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REVIEW ARTICLE

Candidate Biomarkers to Evaluate the Association Between Psychosocial Stressors and Cardiovascular Diseases

A Short Review

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Introduction: The association between psychosocial stressors and cardiovascular diseases had been suggested.
Aims: This review was performed to assess, from literature data, the pertinence of using new biomarkers in the occurrence or prognosis of cardiovascular diseases in a psychosocial context.
Methods: We choose to consider wide-ranging descriptions of psychological stressors (occupational stress, financial strain, marital stress, social isolation, etc.) that may induce or influence the cardiovascular diseases' outcome. We addressed literature data confirming the link between candidate biomarkers, such as cortisol, endothelial dysfunction, pro-inflammatory cytokines, allostatic load, and cardiovascular diseases.
Results and Conclusion: Herein we showed a link between cortisol, endothelial dysfunction, pro-inflammatory cytokines, and the incidence or prognosis of cardiovascular diseases in a psychosocial context of stress. Allostatic load index was also identified as a pertinent tool in the assessment of the cumulative psychosocial stressors' burden exerted on the body.

Keywords: psychosocial stressors, cortisol, endothelial dysfunction, inflammation markers, allostatic load

Introduction

Cardiovascular diseases include pathological processes along the brain-heart and blood vessel axes such as intracerebral hemorrhage (ICH), transient ischemic attack (TIA), acute myocardial infarction (AMI), and peripheral arterial disease. They are considered the most frequent complications of atherosclerosis (Ross & Glomset, 1976, Roger et al., 2012). Yet, acute thrombotic complications of atherosclerosis such as ischemic stroke and myocardial infarction remain global leading causes of disability and mortality (Liberale et al., 2021). An estimated 17.9 million people died of these diseases in 2019 worldwide, representing 32% of all deaths. These deaths are mainly due to heart attacks and stroke (World Health Organization, 2021). The number of fatalities is estimated to increase to over 24 million a year by 2030, which imposes huge disability and healthcare costs (Yazdanyar & Newman, 2009).

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In addition to classic cardiovascular disease risk factors such as hypertension, dyslipidemia, visceral obesity, and diabetes (Paoletti et al., 2004), recent works have examined the role of psychosocial stressors as a potential cause of these diseases (Brotman et al., 2007; Kivimäki & Steptoe, 2018; Hagström et al., 2018; Scott-Storey et al., 2019; Peterson, 2020; Osborne et al., 2020). Major psychosocial stressors include occupational stress, financial strain, low socioeconomic status, marital stress, social isolation, perceived loneliness, and anxiety. The different components of psychosocial stressors may act alone or combine in a group and exert effects at different life course stages (Marmot, 1998; Hemingway & Marmot, 1999).

Three decades of research based on cohort studies provided evidence for psychosocial pathways leading to cardiovascular morbidity and mortality (Brunner, 2017). For example, across multiple international cohorts, unmarried patients, including those who are divorced, separated, widowed, or never married, have an increased prevalence of adverse cardiovascular events when compared to their married counterparts (Dhindsa et al., 2020). Besides, a high prevalence of cardiovascular diseases in patients with post-traumatic stress disorder was reported (Šagud et al., 2017).

The strong association between psychosocial stressors and heart diseases had been suggested in a wide range of populations, including young, older, men, women, socioeconomic strata, lifestyle, and conventional risk factors (Marmot, 1998, Yusuf et al., 2004; Rosengren et al., 2004; Nyberg et al., 2013; Diaz et al., 2014; Celano et al., 2016). Low socioeconomic status is inversely associated with coronary heart disease and it has been proposed that psychosocial pathways may play a mediating role (Matthews & Gallo, 2011; Schultz et al., 2018; Baggett et al., 2018). In addition, there is a clear social gradient in stroke mortality and morbidity, as lower socioeconomic groups worldwide have consistently higher rates of stroke than higher socioeconomic groups (Fransson et al., 2015; Booth et al., 2015; Havranek et al., 2015).

Two main mechanisms have been suggested to explain the link between stress exposure and cardiovascular disease incidence or prognosis in established diseases. The first hypothesis proposes that psychosocial stressors affect cardiovascular health indirectly, through the modification of lifestyle behaviors such as smoking, poor dietary habits, physical inactivity, medication nonadherence, alcohol consumption, and weak sleep duration (Kivimäki et al., 2012; Diaz et al., 2014; Virtanen et al., 2015). But this hypothesis does not entirely explain the link between adverse behavioral risk profiles and stress-related disorders. The second hypothesis involves a direct pathway, through dysregulation of the sympathetic nervous system (SNS) and the hypothalamus-pituitary-adrenal axis (HPA), that could induce inflammatory, metabolic, and hemostatic changes which have atherogenic effects and increase the risk of cardiovascular events (Alboni & Alboni, 2006; Pajer, 2007; Chen et al., 2013; Dich et al., 2015).

The aim of the current review is mainly focused on the identification of candidate biomarkers in cardiovascular diseases related to stress. We chose to consider wide-ranging descriptions of psychosocial stressors (occupational stress, financial strain, marital stress, social isolation…). Regarding biomarkers, special attention will be given to cortisol, endothelial function, inflammatory markers, and allostatic load.

Literature Data About Biomarkers Of Cardiovascular Diseases In A Psychosocial Stress Context

Cortisol As A Biomarker Of Cardiovascular Diseases Related To Psychosocial Stress

The adrenal cortex secretes cortisol after the activation of the Hypothalamus-Pituitary-Adrenal axis (HPA axis). This steroid hormone is involved in regulating a large panel of physiologic functions such as glucose and lipid metabolisms, body composition, and the immune system (Stalder et al., 2013). Cortisol is also called the stress hormone. The prolonged activation of the HPA axis by chronic stress may result in cortisol disruption and important metabolic dysfunction such as elevated fasting insulin and HOMA insulin-resistance index, dyslipidemia, visceral obesity, hypertension, and arterial stiffness, which is the main cause leading to cardiovascular diseases (Rosmond, 2003; Gaete, 2015; Pivonello et al., 2016; Cozma et al., 2017).

The incidence and prognosis impact of cortisol on cardiovascular diseases related to stress were widely studied. Hamer et al. provide support for the hypothesis that hyper-reactivity of the HPA axis is one of the mechanisms through which psychosocial stress may influence the risk of coronary heart disease. The authors included healthy men and women participants without history or objective signs of coronary heart disease, and they showed a prospective association between cortisol stress reactivity and progression of sub-clinical atheroscle-

rosis state, coronary artery calcification, which may lead to clinical endpoint (coronary heart disease). This association was largely independent of conventional risk factors and was most evident in participants without detectable coronary artery calcification at baseline, which further supports the notion that heightened cortisol reactivity might be important in the etiology of atherosclerosis and is not a simple marker of disease progression (Hamer et al., 2012).

Of note, the single serum cortisol measurement may be influenced by the physical stress due to the actuated illness or the emotional stress associated with hospital admission. Measurements of only one-time point may yield inconclusive results. This is especially true when we know that some other studies, using serum or saliva specimen collection, have not shown associations between cortisol and cardiovascular risk factors (Smith et al., 2005; et al., 2010); nor was it reported that low cortisol levels were associated with cardiovascular risk factors (DeSantis et al., 2011). Cortisol is an HPA axis-related hormone with a robust circadian rhythm where levels typically peak in the morning hours and decline across the day (Fiorentino et al., 2012). So, the single serum cortisol measurement may be biased by confounding factors. Scalp hair is a novel matrix that allows for the measurement hormones over several months and it is easy to assess using an Enzyme-Linked Immunosorbent Assay (ELISA) method (Wester & Van Rossum, 2015).

We cannot rule out the role of unmeasured confounding risk factors or genetic influences that might account for cortisol response patterns and cardiovascular disease risks such as Glucocorticoid Receptor (GR) polymorphism, which may be related to higher pro-inflammatory activity and greater risk (Van den Akker et al., 2008).

Endothelial Dysfunction As A Biomarker Of Cardiovascular Diseases Related To Psychosocial Stress

Endothelial dysfunction, a well-established response to cardiovascular risk factors and that precedes the development of atherosclerosis, is associated with an increased risk of plaque rupture and many adverse outcomes' manifestation. It is characterized by reducing the bioavailability of vasodilators. particularly Nitric Oxide (NO) and/or an increase in endothelium-derived contracting factors. The resulting imbalance leads to an impairment of endothelium-dependent vasodilation, which is the functional characteristic of endothelial dysfunction (Lerman & Burnett, 1992).

Evidence exists for a robust link between cardiovascular diseases and endothelial dysfunction under the effect of psychosocial stressors. In fact, in animal models – particularly non-human primates – it was shown that experimentally induced psychosocial stress, by changing the social status of female monkeys from dominant to subordinate, causes endothelial damage and accelerates atherosclerosis which in turn might impact the development and progression of cardiovascular diseases (Shively et al., 1997).

Of note, Flow-Mediated Dilation (FMD) of the brachial artery is the reference technique to measure arterial tonometry, and decreased FMD reflects decreased/impaired endothelial function. This concept has emerged as an essential indicator to predict recurrent cardiovascular events. In this context, using a community-based sample of employed individuals, Charles et al. demonstrated that female blue-collar workers had the lowest mean FMD value and those in the management/professional and services categories (white-collar) had the highest mean values. These findings suggest, moreover, that alterations in endothelial function may be one of the pathways linking occupational categories to FMD (Charles et al., 2014). It was proposed that there are several mechanisms through which occupational category may be associated with endothelial function and they include psychological stress and unhealthy lifestyle behaviors (Siasos et al., 2013). Similarly, a previous study demonstrated that participants perceiving themselves to be of lower social status in their communities exhibited reduced endothelial function (lower FMD) (Cooper et al., 2010). Furthermore, Chen et al. showed that stress score, as measured by the Depression Anxiety Stress Scales, was a powerful independent predictor for decreased brachial FMD (Chen et al., 2013). Depression, which is considered a risk factor for poor prognosis after an acute coronary syndrome (Mehta, 2011), was characterized by endothelial dysfunction and may contribute to the development of coronary artery disease (Lichtman et al., 2014).

Social isolation and perceived loneliness are also major psychosocial stressors (Udell et al., 2012; Perissinotto et al., 2012). In this regard, the best illustration of the deleterious effect of this psychosocial stress in animal research is provided by the report of Peuler et al. The authors showed, using a model system of social stressors, that the prairie vole, *Microtus ochrogaster,* a highly social rodent species, develops an impairment of vascular endothelial function after experimental isolation. This impaired endothelium-dependent vasodilation was not observed in wild animals. These findings confirm clearly that psychosocial stressors may play a role in endothelial dysfunction (Peuler et al., 2012).

Carotid Intima-Media Thickness (IMT) and ankle-brachial index are used to estimate the burden of atherosclerosis when patients are still asymptomatic. Overall increases in vascular wall thickness could indicate general vascular dysfunction. Local increases in vascular wall thickness are likely indicative of vascular remodeling and plaque formation, which precede vessel occlusion and ischemic events. Charles et al. have shown that job strain, represented by longer hours of work, is associated with higher IMT. Significant positive associations were observed between work hours and common carotid IMT among women, even after adjustment for age, race/ethnicity, education, annual household income, and cardiovascular disease-related risk factors. Moreover, longer hours of work were significantly associated with lower levels of the ankle-brachial index, which is an indicator of atherosclerosis and can serve as a prognostic marker for cardiovascular events among men (Charles et al., 2012).

Blocking cortisol production with metyrapone in healthy participants prevented adverse clinical effects such as mental stress-induced endothelial dysfunction (FMD) (Van den Akker et al., 2008). Based on the aforementioned case, it is reasonable to speculate that a strong link between cortisol and endothelial dysfunction/FMD exists. On the other hand, it is known that glucocorticoids strongly stimulate the production and release of endothelin (ET), a potent vasoconstrictor, by vascular smooth muscle cells (Provencher et al., 1998). Conversely, glucocorticoids are known to inhibit the NO Synthase (NOS), which is an enzyme catalyzing the production of NO, a powerful vasodilator and the key factor involved in the phenomenon of FMD. Taken together, this information provides arguments in favor of the role of glucocorticoids in the impairment of endothelial function in cell and tissue models (Wallerath et al., 1999; Simmons et al., 1996; Johns et al., 2001; Rogers et al., 2002). Consequently, it is no wonder that cortisol mediates the mental stress-induced impairment of endothelial function in humans.

Inflammation As A Biomarker Of Cardiovascular Diseases Related To Psychosocial Stress

Inflammation may be the starting point of the atherosclerotic process that results ultimately in a host of clinical complications, including ischemia, acute coronary syndrome, and stroke (Ross & Glomset, 1976; Paoletti et al., 2004; Deuchar et al., 2011).

Accumulating data provided an argument in favor of a positive association between stressful events, especially workplace stressors and the increased production of pro-inflammatory cytokines, such as C-Reactive Protein (CRP) and Tumor Necrosis Factor-α (TNF-α), which are closely associated with a spectrum of age-related diseases such as heart diseases and stroke (Glaser & Kiecolt-Glaser, 2005; Fioranelli et al., 2018, Eguchi et al., 2018). Similarly, it was demonstrated that psychological stress is an independent coronary heart disease risk factor associated with increased inflammation (Wirtz & von Känel, 2017).

The study of Epel et al. provided a better understanding of the underlying mechanism. According to this study, chronic stress might be associated with the premature aging of immune cells. Telomerase activity and telomere length, which are two cellular markers indicating cell aging, were measured in peripheral blood mononuclear cells obtained from mothers caring for a chronically ill child, as well as from mothers of healthy children. Of note, caregivers reported greater stress than controls. The clinical investigations demonstrated that a higher level of stress was associated with lower telomerase activity and shorter telomere length (Epel et al., 2004).

A link between stress-induced immune dysregulation and endothelial dysfunction is plausible. Thakore et al. found a positive relation between stress at work and increased perivascular inflammation (using CRP dosage) as well as endothelial dysfunction (as measured by IMT) (Thakore et al., 2007). Examining the inter-relationship among cortisol, inflammatory markers and endothelial function in a psychosocial stress-induced context would be of great interest to identify new biomarkers. Based on literature data, glucocorticoids may have a pro-inflammatory effect on the endothelium, so it is hardly surprising that cortisol is linked to the inflammatory mechanism and endothelial dysfunction (McEwen, 1998; McEwen, 2008; Kunz-Ebrecht et al., 2003; Deuchar et al., 2011).

Allostatic Load As A Group Of Physiological Biomarkers Of Cardiovascular Diseases Related To Psychosocial Stress

As we illustrated above, stress is known to lead to adverse changes in multiple biological systems, including endocrine, metabolic, and immune systems, which may eventually cause cardiovascular diseases (Juster et al., 2010). A large body of literature on stress and physiological functioning has focused on single biological markers such as cortisol and interleukin levels. Emerging research on stress, however, argues for the importance of simultaneously considering multiple processes rather than a single underlying mechanism (McEwen, 2003).

Allostatic Load (AL), a multisystem indicator of physiological changes resulting from stress, is computed using biological markers of multiple biological systems simultaneously (Juster et al., 2010). AL aims to summarize levels of physiological activity across a range of regulatory systems related to the stress response. The original formulation focused on different markers, including cardiovascular risk factors, HPA-axis activity, SNS activity, and biomarkers obtained from fasting blood (Seeman et al., 1997). Due to this multidimensionality, AL is thought to be a more comprehensive and sensitive measure of the effects of chronic stress on the body than any single biomarker (Juster et al., 2010; Gallo et al., 2014). Even when the changes in each one of these systems are modest and not predictive of health outcomes, the cluster of changes across different multiple physiological systems presents a health risk (Seeman et al., 2001). There is growing evidence that AL can measure stress-related wear and tear of the body (Mauss et al., 2015; 2016).

The traditional way of calculating an AL index has focused on the distribution of biomarkers within a given sample and then counting the number of dysregulated biomarkers for each individual (Seeman et al., 1997). AL index is constructed based on predefined cut-off values of many clinical biomarkers. Juster et al., used cortisol, Dehydroepiandrosterone-Sulphate (DHEA-S), CRP, fibrinogen, insulin, glycosylated hemoglobin, albumin, creatinine, pancreatic amylase, total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol), and triglycerides. Systolic and diastolic blood pressure values based on three resting oscillometric recordings were included; in addition, visceral obesity was assessed by waist-hip ratio. AL indices ranged from 0 to 15 (Juster et al., 2011).

Increased AL is associated with higher job demands in industrial workers in Germany and lower decision latitude and job strain in healthy Montreal workers; as well as burnout, career instability, effort-reward imbalance, and exhaustion (Schnorpfeil et al., 2003; Bellingrath et al., 2009; Juster et al., 2011; Juster et al., 2013; Mauss et al., 2015; 2016). It is worth noting that the study of Mauss et al., published in 2016 replicates the former results published in 2015 in a large sample of German industrial employees using a short form of AL. The revised form of AL included diastolic blood pressure, waist circumference, glycosylated hemoglobin, low-density lipoprotein, and heart rate variability. This short form of AL corroborated data obtained from the original one, which comprised 15 parameters. Based on these findings, the AL index is a pertinent tool in the assessment of the cumulative burden exerted on the body through variation to adapt to life's strain (Mauss et al., 2015; 2016; Gillespie et al., 2019; Veronesi et al., 2019).

Other studies found no effect of job strain on AL (Langelaan et al., 2007; Johansson et al., 2007). The number and type of biomarkers vary by study, which may explain this difference.

Strengths and Weaknesses of these Biomarkers

From the key papers that constitute this review, the data about the psychosocial stress impact on cardiovascular diseases are reliable. The evaluations of these papers used rigorous methodology which then led us to draw firm conclusions. This review highlights the potential of new biomarkers to reveal cardiovascular disease occurrence and prognosis in a psychosocial context. Biomarkers may identify new pathophysiological pathways, and help diagnosing and managing the diseases. Moreover, biomarkers able to detect earlier phases of disease development would facilitate targeted strategies to prevent pathological complications. These strategies have prognostic significance, thus they help improve patient outcomes and can assess the risk stratification in asymptomatic individuals at higher risk (Meune et al., 2014; McCarty, 2016; Smolderen et al., 2019).

Although much recent progress has occurred in identifying cardiovascular disease risk biomarkers related to psychosocial stress context, the emergence of each new biomarker or group of biomarkers raises questions of mechanistic relevance. In other words: (1) How much are these new markers worth? (2) Are the target molecules a biomarker, or are they related in a causal way to the disease pathogenesis? (3) Will the biomarkers help clinicians to improve patient outcomes? (4) How should clinicians incorporate these new biomarkers into clinical practice/standard care? (5) What overall diagnostic improvement do these new biomarkers offer? (6) Several differences exist between women and men in the incidence, clinical course, outcome, and comorbidities, so more attention should be given to the above differences to counteract these confounding factors (Vaccarino & Bremner, 2016; Vaccarino et al., 2016). (7) The potential role of genetics in these complex relationships is unknown. Individuals who have special variants of the polymorphisms associated with an increased production of cortisol, for example, may show worse immunological dysregulation when confronted with stressful events. (8) We should keep in mind that overall, the most powerful indexes are based on a combination of data, including clinical, electrocardiographic, and biological measurements (Meune et al., 2014; Dona et al., 2016; Emdin et al., 2016). Finally,

data replication in larger studies remains necessary to reveal the concrete significance of these biomarkers in the development or prognosis of cardiovascular diseases.

Conclusion

Our study mainly focuses on identifying new candidate biomarkers for cardiovascular diseases related to psychosocial stress. In this review, we addressed literature data approving the link between cortisol, endothelial dysfunction, inflammation, and AL in the development and progression of these diseases. Of note, alterations in neurohormonal stress response systems (catecholamines) happen quickly following an exposure to stress and cannot be used as a biomarker to traduce underlying chronic psychosocial stress exposure (Kvetnansky et al., 2013; Carter & Goldstein, 2015).

Here we chose to collect data from a wide range of cardiovascular diseases to garner more information on the effect of psychosocial stress. We considered wide-ranging descriptions of psychosocial stressors that may influence a physical health outcome through a psychological mechanism.

Psychosocial stress is theoretically modifiable. It is currently the subject of increased attention through interventions based on stress reduction. Many studies are addressing the role of stress prevention in cardiovascular disease development and progression in comparison with lifestyle risk factors and standard risk factors. Most behavioral interventions designed to attenuate the stress based on health educational program, music therapy (Orth-Gomér, 2012; Atiwannapat et al., 2016), and pharmacological tests, based on randomized controlled trials of anti-depressant treatment (Baumeister et al., 2012), to reduce psychosocial stress in the primary and secondary prevention of cardiovascular diseases, have not shown a real benefit. However, mind-body interventions such as regular yoga practice and tai chi seem very promising in this field. Curiously, compelling evidence suggests that these practices have generally produced positive immune and endocrine changes and might be the main strategies to avoid the negative effects of occupational stress (Antoni et al., 2000; Irwin et al., 2003; Andersen et al., 2004; Segerstrom & Miller, 2004; Huang et al., 2013/4; Manchanda & Madan, 2014; Tyagi et al., 2016; Chan et al., 2018).

Recent technological advances, including the signature emerging from multiple omics approaches. For instance, transcriptomics could potentially capture the inherent biological state during psychological stress. The approach using data-driven computational modeling has raised the prospect of identifying the potential of new candidate biomarkers. The further assessment of these signatures regarding for example oxidative stress, inflammation, vascular smooth muscle cell proliferation, and thrombosis in diverse populations, will be essential to make the underlying pathological process of cardiovascular diseases related to psychological stress context more comprehensive. We posit that this strategy may contribute to determining and deciphering the complex underlying process and merits further attention, particularly when considering the impact of such cardiovascular disorders on public health.

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Author contributions

Hanène Ayari: conceptualization, design, methodology, investigation, project administration, data management, formal analysis, interpretation, writing original draft, writing review and editing.
Marianne Zeller: supervision, writing review and editing.
All authors gave their final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors declare no conflicts of interest to disclose.

Ethical Statement

This manuscript is the authors' original work.

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Abbreviation's list:
AMI: Acute Myocardial Infarction
AL: Allostatic Load
CRP: C-Reactive Protein
DHEA-S: Dehydroepiandrosterone-Sulphate
ELISA: Enzyme-Linked Immunosorbent Assay
ET: Endothelin
FMD: Flow-Mediated Dilation
GR: Glucocorticoid Receptor
HDL-cholesterol: High-Density Lipoprotein-Cholesterol
HPA axis: Hypothalamus-Pituitary-Adrenal axis
ICH: Intra-Cerebral Hemorrhage
IMT: Intima-Media Thickness
NO: Nitric Oxide
NOS: Nitric Oxide Synthase
SNS: Sympathetic Nervous System
TIA: Transient Ischemic Attack
TNF-α: Tumour Necrosis Factor-α

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