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Dietary and Lifestyle Cardiometabolic Risk Reduction Strategies in Pro-inflammatory Diseases

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Introduction

Appropriate regulation of both innate and adaptive immunity is a critical component of host defense, wound healing, and physiologic regulation (among many other functions) [1]. Immune system activation with concomitant upregulated chemotactic cytokines, termed systemic inflammation for the purpose of this chapter, are a response to changes in physiologic and pathophysiologic conditions (e.g., viral/bacterial infections). When this response is maladaptive or directed against the host, as is the case with autoimmune and autoinflammatory conditions, an inappropriate pro-inflammatory state develops. This dysregulated immune response characterizes such conditions as psoriasis, inflammatory arthritis, inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), and human immunodeficiency virus (HIV).

The concept that pro-inflammatory conditions relate to vascular disease dates back over 60 years, when physicians recognized the systemic cardiovascular disease (CVD) complications of many autoimmune conditions [2]. Relatively more recently, innate and adaptive immune activation came to also be considered a core component of CVD development [3]. It is now well recognized and supported by large epidemiologic and clinical-translational literature that atherosclerotic cardiovascular (CV) events are a complication of pro-inflammatory conditions. Professional societies including the American Heart Association (AHA) and American College of Cardiology (ACC) now consider pro-inflammatory diseases as CV risk enhancers and place emphasis on the need to provide appropriate CV risk reduction therapies to these patients outside of other risk factors [4]. Recognizing this inherent increased CV risk, the aim of this chapter is to discuss dietary and lifestyle interventions in these patient populations in an attempt to improve CV-related outcomes.

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M. J. Wilkinson et al. (eds.), *Prevention and Treatment of Cardiovascular Disease*, Contemporary Cardiology, https://doi.org/10.1007/978-3-030-78177-4_12

Inflammation, Atherosclerosis, and Clinical CVD

The development and progression of atherosclerosis is a lifelong process and involves a complex interplay between the endothelium, circulating lipids, platelets, and one's innate and adaptive immunity [5]. On a pathologic level, progression of atherosclerosis includes endothelial dysfunction, lipid accumulation with intimal fatty streak formation, translocation of leukocytes and foam cell formation, and lesion progression including smooth muscle cell migration and synthesis of extracellular matrix proteinases [5]. At each stage, immune system activation is a key regulator of this process.

The impact of systemic inflammation on atherosclerosis development is seen early as endothelial pro-inflammatory activation occurs via cytokine stimulation. Upregulated vascular adhesion and chemotactic molecules attract immune cells including monocyte and T lymphocytes. Intimal monocytes mature into macrophages that phagocytose modified lipid particles. Foam cells are formed with enhanced local singling driving smooth muscle cell proliferation [6]. Modified lipoproteins and activated platelets adhering to damaged endothelium send their own pro-inflammatory signals (e.g., S100A8/A9), thus further enhancing the inflammatory milieu in atherosclerosis [6]. In summary, an atherosclerotic plaque is a heterogeneous composite of not just monocyte-derived lipid laden macrophages, but also B and T lymphocytes, mast cells, and neutrophils. [6]

A variety of pro-inflammatory cytokines including chemokines and those from the interleukin (IL), tumor necrosis factor (TNF), interferon (IFN), and colony-stimulating factor (CSF) families are each implicated in atherosclerosis and are shown to correlate with clinical CVD (Fig. 12.1). [7] Key inflammatory cytokines promoting this atherosclerotic march include NLRP3 inflammasome-activated IL-1β and IL-18 with downstream IL-6 production [8]. The clinical importance of this pathway has since been confirmed in clinical trials in which inhibiting IL-1β in patients with a history of myocardial infarction and elevated high-sensitivity C-reactive protein (hs-CRP) reduced recurrent cardiac events [9]. Other pro-atherosclerotic and pro-inflammatory cytokines include TNFα and IFNɣ [10]. Based on this evolving understanding of pathophysiology, it is not surprising that pro-inflammatory conditions in which the primary disturbances are those of either innate or adaptive immunity also potentiate atherosclerosis and elevate CV risk.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis affecting up to 1% of the US population [11]. The incidence of RA is twice as high in women as men with the highest incidence occurring in middle-aged to older individuals [11]. The pathogenesis of RA is multifactorial owing to a combination of genetic and environmental causes. Post-translational protein citrullination by peptidylarginine deiminase is a major contributor to self-antigen production and immune stimulation. [12] The resultant citrullinated peptides cause innate immune activation; a first step in systemic and synovial inflammation [12]. An adaptive immune response is elicited in lymphoid tissues with T-cell and B-cell activation, thus producing antibodies including anti-citrullinated peptide (CCP) antibodies and rheumatoid factor [12]. The synovium is the primary target of a systemic immune response in RA. Innate immune cells and macrophage-like synoviocytes produce cytokines and chemokines that attract a host of leukocytes, most notably memory $CD4^+$ T cells. Interestingly, these T cells form ectopic germinal centers with mature B cells in the synovium causing the production of auto-antibodies in the joint tissue [12]. Cytokine signatures in RA are characterized by pro-atherosclerotic mediators including IL-1, IL-6, and TNFα [12].

In comparison to individuals without RA, CV mortality and ischemic heart disease in patients with RA are up to 50% and 59% higher, respectively [13]. Chronic systemic and vascular inflammation is felt to play a dominant role in enhancing CV risk [13]. Vascular arterial FDG-

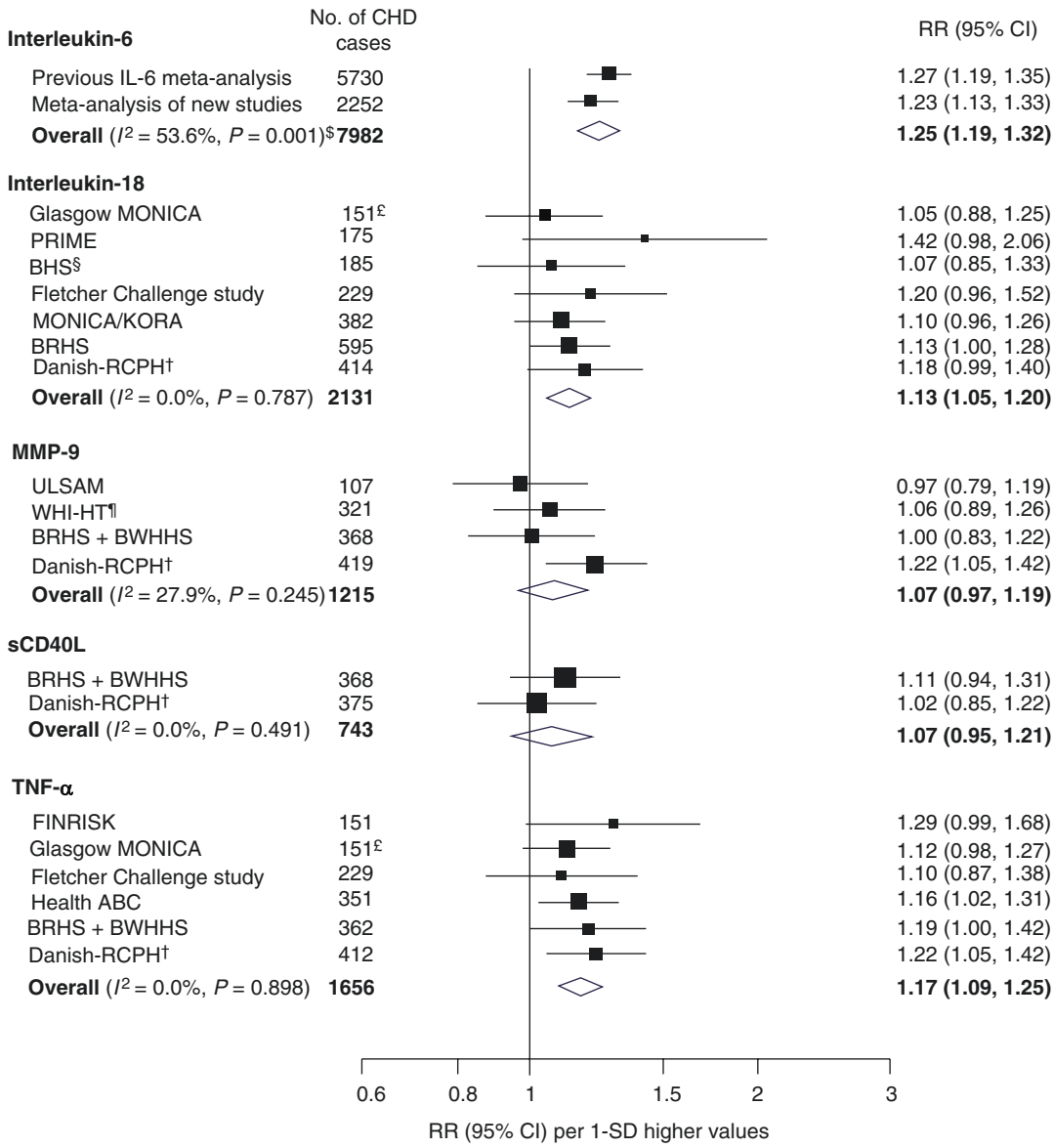

Fig. 12.1 Meta-analysis assessing the association between pro-inflammatory cytokines and risk of non-fatal myocardial infarction or coronary heart disease death. Box with line indicates relative risk with 95% confidence interval. Diamond indicates composite relative risk with 95% confidence interval. (Adapted from Kaptoge et al. [7])

PET studies show that disease activity, presence of rheumatoid nodules, and higher anti-CCP antibody titers are associated with ascending aortic inflammation [14]. ESR and hs-CRP in RA also track with enhanced CV risk [15]. While specific mechanisms to explain vascular inflammation in RA remain under investigation, upregulated IL-6 and TNFα, a dominant role of T lymphocytes and macrophages, along with the contribution of endothelial dysfunction, platelet activation and hypercoagulability promote atherosclerosis [13]. Patients with RA are also often prescribed glucocorticoids and NSAIDs, which can independently elevate risk further [12]. Tofacitinib, a JAK inhibitor approved for the treatment of rheumatoid arthritis (and ulcerative colitis), may fur-

ther elevate the risk of thrombosis [16]. Finally, a well-described lipid paradox exists, whereby higher RA activity is associated with lower circulating LDL-cholesterol and unexpectedly higher CV events [15].

Lifestyle Management in RA to Reduce CV Risk

Identification of elevated CV risk in RA is key and major medical societies now consider RA to be a risk enhancing condition [4]. A 1.5 multiplier to traditional CV risk estimators is suggested to calculate total risk in RA patients [17]. Similar to a patient without RA, risk reduction strategies include recognition and treatment of traditional risk factors, especially as higher rates of metabolic syndrome (upwards of 30%) [18], smoking, and obesity are present [18]. Smoking is not only associated with RA, but also contributes to disease pathogenesis, with active smoking increasing the odds of developing RA up to two-fold [19]. Among many other pathologic changes, smoking is shown to potentiate anti-CCP antibodies and elevate levels of hs-CRP, IL-6, TNFα, and the IL-1 family of cytokines, thereby potentiating both RA and atherosclerosis [19]. Therefore, smoking cessation must be aggressively emphasized, for both the CV health benefits and to alleviate RA symptomatology [19].

Another consideration in RA is the unique physical activity and mobility restriction which may make a recommended 30 minutes a day 5 days a week of aerobic activity particularly challenging. It is not yet clear if exercise regimens in the RA population lead to a decrease in biomarkers of inflammation [20]. However, clinical trials in the RA population show that aerobic activity is feasible and safe with 70% of RA patients able to tolerate prescribed exercise programs. The beneficial CV health impact of exercise is similar among patients with and without RA and such activity should be encouraged [21].

Dietary Considerations to Reduce CV Risk

The overlap between RA and diet with regard to systemic inflammation and gut microbial changes makes diet another key part of CV risk management of patients with RA. Studies of vegan and Mediterranean diets in the RA population have shown a reduction in pro-atherosclerotic inflammatory biomarkers, decreased BMI, circulating lipids, and improvement in RA disease severity and progression [22]. Finally, fish-oil supplementation, both via dietary consumption and oral supplementation with Omega-3 derivatives, was shown to improve RA clinical severity in randomized clinical trials [22]. These data portray the impact dietary counseling can have on systemic inflammatory profiles and CV risk in RA.

Psoriasis

Psoriasis is a chronic, pro-inflammatory condition of the skin presenting primarily as thick, well-demarcated, and erythematous scaly plaques [23]. Upwards of 20% also have joint involvement (psoriatic arthritis) [23]. Psoriasis affects 2–3% of all Americans [23]. There is no obvious gender predilection and studies suggest a bimodal age distribution with incidence peaking between 30–39 and 50–69 years of age [23]. Skin lesions of psoriasis start through a combination of environmental stimuli and genetic predisposition driving an inflammatory cascade (termed initiation phase) composed of dendritic cells, T cells, keratinocytes, and neutrophils. Cytokines produced during this process include type I and II interferons, TNFα, IL-6, and IL-1β. Activation of myeloid dendritic cells produces IL-12/23 leading to further T-cell differentiation with the production of IL-17 family of cytokines. Inflammatory mediators and cross-talk between the innate and adaptive immune systems drive keratinocyte activation and proliferation. A pro-inflammatory feedback loop is generated with Th17 production of

IL17A [23]. Breaking of the positive feedback loop is a mainstay of anti-inflammatory therapies in psoriasis.

Meta-analyses support an approximate 50% increased risk of CVD in patients with psoriasis, and CV-risk stratification guidelines now consider psoriasis a risk enhancing condition [24]. Psoriasis disease severity directly associates with not just pro-atherosclerotic biomarkers such as IL-6 and hs-CRP, but also endothelial and vascular inflammation [25]. Inflammasome signaling, IL-6 [26], and a synergistic component of IFNɣ, TNFα, and the IL17 family contribute to vascular arterial inflammation in psoraisis [25, 27]. Direct immunologic mechanisms linking psoriasis with early atherosclerosis are heterogeneous and still under investigation. Lymphoid abnormalities (including upregulated TH1 and TH17 cells) associate with many pro-inflammatory pro-atherosclerotic processes in psoriasis [28]. However, recent work has shifted to the contribution of myeloid cells including neutrophils, classical monocytes, and platelet activation to further explain mechanisms that drive atherosclerosis in psoriasis [29].

Lifestyle Management in Psoriasis to Reduce Cardiometabolic Disease

Comorbidities in psoriasis are frequently underdiagnosed and undertreated [30]. The odds of having a coexisting CV risk factor (obesity, smoking, hypertension, and hyperlipidemia) with psoriasis varies depending on the population studied but can range between 1.03–1.31 for mild and 1.31–2.23 for severe psoriasis [30]. For example, obesity doubles the risk of developing psoriasis [31] and enhances vascular inflammation [32]. The odds of metabolic syndrome is up to two-fold higher and hyperlipidemia upwards of four-fold higher than controls [33]. Smoking itself can increase the risk of psoriasis by over 70% (in some studies up to two-fold) and worsens the severity of psoriasis [34]. Therefore, management of CV risk in psoriasis requires aggressive lifestyle modification to reduce and treat known CV risk factors.

In obese psoriasis patients, a hypocaloric diet and those patient who undergo bariatric surgery for weight loss (specifically those with initial BMI > 40 kg/m^2) have a 50% reduced risk of psoriasis disease progression in addition to other CV benefits [35]. In a Cochrane review of over 1000 obese patients with psoriasis or psoriatic arthritis, structured exercise along with dietary programs to achieve weight loss improved quality of life and provided up to a 75% improvement in the severity of psoriasis skin lesions [36]. These data suggest obesity assessment and treatment is a critical part of psoriasis management. Finally, while smoking cessation should strongly be encouraged and probably improves psoriasis severity [37], clinical trials evaluating this are limited [36].

Specific Dietary Consideration in Psoriasis to Reduce Cardiometabolic Disease

Dietary free fatty acids (such as in fried foods) in psoriasis are shown to amplify the pro-inflammatory phenotype and skin inflammation in psoriasis including enhanced inflammasome production of IL-1β and IL-18 [31]. As such, specific diets have been evaluated in overweight-obese psoriasis including the Ornish and South Beach to induce weight loss, but it is not clear if these specifically improve psoriasis severity [38]. Gluten-free diets are shown to improve psoriasis severity only in those with known celiac disease [38]. Recognizing the impact weight and diet can have on psoriasis severity and CV risk, the National Psoriasis Foundation recently published dietary recommendations [38]. Overall, a generalized hypocaloric diet is recommended in psoriasis. However, a Mediterranean diet should be considered due to its known CV benefits and high in omega-3 fatty acid content, as well as association with reduced psoriasis skin severity and systemic inflammatory markers such as hs-CRP [38].

Systemic Lupus Erythematosus

SLE is a heterogeneous clinical autoimmune disorder characterized by systemic immune activation and multi-organ system tissue injury [39]. In a recent US population-based registry, prevalent SLE was found to be 62.2 per 100,000 person years with nine-fold higher rates in women compared to men [40]. SLE disproportionately affects racial and ethnic minorities with three- and two-fold higher rates in non-Hispanic Black and Hispanic women, respectively [40]. SLE pathogenesis is driven both by dysfunctional clearance of apoptotic debris, and the production of auto-reactive antibodies [41]. Apoptotic-derived nucleic acids stimulate pattern recognition receptors, most notably toll-like receptors (TLRs), which are an integral part of the innate and adaptive immune response to viral pathogens [41]. TLR ligation produces type I IFNs, strongly associated with SLE, which promote B-cell differentiation and loss of adaptive immune tolerance [41]. Persistent auto-reactive B cells produce the somatically mutated IgG anti-nuclear antibodies pathognomonic of SLE [41].

Importantly SLE carries a significant risk of morbidity and mortality with late deaths most often due to CV [42]. In a recent nested case–control study using the National Inpatient Sample, SLE patients exhibited higher prevalent atherosclerotic CVD compared to age- and sex-matched controls at an adjusted odds ratio of 1.46 [43]. Notably, the CVD prevalence disparity was most pronounced at younger ages with SLE patients developing atherosclerosis in their 20s [43]. SLE patients have increased carotid artery intima-media thickness with plaque detected in 21% of patients under 35, and nearly 100% of those over 65 years of age [44]. Clinically, SLE can produce CVD by several mechanisms including accelerated atherosclerosis, arteritis, thrombosis, and vasospasm among others [45]. As a primary target of inflammatory cytokines, the endothelial barrier function is compromised in SLE [39]. Pro-inflammatory soluble mediators, such as TNF-α and IL-1, cause the endothelium to express adhesion molecules and chemokines [46]. Macrophages, foam cells, platelet activation, and reactive oxygen species all drive endothelial dysfunction and accelerated atherosclerotic plaque production in SLE [39].

Lifestyle Management in SLE to Reduce Cardiometabolic Disease

Risk assessment, the first step in reduction, is notoriously difficult in SLE due to disease heterogeneity [47]. Though SLE patients tend to have high prevalence of traditional CV risk factors, this phenomenon does not fully account for excess atherosclerotic disease [48]. SLE activity, medication use, particularly prednisone, and prevalence of anti-phospholipid antibodies are all contributory [45]. CV risk scores developed in general populations such as Framingham (FRS) and the American College of Cardiology/American Heart Association (ACC/AHA) pooled cohort equation consistently under-estimate risk in SLE patients [49].

The approach to CV risk reduction in SLE should be aimed at healthful behavior change in addition to pharmacological interventions. Counseling on diet and exercise is of crucial importance [50]. SLE patients often experience fatigue, musculoskeletal pain, and/or require prednisone, all of which may reduce the opportunity for exercise and promote obesity [51]. Sleeplessness and fatigue are widely reported in SLE and are major barriers to maintaining healthy lifestyle choices that prevent CVD [51]. SLE patients experiencing high levels of fatigue, are shown to sleep less, exercise less, and smoke more [51]. Strategies to improve fatigue and, therefore, quality of life include recommending greater than 7 h of sleep per night, and a regular exercise regimen [51]. Aerobic exercise at least three times per week has been shown to improve exercise tolerance, fatigue scores, and maximum oxygen consumption [19]. Exercise also improves brachial artery flow-mediated dilation over 16 weeks, a proxy for vascular health [52]. Finally, smoking cessation should be a cornerstone of CV risk management in SLE [44]. Smoking has been associated both with worsened

SLE disease activity and CVD events in multiple, high-quality observational studies [53].

Dietary Consideration in SLE to Reduce Cardiometabolic Disease

A balanced heart-healthy diet should be aimed at maintaining a BMI less than 25 kg/m^2 with both low-calorie and low-glycemic-index diets shown to promote healthy body weight in SLE [50]. Upwards of 60% of SLE patients have a co-existing diagnosis of dyslipidemia characterized by elevated total cholesterol, triglycerides, and LDL-C, along with decreased HDL-C [54]. Dyslipidemia and particularly elevated triglycerides have been independently associated with CV events in SLE, and therefore, should be managed aggressively through diet, pharmacologic interventions, and minimizing glucocorticoid dosing [55]. Omega-3 fatty acid supplementation may also be beneficial to improving endothelial function as measured by FMD in SLE patients [50]. Supporting this, in an observational study of 114 patients with SLE, higher adipose tissue EPA and DHA levels associated with a lower incidence of carotid intimal medial thickness in SLE [56]. Conversely, diets high in carbohydrates associate with SLE-characteristic dyslipidemia [56]. SLE patients should be monitored for adequate vitamin D levels, and supplementation should be provided if required, as low vitamin D levels in SLE track with elevated CV risk factors including hypertension, hyperlipidemia, elevated CRP, higher SLE disease activity, and CV events [57].

Inflammatory Bowel Disease

Inflammatory bowel disease, including Crohn's disease and ulcerative colitis (UC), is a chronic inflammatory disease of the gastrointestinal (GI) tract. The incidence of IBD is rising worldwide, with overall prevalence expected to soon reach 1% [58]. Its pathophysiology involves an interaction between environmental, genetic, and host–microbial commensal flora that initiates a localized autoimmune reaction including epithelial damage within the GI tract [59]. The resulting inflammatory cascade occurs across multiple cell lines such as those of myeloid lineage and CD4$^+$ Th1-derived T lymphocytes. Upregulated cytokines in this process include TNF, IL-1β, IFNs, IL-12/23 along with disturbances in the TH17 and IL-17 pathways, which are critical for maintaining gut epithelial homeostasis [59]. The importance of these cytokines in the pathogenesis of IBD is further emphasized by the efficacy of treatment with anti-TNF and IL-12/23 biologics and the potential worsening of disease in those given IL-17 inhibitors [60].

With regard to vascular complications, venous thromboembolism (VTE) may be the most common and is reported to be between 1.7-fold and 5.5-fold higher than in those without IBD [61]. Atherosclerotic and arterial thromboembolic CV complications are also elevated, with rates approximately 20% higher than patients without IBD [62]. The relative impact of IBD on CV risk may be higher in women (RR 1.35; 95% CI [1.21–1.51]) with IBD as compared to males (RR 1.19; 95% CI [1.03–1.38]) [63]. As opposed to other pro-inflammatory conditions, it is not yet clear if traditional CVD risk factors in IBD including obesity, metabolic syndrome, and hypertension exhibit a higher prevalence [64]. In fact, circulating lipids may actually be lower when compared to matched non-IBD patients [65]. Therefore, hypothesized mechanisms to relate IBD to CVD focus less on the impact of traditional CV risk factors and more on how cytokines such as IL-6, TNFα, and low-grade endotoxemia driven by disturbances in intestinal barrier homeostasis impart-elevated CV risk [66].

Lifestyle Management to Reduce Cardiometabolic Disease in IBD

While minimal data exist on how lifestyle and dietary management can improve CV risk specifically in the IBD population, recommendations to reduce inflammatory activity in IBD often overlap with standard CVD prevention techniques. Similar to other pro-inflammatory conditions, smoking is shown to promote inflammation

in Crohn's disease and patients with Crohn's who smoke have worse outcomes, further highlighting the importance of smoking cessation in this population [67]. Physical activity is also associated with a lower incidence of Crohn's disease and in some studies was shown to decrease disease flares [68].

Dietary Considerations to Reduce Cardiometabolic Disease in IBD

Although the etiology of IBD is clearly multifactorial, epidemiologic data point to a definite role of environmental factors in triggering the inflammation underlying the disease, and a growing body of evidence supports diet and its effect on the microbiome playing at least part of that environmental role. A "Western diet," high in saturated fat and animal intake and low in plants is linked to not just enhanced CVD but also felt to be associated with the development of IBD [69]. In addition, some evidence suggests that high fiber intake – and foods rich in Omega-3 and Omega-6, which are important in CV prevention – are associated with a lower risk of development of IBD, most notably Crohn's disease, and maybe beneficial in those diagnosed with Crohn's [70].

While its evidence base is quite limited, the most well-known diet promoted to reduce intestinal inflammation is the specific carbohydrate diet, a restrictive diet that eliminates poorly absorbed carbohydrates under the theory that these lead to intestinal damage via promotion of a pro-inflammatory gut microbiome. Other proposed diets or dietary modifications to reduce inflammation in IBD (and presumably reduce CV risk) include a semi-vegetarian diet, the Mediterranean diet, red meat reduction, and increasing fruit and vegetable intake (importantly, in those with Crohn's this last dietary modification includes only those patients who do not have intestinal strictures) [71]. Finally, a unique consideration in IBD patients, as compared to other populations with pro-inflammatory conditions, is the risk for protein-calorie malnutrition [72]. Protein-calorie malnutrition in IBD is associated with a 3.5-fold in-hospital mortality likely reflecting a substantial burden of disease in this population [73]. In summary, nutritional status and nutrient intake play an important role in IBD management which may also have implications for CV outcomes.

Human Immunodeficiency Virus

HIV infection can be divided into three phases: the viral transmission phase, the acute phase, and then chronic phase, which eventually progresses into acquired immunodeficiency syndrome (AIDS). The advent of effective antiretroviral therapy (ART) has transformed HIV from almost uniformly fatal, into a chronic illness where the causes of morbidity and mortality are often no longer AIDS-related complications but rather CVD [74]. In a simplified manner, HIV infection is characterized by a destruction and dysregulation of $CD4^+$ T cells and activation of cytotoxic $CD8^+$ T cells. While many immune system abnormalities normalize after initiation of ART, others do not. Specifically in chronic, treated HIV, destruction of $CD4^+$ Th17 T cells, essential in gut epithelial homeostasis, lead to chronic microbial translocation and endotoxemia driving monocyte activation and pro-inflammatory cytokines such as IL-6, IL-1β, TNFα, MCP1 as well as platelet activation [75]. Increased B-cell activation is also present often leading to a higher percentage of B-cell malignancies. [76] Finally, a strong type I IFN signature is also felt to play a role in the chronic inflammation of HIV [77].

Not surprisingly, and in part because of these immune abnormalities, CVD plays a significant role in enhanced morbidity and mortality of HIV with a 1.5–2-fold increased rate of CV events compared to those not infected with HIV [74]. Dyslipidemia, particularly hypertriglyceridemia, is common in HIV and correlated with the degree of viremia [74]. Hypertension, metabolic syndrome, diabetes, smoking, and heavy alcohol use are also more prevalent, especially in developed nations. Although multifactorial, the pro-inflammatory disease state which defines chronic HIV is felt to play a role in potentiating CV risk [74]. For example, in the Strategies for Management of Antiretroviral Therapy (SMART)

study to test CD4 guided vs continuous ART, higher CRP and IL-6 levels were associated with an eight-fold increase in risk of all-cause mortality [78]. Both endothelial damage and vascular inflammation (in FDG-PET studies) are increased in HIV and associated with monocyte activation [79], thus enhancing atherosclerosis development. Based on these observations, CV guidelines now recommend treating HIV as a CV risk enhancing condition [80].

Lifestyle Management in HIV to Reduce Cardiometabolic Disease

The conventional lifestyle and unhealthy dietary patterns that drive CVD development in the non-HIV population have also been studied in the HIV population [74]. In developed nations, up to 40% of those with HIV are active smokers, highlighting the importance of smoking cessation [74]. Those HIV patients with low-physical activity, also exhibit depression, reduced adherence to ART, and higher viral load [74]. In survey studies of HIV individuals, specific barriers to a healthy lifestyle include the higher cost of obtaining nutritious foods, an environment not conducive toward healthy eating, and lack of a social support system [81]. For example, having a strong patient–provider relationship improves ART adherence and healthy behavior patterns [81]. Finally, dietary and lifestyle interventions can work and are beneficial in HIV [82]. Regular exercise (e.g., 1-h, 3× week gym class combined with nutritional counseling) is shown to decrease fat mass, waist circumference, and glucose while raising $CD4^+$ T cells, muscle mass, and improving quality of life [82]. These data suggest that in HIV individuals, similar to the general population, adherence to healthy diet and exercise regimens can improve patient CV outcomes.

Dietary Consideration in HIV to Reduce Cardiometabolic Disease

The appropriate macro- and micro-nutrient intake of the HIV individual potentially impacting overall CV health is an active area of investigation. While we have discussed many of the increased risks in the developed world, the developing world often faces different problems. The resting energy expenditure of HIV is approximately 10% higher than in healthy individuals [83], exacerbating problems of malnutrition due to food insecurity and poverty in HIV health and management. In these countries, supplementation with multivitamins including vitamin D, and increasing protein intake can increase CD4 count, potentially reduce hs-CRP [84], and subsequently reduce HIV progression and mortality [83]. These data have led to position statements from the American Dietetic Association highlighting the importance of food security, nutrition education, and nutrition supplementation when appropriate in the individual living with HIV [85].

In chronic HIV infection, especially in developed nations for those on ART, obesity, metabolic syndrome, hyperlipidemia, and hypertriglyceridemia are of significant concern and have dietary implications. Studies evaluating nutrient intervention in HIV show a beneficial impact on overall health. In a randomized trial of a reduced-fat diet in HIV individuals initiated on ART, those who underwent dietary intervention reduced triglycerides by 25%. At the end of the study, 21% in the treated and 68% in the untreated groups met the criteria for dyslipidemia [86]. Given its CV risk reduction benefits, the Mediterranean diet has also been studied in HIV. Adherence to a Mediterranean lifestyle in HIV is associated with less insulin resistance, higher HDL-C, and a trend toward lower triglycerides [87]. Omega-3 supplementation, especially in those with hypertriglyceridemia, is shown to be effective, and in light of the negative impact of elevated triglycerides in CVD progression, can be considered in those with have an inadequate response to dietary interventions [88]. In summary, a dietary approach to reduce CV risk in chronic HIV has to be customized to baseline nutritional status, feasibility, and individual metabolic abnormalities. Interventions designed to improve cardiometabolic profiles in HIV are shown to be successful and should be considered in those with HIV.

Conclusion

In summary, atherosclerosis development is a complex interplay between the endothelium, vasculature, lipids, platelets, innate, and adaptive immunity. The systemic inflammation derived from autoimmune and autoinflammatory conditions creates a predisposition to atherosclerosis development, thus leading to elevated rates of adverse CV events. A general approach to managing CV risk in these patients is to ensure appropriate screening of traditional CV risk factors (hypertension, obesity, smoking, dyslipidemia, and diabetes). Once recognized, lifestyle modification including smoking cessation, exercise, and dietary regimens (including omega-3 and vitamin D supplementation) can have an impact not just on CV risk, but also on autoimmune disease severity and control.

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