanism among subjects both with features of insulin resistance and with clinically overt DM

363   [170,171]. In subjects with type 2 DM, a correlation was observed between high-sensitive CRP and IL-

364   6 with HbA1c independent of the presence of coronary heart disease [172,173]. Furthermore, serum

365   levels of TNF-α were associated with the level of insulin resistance and with HbA1c in diabetic subjects

366   [174].

367   Diabetic hyperglycemia increases oxidative stress by excessive intracellular ROS generation, which

368   in turn leads to activation of the NF-κB pathway resulting in the production of major pro-inflammatory

369   cytokines. Hyperglycemia-induced oxidative stress increases the formation of advanced glycation end

370   products (AGEs), which results in increased insulin resistance. Moreover, receptors for advanced

371   glycation end products (RAGE) are involved directly in inflammatory cell recruitment [175,176].

372   Insulin resistance is associated with endothelial dysfunction. In particular, the endothelial balance

373   between NO-mediated vasodilator actions and ET-1-mediated vasoconstrictor effects of insulin are

374   regulated via phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK)

375   pathways, respectively. In states of insulin resistance, dysregulation of PI3K-dependent signaling may

376   cause an imbalance between the NO production and secretion of ET-1 [177]. Thus, insulin resistance

377   induces vasoconstriction and VSMCs proliferation and plays a significant role in the occurrence of

378   endothelial dysfunction [178]. Indeed, markers of insulin resistance are associated with abnormal

379   arterial elastic properties and impaired coronary microvascular function not only in dysglycaemic

380   subjects but also in first-degree relatives of diabetic subjects before the development of impaired

381   glucose tolerance or DM [179].

382   Furthermore, oxidative stress is characterized by the production of peroxynitrite that down-

383   regulates NO bioavailability and leads to vasoconstriction. Also, the accumulation of ROS promotes

384   the apoptosis of ECs and augment the expression of intercellular adhesion molecule-1 (ICAM-1),

385 vascular cell adhesion molecule-1 (VCAM-1), and E-selectin resulting in microvascular inflammation

386 and hypercoagulability [180]. Chronic inflammation inhibits the production of endothelial eNOS and

387 promotes the expression of ICAM-1, VCAM-1 and ET-1, further damaging endothelial integrity [181].

388 Acute and long-term hyperglycaemia have a detrimental effect on endothelial glycocalyx integrity

389 [182-184]. The glycocalyx is a gel-like layer composed of sulfated proteoglycans and glycoproteins

390 that prevents the direct contact of circulating inflammatory cells to the luminal surface of the

391 endothelium [185]. Intriguingly, HbA1c is associated with the impaired perfused boundary region, a

392 marker of the microvascular glycocalyx thickness, while intensified glycaemic control ameliorates

393 glycocalyx integrity in diabetic subjects at the 1-year follow-up [186]. The impaired glycocalyx is an

394 independent predictor of adverse outcomes in subjects without established CV disease [43].

395 Besides hyperglycemia, high free fatty acid levels (FFA) may stimulate ROS production via protein

396 kinase C (PKC)-dependent activation of NADPH oxidase in both VSMCs and ECs. This finding may

397 explain the excessive acceleration of atherosclerosis and microcirculation damage in diabetic subjects

398 [187]. In addition, hyperglycemia and lipotoxicity lead to hyperactivation of NLRP3 inflammasome,

399 which mediates caspase-1 activation and the secretion of pro-inflammatory cytokines IL-1β and IL-18.

400 Thus, NLRP3 inflammasome activation in DM leads to chronic inflammation and increased vascular

401 permeability [188].

402 The most common microvascular complication of DM is diabetic retinopathy. Ocular

403 microcirculatory damage on the grounds of hyperglycemia causes capillary occlusion leading to retinal

404 ischemia and neovascularization [189]. Interestingly, experimental data show that microcirculatory

405 changes, including adherence of neutrophils and leukostasis, in non-ocular tissues of diabetic mice

406 appear to be related and reflect retinal microvascular lesions in the context of diabetic retinopathy [190].

407 Underlying retinal microvascular dysfunction seems to precede the clinical manifestation of DM-

408 associated CV disease [191]. New advances in retinal vessel analysis provide useful diagnostic tools to

409 improve the prediction and risk stratification of CV disease [192]. However, there is also evidence of

410 non-retinal MD in diabetes: diabetic subjects have impaired dermal microvascular hyperemia response

411 to local skin heating [193], reduced glycocalyx thickness (**Figure 3C**) [194]. Similarly, digital pulse

412 amplitude tonometry (PAT) is impaired in type 2 diabetes and influenced by glucose level fluctuations

413 [195].

414 Finally, it should be mentioned that several of the novel antidiabetic agents, namely dipeptidyl

415 peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium-

416 glucose cotransporter-2 inhibitors (SGLT-2i), have potential anti-inflammatory properties and improve

417 endothelial function and presumably microcirculation [194,196-200], and this might be - at least

418 partially - responsible of the significant benefit observed in terms of reduction of CV risk [201].

419

420 *Statement: Hyperglycaemia and FFA-derived ROS produce a substantial increase in oxidative*

421 *stress, directly affecting microvascular inflammation and promoting an AGE/RAGE and lipotoxic*

422 *environment, which determines peripheral insulin resistance, further worsening the low-grade*

423 *inflammatory response.*

424

425 *3.4. Arterial hypertension*

426 Arterial hypertension is characterised by diffuse microvascular damage (**Figure 3D,**

427 **Supplementary Figure 1**) [202-206]. Hypertension and inflammation have a bidirectional

428 physiological and pathophysiological background [207,208]. Several human studies have evaluated the

429 relationship between inflammation and essential hypertension. In a meta-analysis (n=21,458 patients),

430 higher levels of circulating CRP, high-sensitivity CRP (hs-CRP), and IL-6, but not IL-1β, were

431 associated with the risk of developing hypertension [209]. Studies have also reported correlative links

432 between arterial stiffness and inflammatory markers in essential hypertension [210].

433 A hallmark of inflammation is the release of inflammatory cytokines such as IL-6, IL-17A,

434 interferon-γ (IFN-γ), and TNF-α by T CD4^{+} cells, and more specifically by subsets of T helper (Th)

435 cells, Th1 and Th17[9,207,208]. Involvement of IL-6 has been shown in mice, where *Il6* knock-out

436 mice showed reduced hypertension severity in response to angiotensin II (AngII) infusion [211].

437 Further, in human renal proximal tubular cells, IL-6 increased angiotensinogen expression [212]. IL-

438   17A affects renal sodium handling [213] and inhibits eNOS, causing impaired vasodilatation and

439   increased peripheral vascular resistance [214]. Long-term effects of IL-17A include the promotion of

440   vascular fibrosis, leading to arterial stiffening [214]. In addition, in mice lacking IL-17A, the number

441   of T cells and macrophages in blood vessels was reduced, illustrating the effect many of these cytokines

442   have in attracting more immune cells, further amplifying the immune response [207]. They induce

443   oxidative stress [215] through enhanced NADPH oxidase subunit expression. Increased oxidative stress

444   affects sodium retention by decreasing the glomerular filtration rate [216]. This, as many of the classical

445   pathophysiological factors in hypertension (ET-1, aldosterone, and AngII), activates the NLRP3

446   inflammasome through NF-κB. NLPR3 activation leads to increased levels of proinflammatory

447   cytokines IL-1β and IL-18, activating immune and vascular cells as T cells (mainly $CD4^+$), monocytes,

448   ECs and VSMCs [217].

449   The contribution of innate and adaptive immune cells to the development of MD leading to

450   hypertension is substantial [218]. Regarding immune cells, in animal models of genetic hypertension,

451   vascular ageing is associated with increased PVAT infiltration of macrophages, neutrophils and natural

452   killer cells (NKs), which promote NADPH oxidase 4-driven microvascular remodeling [9,219,220].

453   Macrophages, as a major source of ROS, are considered important in this process, although the precise

454   mechanisms by which they are involved remain unclear [9]. Similarly, NKs are found to increase before

455   the development of hypertension in spontaneously hypertensive rats [219]. Neutrophils from the plasma

456   of untreated patients with essential hypertension generate neutrophil extracellular traps that lead to

457   collagen production and consequent microvascular remodelling [221]. In adaptive immunity, T cells

458   are considered to play a predominant role. Following antigen recognition, CD4+ T cells are activated

459   and differentiate into T effectors (Th1, Th2 and Th17) or T regulatory cells (T_{reg}), the balance of which

460   influences the inflammatory response [9]. In experimental models of hypertension, as well as in

461   hypertensive patients, the inflammatory response generated by the ratio of T helper lymphocytes (Th)

462   1/17 (Th1/Th17) is not adequately balanced by the pool of regulatory T lymphocytes (Treg), thus

463   contributing to structural damage of the microcirculation [9]. Recently, it was discovered that the T cell

464   mir214 partially recapitulates and transduces the fibrotic effects of the immune system to the

465   microvasculature, leading to vascular fibrosis, vascular stiffening and remodelling. In particular,

466   cytokines released from PVAT mediate these effects [220]. It is thus clear that the immune system is

467   one of the leading mechanisms supporting the cross-talk between vascular inflammation and

468   hypertension. However, it should be noted that most of the evidence comes from in vivo studies, as

469   further investigations in patients are needed [9].

470   However, over the last years, evidence has been accumulated showing that this dialogue also

471   involves the sympathetic nervous system [222,223]: (i) an increase in sympathetic activity elicits T-

472   lymphocytes activation and vascular inflammation [224]; (ii) significant correlations have been found

473   between circulating plasma norepinephrine, and IL-6 produced by T-lymphocytes as well as TNF-α

474   produced by macrophages and monocytes [225]; (iii) chronic sympathetic activation in patients with a

475   peculiar form of high blood pressure desensitizes lymphocyte β_2-adrenoceptors and thereby alters

476   immune function [225]. On the other hand, inflammation and T-lymphocytes activation, which are both

477   triggered by oxidative stress [226], may favour sympathetic activation, as already shown in other

478   diseases characterized by an adrenergic overdrive, including essential hypertension [222]. In any case,

479   pro-inflammatory substances and mediators may trigger signals to the central nervous system activating

480   the sympathetic neural component [222].

481

482   *Statement: arterial hypertension is characterised by increased sodium retention and higher*

483   *levels of ET-1, aldosterone and AngII, which disrupt the microvascular environment by promoting*

484   *NAPDH-derived endothelial dysfunction and IL-6, IL-17 and TNF-α-driven inflammatory responses.*

485   *The innate and adaptive immune systems play a central role. In particular, a balance between effectors*

486   *(Th1, Th17) and regulators (Treg) T cells orchestrates microvascular inflammation and consequent*

487   *microvascular remodelling.*

488

489   *3.5.   Neurodegenerative diseases*

490   The cerebral vasculature is unique in its anatomy and physiology. It constructs a highly

491   specialized blood-brain barrier (BBB) that controls the admission of solvents and ions into the brain

492   and clearance into the blood metabolic end products or endogenous neurotoxin produced by the brain

493   [227,228]. The BBB, therefore, play a critical role in maintaining brain homeostasis. It comprises

494   endothelial cells, basement membrane, pericytes and VSMCs, astrocytes, microglia and neurons

495   [229,230]. Vascular ECs are known to secrete vasoactive substances implicated in regulating cerebral

496   flow, intravascular blood coagulation, and preserving the integrity of the BBB. Their atheroprotective

497   role and homeostasis are controlled by releasing vasoactive factors, especially NO. This leads to cGMP-

498   mediated cerebral vessel relaxation and proper blood supply to the brain tissue and autophagy [231].

499   Pericytes (PCs) directly encircle endothelial cells and VSMCs and are considered vascular mural cells.

500   ECs and PCs have direct contact through gap junctions and contribute to blood vessel formation and

501   BBB function maintenance by regulating immune cells' entry (CD4$^+$ and CD8$^+$ T cells, peripheral

502   macrophages and neutrophils) to the central nervous system [232-234].

503   Similar to the peripheral circulation, impairment in NO production, inflammation and enhanced

504   ROS production [235,236] are vital in promoting ECs dysfunction manifested by increased expression

505   of leukocyte adhesion molecules such as ICAM-1, VCAM-1 and E-selectin. These molecules promote

506   higher immune-endothelial cell interaction and accumulation of inflammatory cells in the vascular and

507   perivascular niches. The higher expression of ICAM-1 and VCAM-1 is observed in cerebral endothelial

508   cells in animal models of cerebral hypoperfusion, while their inhibition protects against cognitive

509   impairment [237,238]. Furthermore, soluble adhesion molecules like sE-selectin, sP-selectin, sICAM-

510   1 and sVCAM-1, considered endothelial dysfunction markers, are elevated in patients with small vessel

511   brain diseases [239].

512   The chemotactic process is strictly controlled by numerous chemokines secreted by the vascular

513   cells [240], pericytes [233], microglia [241], and astrocytes [242] in a concentration-directed gradient.

514   Recent studies have implicated the importance of CCL2, CCL3, CCL5 and CXCL8 in many vascular

515   and neurogenerative diseases, including cognitive impairment, stroke and neuroinflammation [243].

516   Microcerebrovascular endothelial cell activation and BBB leakage promote the migration and

517   accumulation of proinflammatory macrophages [244] and T cells [245,246] in perivascular space

518   (**Supplementary Figure 2**). The role of various immune cells in the pathogenesis of endothelial

519   dysfunction and vascular inflammation in CV diseases has been well established [220,247]. Activated

520 immune cells release diverse pro-inflammatory mediators, which propagate microvascular

521 inflammation and may provoke microhemorrhages, further escalating the inflammatory process. Co-

522 involvement of IL-1β, IL-6 and TNF-α, in microvascular brain injury and inflammation has been widely

523 reported [248,249]. IL-1β is considered the main proinflammatory cytokine that increases the astrocytic

524 production of CCL2, CCL20 and CXCl2 [250]. In addition, IL-1β impairs microvascular ECs by

525 disturbing tight and adherent junctional proteins and increasing adhesion molecules expression,

526 prompting vascular leakage and the parenchymal infiltration of leukocytes. In contrast, anti-IL-1β

527 treatment blunts cerebrovascular inflammation and improve outcome in a mouse model of acute

528 ischaemic stroke [251]. IL-6 is a pleiotropic inflammatory cytokine produced by infliltrating leukocytes,

529 ECs, activated microglia and astrocytes. Its expression affects many neuroinflammatory and

530 neurodegenerative conditions [252-254]. IL-6 mediates the elevation of superoxide production and

531 endothelial impairment by affecting NO-cGMP signalling pathway [255]. In addition, it may enhance

532 CRP released by brain cells [256]. Similarly to IL-6, TNF-α affects proper endothelial function by

533 decreasing eNOS levels by destabilising its mRNA expression. Furthermore, TNF-α activates NF-κB,

534 a major regulatory transcription factor, playing a pivotal role in regulating various inflammation-related

535 genes, including key inflammatory cytokines (along with IL-1β and IL-6), chemokines and adhesion

536 molecules.

537 Cognitive impairment is a hallmark of numerous CV diseases [257]. In hypertension, white

538 matter hyperintensities (WMH) are a critical imaging biomarker linked to this process (**Figure 3E**).

539 Indeed, neurovascular inflammation is involved in the aetiology of WMH [258]. Similarly, cerebral

540 small vessel disease has been identified as a key hallmark of a broad range of neurodegenerative

541 conditions. Human neuroimaging and genetic studies show that it is characterised by microvascular

542 endothelial dysfunction impacting cell-cell interactions and leading to brain damage [259]. One broadly

543 studied model of cerebral small vessel disease caused by NOTCH3 mutations, CADASIL (Cerebral

544 autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) [260], is

545 characterised by accelerated cognitive decline and dementia, recurrent stroke without vascular risk

546   factors, and mood disturbances. This hereditary disorder provides a unique opportunity to understand

547   some of the molecular mechanisms of small vessel disease [261].

548   Elevation of proinflammatory mediators such as IL-1β, IL-6, TNFα and CRP has been linked

549   with cognitive impairment in humans [262,263]. Furthermore, proinflammatory cytokines secreted by

550   immune and vascular cells have direct neurotoxic and apoptotic properties [264], which could

551   perpetuate local neuroinflammation and neurodegradation. Interestingly, neuroinflammatory changes

552   found in the brains of COVID-19 patients were accompanied by the presence of macrophages and T

553   cells in the perivascular space [265], suggesting higher microvascular inflammation caused by a

554   cytokine storm which might affect the proper BBB function [266]. Furthermore, cerebral microvascular

555   inflammation enhances the prevalence of cognitive impairment even in mild symptomatic COVID-19

556   subjects [267]. Similarly, experimental and epidemiological studies indicate a relationship between

557   cognitive decline and CV diseases [228,268-270], associated with chronic low-grade inflammation and

558   dysregulation of the immune system [271,272]. In particular AngII is at the crossroad, acting as

559   cardiovascular and immune systems modulator, initiating inflammation by indirect promotion of

560   vascular permeability and the recruitment of peripheral macrophages and CD4$^+$ and CD8$^+$ T cells

561   [273,274]. In turn, augmented permeabilty leads to further inflammation and secondary damage to the

562   BBB, with the entry of plasma proteins and neurotoxic substances [275].

563   The most prevalent form of dementia, AD, is marked by a steady decline in cognitive function

564   and neurodegeneration. The vascular hypothesis suggests that cerebral microvascular alterations are

565   central to the pathogenesis of AD, providing a link with CV disease [276]. Possible mechanisms include

566   neurovascular coupling imbalances and BBB disruption [276]. Impaired removal of beta-amyloid may

567   be a consequence of these neurovascular changes: vascular changes may precede the development of

568   tau pathology [277]. A two-hit hypothesis has been developed in which classical risk factors leading to

569   the development of microvascular dysfunction facilitate AD-specific pathology. This is linked with the

570   development of a vicious cycle between microvascular damage and beta-amyloid aggregates that

571   contribute to AD development. Brain imaging supports these observations, as well as chronic cerebral

572   hypoperfusion, microvascular dysfunction, and perivascular space enlargement - hallmarks of small

573 vessel disease - precede cognitive decline and changes in conventional biomarkers [276]. These

574 mechanisms of small vessel disease are shared between vascular dementia and AD: assessment of

575 retinal microvasculature has shown apparent microvascular dysfunction and remodelling in

576 neurodegenerative diseases [278,279].

577

578 Statement: *In neurodegenerative disease, MD favours the increased BBB dysfunction and*

579 *leakage paired with higher NF-κB activation and consequent microvascular levels of IL-1β, IL-6, TNF-*

580 *α, which promotes the onset of a vicious cycle leading to progressive cognitive impairment and*

581 *increased predisposition to tau pathology.*

582

583 *3.6.   Autoimmune rheumatic diseases*

584 Autoimmune rheumatic diseases (ARD) are distinct heterogeneous disorders with common

585 immune responses against self-antigens arising from genetic predisposition, dysregulation of the

586 immune system and environmental factors. Among them, chronic inflammatory rheumatic conditions,

587 mainly represented by rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and

588 spondyloarthritis (ankylosing spondylitis (AS) and psoriatic arthritis (PA)) are those further

589 characterized by increased and premature CV morbidity and mortality [280]. Atheromatosis is a chronic

590 inflammatory process in which the immune system, blood and vascular cells, and several hormonal

591 systems are primarily involved in the structural and functional damage of the small vessels [281].

592 Microangiopathy has been used as an important subclinical CV risk indicator, and ARD patients

593 [282,283] have an increased prevalence of CV diseases which cannot be fully explained by the classical

594 CV risk factors [284].

595 In ARD, a combination of elements is able to contribute specifically to MD and microvascular

596 inflammation: (i) genetic predisposition due to the polymorphism in *MTHFR*, *TNF*, *IL6* loci and the

597 *HLA-DRB1* status [285]; (ii) activation of IL-1β, IL-6, IL-17 and TNF-α pathways [285]; (iii) enhanced

598 ECs activation with the expression of ICAM-1, VCAM-1, E-selectin [286]; (iv) the increase in

599 NAPDH-derived ROS production, leading to eNOS uncoupling and formation of 3-nitrotyrosine.

600 RA is the most prevalent autoimmune inflammatory rheumatic disease [287], characterized by

601 a 50% excess in CV mortality compared to the general population [288]. RA has been associated with

602 diffuse microvascular injury (**Figure 3G**) [24] documented by decreased myocardial perfusion

603 (**Supplementary Figure 3**) [289], altered retinal arteriolar diameters [290,291], and dermal capillary

604 density assessed with nailfold capillaroscopy [292], as well as impaired coronary microcirculation

605 evaluated by coronary flow reserve (CFR) [293] and impaired endothelial glycocalyx integrity [294]

606 even in the absence of overt CV disease. This is paired with an attenuated microvascular response to

607 different stimuli, assessed with venous occlusion plethysmography [295,296], and an increased

608 hyperaemic vasodilatory response [297] in RA patients compared to healthy controls. Pronounced

609 impairment of microcirculatory blood flow responses assessed by laser speckle contrast imaging (LSCI)

610 and decreased coronary microvascular perfusion has also been found in RA individuals free from CV

611 disease [298] (**Supplementary Figure 4**).

612 In SLE, prevalent in about 0.1% of the general population, apart from the widespread

613 inflammation and tissue damage in the affected organs, the blood vessels, especially the brain and

614 kidneys, could also be severely impaired. Since vascular involvement, presenting as noninflammatory

615 necrotic vasculopathy, thrombotic microangiopathy, and lupus vasculitis, is considered the leading

616 cause of death in patients with SLE, interest has been focused on identifying the presence and role of

617 early, subclinical microcirculation alterations, potentially anticipated before the establishment of CV

618 events [25]. In addition to the classical subclinical structural changes (cortical atrophy and white matter

619 hyperintensities), identified mostly by conventional MRI in patients with SLE regardless of the presence

620 of neuropsychiatric manifestations, functional changes such as a blunted increase in cerebral

621 oxygenation during exercise assessed with near infra-red spectroscopy [299] and hypoperfusion lesions

622 with single-photon emission tomography (SPECT) in comparison to controls [300] are present. They

623 often precede the permanent changes identified by conventional imaging [301] and are also found in

624 sites different from the classical one targeted by lupus vasculopathy (e.g., SLE nephritis): the fundus

625 [26,302,303], the skin, with capillaroscopic alterations concerning density, dimensions, morphology

626 and haemorrhages, and the myocardium, presenting coronary microvascular dysfunction [304-306].

627 Functional microcirculation studies with digital PAT [307,308], Portable Oxygen Transmitter [309] and

628 LSCI [310,311] document reduced peripheral perfusion and impaired microvascular reactivity in SLE

629 patients (**Supplementary Figure 4**).

630 Subclinical microvascular alterations in psoriatic disease, inflammatory bowel disease,

631 vasculitis and AS have also been studied [312-314]. Psoriatic patients and patients with inflammatory

632 bowel disease present coronary microcirculatory dysfunction, as assessed by CFR, reduced endothelial

633 glycocalyx thickness and microvascular perfusion impairment leading to impaired cardiac function

634 (**Supplementary Figure 4**) [27,28,315-318].

635 Remarkably, biological anti-inflammatory therapies and statins in autoimmune diseases

636 improve endothelial glycocalyx and function, as well as coronary and peripheral microcirculation and

637 thus, have beneficial effects on CV function [28,317,319,320], providing indirect evidence of the

638 beneficial impact of targeting microvascular inflammation. Nonetheless, the precise role of MD and

639 microvascular inflammation, in terms of risk prediction and therapeutic target, needs to be addressed

640 appropriately by rigorous prospective studies.

641

642 *Statement: ARD are a heterogeneous group of diseases characterised by MD and microvascular*

643 *inflammation, driven by the combination of genetic predisposition and innate immunity hyperactivation*

644 *via IL-1β, IL-6, IL-17 and TNF-α pathways. The beneficial effects of anti-inflammatory drugs in terms*

645 *of CV risk reduction provide indirect evidence of the centrality of microvascular inflammation in ARD.*

646

647 *3.7. Oncologic disease*

648 As previously mentioned, systemic and local inflammation have a major role in the development

649 and maintenance of microvascular structural alterations [9]. Oncologic diseases may cause or be

650 associated with systemic inflammation, possibly contributing to the development of hypertension and

651 CV diseases, thus reducing overall survival in these patients [321]. However, due to many clinical

652   reasons, including relatively short follow-up periods, few data are available about microvascular

653   alterations in cancer patients *per se.*

654   Cancer primarily shares with CV disease several pathophysiological mechanisms and similar risk

655   factors. In this respect, chronic inflammation is a crucial feature in the pathogenesis and progression of

656   both CV disease and cancer. It may be directly involved in the induction of some cancer types (*e.g.* H-

657   pylori and stomach cancer) or indirectly promote local carcinogenesis and its progression by releasing

658   inflammatory mediators and recruiting immune cells within the tumor microenvironment [29]. Other

659   mechanisms such as oxidative stress, cytokines, hormones (*e.g.* leptin), growth and metabolic factors

660   have also been proposed to connect both diseases. However, a clear pathogenetic understanding is still

661   lacking: although T cells appear to be involved, which specific subtype and by which mechanism they

662   induce MD requires further investigation. [29]. The concomitant presence of CV risk factors or

663   conditions such as physical inactivity, smoking, obesity, and diabetes may further induce inflammation

664   worsening the prognosis of cancer and cancer survivor patients [30]. Cancer cells secrete VEGF to

665   stimulate tumor vascularization, which increases vascular permeability and may contribute to

666   microcirculation structural remodeling and perivascular fibrosis [31,32].

667   Particularly relevant is that several cancer treatments present CV toxicity and may cause MD,

668   microvascular inflammation, hypertension and thus, an increase in CV events [321,322]. While

669   anthracyclines have been mostly related to specific cardiotoxicity [323], VEGF and other tyrosine

670   kinase inhibitors are the most frequently associated anti-cancer drugs with a dose-dependent increase

671   in blood pressure both in hypertensive patients and in normotensive subjects [322,324,325]. These drugs

672   enormously improve the prognosis for several solid tumors [326], targeting specific pro-angiogenic

673   VEGF signaling involved in the neovascularization of tumors in vivo [327]. A consequent increase in

674   blood pressure has been suggested as a pharmacodynamic biomarker and predictor of therapeutic

675   efficacy [328,329]. However, this was not confirmed by other studies [330], and, what is more, poorly

676   controlled hypertension leads to an increase in CV events, causing the discontinuation of anticancer

677   therapy and thus hindering its clinical benefit.

678   The mechanism underlying vascular toxicity and hypertension induced by VEGF inhibitors is

679   still debated. VEGF-A, the most important isoform of VEGF, may promote the proliferation,

680 differentiation, and migration of endothelial cells by interacting with the VEGF-A receptor, as well as

681 NO production [331]. Accordingly, VEGF inhibition is associated with reduced NO bioavailability

682 because of the inhibition of eNOS and concomitant increase in vascular ROS [324,332], resulting in

683 MD [31]. Activation of the ET-1 system with increased concentrations of ET-1, nephrotoxicity and

684 impaired natriuresis induces hypertension along with the inhibition of other growth factors, including

685 platelet-derived or fibroblast growth factor, c-Kit and FMS-like tyrosine kinase 3 [333]. Recently, a

686 novel molecular mechanism involving the interplay between endothelial microparticles, the endothelin

687 system and endothelial cell pro-inflammatory and redox signaling have been described; such

688 interactions could be important in CV toxicity and hypertension associated with VEGF inhibitors [334].

689 All these events would favour an increase in peripheral resistance, further increasing MD.

690 Another consequence of antiangiogenic drugs leading to vascular resistance increase and

691 elevated blood pressure is microvascular rarefaction. A reduction of capillary density during

692 antiangiogenic treatment, reversible with cancer drug discontinuation [335], was observed in some

693 [336-339] but not in other studies [340]. In one of these studies [338], the effect of antiangiogenic drugs

694 on the structure of retinal arterioles and capillary density was investigated in 20 patients with cancer.

695 No change in systolic or diastolic blood pressure values during treatment was observed [338]; however,

696 during the study, antihypertensive treatment was optimized in most patients. Although no difference

697 was observed in the retinal arteriole wall-to-lumen ratio [19], capillary density was reduced by

698 antiangiogenic drugs after three or six months (**Figure 3F**) [338]. These findings might imply that an

699 up-titration antihypertensive treatment is necessary for patients treated with tyrosine kinase inhibitors

700 or a VEGF inhibitor. Indeed, under adequate blood pressure control, microvasculature seems preserved

701 [338]. Since the efficacy of these drugs could be related to the extent of the antiangiogenic effect, the

702 non-invasive evaluation of capillary density should be evaluated by further studies as a predictive

703 parameter of drug efficacy. The better identification of the mechanisms underlying adverse cardiac and

704 vascular effects of anti-cancer therapies may allow to develop novel vasculoprotective strategies. Only

705 by doing so will patients achieve optimal cancer treatment at the minimum cost to cardiac and vascular

706 health [323].

707

708   *Statement: In oncological disease, the pan-activation of inflammatory response concurs to*

709   *induce MD and microvascular inflammation. Even more relevant is that anti-cancer drugs, particularly*

710   *anti-VEGF, might cause detrimental derangement in microvascular function and inflammation, thus*

711   *attenuating their medium/long-term beneficial effects in terms of survival. An adequate increase in*

712   *treatment to achieve a stronger control of age-related disease (in particular, hypertension) is thus*

713   *required.*

714

Conclusions

716   Ageing and age-related diseases are all characterised by different degrees of MD, leading to high-CV

717   morbidity and mortality. As microvascular inflammation is both the consequence of environmental

718   stressors and the perpetrator of age-related damage, its centrality in CV risk is apparent. However,

719   though damage pathways have been extensively studied over the last decades, a clear understanding of

720   their involvement's temporal and spatial sequence across the age-related disease spectrum is missing.

721   In particular, although the interaction between immune and non-immune cells is receiving increasing

722   attention, a precise definition of their cross-talk in the context of MD is lacking. Preventing their

723   detrimental dialogue may be crucial to stopping the disease at a very early stage. This gap of knowledge

724   substantially limits the translation in terms of clinical strategies. Targeting microvascular inflammation

725   is still a difficult road to travel: as the microvascular damage leverage epigenetic remodeling [52], early

726   or intensive treatment is required to revert it. However, even as some interventions have demonstrated

727   a potential benefit in terms of rescuing MD (e.g., physical activity, weight loss [166,167], SGLT-2i

728   [200]) and inflammation [104], translational studies addressing microvascular inflammation to identify

729   either early common or disease-specific targets are required. At the same time, we need to clearly

730   understand the strengths and limitations of each technique used to assess MD, as well as the ability to

731   distinguish between microvascular and macrovascular. Efforts towards standardisation are needed to

732   obtain interpretable results from studies.

Table 1. Currently available methods for assessment of microcirculatory function in humans.

Technique	Tissue	Method of assessment	Advantages	Limitations
Peripheral arterial network				
Finger plethysmography	Arteries of fingers	Reactive hyperemia index in finger blood flow measured by using finger probes.	-Safe and non-invasive -No need for specific training -Totally non-operator-dependent -Prognostic value for adverse CV events	-More expensive -Environmental conditions and the autonomic nervous system may affect measurements
Antebrachial plethysmography	Brachial artery	Quantification of forearm blood flow by means of plethysmography during infusion of vasoactive drugs in the brachial artery immediately after cuff deflation and again at 1 and 5 minutes of reperfusion.	-Safe, noninvasive -It allows the simultaneous study of large conduit vessels and small arteries.	-Inexpensive -Small errors in the measurement of arterial diameter will result in large errors in the calculation of flow -Room temperature may affect measurements -Measures the local arterial extensibility
Transcutaneous oxygen tension	Skin	Quantity of oxygen molecules transferred to the skin microcirculation after heating skin>40°C.	-Wide availability	-Time-consuming -Does not assess all ischemic regions
Flow mediated skin fluorescence	Skin	Assessment of microcirculation and metabolic regulation based on the measurements of NADH fluorescence intensity in epidermis.	-Quick and simple -Good reproducibility -Flowmotion analysis -Correlated with endothelial biomarkers	- Lack of robust evidence on the prognostic value
Iontophoresis	Subpapillary plexus, nutritional capillaries, nerve-axon reflex	Delivery of vasodilators (acetylcholine/ SNP) subdermally and measurement of microcirculatory flow with laser Doppler fluxmetry or single-point probes.	-Quick and simple -Small coefficients of variation -Correlated with other microvascular beds -Isolation of nerve-axon reflex	-Cannot distinguish subpapillary plexus from nutritional capillaries in glabrous skin
Skin pulp blood flow	Nutritional capillaries and AV shunts	Assessment of microcirculation of pulp skin of the toes with laser Doppler fluxmetry or heat and/or radioisotope washout methods.	-Simple, can be performed on any area of skin quickly -Distinguishes nutritional capillaries and AV shunts in glabrous skin	-Not correlated with other tissue beds
Capillaroscopy	Subpapillary plexus, nutritional capillaries	Evaluation of morphology and blood flow by studying capillary changes with light microscopy or fluorescent dye dynamic capillaroscopy.	-Distinguishes microvascular from the interstitial compartments, assesses transcapillary diffusion -Distinguishes subpapillary plexus from nutritional capillaries	-Cost and availability of the equipment -Patients need to be placed in the sitting position -Qualitative evaluation is largely dependent on the operator experience

				-Need for readily available software among different centers for quantitave evaluation of MD parameters
Hand-held vital-microscope device	Sublingual microcirculation, microvascular beds of different types of mucosa and solid organ surfaces	Video observation of the flowing RBCs of the microcirculation (3rd generation device -the newest technology- uses incident darkfield illumination for this purpose) and diffuse capacity.	-Noninvasive monitoring of the microcirculation at the bedside -Alterations in sublingual microcirculation are highly sensitive and specific, predicting adverse outcomes *3rd generation device* -Computer-controlled image sensor -Better image quality -Evaluation of 30% more capillaries	- Microcirculation can be visualized only if the epithelial layer of the area of interest is thin - Presence of artefacts due to movement - Variability with the use of different generations of HVM
Micromyography	Subcutaneous tissues	Measurement of MLR or WLR of small subcutaneous vessels dissected from tissue biopsies by pressure or wire micromyography.	-Gold-standard method -Precise and reliable -The most potent predictor of CV events in hypertensive patients	-Locally invasive
Laser speckle contrast imaging	Skin and subcutaneous tissues, Retinal and choroidal microcirculation	Mesurements of peripheral microcirculatory perfusion on a wide area of tissue LSCI coupled with vascular reactivity tests enables to assess endothelial function Complementary use of a fundus camera with a laser diode or a blue component argon laser for assessment of deep or superficial retinal flow, respectively.	-Dynamic, real-time perfusion monitoring -Very good spatial and temporal resolution -Improved spatial and temporal reproducibility as compared to conventional laser Doppler flowmetry -Excellent reproducibility -Safe, noninvasive	-Cost and availability of the equipment -Lack of robust evidence on the prognostic value -Interference by movement artifacts -Limited interpatient comparability -Complexity of quantitative measurements
Scanning laser Doppler flowmetry	Retinal vascular district	Quantification of the WLR of retinal arterioles using scanning laser Doppler flowmetry.	-Easy repeatability and comfortable for patients -Good agreement with wire micromyography	-Lack of robust evidence on the prognostic value -Suboptimal variability in real-life situations due to the indirect nature of the measurement
Nears Infrared Spectroscopy	Muscle and brain microcirculation	Noninvasively assessment of (i) microvascular reactivity, (ii) skeletal muscle and brain oxygenation via continuous monitoring of functional changes in oxygenated hemoglobin dissociation.	-Easy repeatability -Precise and reliable -Correlated with other microvascular beds	-Lack of prospectives and large epidemiological studies
Adaptive optics	Retinal vascular district	Direct measurement of WLR of retinal arterioles by an adaptive optics imaging system using a beam of light.	-Better reproducibility than scanning laser Doppler flowmetry	-Lack of robust evidence on the prognostic value

Retinal Vessel Diameter	Retinal vascular district	Direct measurement of arteriolar and venular vessels diameter from fundus photographs.	-Safe and non-invasive -Low cost and quick -Applicable in large populations -Implicated in large epidemiological studies predicting CV events -correlated with macro- and other microvascular beds	-Lack of normal values -Lack of studies investigating the changes after drug treatment
Coronary arterial network				
Coronary angiography-derived index of microcirculatory resistance	Coronary arteries	Physiological assessment of microvascular disease in coronary circulation from angiographic images.	-May predict adverse CV outcome and extensive myocardial injury -Highly reproducible and excellent diagnostic accuracy, not affected by hemodynamic changes - Relatively independent of epicardial coronary disease	-Invasive method -Limited in clinical practice due to required additional procedural time, cost and technical complexity (in non-STEMI patients)
Coronary flow reserve	Coronary arteries	The ratio of the maximal or hyperemic flow down a coronary vessel to the resting flow.	-Prognostic value for all-cause mortality and CV events -Quantitative and global physiological interrogation of the coronary circulation -Can be measured using non-invasive modalities, including echocardiography, PET and CMR	-Invasive method using a Doppler-tipped coronary guidewire -Difficulty in obtaining a suitable Doppler signal -Suboptimal repeatability of measurements - Lack of a clear cut-off between normal and abnormal CFR

Abbreviations: SNP, sodium nitroprusside; AV, arteriovenous; RBCs, red blood cells; HVM, hand-held vital microscope; MLR, media thickness to internal lumen ratio of subcutaneous small resistance arteries; WLR, wall-lumen ratio; CV, cardiovascular; STEMI, ST-elevation myocardial infarction; PET, positron emission tomography; CMR, cardiac magnetic resonance; CFR, coronary flow reserve; EndoPAT, non-invasive peripheral arterial tonometry.

Figure1

Endothelial dysfunction

Capillary density

Microcirculatory remodeling

Microcirculatory plugging

Oxidative stress

Activation of immune cells

Microcirculatory dysfunction

Development of cardiovascular disease

Idiopathic dilated cardiomyopathy

Hypertrophic cardiomyopathy

Stable obstructive CAD

Myocardial infarction

MINOCA/ INOCA

Takotsubo syndrome

Microvascular angina

HFpEF

Infiltrative cardiac diseases

Figure2

Environmental stressors and bad lifestyle habits

Microvascular inflammation

Microvascular dysfunction

Microvascular ageing

Microvascular inflammation

Ageing and age-related diseases

Environmental stressors and bad lifestyle habits

Healthy ageing

Age

Physiological ageing

↑SASP (↑IL-1β,↑IL-6,↑TNF-α)
↓autophagy
↑oxidative stress
↑NLRP3,↑NFκB,↑TLRs

Diabetes

↑AGE, ↑RAGE
↑Hyperglycaemia-derived ROS
↑FFA-derived ROS
↑Insulin resistance (↓ET$_A$/NO ratio)
↑FFA-activated NLRP3
↑IL-6,↑IL-18,↑TNF-α
↑ICAM-1,↑VCAM-1

Obesity

↑PVAT dysfunction (↑IL-6,↑TNF-α,
↑leptin,↓anti-contractile)
↑ET$_A$/NO ratio
↑AGO1 (impaired angiogenesis)
↑mitochondria dysfunction

Ageing and age-related diseases

Neurodegenerative disease

↑BBB leakage and dysfunction
↑ICAM-1,↑VCAM-1
↑NFκB,↑IL-1β,↑IL-6,↑TNF-α
↑chemokines

Hypertension

↑NADPH-ROS
↑ET-1
↑AngII (↑IL-6,↑IL-17,
↑TNF-α,↑IFN-γ)
↑NLRP3,↑NFκB

Oncologic disease

↑ROS,↑IL-1β,↑IL-6,↑TNF-α,↑leptin
↑VEGF (↑impaired angiogensis)
anti-VEGF:↑ROS,↓eNOS,↑ET-1)

Autoimmune rheumatic disease

MTHFR, TNF, IL6 polymorphisms
↑IL-1β, ↑IL-6, ↑IL-17,↑TNF-α
↑ICAM-1,↑VCAM-1,↑E-selectin
↑NADPH-derived ROS

Event-free CV outcomes

100
80
60
40
20
0

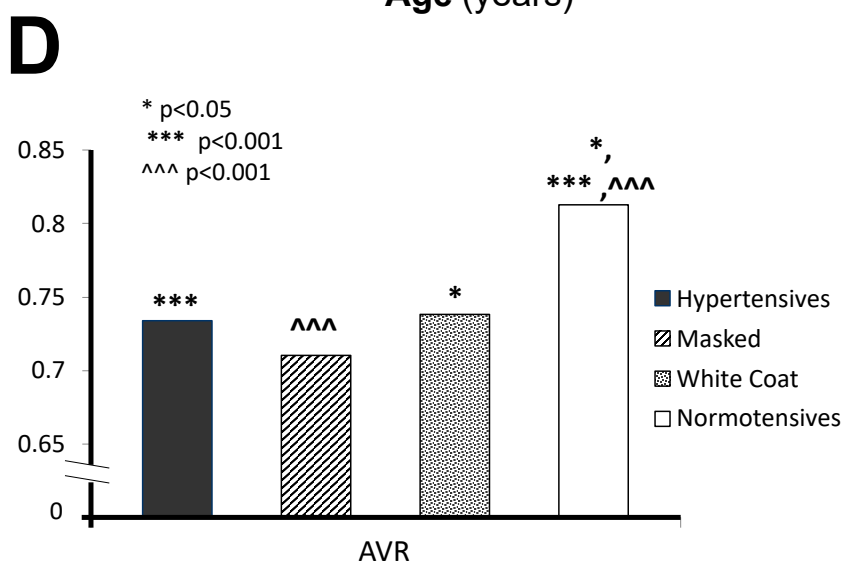Low microvascular inflammation
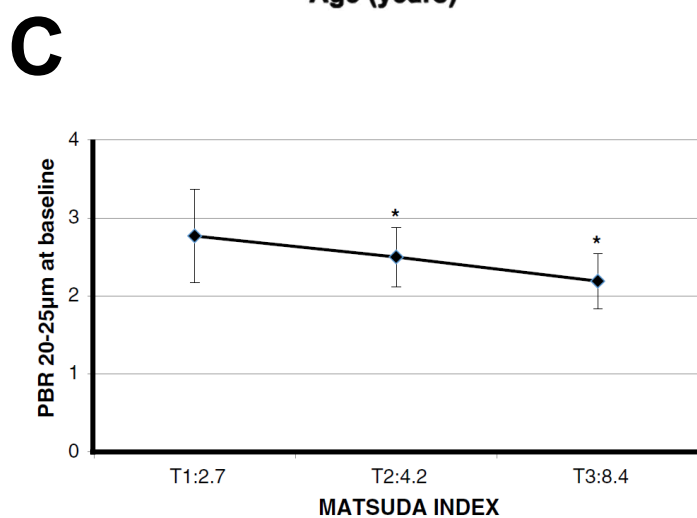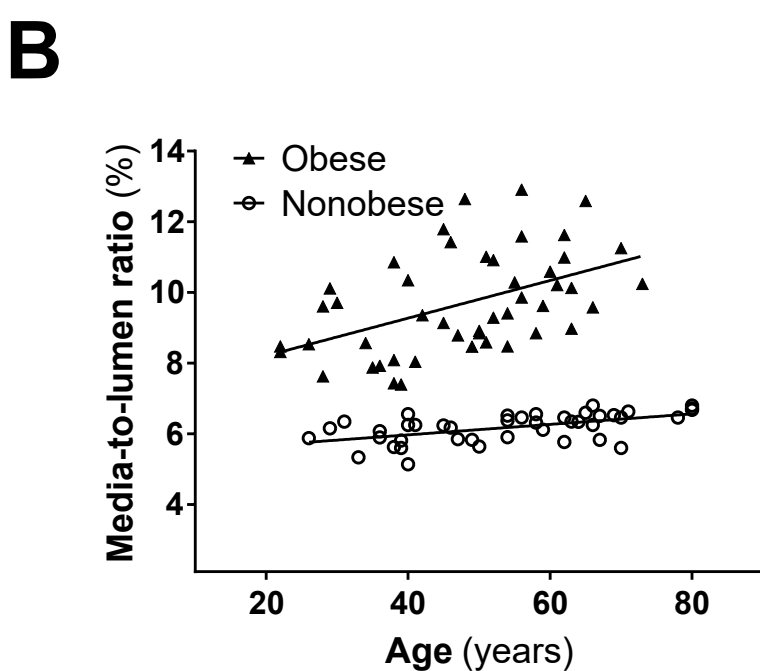
High microvascular inflammation

Time to-event
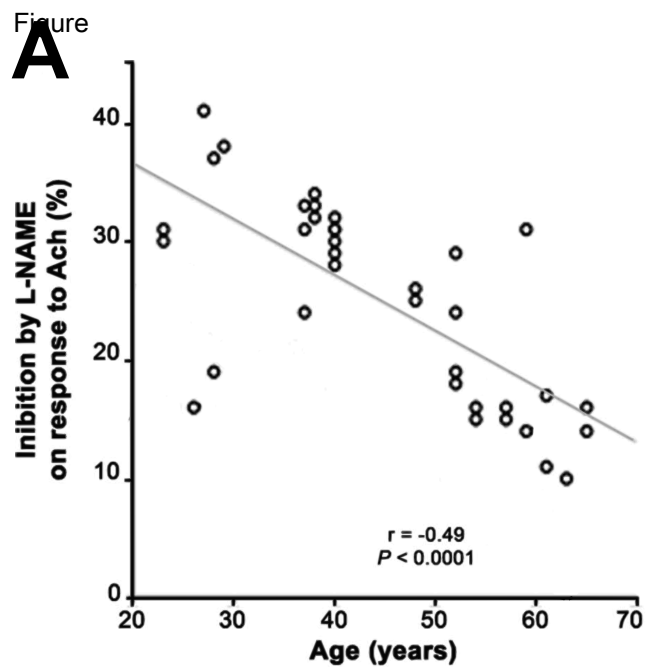
Figure

1   **Legends to the figures.**

2   **Figure 1. Mechanisms linking microcirculatory dysfunction with multiple manifestations of cardiovascular**

3   **disease.** *Abbreviations: CAD: coronary artery disease; MINOCA: myocardial infarction with non-obstructive*

4   *coronary arteries; INOCA: ischemia with non-obstructive coronary arteries; HFpEF, heart failure with preserved*

5   *ejection fraction.*

6

7   **Figure 2. Graphical abstract. Microvascular inflammation links environmental stressors to microvascular**

8   **ageing**. Environmental stressors induce microvascular dysfunction, which in turn promotes microvascular

9   inflammation. When microvascular inflammation causes permanent changes in vascular structure and function,

10   microvascular age and biological age diverge. The vessel becomes the architect of microvascular inflammation,

11   exposing the microcirculation to further damage from environmental stressors and thus promoting the onset of

12   cardiometabolic disease, exponentially increasing the degree of microvascular inflammation and the individual

13   cardiovascular risk. The major common and distinct molecular-, cell- and tissue-level mechanisms involved in

14   microvascular inflammation are summarized. *AGE: advanced glycation end products; AGO1: argonaute 1; BBB:*

15   *blood-brain barrier; eNOS: endothelial nitric oxide synthase; ET-1: endothelin-1; ET_A: endothelin-1 receptor A;*

16   *FFA: free fatty acids; ICAM: intercellular adhesion molecule-1; IFN: interferon-γ; IL: interleukin; MTHFR:*

17   *Methylene-tetrahydrofolate reductase; NADPH: nicotinamide adenine dinucleotide phosphate; NF-κB: nuclear*

18   *factor kappa-B; NLRP3: NOD-like receptor family pyrin domain containing 3; NO: nitric oxide; PVAT: perivascular*

19   *adipose tissue; ROS: reactive oxygen species; SASP: senescent-associated secretory phenotype; TLR: toll-like*

20   *receptors; TNF-α: tumor necrosis factor; VCAM-1: vascular cell adhesion molecule-1; VEGF: vascular epithelial*

21   *growth factor.*

22

23   **Figure 3. Microvascular inflammation and its impact on microvascular dysfunction across ageing and age-**

24   **related disease.** (**A**) Relationship between age (x axis) and the inhibition by N-nitro-l-arginine methylester (L-

25   NAME) on maximal response to acetylcholine (y axis) in normotensive subjects (n=41). Adapted from [108]. (**B**)

26   Increased Media-to-Lumen (M/L) ratio per year of age in healthy nonobese (white circle; n=42) and obese with no

other comorbidities (black triangle; n=47) subjects. Regression lines for each group are shown. The M/L ratio is expressed as a percentage (%). Age and M/L are tightly related in both groups (obese: r=0.487, p <0.01; nonobese: r=0.555, p=0.001). The slope is five-fold steeper in the obese group. Figure and captions adapted from [125]. (**C**) Association of tertiles (T1-T2-T3) of Matsuda index with perfused boundary region (PBR) measured in the microvessels ranged from 20 to 25 μm indicating an association between insulin resistance and damaged glycocalyx (F=4.8, p=0.03) in n=100 subjects with different degrees of insulin resistance (n=40 first-degree relatives of type-2 diabetes patients, n=40 subjects with abnormal oral glucose tolerance test and 20 subjects with normal oral glucose tolerance test without parental history of diabetes). Adapted from [182]. (**D**) Comparison of the retinal arteriovenous ratio (AVR) in n=201 newly diagnosed individuals with hypertension of different phenotypes and normotension. Intergroup comparisons were made with analysis of variance ANOVA with Bonferroni correction after adjustment for age, sex, body mass index (BMI). Individuals with sustained hypertension (n=103), masked hypertension (MHT; n=28) and white coat hypertension (WCH; n=20) had significantly lower AVR than normotensive subjects (n=50;p<0.05). Adapted from [206]. (**E**) Observational, standardised coefficients concerning 242 brain imaging-derived phenotypes genetically affected by SBP corresponding to their association with cognitive function or SBP at the imaging visit. Hypertension was used as a model associated with microvascular inflammation. Figure and caption adapted form [257]. (**F**) Altered capillaroscopy in oncologic disease. Basal capillary density in the dorsum of the 4th finger (Dpre_basal) in patients (n=20) with cancer and treated with either a tyrosine kinase inhibitor or a vascular epithelial growth factor inhibitor at the different time points (T0, T3, T6). *T3 vs T0 p=0.03 ; #T6 vs T0 p=0.02. Data are expressed as mean+standard deviation. Adapted from [338]. (**G**) Accumulative data of near-infrared-spectroscopy cerebral responses during exercise in systemic lupus erythematosus (SLE; n=26) versus control (n=27) group. Oxygenated haemoglobin (O_2Hb), deoxygenated haemoglobin (HHb) and total haemoglobin (tHb) levels were measured. Cerebral O_2Hb continuously increased during exercise in the control group, whereas the SLE group exhibited a plateau in O_2Hb after the first minute of exercise (p<0.01). During exercise, the SLE group exhibited significantly lower average-O_2Hb (1.20±0.89 vs. 2.69±2.46, p=0.001), and a lower peak-O_2Hb) response (2.89±1.56 vs. 5.83±4.59, p=0.004) compared with the control group. No differences were detected in the average HHb responses between groups. Adapted from [299].

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