



Inflammation Atherosclerosis and Psychological Factors

35

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Abstract

Inflammation plays an important role in the etiology and pathophysiology of cardiovascular disease and its most common form, atherosclerosis. The present chapter provides the reader a short synopsis of the role of inflammation in the etiology of atherosclerotic cardiovascular disease (ACVD) and lists the most commonly used markers of inflammation and corresponding measurement

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techniques. With respect to behavioral and psychological factors, this review focuses on relevant studies that have examined the unique associations between inflammatory markers and psychological and behavioral factors associated with an increased risk of cardiovascular disease. These factors include major depressive disorder, severity of depressive symptoms, hostility, and anger. This review also describes an emerging body of evidence suggesting that combinations of psychological factors, and most prominently the combination of hostility and depressive symptoms, may be better predictors of inflammation than any single factor. The chapter concludes with a discussion of the bidirectional nature of the relationship between inflammation and psychological factors as well as the mechanisms potentially underlying these associations.

Keywords

Inflammation · Behavioral factors · Psychological factors · Depression · Hostility

In the last 70 years, significant progress has been made in our understanding of the etiology and pathophysiology of cardiovascular disease and its most common form, atherosclerosis [91]. Despite these advances, cardiovascular disease remains the number one cause of death worldwide with one-third of all deaths globally due to cardiovascular disease [178]. Such numbers underscore the challenges posed by the complex and multifactorial nature of cardiovascular disease and how to translate laboratory and experimental findings to clinical applications. The same is true for the area of cardiovascular behavioral medicine, where researchers and healthcare providers face not only the complexities of the atherosclerotic disease processes but also the multidimensionality and variability of human behavior, psychological traits and states, and their putative influences on cardiovascular disease onset and progression.

Including a chapter on inflammation in this volume attests to its critical role in the etiology and pathophysiology of cardiovascular disease and the progress that has been made in understanding its association with behavioral, psychological, and stress-related factors. For the most part, prior to 1990, atherosclerosis was viewed simply as a lipid storage disease. During this same period, researchers in the area of cardiovascular behavioral medicine focused their efforts on identifying whether lipid levels were associated or predicted by lifestyle factors (e.g., obesity, sedentary lifestyle, smoking, high-fat diets) and the Type A behavior pattern [131–133]. Today, the inflammatory nature of atherosclerosis has stimulated behavioral scientists to examine the relation of psychological, behavioral, and stress-related factors to peripheral measures of inflammation and aspects of the inflammatory response system. Accordingly, in this chapter, I review evidence for the relation of psychological factors to cellular-mediated immune responses and inflammation that contribute to atherogenesis (i.e., steps leading to formation of fatty deposits and plaque in the inner lining of the arteries). While there remain many unanswered questions

about the relation of inflammation to psychosocial and behavioral factors, the weight of the evidence suggests that psychological factors, and especially those aspects associated with negative traits and affective states, are associated with inflammation as indexed by elevations in inflammatory markers such as increases in white blood cell count [36], higher levels of circulating inflammatory proteins [159], and cell-mediated immune activation as measured by production and expression of pro-inflammatory cytokines [96]. Ultimately, testing the causal association between inflammation and psychological factors may require longitudinal studies and randomized controlled trials that may shed light on the nature of this association.

This chapter first provides a short review of the role of inflammatory processes in atherosclerosis and factors that potentially initiate and promote inflammation. This section is followed by a short section describing available techniques useful in measuring inflammation relevant to research in cardiovascular behavioral medicine. Lastly, I review the evidence stemming from studies that have examined the relation of inflammatory markers to putative psychological and behavioral risk factors of cardiovascular disease with an emphasis on major depressive disorder [174], depressive symptoms severity [78], hostility [175], anger [164], Type D personality, and their combinations [164].

The Inflammatory Response

Inflammation has long been recognized in the history of medical literature. *De Medicina*, a tome published in the first century by Celsius, included a description of the observable consequences of inflammation: *rubor* (redness), *tumor* (swelling), *calor* (heat), and *dolor* (pain) [52, 151]. Today, we recognize that at its most basic function, inflammation is a protective mechanism activated in response to injury, infection, or irritation [104]. The body's inflammatory responses serve not only to protect the host but also to remove the injurious stimuli and to promote healing, processes necessary for maintaining homeostasis [129]. The failure of an inflammatory response to terminate, however, raises significant health consequences to the host, and this is now understood to be the case for the effects of chronic inflammation in the pathophysiology of atherosclerotic cardiovascular disease (ACVD) [90].

Inflammation can be characterized on the basis of its duration and clinical appearance. Active (or acute) inflammation is the process that occurs within a few hours to days following an injury and acute infection. Acute inflammation exhibits the four cardinal signs of inflammation (redness, swelling, heat, and pain) and represents the body's effort to eliminate the injurious agent/factor and allow the process of healing and repairing to begin. Chronic inflammation refers to a pathological condition characterized by continued inflammatory activities over long periods of time. Although asymptomatic at times, chronic inflammation may include the loss of proper function of the affected tissues such as that observed in many autoimmune diseases [87].

Components of the Inflammatory Response: Proinflammatory and Anti-inflammatory Cytokines

Immune system responses are regulated by antigen-presenting cells (APC). The APC include cellular components of innate immunity, such as phagocytic cells (e.g., monocytes, macrophages, dendritic cells), natural killer cells, mast cells, eosinophils, and basophils, and of acquired (or adaptive) immunity, such as T-lymphocytes and B-cells. As its name suggests, acquired immunity is not present at birth but develops as individuals are exposed to foreign substances (antigens) such as viral and bacterial infections as well as vaccinations. For adaptive immunity, exposure leads cells to acquire memory for how to attack antigens, adapt to responding to the antigens, and remember how to respond. It has been suggested that the pathogenesis of atherosclerosis involves both innate and adaptive immunity [64]. T-lymphocytes are differentiated into cytotoxic and helper cells by surface marker with T-helper (Th) cells further separated into two subtypes depending on patterns of secreted cytokines [156]. The Th1 cells promote cellular immunity and secrete Th1-type cytokines that include interferon (IFN)- γ , interleukin (IL)-2, and tumor necrosis factor (TNF)- α ; Th2 cells secrete Th2-type cytokines that include IL-4, IL-13, and IL-17. With the framework of ACVD, Th1 cytokines, the principal being IFN- γ , initiate and amplify the proinflammatory response thought to underlie atherosclerosis [50]. Th2 cytokines are anti-inflammatory and thus counteract the effects of Th1 cytokines by protecting the host. In studies that evaluate cellular-mediated responses, researchers have used the Th1-to-Th2 ratio to better characterize patterns of cytokine responses with higher Th1/Th2 ratio values, or a dominance of Th1-type cytokines, suggestive of an inflammatory response. Not surprisingly, higher Th1/Th2 ratio values have been associated with a range of inflammatory conditions including coronary artery disease [167].

Triggers of Chronic Inflammation

A wealth of evidence suggests a link between inflammation and traditional risk factors such as smoking [69], hypertension [48, 143], diabetes mellitus [7], abdominal obesity [122], sedentary lifestyle [1], (pre)diabetes [61], insulin resistance [28, 49, 48], and metabolic and hemostatic factors [115] and to a lesser extent lipid constituents [56]. It has also been suggested that inflammation is associated with poor oral hygiene, a putative risk factor for ACVD [37]. The associations between inflammation and traditional risk factors appear to be robust and have been reported in disparate subgroups such as healthy middle-aged and elderly adults [73] and adolescents and children [44] and in a variety of patient populations [108, 182]. In addition to cardiovascular disease, chronic inflammation has also been identified as a key feature of many chronic diseases including chronic obstructive pulmonary diseases (COPD) [51], asthma [107], rheumatoid arthritis [38], systemic lupus erythematosus (SLE), psoriasis, and cancer [35]. For these conditions, inflammation

is thought to be a part of the specific disease process that contributes to the increased risk of ACVD observed in individuals with these conditions (e.g., [62, 63, 71]).

Although the associations between markers of inflammation and traditional risk factors of ACVD have been well characterized, emerging evidence suggests that inflammation is also linked to psychological factors associated with an increased risk of ACVD. These include stress-related negative emotions (anger, depressive mood, anxiety) and personality traits (hostility, optimism, type D). In addition, inflammation has also been associated with stress-related mental disorders such as major depressive disorder [130], post-traumatic stress disorder [54], anxiety disorders [173], and schizophrenia [75], disorders also associated with increased risk of cardiovascular disease. If psychological and behavioral factors, as well as clinical disorders, are associated with inflammation, then an important question to address is whether these associations are causal (psychological factors precede and promote) or correlative (are psychological factors correlated with inflammation) or both [9]. As described in this chapter, evidence supports an association between measures of inflammation and psychosocial factors associated with increased risk of coronary artery disease (CAD) [137]. It is not well understood, however, if psychological factors precede inflammation and thus potentially act as triggers of inflammation. Preliminary evidence suggests that stress-related neuroendocrine and adrenergic responses, associated with personality traits (e.g., hostility) and states (e.g., anger), may influence inflammation via inhibition (via cortisol) or activation (via catecholamines) of the transcription factor called nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) [12]. Activation of the NF- κ B pathway promotes the expression of a number of genes required to upregulate cytokine-producing immune cells [105, 180].

Atherosclerosis as an Inflammatory Disease: The Development of Hypotheses

The Atherosclerosis and Lipid Hypothesis

It was originally speculated that atherosclerosis and its clinical sequelae were degenerative diseases associated with aging [43]. This original assumption was challenged by Anichkov in the early 1900s who showed that rabbits fed a cholesterol diet developed atherosclerosis [43, 153]. Surprisingly, Anichkov's findings were not well recognized, and it was not until 1950 that Gofman and his colleagues acknowledged the early work of Anichkov and replicated his early findings [57]. Gofman et al. also discovered differences in cholesterol molecules as a function of molecular weight, recognized today as low-density lipoprotein (LDL) and high-density lipoprotein (HDL) [57]. Gofman et al. [57] observed that the low molecular weight molecule, LDL, was elevated not only in patients with documented myocardial infarction (MI) but also in patients with diabetes. The latter observations in individuals with diabetes were particularly insightful at the time since it was recognized that diabetes was associated with cardiovascular disease (CVD) and CVD-related death.

The 1950s and 1960s saw a wealth of information emerge from the Framingham Heart Study, evidence that further strengthened the role of cholesterol and its constituents in the onset and progression of atherosclerosis [22]. Among the many landmark findings from the Framingham Heart Study was evidence suggesting that the risk of ACVD reflected the presence of a number of (risk) factors that included cholesterol, triglycerides, and HDL [22]. The risk of ACVD appeared to increase with higher levels of cholesterol *and* decrease with higher HDL levels [23, 24]. Together, the evidence from the Framingham Heart Study strengthened the argument that ACVD is multifactorial with cholesterol and fat intake as central components. Even after 50 years since those early Framingham publications, those early findings form the bases for current intervention and cardiac rehabilitation programs that focus on reducing cholesterol and fat intake.

Atherosclerosis and the Response to Injury Hypothesis

The mid-1970s was another period of significant advances in our understanding of atherosclerosis. Ross and Glomset proposed that the initiation and progression of atherosclerotic lesions (atheroma) were characterized by *cellular responses to endothelial dysfunction* attributed to injury [136]. As proposed, vascular responses to injury include the migration and proliferation of smooth muscle cell (SMC) in the outer part of the blood vessel [136]. In addition to hyperlipidemia, Ross and Glomset postulated that sources of injury to the endothelium included homocysteine (a common amino acid), uremia (imbalance of fluid, electrolytes, and hormones due to poor kidney functioning), metabolites, infection, immunologic injury, and mechanical forces. It was speculated that injury to the blood vessel altered the relationship between endothelial cells (EC, cells that line the interior surface of blood vessels) and the underlying layer of connective tissue, changes that facilitated the detachment of EC from the artery wall. Endothelial dysfunction also promoted adherence and aggregation of platelets at the site of the injury. Platelets released platelet-derived factors (proteins that regulate cell growth of blood vessel tissue) at the site of the injury and, in conjunction with lipoproteins, promoted SMC proliferation and/or continued proliferation by already existing SMC, the latter suggestive of the progressive nature of the disease. As initially described, the response-to-injury hypothesis emphasized *endothelial dysfunction* as the critical first step in atherogenesis. It would not be until the mid-1980s to early 1990s that atherosclerosis would be recognized as an inflammatory disease [134, 135].

Atherosclerosis and the Inflammation Hypothesis

The response to injury hypothesis underwent several revisions. As initially proposed, the emphasis was placed on *endothelial dysfunction* as the critical first step in atherogenesis. Current versions of the hypothesis, however, point to *endothelial*

dysfunction in response to injury as the potential first step [135]. *Endothelial dysfunction* is a pathophysiological state whereby the inner lining of blood vessels (endothelium) fails to maintain homeostatic balance between vasoconstriction and vasodilation. It has been posited that factors that cause “injury” not only promoted endothelial dysfunction and vascular permeability but also stimulated EC to express vascular adhesion molecules and to secrete cytokines (signaling molecules of the immune system) that are chemotactic (factors that influence cells to migrate toward or away from stimuli) to circulating leukocytes and SMC. In characterizing atherosclerosis, Ross suggested that regardless of what first event occurs, whether EC detachment or endothelial dysfunction, the progression of atherosclerosis included cellular and molecular constituents consistent with chronic inflammation in the artery [134, 135]. As postulated by Ross, the role of inflammation in ACVD echoed an early hypothesis by Rudolf Virchow who in 1856 posited that atherosclerosis was caused by plasma components that evoke an inflammatory response in the arterial wall [183]. Today, chronic and excessive inflammatory responses to injury either precede or accompany a fibroproliferative response [86]—a combination that characterizes atherosclerotic lesions.

The significance of inflammation in atherosclerosis is such that its impact on disease risk is noted even in the absence of elevated lipids and other traditional risk factors [126]. Thus, elevations in C-reactive protein (CRP), an acute phase protein commonly used to assess non-specific inflammation, have been consistently shown to provide prognostic information on the risk of future vascular events [124]—information that is comparable to that provided by elevations in cholesterol and blood pressure [13, 125]. Inflammation is implicated not only in the initial response to injury but also at all stages of atherogenesis, from initiation and growth of lesions to complications of the atherosclerotic plaque [88, 119]. In atherosclerosis, the effects of inflammation represent a significant departure from its primary role as a protective response [104].

The earliest type of atherosclerotic lesion is the fatty streak. The fatty streak consists of lipids and inflammatory cells such as monocyte-derived macrophages and T lymphocytes. At this early stage, inspection of the vessel wall shows small formation of isolated groups of macrophages containing lipid droplets (foam cells) [152]. Formation of foam cells is the result of macrophages ingesting lipids (low-density lipoprotein (LDL), including oxidized and minimally modified LDL), via scavenger receptors [144]. The modified LDL stimulates the innate and adaptive immune system to mount an inflammatory response that includes activation of T cells that release IFN- γ and lymphotoxins (a cytokine previously referred to as tumor necrosis factor- α) that subsequently stimulate macrophages, vascular EC, and SMC. The presence of macrophage foam cells represents not only an immune response to atherogenic lipoproteins, such as minimally modified LDL and oxidized LDL, but also an indicator of lipoprotein accumulation in the blood vessel. Progression of the fatty streak is accompanied by stratification of macrophage foam cells in adjacent layers and the incorporation of lipids into intimal SMC. Overall, these vascular changes are considered characteristics of early lesions, the fatty streaks,

which have been observed in animal models of early stages of atherosclerosis [72] and in arteries of young adults and children [8, 116], even though they are at low risk of developing clinically important atherosclerosis.

Progression of early lesions (asymptomatic phase) to clinically symptomatic lesions involves mechanical forces that act on the vessel walls. For example, shear stress acts on the vessel wall and particularly at locations of the arterial tree that are prone to develop fatty deposits. Low shear stress promotes permeability of the vessel wall promoting longer periods of interaction between circulating atherogenic particles, such as LDL, and the artery wall. In these areas, lipid accumulation promotes the development of additional layers of macrophage foam cells that grow with time. In individuals with elevated cholesterol levels, these conditions are likely to be more pronounced, thus hastening the progression of asymptomatic lesions to more advanced symptomatic lesions. In advanced stages of the atherosclerosis, lesions show physical changes that reflect accumulation and development of the lipid core—a condition that characterizes the most advanced lesions. The advanced lesion associated with ischemic events (a condition in which blood flow is restricted, thus reducing oxygen to that area) is characterized not only by the presence of the lipid core but also by structural changes in the intima. In the advanced stage, inflammatory cells continue to play a role in precipitating events leading to an acute coronary event—the rupture of the lesion due to the instability of the fibrous cap. It is important to state that not all fibrous caps are unstable. The stability of the cap depends upon its characteristics. For unstable lesions, production of certain enzymes by macrophages alters the strength of the plaque's cap, making it thin and unstable and therefore more likely to rupture [89]. In addition to macrophage-produced enzymes, activated T cells produce IFN- γ that halts collagen synthesis by SMC which contributes to an unstable fibrous cap. Other inflammatory mediators, such as macrophage-derived tissue factor, act as the major procoagulant and trigger the formation of the thrombosis due to plaque rupture.

That inflammation plays a key role in the onset and progression of ACVD is no longer in question. What is not well understood, however, is whether inflammation precedes disease or is a risk marker (concomitant presence with disease) [117]. It may be the case that inflammation plays an active *causal* role leading to atherosclerosis or is it a measured indicator of the disease process itself? While addressing these issues is beyond the scope of this chapter, it is important that the reader keeps these two possibilities in mind. What is reasonable to state at this time is that inflammation appear to be not only a consequence of ACVD [76] but also a precipitating causal contributor [25].

In the following sections, a similar issue is raised with respect to the relationship between depression and inflammation; is inflammation a causal factor of depression and/or low mood *or* is inflammation a correlate of depression? This question arises from the possibility that the relationship between inflammation and depression is bidirectional such that depression precedes inflammation and that inflammation promotes depression [121]. The bidirectional nature of this link has been at the center of discussions that focus on understanding the high prevalence of mood disorders in many inflammatory conditions such as cardiovascular disease [124].

Measures of Inflammation in Clinical and Research Settings: Relevance to Cardiovascular Behavioral Medicine

In the last few decades, considerable technical advances have been made for assessing inflammation and its components. Early studies that assessed inflammation relied on measures of white blood cells and fibrinogen [70, 102, 181]. Today, the array of inflammatory markers that can be measured is considerable given the advancement of techniques that detect relatively low levels of systemic inflammation, levels that are considerably lower than those levels associated with acute trauma or clinical diseases. Progress in this area is best illustrated by the development of the high sensitivity (hs) CRP assay which allows for very low CRP levels to be detected—levels that are considered within the normal range [124]. While CRP, a prototype marker of the inflammatory process, is elevated in many inflammatory disorders and can increase 1000-fold in response to inflammatory stimuli, levels of CRP associated with increased risk of cardiovascular disease are usually below 10 mg/L, a range not associated with acute infections, trauma, or active inflammatory diseases.

C-reactive protein was discovered in 1930. It was not until the 1940s that CRP was described as an acute-phase reactant that appeared to be elevated among patients with conditions characterized by inflammation [101]. In addition to CRP, acute-phase reactants include serum ferritin, serum albumins, serum amyloid A, and transferrin, proteins that are continually produced in the liver and rise in concentration during inflammation and in response to the release of cytokines from macrophages and monocytes. In the 1980s and 1990s, publications of numerous prospective and cross-sectional studies linked CRP to atherosclerosis [79]. The challenge, however, was that CRP levels associated with cardiovascular risk, but not an acute cardiac event, are often below the detectable levels of available assays. This stimulated the development and validation of the high sensitivity assay [113]. Today, the commercial availability of high sensitivity (hs) CRP assays allows physicians and researchers to evaluate CRP *in vivo* with greater sensitivity and reliability. The hsCRP assay is just one of numerous *in vivo* tests used to examine immune system status and responses *in situ*. These new tests include commercially available kits for humoral measures of complement (e.g., C3, C4), α 1-acid glycoprotein, α 1-antitrypsin haptoglobin, immunoglobulin, and measures of circulating cytokines and their soluble receptors.

With technical developments in methods to assess inflammatory markers, the selection of assay in clinical settings remains a clinical judgment guided by the relevance of the marker for diagnosis and risk determination [124] and treatment [111]. Selection of assays in the research settings, however, should take into account additional factors including characteristics of the study population (e.g., age, sex, health status, medication use), sampling rates (e.g., hours vs. days vs. years vs. decades), and storage (e.g., fresh vs. frozen samples; see below), within the context of the scientific question being addressed. With respect to the aims of the study, researchers must consider whether assessment of inflammation is best done by measuring humoral factors or by procedures used to assess enumerative and functional aspects of cellular inflammatory responses. For example, assessing enumerative changes (changes in cell subpopulations characterized by specific cell markers) can be done by flow cytometry that measures the number and percentages of various

immune cell subpopulations by detecting (referred to as gating) specific cellular markers expressed by the selected cell population of interest (e.g., positive on the expression of cellular surface markers such as CD14, CD56, CD11/CD18). Flow cytometry has also been used in measuring intracellular cytokine expression by specific cell types that are identified by the presence of a surface marker [68]. Flow cytometry can be used in samples that are unstimulated by laboratory exposure to inflammatory stimuli and stimulated (e.g., exposure to lipopolysaccharide (LPS) and phytohemagglutinin (PHA)) so as to evoke an inflammatory immune response.

A cursory review of articles published in recent years shows that the most frequently used commercial assays to assess circulating levels of inflammatory biomarkers are those that assess (a) soluble adhesion molecules such as E-selectin, P-selectin, intracellular adhesion molecules-1, and vascular cell adhesion molecules-1; (b) cytokines such as interleukin (IL)-1[β], IL-6, IL-8, and IL-10 and tumor necrosis factor- α ; (c) acute-phase reactants such as fibrinogen and hsCRP serum amyloid A; and (d) white blood cell counts (e.g., total white blood cells, number of mononuclear blood cells). While this list is not exhaustive, it provides the reader with a sense of the arsenal of techniques used to measure inflammation within the context of ACVD.

The above-listed assays allow clinicians and researchers to assess circulating and cellular levels of biomarkers associated with inflammation with relative ease. Markers of inflammation such as white blood cells are simple to perform. In the case of hsCRP, commercially available assay kits allow not only measurement of low levels but also comparison of results across research studies. Selecting the appropriate assay also takes into account the research questions. Does the question address inflammation per se that is independent of source? If this is the aim of the researchers, assays that assess non-specific measures of inflammation are appropriate. This is the case for CRP, which is released by the liver, and IL-6, which is released by adipose tissue, monocytes, and macrophages, and thus they do not reflect any specific disease, disease process, or injury but are non-specific indicators of an inflammatory response. Thus, elevated IL-6 and hsCRP levels may reflect various factors including adiposity, smoking, physical activity, asymptomatic disease, acute infection, and injury. Interpreting results takes into account characteristics of the study samples including overall health status and vitals such as weight, age, and medications. Given the non-specific nature of some peripheral markers of inflammation, it is not unusual for reported statistical associations between non-specific markers of inflammation and psychosocial variables to diminish or disappear in models that statistically adjust for potential confounding factors such as age, adiposity, smoking, gender, dietary or multivitamin supplements, exogenous hormones, etc. (e.g., [146]).

Inflammation in Cardiovascular Behavioral Medicine: Shared Genetic Influences

Advances in genome-wide association studies have led to important new evidence for common genetic factors that influence both inflammation and psychosocial

factors, most noticeably depression [157, 170]. For example, in one study, genetic modeling found a significant association between depressive symptoms and IL-6 indicating that approximately 66% of the covariance was explained by shared genetic influences [157]. In a study of male-male twins, it was found that a history of depression was a risk factor for incident heart disease (IHD) with twins with both high genetic vulnerability for IHD and phenotypic expression of depression at greatest risk for IHD, suggesting that genetic influences of IHD are shared with depression [179]. While there is much to be done in this area, it is important that researchers are aware of the complex nature of inflammation and the potential role of genetic influence on both cardiovascular disease and psychological factors.

Inflammation and Psychological Factors: A Biopsychosocial Model of ACVD

In this section, I review the evidence for the relation of inflammation to psychological factors. In doing so, the following will be addressed: (a) the combined or joint effects of psychological factors on inflammation and (b) how inflammatory conditions and medical treatments that evoke inflammation often induce behavioral symptoms associated with depression. The focus of the review is on factors that have been rigorously tested and shown to prospectively predict ACVD severity and clinical manifestations: negative emotional states such as depression, depressed mood, anxiety and anger, and dispositional traits such as neuroticism, hostility, and optimism/pessimism. While this list is not exhaustive, it represents the range of psychological and behavioral factors that have been linked with an increased risk of CVD.

Personality Traits and Inflammation

The prevailing framework used to describe normal personality is the Five Factor model (sometimes referred to as the Big-Five of personality) [58, 176]. Personality theorists suggest that normal personality can be described using five dimensions: neuroticism (N), extraversion (E), openness (O), agreeableness (A), and conscientiousness (C) [58]. A number of self-report scales have been developed to assess these five dimensions, one example being the NEO-Personality Inventory (PI) [34]. The NEO-PI yields scores on the five principal domains (dimensions) of personality as well as subscores on underlying traits (or facets) [34]. Poor cardiovascular outcomes have been independently associated with N, O, A, and C [141] with evidence also suggesting that ACVD is associated with the individual trait components depression, anxiety, and angry hostility [67].

Another personality trait associated with increased risk of ACVD is the Type D personality construct [80]. The Type D personality is an individual's tendency to experience negative emotions and social inhibition [39]. In a number of studies, Type D personality has been associated with CVD [39]. Risk of CVD has also been

associated with hostility [29], a multidimensional dispositional trait. Emphasizing the positive dimensions of personality, there is evidence suggesting that optimism is negatively associated with cardiovascular disease outcomes [123]. In general, evidence suggests that neuroticism [147, 168], Type D personality [42], trait hostility, and trait anger [29, 168, 177] are significantly associated with progression and severity of atherosclerotic disease and future risk of CVD and, in patient populations, poor prognosis [80, 142].

Personality Factors and Markers of Inflammation

A number of studies have examined the relation of the five dimensions of personality to markers of inflammation in both healthy adults and patient samples. Although negative findings have been reported [26], it appears that the domains of (high) N, (low) C, and (low) O, alone or in combination, are associated with elevations in interleukin (IL)-6 [16, 26, 27, 165, 166]. The association between C and inflammation was further supported by results of a recent meta-analytic study whereby high CRP and IL-6 were associated with low C, an association that remained even after statistically adjusting for the effects of smoking and adiposity [95]. In that same meta-analysis, N, E, and A were not associated with CRP and IL-6.

In addition to the Big Five, inflammation has been linked to individual personality facets. For example, higher level of IL-6 is associated with higher scores on the NEO-PI subscales of angry hostility [100] and impulsiveness [166], both facets of N. To date, few studies have evaluated the *prospective* relation of personality and inflammatory markers. In a 4-year longitudinal study that employed the NEO-PI, changes in CRP and fibrinogen were independently associated with high neuroticism and low extraversion [6]. Moreover, the study also found synergistic effects of high neuroticism and physical inactivity at entry and at 4-year follow-up for CRP and fibrinogen but not with changes in levels over time. In contrast, Boyle et al. [17] observed changes in C3 over a 10-year follow-up period. In that study, subscales of the Minnesota Multiphasic Personality Inventory (MMPI) were used to assess depression, anger, and hostility. Over a 10-year period, increases in C3, but not C4, were associated with higher depression, anger, and hostility and with the combination of the three factors [17]. Complement C3 is produced by liver, adipocytes, and macrophages at inflammation sites, and it is associated with CRP and waist circumference. Using the NEO-PI, Chapman et al. [27] showed that in a 34-week follow-up period, low conscientiousness and openness was associated with higher IL-6. While there is a paucity of evidence, the data suggest that personality factors at entry predict increases in inflammatory markers over time with some evidence for synergism between factors and with demographic variables such as sedentary lifestyle.

Trait Hostility and Anger

One of the first studies to report a relationship between hostility, anger, and inflammation was published in 2002 [161]. In that study, hostility and its components were

assessed using the Buss-Perry Aggression Questionnaire (BPAQ), a scale that purports to assess four dimensions of aggression: hostility, anger, physical aggression, and verbal aggression [10]. Inflammation was assessed using *in vitro* LPS-stimulated expression of TNF- α by peripheral monocytes. In a fully adjusted model, greater stimulated production of TNF- α was associated with greater overall aggression (total score) as well as greater hostility, physical, and verbal aggression [161]. These initial findings were subsequently extended by Coccaro [31] who showed that increases in CRP were associated with higher hostility and aggression scores on subscales of the Buss-Durkee Aggression Questionnaire, the predecessor to the BPAQ. Consistent with the original findings in 2002, the observations by Coccaro were not attenuated by adjusting for potential confounders.

Other measures of inflammation have been linked to hostility and anger. For example, Shivpuri et al. [148] examined the effects of trait cynical hostility and trait anger on soluble intracellular adhesion molecule (sICAM) in healthy middle-aged Mexican-American women. In that study, the Spielberger's Trait Anger scale was used to assess anger, anger temperament, and anger reaction, the latter two dimensions of anger. Anger temperament is thought to reflect a predisposition toward quick, unprovoked or minimally provoked anger, whereas anger reaction corresponds to an individual's propensity toward anger in response to frustration, criticism, or unfair treatment. Trait hostility was measured using the six-item cynicism scale from the Cook-Medley Hostility Inventory. Consistent with previous findings, hostility was significantly associated with sICAM-1, even after controlling for potential confounding factors. Anger reaction was marginally associated with sICAM-1.

Both Janicki-Deverts et al. [66] and Mommersteeg et al. [109] assessed inflammation using *in vitro* stimulated production of proinflammatory and anti-inflammatory cytokines. Janicki-Deverts et al. [66] examined the relation of hostility to stimulated production of the Th1 cytokines IL-2, TNF- α , IFN- γ and the Th2 cytokines IL-4, IL-5, and IL-10 in a sample of healthy men and women. Hostility was assessed using the 20-item Cook-Medley Hostility (CMHO) scale. The primary analysis used the total CMHO score, while exploratory analysis examined the relation of the cynicism, hostile affect, and aggression subscales of the CMHO to inflammation markers. When adjusting for confounding variables including severity of depressive symptoms, the total CMHO score was associated with both stimulated production of Th1 cytokines TNF- α and IFN- γ replicating and extending the findings of Suarez et al. [162]. In contrast, CMHO failed to predict Th2 cytokines. Results of exploratory analysis suggested that all three Th1 cytokines were associated with cynical hostility but not hostile affect and aggressive responding. The authors concluded that hostility, and particularly the cognitive component of hostility, is associated with a proinflammatory state.

Two prospective studies have examined whether hostility and anger precede inflammation [17, 47]. In a study of male Vietnam veterans, Boyle et al. [17] showed that MMPI-derived measures of hostility and anger independently predicted 10-year increases in C3, but not C4, complement. Elovainio et al. [47] used the score on the 7-item cynicism scale from the CMHO to predict CRP measured 9 years later. Study

participants were Finnish children and adolescents of the Young Finns Study. Hostility was measured at baseline when participants were 3–18 years, and CRP was measured 9 years later when participants were 24–39 years of age. After adjusting for demographic, metabolic and behavioral factors, and baseline level of CRP, cynical hostility was associated with CRP in women but not in men. In this same study, hostility also predicted aspects of the metabolic syndrome in women but not in men. Given that CRP is associated with the metabolic syndrome, the observed sex-related disparity is not surprising (e.g., [160]). The findings by Elvainio et al. were subsequently replicated by Boisclair Demarble et al. [15] who showed that inflammation, as indexed by IL-6 and TNF- α , were associated with cynical hostility score from the Cook-Medley scale for women but not men. Similarly, Girard et al. [55] observed that higher Cook-Medley hostility score was associated with smaller IL-10 response to four interpersonal stressors in women but not in men suggesting that hostility was associated with a diminished anti-inflammatory response.

Type D Personality

A small number of studies have examined the relation of the Type D personality to inflammation markers [40, 41, 150, 172]. These studies have shown that the Type D personality is associated with inflammation as indexed by levels of circulating CRP in healthy volunteers [46] and, more prominently, with proinflammatory cytokines in cardiac patients [33, 40, 41]. In the von Doornan study, Type D personality was associated with an inflammatory sum score composed of CRP, TNF- α , IL-6, IL-8, and sICAM-1, although individual inflammatory markers did not show an association with Type D personality [172].

Life Orientation Optimism and Pessimism

A large population study of adults without a history of clinical cardiovascular disease examined the relation of peripheral measures of inflammation and the Life Orientation Test (LOT) which is used to measure dispositional optimism and pessimism. While optimism was associated with lower concentrations of IL-6, fibrinogen, and homocysteine, the associations between pessimism and inflammation markers were stronger. The relation of pessimism to inflammation remained significant, but somewhat attenuated, when measures of psychosocial and biological factors were incorporated in the statistical model.

Negative Affective States Anxiety Mood Disorders and Inflammation

Negative affective states, particularly depressed mood and high levels of symptoms of anxiety, have been associated with ACVD with considerable attention paid to depression, operationalized either as a clinical diagnosis or as depressive symptom severity [14]. There is a wealth of evidence suggesting that Major Depressive Disorder (MDD) is associated with ACVD with population studies suggesting a risk gradient between depressive symptom severity and future CVD with MDD conferring the highest risk [137]. Less widely studied has been the role of anxiety and anxiety disorders. While there is a paucity of evidence, the evidence suggests an

association between anxiety and cardiac death such that increased severity of anxiety incurs greater risk [137]. These findings have led researchers to examine the relation of inflammation to MDD, depressive symptom severity, and anxiety.

Although some studies have reported no association (e.g., [154]), results of a meta-analysis suggest that MDD is associated with systemic markers of inflammation and specifically CRP, IL-1, and IL-6 [65]. These observations are consistent with evidence suggesting a relationship between measures of cell-mediated inflammation, MDD [96], and severity of depressive symptoms [99, 161, 163]. While fewer studies have been conducted, measures of anxiety have also been associated with both peripheral and cell-mediated markers of inflammation [92, 118]. Additional evidence has also emerged for a relationship between anxiety and inflammation [139]. For example, a recent study by Vogelzangs et al. [173] compared adults with a current or remitted anxiety disorder to healthy control. Results revealed that CRP was elevated in men with a current anxiety disorder but not women. Moreover, among those with current anxiety disorders, women with social phobia had lower CRP and IL-6, whereas CRP and IL-6 were elevated in individuals with an onset of anxiety disorder at older age. Lastly, one study of healthy adults examined the effects of experimentally induced anxiety and anger on stress-induced inflammatory responses [110]. A writing-based induction method was used to evoke anger and anxiety. Results suggested that anxiety, but not anger, was associated with stress-induced increases in IFN- γ and IL-1 $[\beta]$. While provocative, the observations by Moons and Shield [110] await replication.

Clustering of Psychosocial Factors and Inflammation

Studies that have evaluated the relation of cardiovascular disease to psychological factors have, for the most part, adopted an approach that focuses on single psychological factors in isolation [164]. It is recognized, however, that both trait and state factors tend to cluster [164]. In the few studies that have examined the combined or interactive effects of two or more psychological factors, risk of CVD appears to increase incrementally with the presence of each additional psychosocial risk factor [138]. For example, in a longitudinal study, trait measures of hostility, anxiety, anger, and depression at entry predicted incidence CHD over a 20+ year follow-up period [18]. While each independent factor significantly predicted incident CHD, the best predictor was the variance shared among these factors [18].

The same approach was taken in studies that have examined the combined effect of depressive symptom severity and hostility on IL-6 and CRP [158, 159]. Even after statistical adjustment for potential confounders, hostility in combination with severity of depressive symptom significantly predicted elevated levels of IL-6 [158] and CRP [159]. The form of the interaction was such that higher hostility scores were associated with higher IL-6 and CRP, but only in those participants with high Beck Depression Inventory (BDI) scores. Conversely, depressive symptom severity was associated with higher IL-6 and CRP but only among hostile men. These initial findings were subsequently replicated by Stewart et al. [155] who showed that trait

hostility was associated with higher levels of CRP and IL-6 but only among those who report high levels of depressive symptoms. That the combination of trait hostility and depressive symptoms also predicted stimulated production of pro-inflammatory cytokines by peripheral monocytes [163] suggests the robust nature of the effect of hostility and depressive symptom severity.

Although a test of the depression by hostility interaction was not performed, a study by Graham et al. [59] in older caregivers and non-caregivers examined the relation of hostility to changes in CRP and IL-6 over a 6-year follow-up period. The CMHO and BDI scales were administered at yearly intervals during the 6-year follow-up period. Using structural equation modeling, Graham et al. developed and used a latent hostility factor with yearly CMHO scores as measured indicators. Graham et al. observed that the latent construct of hostility predicted CRP, but not IL-6 level, and that this association was independent of demographic, behavioral, and biomedical factors as well as caregiver status. What is interesting to note is that inclusion of the BDI in the structural equation model attenuated the relation between CRP and the latent construct of hostility even though the BDI was not associated with CRP or IL-6 but was correlated with hostility. The pattern of observations led the authors to conclude that depressed mood may have an indirect effect on CRP via hostility, a supposition consistent with previous observations that depressed mood influences the relationship between hostility and markers of inflammation.

One study of the interaction between hostility and depression resulted in a different form of the interaction. In a study of 100 healthy adults with half the sample having a diagnosis of MDD, Miller et al. [106] reported a significant hostility by severity of depressive symptom interaction predicting circulating levels of IL-6 and TNF- α . The form of the interaction, however, differed from previously reported findings [155, 158]. Using the Cook-Medley Hostility (CMHO) and BDI, Miller et al. showed that increases in hostility were associated with higher circulating TNF- α and IL-6, but only among those individuals reporting *low* levels of depressive symptoms. Hostility was not significantly associated with either marker in individuals reporting *moderate to high* levels of depressive symptoms. It may be that differences in the form of the interaction reflect differences in participant characteristics with the Miller et al. study enrolling individuals diagnosed with MDD, whereas the studies of Suarez et al. and Stewart et al. enrolled community volunteers.

While only measuring one cytokine, Sjögren et al. [149] examined the relation of IL-6 in saliva, serum, and supernatant of peripheral blood mononuclear cells (PBMC) before and after stimulation with lipopolysaccharide (LPS) to psychosocial measures of hostility (CMHO), severity of depressive state (Major Depressive Scale), vital exhaustion (Maastricht Vital Exhaustion scale), hopelessness (2 items from the Kuopio study), and self-esteem/coping (Pearlin's scale). Adjusting for demographic, health, and behavioral factors, correlational analysis revealed that *serum* IL-6 was positively correlated with CMHO subscale of cynicism, hostile affect, and hopelessness, severity of depressed mood, and vital exhaustion. In contrast, *stimulated* production of IL-6 was negatively correlated with cynicism, severity of depressed mood, and vital exhaustion. The results using serum IL-6

replicate and extend previous observations of the relation of hostility and depressed mood to IL-6 [158]. However, that cynicism and depressed mood are negatively associated with stimulated production of IL-6 is in contrast to earlier reports of positive associations among these measures. At this time, it is not understood why correlations differed so dramatically when using *in vivo* and *in vitro* measures of IL-6. It is possible that salivary, serum, and stimulated production assess different regulatory mechanisms given that *in vivo* and *in vitro* measures of IL-6 appear not to be significantly correlated.

Psychological Factors and Inflammation: Potential Bidirectional Pathways

If psychological factors are associated with inflammation, then it is reasonable to ask whether the relationships are causative or correlative or both [9]. While exact mechanisms are not well understood, it has been speculated that psychological factors may precede and promote inflammation via various pathways that include behaviors such as smoking [20, 84], poor sleep [19, 30], sedentary lifestyle [85, 98], poor diet [74] and especially high-fat diets [45], poor dental hygiene as well as through stress-induced adrenergic responses that activate the NF- κ B [82, 140] and cAMP-protein kinase A [93] signaling pathways. Conversely, it has also been speculated that inflammation precedes and promotes the onset of mood states and most prominently depressed mood [97] and anger [94]. Support for the causal nature of inflammation arousal of negative affect has been reported in studies of patients undergoing cytokine therapies [169] and in experimental models of endotoxemia where increases in inflammation correlate with decreased mood, reduced motivation, and somatic symptoms such as fatigue [81]. Lastly, inflammation and psychological factors may share a common underlying factor or mechanism(s) that give rise to inflammation and low mood.

The hypothesis that inflammation precedes the onset and progression of depression and depressive states has received considerable attention [97]. It is thought that inflammatory mediators, such as proinflammatory cytokines and reactive oxygen species (ROS), metabolize tryptophan into kynurenine resulting in a reduced bioavailability of tryptophan and serotonin (5-HT) synthesis in the brain. It is the reduction of 5-HT synthesis that many have speculated promotes low mood and subsequent depression. The causal nature of inflammation on the onset and progression of clinical depression and depressive symptoms has led to depression being considered an inflammatory disease [96]. In support of this possibility, proponents of this hypothesis point to the higher incidence of depression and depressed mood in conditions in inflammatory conditions such as ACVD [112].

It has also been speculated that psychological factors precede inflammation. In this model, the mechanisms of action are not well established although one hypothesis suggests that psychological factors promote endothelial dysfunction that subsequently initiates an inflammatory response to injury [135]. As previously noted, a healthy endothelium is anti-atherogenic [4]. Endothelial dysfunction, on the other

hand, is characterized by impairment of endothelium-dependent vasodilation [4]. Endothelial dysfunction also encompasses abnormalities such as endothelial interactions with leukocytes, platelets, and regulatory and increased permeability. It has been speculated that one putative mechanism linking traditional risk factors to CAD is endothelial dysfunction [5, 128, 171]. Evidence suggests that even modest increases in weight (~4 kg or ~9 lb) promote endothelial dysfunction consistent with a risk gradient [128]. Such evidence suggests that endothelial dysfunction can already emerge at modest levels of risk. Similar to traditional risk factors, psychological factors are also associated with endothelial dysfunction, an association thought to reflect the disruption of vascular responses by chronic mental stress [53]. While the cause of inflammation is multifactorial, stress-induced endothelial dysfunction promoted in inflammation via increases in ROS and decreases in nitric oxide (NO), consequences that activate the NF- κ B pathway [184].

Another pathway whereby psychological factors promote inflammation is by direct regulation of peripheral leukocyte actions and especially monocyte and macrophage activities via adrenergic and glucocorticoid receptors [2]. For example, in healthy men and women, arousal of negative affect promoted increased expression of adhesion molecules on peripheral monocytes [60]. This effect was attributed to stress-induced increases in norepinephrine and diastolic blood pressure. Relative to healthy controls, patients with coronary artery disease responded to mental stressors (e.g., mental arithmetic and anger recall) with greater increases in CRP and IL-6, changes that were correlated with norepinephrine responses to challenges [77]. Other studies have examined the relation of glucocorticoid (GC) receptor sensitivity to stimulated production of IL-6 and TNF- α and cortisol responses to a laboratory stress protocol [127]. Following the stress protocol, the relation of GC receptor sensitivity to stimulated cytokine production differed in healthy men and women with men showing reduced IL-6 production and increased GC receptor sensitivity. In women, however, stress-induced increases in IL-6 were associated with decreased GC receptor sensitivity. Such differences underscore the significant influence of sex on the relation of inflammatory stress responses to GC receptor function. Furthermore, psychological stressors may also initiate inflammation via activation of transcription factors and specifically NF- κ B [11, 12]. The transcription factor NF- κ B is known to initiate the inflammatory response in target tissue and cell [83].

It may also be the case that the association between psychological factors and inflammation reflects common causative processes. This hypothesis is particularly relevant to genomic determinants of inflammation and psychological factors with emerging evidence suggesting that a polymorphism of the CRP gene is associated with higher levels of CRP and depressed mood [3]. Moreover, Coles et al. observed that persons who experience social isolation show increased activity of pro-inflammatory transcription control pathways [32]. In addition to general age-related processes, other common factors underlying both inflammation and psychological factors include adiposity [21, 145, 146] and exposure to air pollution [114, 120].

Conclusions

Atherosclerosis is an inflammatory disease characterized by the presence of monocytes/macrophages and T lymphocytes as well as the proliferation of SMC, elaboration of extracellular matrix, and neovascularization [135]. There is a wealth of evidence suggesting that traditional risk factors of CAD are associated with inflammation [103]. As described in this chapter, emerging evidence also suggests an association between inflammation and psychological and behavioral factors associated with an increased risk of ACVD. Evidence stemming from both cross-sectional and prospective studies suggests that personality traits and psychological states associated with an increased risk of ACVD are positively associated with *in vivo* and *in vitro* measures of inflammation in healthy adults and patient populations. In some, but not all studies, these associations appear to be independent of socio-demographic, behavioral (e.g., smoking, sedentary lifestyle), and biological (e.g., lipids, blood pressure) factors although some have speculated that adiposity may be an important mediating factor linking depression and inflammation [146]. To date, the most consistent findings suggest that MDD, depressive symptom severity, and hostility are associated with cell-mediated immunity and inflammation with some studies suggesting that the presence of more than one of these factors, and most prominently the combination of depressive symptom severity and trait hostility, is potentially synergistic in promoting inflammation. Although psychological traits and states are associated with inflammation markers, the magnitude of the associations is relatively low, and therefore it is unlikely that inflammatory processes alone explain the association between psychological factors and CAD onset and progression.

Limitations

With few exceptions, the available evidence stems from cross-sectional studies and suggests that psychological factors associated with increased risk of ACVD are also associated with inflammation. Of the few prospective studies, the evidence indicates that psychological measures at entry predict increases in inflammation marker in follow-up periods as long as 10 years suggesting that psychological factors precede and promote inflammation. Other causal pathways, however, suggest that inflammation evokes psychological states, and specifically depressed mood, associated with ACVD. The bidirectional nature of the association between psychological factors and inflammation combined with the contributions of common underlying mechanisms is likely to promote the development of atherosclerotic disease processes and increase the risk of adverse clinical outcomes such as myocardial infarction and stroke. Future studies should aim at providing a more completely defined picture of the relationship between inflammation and psychological factors associated with diseases in which atherosclerosis plays a primary role.

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