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The link between depression and atherosclerosis through the pathways of inflammation and endothelium dysfunction

Christina Chrysohoou[a,*], Natasa Kollia[b], Dimitris Tousoulis[a]

[a] First Cardiology Clinic, School of Medicine, University of Athens, Athens, Greece
[b] Department of Nutrition & Dietetics, School of Health Science and Education, Harokopio University, Athens, Greece

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ABSTRACT

A large body of evidence suggests that depression increases the risk of cardiovascular morbidity and mortality. The elevated risk associated with depression is not limited to clinical major depressive disorder but also extends to sub-syndromal depressive symptoms and constructs with overlapping characteristics, such as vital exhaustion. Multiple pathophysiological pathways are involved in the relationship between depressive symptoms and atherosclerosis and its clinical manifestations and progression. These underlying mechanisms are not yet fully understood and need further clarification. This review examines inflammation and endothelium dysfunction as potential biological factors involved in the relationship between depressive symptoms and atherosclerosis. It has been reported that systemic inflammation and psychological factors interact through complex pathophysiological and behavioral mechanisms and one question that has been raised concerns whether the inflammation drives depression or vice versa, or whether the association is merely coincidental. Although further investigation is needed, including well-designed prospective studies, to address this question thoroughly, it seems that there is a feedback relationship, although the biological pathways of each direction may be distinct.

1. Introduction

Depression is a serious public health concern, estimated to affect 350 million people worldwide, mainly women and older adults [1–3]. Atherosclerosis and depression are listed between the four more common medical conditions related to increased mortality and morbidity [4]; in particular, the World Health Organization has ranked atherosclerosis as the 1 st leading cause and depression the 4th leading cause of disability worldwide and projects that by 2030, depression will be the first cause. The fact that depressive disorders are more frequently characterize women and older people, in which cardiovascular disease is often underestimated and or not well managed, highlight the need for effective preventive actions in the aforementioned groups of individuals. There is a significant scientific body of evidence linking depression with atherosclerosis through various pathways, mainly through unhealthy lifestyle behaviours and neuro-hormonal system activation. However, the exact patho-biological mechanisms are not well understood and appreciated. Thus, the scope of this review was to illustrate pathophysiological pathways of depression on endothelial function and vascular pathology, which act as surrogate markers of atherosclerotic disease.

2. Methothology

A mini-review of the relevant studies performed over the time period January 2000–October 2017 was conducted in order to summarize the mechanisms underlying the depression-atherosclerosis association focusing on the role of inflammation and endothelial dysfunction.

A literature search was conducted in October 2017. The Plumbed database was used by applying the following title keyword search terms and their combinations: depression OR depressive AND atherosclerosis OR cardiovascular AND endothelium OR endothelial OR inflammation OR inflammatory; limited to studies published as journal articles in the English language. The reference lists of these manuscripts were then examined for additional titles; and the most relevant manuscripts were selected for citation based on the predetermined subheadings of the review. Reviews and meta-analyses were preferred. A narrative summary of the findings of these studies is provided.

2.1. Depression and atherosclerosis

Depression is a common mental disorder, which is currently the leading cause of disability worldwide, and is a major contributor to the

* Corresponding author at: 46 Paleon Polemiston St., Glyfada, 166 74, Attica, Greece.
E-mail address: chrysohoou@usa.net (C. Chrysohoou).

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overall global burden of disease [1,2]. It is an important public health issue with a lifetime prevalence of 4.4% to 20% in the general population [3]. A large body of evidence indicates the existence of a relationship between psychological function and atherosclerosis [4]; particularly depression has been repeatedly emerged as an etiological or prognostic factor in cardiovascular disease (CVD) development and/or prognosis [5–7]. In this association several linking mechanisms have been proposed, including unhealthy lifestyle behaviours (e.g., diet, inactivity, smoking) [8–10] as well as biological pathways (e.g., metabolic syndrome, inflammation) [11,12]. Such mechanisms could be presented in two parts: a) the first part representing the causal relationship between depression and the mediator (e.g., inflammation and/or endothelium dysfunction) and b) the second part representing the causal pathway from the mediator to atherosclerosis. Considering the widening of depression prevalence worldwide [13] and the growing body of evidence indicating widespread under-recognition and/or under-treatment of depressive disorders despite the availability of effective treatments [14], identifying and interrupting the linking pathways between depression and CVD becomes imperative.

The present work reviewed the literature on the mediating role of inflammation and endothelium dysfunction on the association between depression and atherosclerosis in order to summarize the already acquired knowledge in this field with the aim of contributing to the selection of appropriate interventions to interrupt the aforementioned risk chain. In this context, given the fact that the pathogenetic mechanisms from inflammation and endothelial dysfunction to atherosclerosis (i.e., the second part of the mediating pathway under study) are very well known, the emphasis was given to the delineation of the positive association between depression and inflammation/endothelial dysfunction (i.e., the first part of the mediating pathway under study).

2.2. The link between depression and inflammation

In relation to mood, beyond reasonable doubt, there is a robust association between inflammation and depressive symptoms. Studies consistently report that groups of individuals with major depressive disorder (MDD) demonstrate increased levels of a variety of peripheral inflammatory biomarkers when compared with groups of non-depressed individuals. Specifically, major depression is accompanied by immune dysregulation; an activation of the inflammatory response system (IRS) has been demonstrated by increased production of proinflammatory cytokines such as interleukin (IL)-1β, IL-2, IL-6, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, the soluble IL-6 receptor (IL-6R), and the IL-1 receptor antagonist (IL-1RA) [3]. One candidate mechanism for the association between pro-inflammatory cytokines and mood is the involvement of the first in the hippocampal neurogenesis which has been implicated as a key contributing mechanism in the pathophysiology and treatment of depression [15]. The influence of inflammatory activity on hippocampal neurogenesis is considered largely inhibitory; the inflammatory system of the central nervous system (CNS) is composed largely of the microglia, which may be overactivated in major depression [16,17]. Activated microglia, employ IL-6 as a key antineurogenic signal, which can interact directly with neural progenitor cells via IL-6 receptors [18]. Similarly, TNF-α has appreciable antiproliferative activity on neuronal progenitor cells via TNF receptor 1 (TNF-R1) receptors [15]. Additionally, the association between proinflammatory cytokines and mood has been related to the induction of the indoleamine-2,3-dioxygenase (IDO) enzyme, which catalyzes the rate-limiting step in the synthesis of kynurenine from dietary tryptophan [19]. Thus, the degradation of tryptophan may contribute to depressive symptoms by reducing the availability of the requisite precursor for the synthesis of serotonin and melatonin [19].

Another traditional hypothesis of depression is that people who are depressed have a deficiency in monoamine neurotransmitters in the body, which leads to low levels of neurotransmitters like serotonin and norephinephrine in the brain [20]. But growing evidence supports that at least some forms of depression may also be linked to ongoing low-grade inflammation in the body [20]. A large number of studies have linked depression with higher level of inflammatory markers compared to people who are not depressed [12,13,21]. Even brain imaging of people with depression shows an increased neuroinflammation [20].

In severe forms of depression, hypercortisolemia and dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis are often found [22]. In the literature it has been proposed that psychological stress activates the HPA axis and sympathetic nervous system, which releases stress hormones [23], while alterations in the autonomic nervous system, platelet receptors and function, coagulopathic factors such as plasminogen activator inhibitor-1 and fibrinogen, pro-inflammatory cytokines, endothelial function, neurohormonal factors, and genetic linkages such as with the serotonin transporter mechanism, are also included [24]. The increment in the circulating stress hormones, together with cytokine release induced by stress, initiate the acute-phase response triggering inflammation.

Furthermore, depression might lead to inflammation mediated by weight gain [25] where depressive symptoms promote weight accumulation, which in turn activates an inflammatory response through two distinct pathways: expanded adipose tissue stimulating the production of acute-phase proteins, including C-reactive protein (CRP) and the release of IL-6 and leptin-induced upregulation of IL-6 release by white blood cells [26].

2.3. The link between depression and endothelium dysfunction

Endothelial dysfunction predicts adult atherosclerosis but it has also been of interest as a possible mechanism linking depression to CVD [27,28]. Endothelium function can be evaluated by examining endothelium-dependent brachial artery flow-mediated dilatation (FMD). In FMD, endothelium-dependent vasodilation is elicited by a reactive hyperaemia-induced rise in endothelial shear stress [29]. In response to the latter, the endothelium increases the release of nitric oxide, which under normal functioning, leads to the relaxation of vascular smooth muscle and increased artery diameter [29]. FMD is quantified as the increase in artery diameter relative to resting baseline. This noninvasive measure correlates with more invasive measures of endothelial functioning [29]. Recent evidence suggests that the depression-CVD association may be mediated through endothelial dysfunction at an early stage of atherosclerosis contributing to depression, supported by an inverse association between depression and FMD [30]. Simultaneously, it has been observed that antidepressants improve FMD suggesting that rather than FMD effecting depression it is that depression has an adverse effect on endothelial function [31]. Additionally, while circulating endothelial progenitor cells (EPCs) are related to endothelial function and progression of atherosclerosis, their depletion has been also observed in depressed patients [32,33]. Alongside, low reactive hyperaemia peripheral arterial tonometry (RH-PAT) levels, soluble tissue factor (sTF), von Willebrand factor (VWF), and soluble intercellular adhesion molecule (sICAM)-1 (i.e., other markers of attenuated endothelial function), have been linked with depression [34,35] and it has been suggested that heightened sympathetic arousal, excessive circulating catecholamines and prolonged noradrenaline responses to stress (common situations in depression) are known to cause direct damage to the endothelium [36,37]. Thus, it has been proposed that stress-related endothelial dysfunction could be prevented by blocking cortisol production with metyrapone, demonstrating a direct or facilitative role for cortisol in the development of endothelial dysfunction [38].

Finally, another mechanism that has been suggested is through alterations in the nitric oxide (NO) system [39]. Endothelium-derived NO, through its vasodilator properties, participates in the modulation of vascular tone and inhibits a number of proatherogenic processes, such as the oxidation of low-density lipoproteins and the proliferation of smooth muscle cells [40]. Both endothelium- and platelet-derived NO