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Review

Nutritional factors in the prevention and management of coronary artery disease and heart failure

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ABSTRACT

Nutritional factors such as magnesium, folic acid, vitamins B_{12} and B_6, L-arginine, and polyunsaturated fatty acids (PUFAs) appear to be significantly beneficial for patients with coronary artery disease (CAD), and in the prevention and arresting the progression of HF and cardiac arrhythmias. Additionally, ingestion of adequate amounts of protein and maintaining normal concentrations of plasma albumin seem to be essential for these patients. These nutrients closely interact with the metabolism of L-arginine–nitric oxide (NO) system, essential fatty acids, and eicosanoids such that beneficial products such as NO, prostaglandin E_1, prostacyclin, prostaglandin I_3, lipoxins, resolvins, and protectins are generated and synthesis of proinflammatory cytokines is suppressed that results in platelet anti-aggregation, vasodilation, angiogenesis, and prevention of CAD, cardiac arrhythmias, and stabilization of HF. This implies that individuals at high risk for CAD, cardiac arrhythmias, and HF and those who have these diseases need to be screened for plasma levels of magnesium, folic acid, vitamins B_{12} and B_6, L-arginine, NO, various PUFAs, lipoxin A_4, resolvins, protectins, asymmetrical dimethylarginine (an endogenous inhibitor of NO), albumin, and various eicosanoids and cytokines and correct their abnormalities to restore normal physiology.

Introduction

Nutrition plays an important role in the pathobiology of obesity, type 2 diabetes mellitus, hypertension, metabolic syndrome, and coronary artery disease (CAD) [1–13]. Malnutrition is the leading cause of disease burden in developing countries with high morbidity and mortality rates. It also is common in North America, especially in hospitalized patients, wherein it is estimated that about 30% to 50% if inpatients are malnourished or at risk for malnutrition. This is especially true in geriatric patients [14–19]. Several studies reported a close association between malnutrition and impaired wound healing, increased postoperative complications, and mortality [20–25]. Furthermore, malnutrition is common in various chronic diseases such as cancer, infections, chronic kidney diseases, and chronic heart failure [26–30]. A close relationship has been described between hospital length of stay and nutritional status: The longer the hospital stay, the greater the chance for undernutrition. At the same time, it was noticed that malnutrition becomes more prevalent as the hospital stay is prolonged [31–33]. This led to routine screening at admission of patients for nutritional status so that they can be offered relevant nutritional support; nutritional risk; and risk for complications [32]. The Nutritional Risk Index (NRI), developed by the Veterans Affairs Total Parenteral Nutrition Cooperative Study Group, is used to assess nutritional status [34]. The NRI uses objective (serum albumin and percent usual body weight) rather than subjective measurements to determine nutritional risk in hospitalized patients [35,36]. The success of the NRI in accurately assessing the nutritional status of

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patients and the interventions instituted as a result led to modifications for use in various groups [36]. Some of these modifications led to the development of a new index, the Geriatric Nutritional Risk Index (GNRI) [36], which essentially measures the nutritional status of patients in terms of their plasma albumin, prealbumin, and body mass index. The GNRI is a simple and accurate tool for predicting the risk for morbidity and mortality in hospitalized geriatic patients [36].

It is important to note that chronic HF is a multisystem disease with multiple comorbidities such as anemia, insulin resistance, autonomic dysfunction, or cardiac cachexia [37]. Patients with HF are more prone to experience malnutrition due to a variety of reasons, including symptomatic anorexia, early satiety and ascites, medications prescribed, and psychological factors or catabolic/anabolic imbalances that lead, to a hypermetabolic state [38–40]. However, to our knowledge, relatively little data is available regarding the clinical significance of malnutrition in patients with HF and the impact that correction of these nutritional deficiencies has on the outcome of the disease. This is important in the light of the observation that acceptable levels of nutritional support led to significant improvements in the general well-being of patients with HF and improved their clinical status without adversely influencing cardiac function [41,42]. This is supported by a recent report [43] demonstrating that low GNRI is common in female patients and is associated with lower serum hemoglobin and sodium, but higher serum blood urea nitrogen (BUN), C-reactive protein (CRP), and B-type natriuretic peptide (BNP) compared with those in the high GNRI group of patients with HF with preserved ejection fraction. It was noted that physical activity at discharge measured by the Barthel index was significantly lower in the low GNRI group than in the high GNRI group ($P < 0.05$), and Cox hazard analysis revealed that lower GNRI predicted increased all-cause mortality independent of age, sex, prior hospitalization for HF, and higher BUN and BNP ($P < 0.01$) [43]. These results highlight the importance of nutrition in the prevention and preservation of cardiac function and decreasing mortality due to HF. In this context, it is important to evaluate the importance of nutritional factors that could play a critical role in the prevention and management of CAD in general and HF in particular. To assess the role of nutritional factors in HF, a PubMed search using the terms *nutrition support improves HF; albumin improves heart failure,* and *PUFAs in heart failure* led to the identification of 23, 51, and 1140 articles, respectively. Of which, 6 articles in the area of nutrition support, 6 on albumin, and several on PUFAs were found to be suitable for the present discussion. Based on these publications, the following assertions have been made.

PUFAs in CAD and HF

It was recently demonstrated [44] that low levels of serum PUFAs, especially of ω-3 eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are associated with worse HF-free survival in patients with acute myocardial infarction (AMI), and particularly with HF hospitalization and all-cause mortality (Fig. 1 shows the metabolism of EPA and DHA and other unsaturated fatty acids of the ω-6 and ω-3 series). The association of low levels of serum EPA and DHA to worse HF-free survival in patients with AMI could be related to the fact that CAD and HF (including asymptomatic HF) are low-grade systemic inflammatory conditions, as noted by elevated plasma levels of high-sensitivity CRP, interleukin (IL)-6, and tumor necrosis factor (TNF)-α [45–48]. One mechanism by which these proinflammatory cytokines are involved in CAD and HF includes their ability to suppress myocardial contractility. In this context, levels of growth-differentiation factor-15 (GDF-15), a stress-responsive transforming growth factor (TGF)-α–related cytokine, are elevated and independently related to an adverse prognosis in CAD and HF [49,50]. Elevated GDF-15 levels seem to be of significant help in identifying patients with non-ST elevation acute coronary syndrome who derive benefit from an invasive treatment strategy. Although the elucidation of the pathobiology and upstream inducers of GDF-15 remain unknown, it is likely that this is related to the elevated levels of proinflammatory cytokines seen in these patients. This is so because TNF-α and IL-6 are proinflammatory cytokines, whereas TGF-α is an anti-inflammatory cytokine [51–54]. This implies that increased production of GDF-15 in CAD and HF could be a compensatory mechanism adopted by the body to neutralize or minimize the cytotoxic actions of TNF-α and IL-6.

The involvement of inflammatory cytokines in CAD and HF is supported by the observation that hypertension, diabetes mellitus, hyperlipidemias, and obesity—diseases that predispose to the development of CAD and HF—are associated with altered metabolism of essential fatty acids (EFAs) such that they are low in plasma phospholipid concentrations of arachidonic acid (AA), EPA, and DHA [55]. This led to the suggestion that because PUFAs have anti-inflammatory actions, their beneficial action in CAD and HF is related to their anti-inflammatory properties, and hence, they may serve as predictors and prognostic markers of CAD [56–59]. An inverse correlation has been reported between circulating ω-3 PUFAs (especially EPA) and inflammatory markers (markers measured included CRP, pentraxin-3, adiponectin, natriuretic peptide, and troponin) and HF severity [60]. Three-month treatment with ω-3 PUFAs markedly enriched circulating EPA and DHA and lowered pentraxin-3 (pentraxin-related protein PTX3, also known as TNF-inducible gene 14 protein [*TSG-14*] is encoded by the *PTX3* gene in humans). Pentraxin-3 (ptx3) is a member of the pentraxin superfamily that is rapidly produced by mononuclear phagocytes, dendritic cells (DCs), fibroblasts, and endothelial cells in response to inflammatory signals such as toll-like receptor (TLR) engagement, TNF-α, and IL-β. PTX3 activates the classical pathway of complement activation and facilitates pathogen recognition by macrophages and DCs [61–64]. Low EPA levels were inversely related to total mortality in patients with chronic HF.

A study summarizing the clinical trials that investigated the use of ω-3 PUFAs in patients with HF with an emphasis on diabetes, revealed that reasonable evidence exists for a beneficial effect of ω-3 PUFA supplementation in patients with HF [65]. The study results demonstrated that in HF patients with diabetes, ω-3 PUFAs might have a preferential therapeutic benefit. This beneficial action has been attributed to the binding of ω-3 PUFAs to the G protein-coupled receptor, GPR120, which could lead to a reduction in the production of proinflammatory cytokines IL-6 and TNF-α and improvement in insulin resistance. This conclusion is supported by the observation that PUFAs suppress HF-induced atrial structural remodeling and atrial fibrillation promotion that has been related to prevention of mitogen-activated protein kinase activation [66]. Additionally, it was reported that supplementation of ω-3 PUFAs reduced platelet activity biomarkers, despite concomitant aspirin and statin therapy [67]. These results are important because platelet activation plays a significant role in atherosclerosis and CAD. Thus, there is reasonable evidence supporting the contention that PUFAs (especially ω-3 series and in particular, EPA and DHA) are beneficial in the prevention of atherosclerosis, CAD, HF, and its associated complications such as arrhythmias [9,68–77].