Biomarkers Related to Endothelial Dysfunction and Vascular Cognitive Impairment: A Systematic Review

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Keywords

Endothelial dysfunction · Vascular cognitive impairment · Vascular dementia · Cerebral small vessel disease

Abstract

Introduction: The damage in the endothelium and the neurovascular unit appears to play a key role in the pathogenesis of vascular cognitive impairment (VCI). Although there have been many advances in understanding the physiopathology of this disease, several questions remain unanswered. The association with other degenerative diseases and the heterogeneity of its clinical spectrum establish a diagnostic problem, compromising a better comprehension of the pathology and halting the development of effective treatments. The investigation of biomarkers is an important movement to the development of novel explicative models and treatment targets involved in VCI. **Methods:** We searched MEDLINE considering the original research based on VCI biomarkers in the past 20 years, following prespecified selection criteria, data extraction, and qualitative synthesis. **Results:** We reviewed 42 articles: 16 investigated plasma markers, 17 analyzed neuropathological markers, 4 studied CSF markers, 4 evaluated neuroimaging markers (ultrasound and MRI),

and 1 used peripheral Doppler perfusion imaging. **Conclusions:** The biomarkers in these studies suggest an intrinsic relationship between endothelial dysfunction and VCI. Nonetheless, there is still a need for identification of a distinctive set of markers that can integrate the clinical approach of VCI, improve diagnostic accuracy, and support the discovery of alternative therapies.

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Introduction

Small vessel disease (SVD) is a clinical-radiological syndrome caused by a disorder in perforating cerebral arterioles, capillaries, and venules, resulting in lesions of cerebral white and deep gray matter [1]. It is responsible for about 20% of strokes and 45% cases of dementia in the world [2, 3]. Endothelial cells appear to have a pivotal role in the pathogenesis of cerebral SVD and vascular dementia (VaD). Endothelial dysfunction (ED) may contribute to SVD pathology through multiple mechanisms, such as blood-brain barrier (BBB) damage, decrease in whole-brain or tissue-resting cerebral blood flow, loss of cerebral vasoreactivity, and increase in intracranial pulsatility [4].

Fig. 1. Flow of information through the different phases of this systematic review. VCI, vascular cognitive impairment.

Moreover, ED may represent a potential link between cerebral SVD and Alzheimer's pathology. For example, the leakage of fibrinogen through vessel walls contributes to amyloid-beta ($A\beta$) plaque formation [1] and disrupted transport across the BBB plays a significant role in determining $A\beta$ concentrations in the central nervous system (CNS) [5, 6].

Recently, Alzheimer's Disease-Related Dementias Summit set the study of small vessel VCI biomarkers as a research priority [7]. Considering that a thorough review analyzing markers of ED in patients with VCI is lacking, we carried out a systematic review on biomarkers of ED in VCI studies undertaken in the last 20 years.

Methods

Search Strategy, Study Selection, and Data Acquisition

We searched MEDLINE for studies investigating ED and VCI with the following free text and Medical Subject Headings (MeSH): "endothelium" or "endothelial" and "cognitive impairment" or "dementia." We limited the search to articles written in English, with human adults as subjects and published in the last 20 years (search period between January 1, 1999, and December 31, 2019).

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [8], 2 investigators (R.K.M.F. and G.R.) searched MEDLINE independently and compared their results. Differences in the screening phase were re-

solved by consensus. Three investigators (R.K.M.F., M.C.Z., and G.R.) carried out data extraction independently. They stored the variables in a spreadsheet especially developed for this review, tabulating the following data: number of participants, population studied, study design, biomarker of interest, source of biomarker, and main results.

Results

The combined terms yielded 74 articles: "endothelial" and "vascular cognitive impairment" – 5 articles; "endothelium" and "vascular cognitive impairment" – 3 articles; "endothelial" and "vascular dementia" – 49 articles; and "endothelium" and "vascular dementia" – 17 articles. After excluding studies in duplicates, 58 articles remained. In sequence, R.K.M.F. and G.R. independently reviewed all identified abstracts and excluded articles that met any of the following criteria: (a) articles not related to VCI; (b) no original research (i.e., reviews, editorials, and letters); (c) research not focused on endothelial biomarkers. Again, any discrepancies were resolved by consensus.

From 58 articles initially identified, we excluded 16 papers in this second phase (9 reviews, 6 not related to VCI, and 1 did not study biomarkers) as shown in Figure 1. From the 42 articles included in the qualitative synthesis,

Table 1. Main biomarkers related to ED in VCI [9, 12–21, 23–30, 35–37, 40, 41, 44, 45, 48, 53–55]

Category	Reference
<i>BBB dysfunction markers</i>	
↑CSF:plasma albumin ratio	[9]
Adhesion molecules: ↑ICAM-1, VCAM-1, and sICAM-1	[9, 12, 13]
Plasmatic inflammatory markers: ↑platelet factor IV, CD40 ligand, homocysteine, interleukin-6, TNF-α, and C-reactive protein	[13–16]
Endothelial function mediators: ↑endothelin-1, natriuretic atrial peptide, von Willebrand factor, and angiopoietin-2; ↓NO synthase	[17–21]
Endothelial assembly: ↑collagen types I and IV, kallikrein 6, occludin, and claudin	[23–27]
<i>Perfusional and hemodynamic markers</i>	
↑VEGF and TGF-β	[9, 29]
No change: VEGF	[28, 30]
Neoangiogenesis	[35, 36]
↓MAG:PLP1 ratio (hypoperfusion)	[37]
↑ANGPTL4, ET-1, thrombomodulin, and dihydroxyeicosatrienoic acid	[40, 41, 44, 55]
<i>Vasoreactivity markers</i>	
↓Cerebral vasoreactivity to CO ₂	[45]
↓Peripheral vasoreactivity	[45]
↓DBF after capsaicin	[48]
<i>Other markers</i>	
↑β-amyloid 40 (vasoconstrictive effect)	[53]
↓CD34 and CD133 (endothelial progenitor cells)	[54]
↑Serum NfL (neuroaxonal damage)	[56]

ED, endothelial dysfunction; VCI, vascular cognitive impairment; BBB, blood-brain barrier; CSF, cerebral spinal fluid; ICAM-1, brain endothelial intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1; sICAM-1, plasma level of soluble intercellular adhesion molecule 1; VEGF, vascular endothelial growth factor; TGF-β, transforming growth factor β; MAG, myelin-associated glycoprotein; PLP1, proteolipid protein 1; ANGPTL4, angiopoietin-like 4; TNF-α, tumor necrosis factor-alpha; NO, nitric oxide; ET-1, endothelin-1; DBF, dermal blood flow; NfL, neurofilament light chain.

16 investigated plasma markers, 17 analyzed neuropathological markers, 4 studied CSF markers, 4 evaluated neuroimaging markers (ultrasound and MRI), and 1 dealt with peripheral Doppler perfusion imaging. The main findings of each study are summarized in online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000510053.

Discussion

Summary of Evidence

This systematic review aims to describe biomarkers that target pathways linking ED with cerebral SVD and VCI. We divided such markers into those related to BBB dysfunction, those related to perfusional and hemodynamic changes, and those that assess cerebrovascular and peripheral reactivity. Table 1 summarizes the most important known facts to each category. Some of the main

markers are represented in a schematic model illustrated in Figure 2.

Blood-Brain Barrier Dysfunction

A functional BBB depends on the adequate interaction between the many components of the neurogliovascular unit to regulate the transit of fluid and nutrients between intravascular and interstitial spaces, maintaining CNS homeostasis [9]. Biochemical markers, found in the CSF and the plasma, are related to BBB dysfunction in patients with VCI.

CSF/Plasma Albumin Ratio

The ratio between albumin levels in CSF and plasma (Qalb), though not specific, represents a commonly used method to measure the degree of disruption of BBB. Janelidze et al. [9] found increased Qalb in participants with multiple forms of dementia, although only slightly higher values were demonstrated among subjects with

Fig. 2. Schematic model illustrating some of the key markers covered in this review (customized with BioRender). ICAM-1, brain endothelial intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1; sICAM-1, plasma level of soluble intercellular adhesion molecule 1; VEGF, vascular endothelial growth factor; MAG, myelin-associated glycoprotein; PLP1, proteolipid protein 1.

VaD. These findings suggest that BBB dysfunction may be a common feature in different dementia types. Interestingly, Qalb was associated with diabetes mellitus (DM) and obesity markers were associated with increased Qalb 2 decades later [9]. These findings are in line with the expected endothelial damage induced by inflammatory and oxidative effects of chronic DM and support the pathophysiological link between vascular risk factors and dementia [9–11].

Adhesion Molecules (ICAM-1, VCAM-1, and sICAM-1)

Endothelial cells express intracellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-

1), which participate in transendothelial migration and endothelial cell activation. ICAM-1 and VCAM-1 were up-regulated in peripheral vascular dysfunction related to DM [9]. In a small subgroup of patients with DM, there is a higher CSF level of ICAM-1 and VCAM-1, which correlated positively with Qalb levels, suggesting that endothelial damage related to DM may affect cerebral vessels [9].

The measure of the plasmatic soluble portion of ICAM-1 (sICAM-1) is an independent factor for the onset and severity of white matter disease in patients older than 60 years without a history of neurological disease. In a study with VaD and AD patients, these vascular adhesion molecules had higher levels in plasma compared with the control group [13].

Plasmatic Inflammatory Markers

Markers such as platelet factor IV, CD40 ligand, homocysteine, and interleukin-6 are associated with radiological progression of cerebral SVD in patients with lacunar stroke, VaD, and vascular parkinsonism [14]. These findings are in line with the increase in interleukin-6 and tumor necrosis factor- α (TNF- α) in patients with VaD compared with late-onset AD [13]. Basolateral interleukin-6 secretion raises in dyslipidemic patients with AD, with or without vascular risk factors [15]. C-reactive protein levels were associated with reduced verbal fluency in nondementia patients with moderate-to-high cardiovascular risk [16].

Endothelial Function Mediators

Endothelial function regulators and vasodilators, such as endothelin-1 (ET-1) and atrial natriuretic peptide, respectively, are associated with an increased risk of VaD [17]. In a randomized clinical trial investigating the use of medicinal herbs in diabetic patients with VaD, both treatments (the investigational herb and the use of pioglitazone) decreased ET-1 levels after the intervention with a concomitant increase in plasma nitric oxide [18]. The nitric oxide (NO), known as an “endogenous anti-atherosclerotic” agent, is a pivotal mediator of endothelial function, and inhibitors of endothelial NO synthase, such as the asymmetric form of dimethylarginine (ADMA), were investigated in 2 registries [16, 19]. In the first, ADMA levels are independently associated with silent cerebral infarcts [19]. In the second, ADMA levels were associated with low verbal memory performance in asymptomatic patients with moderate-to-high cardiovascular risk [16].

In TREX1 mutation carriers, a genetic cause of SVD triggered primarily by ED, levels of von Willebrand factor (VWF), and angiopoietin-2 were increased. They were also related to disease activity, mainly in individuals older than 40 years [20, 21].

On the other hand, antibodies against heparan sulfate (HS Abs), a glycosaminoglycan present in endothelial cells, which plays an important role in angiogenesis, the integrity of vessels' barrier, and processes of cell adhesion were similar in patients with dementia (VaD and AD) and controls [22].

Neuropathological Findings

Neuropathological studies show structural changes in the BBB of patients with VaD with an increment in collagen types I and IV and fibrohyalinosis in brain vessels of VaD subjects [23]. In addition, there is a higher expres-

sion of kallikrein 6, whose substrates include fibronectin, fibrinogen, collagen types I and VI, and laminin [24, 25].

Tight junctions form an essential structure for the correct functioning of the BBB, and its main components are claudin and occludin proteins. In individuals with VaD, there is a rise in occludin and claudin expression, suggesting a possible compensatory phenomenon [26, 27].

Markers Related to Perfusional and Hemodynamic Changes

Angiogenic Factors (HIF-1 α , VEGF, TNF- α , TGF- β , NGF, and BDNF)

Multiple cytokines have been recently studied for their interconnected role in neuroprotective pathways associated with ischemia and hypoxia-induced brain injury. Many of these cytokines have in common a regulatory effect on the secretion of vascular endothelial growth factor (VEGF). VEGF is a cytokine secreted by astrocytes with significant neurotrophic and neuroprotective effects that binds to endothelial cells to regulate angiogenesis and vascular permeability [26–28, 31]. Hypoxia-inducible factor (HIF) is a transcription factor that mediates neuroprotective effects related to hypoxia conditioning and ischemia and induces upregulation of VEGF [28]. Nerve growth factor (NGF) and brain-derived neurotrophic growth factor (BDNF) have also demonstrated neuroprotective effects under hypoxia/ischemia-induced brain injury by inducing expression of VEGF, through a pathway dependent on HIF-1 α [28]. TNF- α is a cytokine with proinflammatory effects that upregulates transforming growth factor β (TGF- β) and induces VEGF production [29]. TGF- β has anti-inflammatory effects and also upregulates VEGF [29]. Animal models suggest that TGF- β is also associated with amyloidogenesis [29].

Janelidze et al. [9] found higher VEGF levels in CSF of patients with different forms of dementia in comparison with controls, with a slightly higher index of bioactive levels of VEGF among patients with VaD, supporting that concomitant vascular factors may participate in the pathogenesis of neurodegenerative diseases. CSF VEGF correlated positively with Qalb, which is in line with the expected increase in BBB permeability induced by VEGF [9]. However, even subgroups without increased Qalb showed higher CSF VEGF levels, which could mean that upregulation of VEGF may precede BBB dysfunction [9]. The GTC haplotype in the VEGF gene is related to VaD, supporting the pathogenic role of this angiogenic factor [33]. There is an increase in CSF VEGF and TGF- β levels in patients with AD and VaD, supporting a potential role in both forms of dementia [29]. Increased levels of intra-

thecal TNF- α have also been described among patients with stroke, AD, and VaD [29].

In contrast, Chakraborty et al. [30] found no significant difference in CSF VEGF levels across patients with VaD, AD, and controls. Ke et al. [28] also did not find significant differences in intrathecal levels of VEGF or BDNF in patients with ischemic cerebrovascular diseases and VCI compared with controls. There were, however, unexpectedly lower levels of HIF-1 α and NGF in pathological groups in comparison with controls, which were hypothesized to be secondary to the limited duration of upregulation of those markers in response to ischemia [28].

In another study, patients with VaD showed decreased secretion of VEGF by peripheral lymphocytes, similar to what was found in the healthy elderly [32]. AD patients showed a more substantial decrease in VEGF secretion, hypothesized to be potentially due to an inhibitory effect of amyloid- β 42, which could be compromising angiogenesis and the ability to maintain oxygen and nutrient delivery to the brain in those subjects [32].

Overall, these inconsistent results suggest that angiogenic factors may play a yet incompletely understood role in multiple forms of dementia, including vascular and neurodegenerative pathologies. Studies with VEGF CSF levels in AD populations have also yielded inconsistent results [29, 30, 34].

Neuropathological Findings

VaD patients have perfusional changes and neovascularization [35]. Burke et al. [36] found a higher length density of hippocampal microvessels in those cases. The vessels were narrower than those without dementia, suggesting an ineffective neoangiogenesis [36].

The white matter hypoperfusion reduces the relation of myelin-associated glycoprotein (MAG) to proteolipid protein 1 (PLP1) [37]. In subjects with VaD, this ratio is decreased [38]. A reduction in MAG:PLP1 values correspond to an elevation in VEGF levels, which associates with a raise in white matter vascular density [37]. However, this increment in VEGF has not been found in subsequent studies [38, 39]. Angiopoietin-like 4 (ANGPTL4) is a protein linked to neovascularization, whose production grows in hypoxia situations [40]. A later study on the brains of VaD patients showed an increase in ANGPTL4 levels in these individuals [41].

Cerebral hypoperfusion triggers compensatory mechanisms to restore blood flow. Endothelin (ET) is a vasoconstrictive peptide produced by endothelial vascular cells and formed by the endothelin-converting enzyme

(ECE) [42]. Therefore, a decrease in MAG:PLP1 values correlates with a decrease in endothelin-1 (ET-1) levels. However, in VaD patients, this protective mechanism fails as there is an increase in ET-1 levels and ECE-1 expression remains normal [37, 43].

Other evidence of hemodynamic changes in brains of patients with VaD is a higher expression of the antithrombotic thrombomodulin in subjects with VaD [44] and raised levels of the vasodilator dihydroxyeicosatrienoic acid (DHET) [55]. The DHET increment is likewise a compensatory mechanism since patients with the R287Q polymorphism in the soluble epoxide hydrolase gene, the enzyme that produces DHET, have a higher volume of white matter lesions [55].

Vasoreactivity

Vasoreactivity represents the vascular ability to undergo adaptive changes in response to vasodilatory stimuli, such as metabolic changes and increases in neuronal activity [1, 45]. Cerebral vasoreactivity (CVR) is strongly dependent on the normal function of the neuroglial vascular unit and may indirectly reflect the efficacy of collateral circulation [46]. Studies suggest that cerebral vasoreactivity may already be impaired when resting cerebral blood flow is still within normal ranges, making vasoreactivity markers particularly promising in patients with SVD [1]. Assessment of cerebral vasoreactivity is possible through multiple techniques, such as single-photon emission tomography (SPECT), PET, and transcranial Doppler ultrasound (TCD) [45].

Cerebral Vasoreactivity Measured through TCD

Assessment of cerebral vasoreactivity through TCD involves the calculation of the percent increase in the mean flow velocity (MFV) of the middle cerebral artery (MCA) in response to different stimuli such as acetazolamide, variation in CO₂ levels (induced by hypo- or hyperventilation), and administration of L-arginine. L-Arginine is the precursor of NO, representing a useful tool to assess vasodilation mediated by endothelial cells and executed by vascular smooth muscle cells (VSMC) [47]. On the other hand, direct administration of sublingual nitroglycerin can assess vasoreactivity independent of endothelial cells, offering a more direct assessment of VSMC function [48].

Staszewski et al. [45] showed diminished CVR in response to breath-holding maneuvers in patients with lacunar stroke, VaD, and vascular parkinsonism compared with matched controls. CVR was reduced among participants with severe brain atrophy, enlarged perivascular

spaces, and extensive white matter lesions. Both white matter lesions and CSVD burden score on MRI correlated with CVR [45].

In CADASIL patients, there is a higher MCA resting pulsatility index and increased L-arginine-induced vasoreactivity when compared with controls. These findings imply that large cerebral arteries of CADASIL subjects may present impaired endothelial function, but inconsistent results and methodological concerns argue against this interpretation [45, 46, 49, 50]. Other findings reinforce that the degeneration of VSMC from small vessels mediates vascular reactivity impairment in CADASIL [47, 48].

Peripheral Vasoreactivity

Extracerebral Vasoreactivity Measured by Doppler US Flow-Mediated Dilatation

Brachial artery flow-mediated dilatation (FMD) is a useful marker of extracerebral endothelial function in conduit vessels [45, 48]. In this technique, the diameter of the brachial artery is measured serially before and after hyperemia induced by deflating a sphygmomanometer cuff distal to the US site. In order to evaluate endothelium-independent vasodilation capacity, NTG can be administered, followed by consecutive measurements of the diameter of the brachial artery [48].

In patients with severe sporadic SVD or VaD, there is a lower FMD when compared with control subjects, in agreement with concomitant findings of reduced CVR [45, 51]. These findings suggest that in the setting of CSVD, the vasoreactivity impairment may also be found in systemic vessels and could be more easily accessible through peripheral vessels than through cerebral vessels [45]. A positive, though weak, correlation between CVR and FMD was found in CSVD patients, suggesting an association between peripheral and cerebral vasoreactivity dysfunction in this population [45]. Moreover, the significant correlation between FMD and Mini-Mental State Examination (MMSE) implies that ED relates to cognitive impairment [51]. Reduced FMD has also been reported among AD subjects, suggesting that ED may also play a role in neurodegenerative pathologies [51].

In the setting of monogenic SVD pathologies, de Boer et al. [48] employed FMD in patients with RVCL-S and with CADASIL and found reduced dilation only in the former group. Even though VSMC degeneration is a feature of CADASIL, de Boer and colleagues did not find a significant reduction in FMD after nitroglycerin administration in this population, which corroborates the belief that small vessels, rather than conduit vessels, are primarily affected in this pathology [48].

Capsaicin-Induced Dermal Blood Flow Variation

Laser Doppler perfusion imaging can access the dermal blood flow (DBF) variation in response to stimuli such as topical administration of capsaicin, with the advantage of providing information about microcirculatory vessels instead of conduit vessels, as is the case with FMD [48]. de Boer et al. [48] found reduced DBF after capsaicin application in patients with CADASIL, which is hypothesized to be associated with impairment of VSMC relaxation in response to endothelial-independent stimuli.

Forearm Resistance Vessel Function Assessment

This technique involves cannulation of the brachial artery and measures variation of forearm blood flow in response to different vasoactive agents, such as acetylcholine (induces vasodilation dependent on endothelial cells), nitroprusside (NO donor that induces vasodilation independent of endothelial function), and verapamil (directly acts on VSMC independently of endothelial cells or NO) [52]. Moser et al. [52] found a significant association between VSMC function, measured with the administration of verapamil, and performance on neuropsychological tests for initiation and processing speed in a population with early-stage atherosclerotic vascular disease. Curiously, the same was not found with endothelial function [52].

Other Markers

In a study of 149 stroke patients with SVD, β -amyloid-40 levels were correlated with diffuse SVD disease rather than isolated lacunar strokes [53]. Such findings may represent a direct and vasoconstrictive toxic effect of this peptide against the endothelium, leading to BBB dysfunction [53].

Quantitative evaluation of endothelial progenitor cells also appears to be associated with VaD and AD. Two markers, CD34 and CD133, are particularly useful in this assessment. CD34 identifies endothelial lineage cells, and CD133 allows the quantification of immature lineages, whereas the double staining of these cells allows a measure of reserve capacity and turnover of endothelial cells [54]. Xiao-dong et al. [54] found a decrease in cell levels with these markers compared with the control group, while patients with AD showed not only a quantitative reduction in progenitor cells but also a correlation with a worse performance in the MMSE.

In addition, SVD burden has been associated with the increment of serum neurofilament light chain (NfL), as demonstrated by Duering et al. [56]. In this study, serum NfL was related to processing speed performance, focal

neurological symptoms, and disability in patients with CADASIL and sporadic SVD. As a marker of neuroaxonal damage, increased NfL levels in this population suggest that axonal lesion and neuronal loss might be the ultimate consequence of a broader cascade of pathological events involved in SVD [56].

Conclusions

This review suggests an intrinsic relationship between ED and VCI, establishing the endothelium as a pivotal target involved in the pathogenesis of the disease. The biomarkers studied indicate a dynamic and whole-brain process. The BBB has its integrity affected, as demonstrated by the higher CSF/plasma albumin ratio and the increment of collagen types I and IV and fibrohyalinosis. Besides, several inflammatory markers (e.g., interleukin-6, TNF- α , and C-reactive protein) are upregulated, also impairing BBB permeability.

Hemodynamic biomarkers' dynamic, for its part, suggests a state of hypoperfusion (e.g., decrease in MAG:PLP1 ratio) and abnormal vasoreactivity (e.g., abnormal CO₂ vasodilation). As a consequence, mechanisms of compensation for ineffective neoangiogenesis (increase in ANGPTL4 and ET-1 levels and decrease in CD34+ and CD133+ progenitor endothelial cells) and antithrombogenicity (higher thrombomodulin levels) would eventually culminate in a vicious cycle of lesion progression. Finally, it is essential to note that the significant heterogeneity of subjects investigated and the multitude of different

markers, some with inconsistent results, compromise its application in clinical practice and highlight the importance of establishing this theme as a research priority.

Statement of Ethics

This research did not involve human participants or animals as this was a systematic review of existing publications, and no primary data were collected. Written informed consent was, therefore, not obtained, and ethical approval was not sought.

Conflict of Interest Statement

Dr. Pontes-Neto received research support from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq: 402388/2013-5), Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP: 2016/15236-8), and CAPES (402388/2013-5). The other authors declare no conflicts of interest.

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Author Contributions

R.K.M.F., M.C.Z., and G.R. carried out the literature search and drafted the manuscript. O.P.N. critically revised the manuscript. All authors read and approved the final version of the manuscript.

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