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A Review on Nutritional Interference in Heart Dysfunction

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Abstract
Western diet, characterized by highly sweetened foods, as well as being rich in fat, fried foods, eggs, red and processed meat, and sweet beverages, may outcome inflammation, leading to oxidative dysfunction in the cardiac ultra-conformation. Oxidative functioning of the myocardium and how oxidative dysfunction grounds pathophysiological restoration, foremost to heart failure (HF), is not well documented. Antioxidants, namely, polyphenolics and flavonoids, omega-3 fatty acids, and other micronutrients, rich in Indo-Mediterranean-type diets, could be protective in sustaining the oxidative functions of the heart. Apart from toxicity due to glucose, lipotoxicity also adversely affects the cardiomyocytes, worsening in the presence of deficiency of endogenous antioxidants and deficiency of exogenous antioxidant nutrients in the diet. The alteration in the biology may initiate with normal cardiac cell remodeling to biological remodeling due to inflammation. Intensification in the fat content of a diet in addition to inducible nitric oxide synthase (NOSi) through N-arginine methyl ester has been noticed to preserve the ejection fraction in HF. It is recommended that a greater intake of high exogenous antioxidant restorative treatment (HEART) diet, polyphenolics and flavonoids, concomitant with cessation of red meat intake and egg, can cause improvement in the oxidative function of the heart, by inhibiting oxidative damage to lipids, proteins and DNA in the cell, resultant in favorable effects in the early stage of the Six Stages of HF. This overview provides new insights into develop an unmet requisite to conduct cohort studies and randomized, controlled studies to validation of the role of the HEART diet in the effective treatment of HF.

Keywords: *Antioxidants, Cardiomyocytes, Heart failure, Myocardium, Oxidative function.*

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I. Introduction

Heart failure (HF) is measured as a present-day epidemic, with about 26 million cases globally, ensuing a load on health care systems; for example, it has been assessed that approximate 2% of the National Health Service (NHS) budget is spent on HF alone [1, 2]. The incidence of HF inclines to increase with age because of age-linked variations in the heart's structure and function, showing HF one of the most common reasons for hospitalization in older adults [3, 4]. The 1-year mortality rate among HF patients admitted to hospital has been assessed at about 30% by the latest Annual National HF Audit in England [5]. Moreover, patients with HF predispose to also have a high hospital readmission rate with almost 25% of patients being readmitted within 30 days [6]. However maintaining a good quality of life is imperative for patients' survival and outlook, it has been shown that the quality of life for patients with HF is lower than in any other chronic disease [5, 6].

Malnutrition is common among patients with HF, and it foretells worse mortality and hospital readmission outcomes [7-9]. The occurrence of malnutrition among such a group of patients has been described to be as high as 70% liable to the screening tool being used, and it can be ascribed to illness-related factors, namely, reduced calorie intake due to medication induced anorexia (e.g. diuretics), anxiety and the lack of energy to prepare food [10]. Also, around 5–15% of HF patients have a tendency to suffer from cardiac cachexia, defined as 'involuntary progressive weight loss consequent to the reduction in skeletal muscle mass with or without depletion of adipose tissue' [11]. Cachexia is initiated by immunological and hormonal deviations, changing the body from an anabolic to a catabolic state by a reduction in the activity and levels of anabolic mediators e.g. insulin and growth hormone and an increase in activity and levels of catabolic mediators such as pro-inflammatory cytokines and glucocorticoids [12]. The above changes lead to a hypermetabolic state [13] and an increase in protein degradation [14], and hence, outcome in muscle wasting.

In view of the pathophysiology of malnutrition and cachexia in HF, it has been hypothesized that the supplementation of protein or the increase in energy intake could reduce catabolic effects and increase in lean body mass tissue in these patients [15]. However, no nutritional strategies for the management of HF presently exist. Although systematic overviews have explored the efficiency of restrictive diets (e.g. low sodium and fluid restriction) for HF patients, no systematic review so far has concentrated on nutritional interventions tackling malnutrition in HF patients. Consequently, this systematic review, being the first of its kind, will highlight on responding the question whether nutritional interventions targeting to increase protein or energy intake for malnourished or at risk of malnutrition or cachexia HF patients are effective at upgrading clinical outcomes including nutritional status, mortality and hospital readmission. The objective is to present the evidence regarding the effectiveness of nutritional interventions, which can effectively aid to make strategies for nutritional support in HF patients, and further to critically appraise the components of nutrition interferences and to establish an evidence base for future advances in HF nutrition research as well as practice as follows:

Nutritional supplementation in heart dysfunction

Chronic heart failure (CHF) is one of leading health problems in industrialized countries. Despite the therapeutical advancement, based on drugs and exercise training, it is still defined by elevated mortality and morbidity [16]. Several pathophysiological mechanisms, predominantly due to the rise in blood hypercatabolic molecules, have been projected to interpret this phenomenon. Nutritional supplementation with proteins, amino acids, vitamins and antioxidants has all been applied for treating malnutrition. However, the success and efficacy of these trials are often conflicting and not convincing. Remarkably, data on exercise training reveal that exercise declines mortality and increases functional ability, whereas it also augments the catabolic state with energy expenditure and nitrogen-providing substrate requirements. Thus, it is focused that the molecular mechanisms of specific nutritional supplementation integrated with exercise training may improve anabolic pathways. Besides, the link between exercise and the mTOR complex subunit as Deptor and/or correlated signaling proteins, such as AMPK or sestrin, is vital. As a consequence, alongwith traditional medical therapies, a combination of personalized and integrated nutritional supplementation, as well as exercise to treat malnutrition, and anthropometric and functional CHF-related disorders. It has been well recognized comprehensive relevant account as follows:

***Clinical Problem*:** CHF is one of major health complications of the industrialized countries. It is a complex syndrome where, though the "*primum movens*" is heart disease, it also affects various organs and systems of the human body [17]. Despite latest therapeutical improvements based on a amalgamation of specific medical approaches/therapies, CHF is still characterized by elevated mortality and morbidity [18]. Recently the benefits of cardiac rehabilitation and exercise training have been remarkably shown in patients with heart dysfunction, concomitant with a decline in morbidity and mortality. Though, data also display that even light exercise causes a significant catabolic destruction of muscular proteins [19]. This catabolic effect of exercise is more noticeable in patients with malnutrition. It must therefore be specified that malnutrition is a generic term including two pathophysiological and clinical conditions, namely, over-nutrition and under-nutrition.

On the other hand, under-nutrition is because of a lack of nutrients, resulting in reduced growth or weight loss according to age and/or concomitant diseases. It should be specified that under-nutrition is an increasing health problem in people aged over 65 years in developed countries, mainly because of physical, psychological and social factors. Indeed, aged people reduce dietary intake because they may have both physical and/or social glitches, such as chewing and swallowing difficulties, depression, intestinal-related diseases, and/or poverty and loneliness. It is also obligatory to specify that iron is essential for other dynamic metabolic processes of cell cycle, including DNA synthesis and matrix metalloprotease activities (MMPs). Besides, MMPs play a central role in degrading both matrix and non-matrix proteins, which in turn affect tissue repair and remodel the reaction to injury, like trauma or necrosis. In addition, MMPs are involved in the development of atheroma and/or chronic diseases. It should also be evoked that hemoglobin is a heme protein. As such, hypo-hemoglobinemia point out that there is a shortage of other heme proteins, together with basic proteins involved in the energy use/production (i.e., cytochrome-c, myoglobin,), in the defense against oxygen free radicals (i.e., catalase, peroxidase) or in inflammatory developments (i.e., cyclooxygenase, NOS) [20]. Noticeably, epidemiological outcomes reveal that protein energy malnutrition is often present in patients with CHF, concomitant with traditional CHF symptoms [21].

It is fascinating to annotation that protein energy malnutrition links with mortality irrespective of heart disease severity in CHF patients [22]. Nonetheless, although protein energy malnutrition has such an imperative clinical impact, it is still too often underestimated and/or not precisely evaluated or counteracted by most of the clinicians [23]. Here, grounded on molecular and pathophysiological evidence, it has been proposed to integrate nutritional supplementation with certain molecules, with exercise training and customary medical therapy to produce a persuasive alliance to treat patients with CHF in the best promising way.

Nutritional supplementation: As hitherto mentioned, data propose that CHF-induced hypercatabolic syndrome reasons AA metabolism alterations and the protein disarrangement of both globular and muscular proteins. Consequently, the exogenous supplementation of food preproteins and/or free AAs could be an effective therapeutical approach to use with CHF patients. However, results also reveal that progression of the metabolic and nutritional status of muscle-depleted CHF patients happens as and when bearable energy protein intake is pooled with a specific mixture of all free forms of essential AAs (EAAs) in a stoichiometric ratio, and not with a simple rise in food protein intake [24, 25].

Interestingly, investigational data display those special EAA mixtures with an EAA/NEAA ratio >1 increase the lifespan and albumin [26], and furthermore decrease inflammation in healthy mice [27, 28]. This proposes that NEAAs are not indispensable for cell cycle and are synthesized as per metabolic necessities if sufficient amounts of EAAs are provided. Besides, data validate that leucine's ketoacid, referred to as beta-hydroxy-beta-methyl butyrate (HMB), as well as EAA mixtures, directly affects protein synthesis, stimulating the regulatory intracellular mTOR system [29, 30]. Besides, EAA mixtures, but not ketoacids (i.e., HMB) and/or certain individual free AAs (i.e., leucine) can provide a adequate concentration of AAs to upkeep protein synthesis and provide a suitable amount of nitrogen essential for nitrogenous base production. These are a requisite part of ATP and/or of NAD-NADH synthesis, which are vital for maintaining cellular redox homeostasis [30]. EAAs can also affect the insulin effects on adipocytes, escalating glucose transport and modulating the use of FFAs. Indeed, EAAs and their metabolites have recently been demarcated as "Metabokine" since they are able to influence local metabolism and systemic physiology [31], not only through direct metabolic influence, but also modifying the gene expression through epigenetic action [31]. Definitely, it has been exposed that monocarboxylic acid, branched-chain essential amino acid (BCEAA) derivatives, 3-methyl-2-oxovaleric acid (MOVA), B-hydroxy-isobutyric acid (BHIBA) and amino acid 5-oxoproline (5OP) control adipocyte and myocyte metabolic gene expression of the enzymes involved in fatty acid oxidation. Moreover, they exert a transcriptional regulation of peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1α) that is a transcriptional coactivator regulating the genes involved in mitochondrial biogenesis and the adaptive metabolic response to exercise [32].

It should be emphasized that nutritional therapies may considerably affect human metabolism, a complex phenomenon characterized by chemical alterations, taking place in the cell following an convoluted network of specific metabolic pathways, which administer physical processes determining the cell physiology and biochemical characteristics. EAA-related metabolism is the sum of all chemical reactions in which one specific chemical compound is transformed into other molecules via a series of steps. Each step is assisted by a specific co-factor (i.e., vitamins, ions and others). The consequence of nutritional metabolic therapeutical methodologies is that nutrition should provide not only one molecule, but all the most dynamic molecules involved in the anabolic EAA-mediated pathways [33]. This approach has been established in relevant recent clinical study. This revealed that a specific mixture of EAAs, competent to match human metabolic requirements, has the best impacts on patients with CHF-induced hypercatabolic syndrome with proteins disarrangement (anaemia) when it is administered with co-factors (vitamin D, B6 and B9, iron) vital for the activation of the anabolic pathways of haemoglobin synthesis.

Furthermore, recent data exhibit that changed intestinal function, such as dysbiosis, and increased permeability are present in patients with CHF, and they adversely affect patient nutrition [33, 34]. A recent comprehensive review paper supports relevant perspective. It analyses the influence of diverse micronutrients (i.e., Q10, L-arginine, antioxidants, vitamins A-C-D-E, ions and others), which have been suggested as influencing cardiovascular risk. Assessment of the literature point out those not all nutritional molecules are equal, given that the requirements of patients may be dissimilar. As a consequence, it is mandatory to provide more personalized and specifically integrated dietary interventions involving combinations of advantageous supplements in acceptable amounts, as per the specific metabolic requirements of each patient [35]. These findings recommend that personalized, functional and integrated nutritional therapies, considering all the noticeable aspects of nutrition and exercise, should be used to perform the best and avoid contrasting results.

Mechanisms of Impairment and Restoration

Despite the recurrent efforts to develop an amalgamating hypothesis, which explains the clinical syndrome of HF, no single theoretical paradigm for HF has endured the test of time. Though clinicians principally observed HF as a problem of extreme salt and water retention that was activated by deviations of renal blood flow (Cardio-renal model) [23, 24], as physicians initiated to accomplish careful hemodynamic measurements, it moreover became noticeable that HF was linked with a reduced cardiac output and excessive peripheral vasoconstriction. This final realization led to develop the "cardiocirculatory" or "hemodynamic" model for HF [23, 24], wherein it was assumed to arise principally consequent to aberrations of the pumping capability of the heart and extreme peripheral vasoconstriction. Although both the cardiorenal and cardiocirculatory models for

HF explained the extreme salt and water retention that heart failure patients experience, neither of these models elucidated the persistent "disease advancement" that happens in this syndrome.

Interruption and cohort studies of several nutrients and Mediterranean diet

The exact pathophysiology of heart failure (HF) is not yet known. Western diet, characterized by highly sweetened foods, as well as being rich in fat, fried foods, red meat and processed meat, eggs, and sweet beverages, may cause inflammation, leading to oxidative dysfunction in the cardiac ultra-structure. Oxidative function of the myocardium and how oxidative dysfunction causes physio-pathological remodeling, leading to HF, is not well known. Antioxidants, such as polyphenolics and flavonoids, omega-3 fatty acids, and other micronutrients that are rich in Indo-Mediterranean-type diets, could be protective in sustaining the oxidative functions of the heart. The cardiomyocytes use glucose and fatty acids for the physiological functions depending upon the metabolic requirements of the heart. Apart from toxicity due to glucose, lipotoxicity also adversely affects the cardiomyocytes, which worsen in the presence of deficiency of endogenous antioxidants and deficiency of exogenous antioxidant nutrients in the diet. The high-sugar-and-high-fat-induced production of ceramide, advanced glycation end products (AGE) and triamino-methyl-N-oxide (TMAO) can predispose individuals to oxidative dysfunction and Ca-overloading. The alteration in the biology may start with normal cardiac cell remodeling to biological remodeling due to inflammation. An increase in the fat content of a diet in combination with inducible nitric oxide synthase (NOSi) via N-arginine methyl ester has been found to preserve the ejection fraction in HF. It is proposed that a greater intake of high exogenous antioxidant restorative treatment (HEART) diet, polyphenolics and flavonoids, as well as cessation of red meat intake and egg, can cause improvement in the oxidative function of the heart, by inhibiting oxidative damage to lipids, proteins and DNA in the cell, resulting in beneficial effects in the early stage of the Six Stages of HF. There is an unmet need to conduct cohort studies and randomized, controlled studies to demonstrate the role of the HEART diet in the treatment of HF.

***Oxidative dysfunction in HF*:** It seems that behavioral risk factors such as Western diet, tobacco and alcohol intake, short sleep, and mental stress can cause an overproduction of free radicals, oxidative myocardial dysfunction and inflammation, which may alter the twist of the heart due to cardiomyocyte dysfunction and physiological remodeling initially [36]. The intracellular oxidative homeostasis in the cardiac cells is closely regulated by the production of ROS with limited intracellular defense mechanisms. If the oxidative dysfunction continues, it may lead to pathological remodeling with cardiac damage in the form of increased high-sensitivity (hs) troponin T, in cardiac cells causing abnormalities in the global longitudinal strain [36]. In the cardiac cells, an overproduction of ROS may lead to the development and progression of maladaptive myocardial remodeling, which may be an early stage of HF [37, 38]. Oxidative stress and ROS directly cause inflammation and impair the electrophysiology of the heart by targeting contractile machinery and cardiac components via the dysfunction of proteins that are crucial to excitation–contraction coupling, including sodium channels, L-type calcium channels, potassium channels, and the sodium–calcium exchanges. Oxidative stress may also cause alteration in the activity of the sarcoplasmic reticulum Ca2+-adenosine triphosphatase (SERCA) as well as reduce myofilament calcium sensitivity [39].

It is proposed that oxidative dysfunction with increased oxidative stress may be the first stage of HF, which may be associated with cardiac damage and dysfunctional twist [40]. If there is a lower availability of endogenous antioxidants, super-oxide-dismutase (SOD), glutathione-peroxidase (GPS) and catalase or coenzyme Q10, it may cause the worsening of cardiac function, resulting in sub-endocardial damage, which may be the second stage of HF [41]. Interestingly, the protective factors, such as the HEART diet may prevent the development of HF, if administered in one or the other of the initial stages of Six Stages of HF [42]. This crucial mechanism is more obviously illustrated in Figure 1.

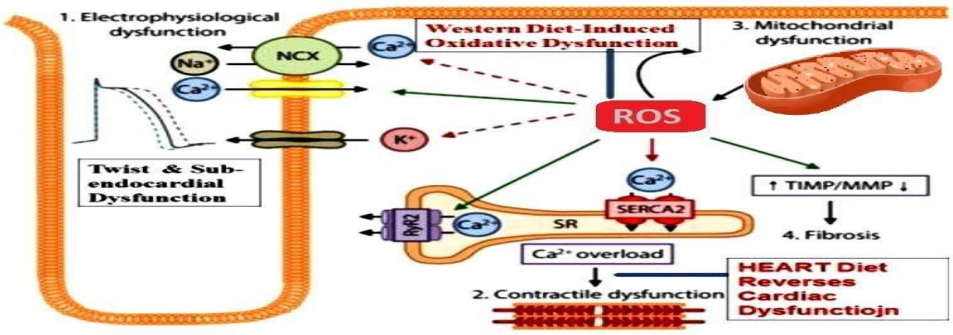

Fig.1: Oxidative dysfunction in the heart due to Western diet, with diminution in antioxidant defenses, causing mitochondrial dysfunction, proceeding to electrophysiological dysfunction with turn and sub-endocardial dysfunction. (Modified from Reference [42]).

***Oxidative dysfunction and inflammation as targets for therapeutic antioxidants*:** Preclinical and clinical studies direct that several therapeutic choices are available to treat oxidative stress-linked cardiovascular diseases (CVDs) [43]. The basic principle of pharmacological prevention of cardiovascular events consists of the control of classical risk factors with specific interventions. This clinical approach has led to an improvement in prognosis, although still far below expectations. In other words, the mere control of hypertension, hypercholesterolaemia, or diabetes, although definitely beneficial, leaves a residual risk, which is still greater than that reduced by treatment [44].

Oxidative stress is an attractive candidate target, as it represents a common mechanism leading from multiple risk factors to disease. At the present time, however, it is not clear which pathogenetic mechanism should be targeted and/or which kind of compounds should be used. Therefore, retrospectively looking, the attempts made in several clinical trials, which mainly obtained negative results, have to be considered premature. Today, we have to recognize that it may be still too early to test this hypothesis in the clinical setting. Further mechanistic studies, both in animals and in humans, are needed in order to achieve a better understanding of the role of ROS in the pathophysiology of atherosclerosis. Further methods that allow a better characterization of the vascular milieu in humans are necessary. Only a more in-depth knowledge of these important pathophysiological mechanisms can allow identifying and testing a therapeutic strategy aimed at oxidative stress as a possible target of cardiovascular therapy. Thus, it is necessary to identify different treatment targets, which could more successfully impact on cardiovascular disease. Thus, it is necessary to identify different treatment targets, which could more successfully impact on cardiovascular disease. Many of the antioxidants, such as dietary content of phytochemicals, and novel polyphenols, have been scrutinized for therapy, in view of the risk factors and inflammatory mediators of HF [44].

It is possible that the cell damage may be reversed by the HEART diet. Experimental and epidemiological studies have also demonstrated that Western-type diets characterized by high sugar and refined carbohydrates with a high glycemic index, as well as high-fat diet, red meat and preserved meat, may predispose individuals to increased risk of HF [45-48], several exogenous antioxidants are available that may be administered for the treatment of HF.

***Shielding dietary patterns in the prevention of heart failure*:** Protective Dietary Patterns in the Prevention of Heart Failure In the USA, as well as in other Western countries, dietary patterns of patients with HF expose a commonly poor Western-type diet that may have a negative impact and a Mediterranean-style diet that may have an advantageous effect on pathophysiology and progression of CVDs and HF [49-51].

The association between glutamate and glutamine in relation to cardiometabolic disorders has been evaluated, in the development of atrial fibrillation (AF) and HF among 509 incident cases of AF, 326 with HF and 618 control subjects [45]. After a follow-up of 10 years, glutamate was associated with a 29% greater risk of HF and glutamine-to-glutamate ratio with a 20% reduced risk. Interestingly, glutamine-to glutamate ratio was also inversely associated with risk of HF (OR per 1-SD increment: 0.80, when comparing extreme quartiles). Increase in glutamate concentrations were found to have a worse risk of cardiometabolic state, whereas a greater glutamine-to-glutamate ratio showed with an improvement in the risk profile. It is possible that high plasma glutamate levels possibly due to changes in the glutamate-glutamine cycle may contribute to the development of HF in subjects at greater risk of CVD [45]. There are no large-scale randomized, controlled intervention trials in patients with HF, to demonstrate the role of the Mediterranean-style diets or the HEART diets in the management of HF.

There is also further evidence from experimental and clinical studies to elucidate the mechanisms of cardiac hypertrophy and HF [49-51]. In a previous study, metabolic products of the intestinal microbiome have been found to predispose individuals to atherosclerosis, which is a risk factor of HF [37, 38]. There is growing evidence on the role of egg on risk of CVDs, which may be erroneous [44]. Cardiac imaging via speckle tracking echocardiography and MRI may be useful in determining the role of nutritional factors and biomarkers in the pathogenesis of HF. The exact pathophysiology of heart failure (HF) is still obscure. Western diet, characterized by highly sweetened foods, as well as being rich in fat, fried foods, red meat and processed meat, eggs, and sweet beverages, may cause inflammation, leading to oxidative dysfunction in the cardiac ultra-structure [52]. Oxidative function of the myocardium and how oxidative dysfunction causes physio-pathological remodeling, leading to HF, is not well known. Antioxidants, such as polyphenolics and flavonoids, omega-3 fatty acids, and other micronutrients that are rich in Indo-Mediterranean-type diets, could be protective in sustaining the oxidative functions of the heart. The cardiomyocytes use glucose and fatty acids for the physiological functions depending upon the metabolic requirements of the heart. Apart from toxicity due to glucose, lipotoxicity also adversely affects the cardiomyocytes, which worsen in the presence of deficiency of endogenous antioxidants and deficiency of exogenous antioxidant nutrients in the diet [52]. The high-sugar-and-high-fat-induced production of ceramide, advanced glycation end products (AGE) and triamino-methyl-N-oxide (TMAO) can predispose individuals to oxidative dysfunction and Ca-overloading. The alteration in the biology may start with normal cardiac cell remodeling to biological remodeling due to inflammation. An increase in the fat content of a diet in

combination with inducible nitric oxide synthase (NOSi) via N-arginine methyl ester has been found to preserve the ejection fraction in HF [52,53]. It is proposed that a greater intake of high exogenous antioxidant restorative treatment (HEART) diet, polyphenolics and flavonoids, as well as cessation of red meat intake and egg, can cause improvement in the oxidative function of the heart, by inhibiting oxidative damage to lipids, proteins and DNA in the cell, resulting in beneficial effects in the early stage of the Six Stages of HF [52].

***Epidemiological studies on diet and risk of HF*:** There are restricted known large-scale epidemiological studies representing the role of dietary factors in the pathogenesis of HF [46-51]. The dietary quality of persons with HF was examined in the NHANES 1999–2006; among the 574 patients, the mean age was 70 years, with 52% being women [53]. The intake of mean sodium was 2719 mg, with 34% consuming less than 2000 mg per day. The intake of potassium was a mean of 2367 mg/day, without consideration for the type of diuretic used or renal disease status. The intake of other nutrients, as per the strategies, was low for some nutrients-13% for calcium, 10% for magnesium, 2% for fish oils, and 4% for fiber-but high (13%) for saturated fat [51]. The dietary quality of persons with self-reported HF was poor. In a case control study from USA among 246 patients, aged mean 61.5 years, with 67% in New York Heart Association class III/IV HF, micronutrient deficiencies were determined. Among 246 patients, 29.8% had hospitalization or death at one year follow-up that included 44.3% in the subgroup with high-deficiency and 25.1% in the rest of them. The distribution of survival exposed significant differences (log rank, $p = 0.0065$). It is likely to conclude from this study that the quality of dietary intakes of the patients with HF may be crucial in determining outcomes [49]. In a different study, comprising 118 patients, 54% were males, aged 66 years (median), with a median ejection fraction of 45% (30–60%), and 49% of patients had CAD [53]. There was a noteworthy association for PUFA; adjusted hazard ratio (HR), 0.67, for consumption as SFA; adjusted HR, 1.15, for consumption as percentage of daily energy. The median of consumption of daily energy was 8.2% for SFA and 5.3% for PUFAs. Remarkably, the consumption of SFA and PUFAs was positively co-related with 1-year all-cause mortality in CHF patients [53-55]. It is possible that decreasing dietary saturated fat with an increase in PUFA consumption should be the approach in these subjects.

Though dietary intakes were not reported in this paper, personal communication revealed that these patients were consuming a meaningfully lower quantity of vegetables, fruits, nuts and legumes. However, beyond these factors, a number of studies have confirmed that following an injury to the cardiomyocyte during a disease, an extreme inflammatory response ensues that predisposes individuals to further damage and the development of cardiac dilatation and thus dysfunction [53, 54]. The injurious biomarkers in failing cardiac cells are as follows: cryopyrin (NLRP3 encodes cryopyrin, which belongs to an emerging family of danger sensors, called NLRs = NOD-like receptors, which are sensor proteins) and the apoptosis-linked speck-like protein containing a CARD (C-terminal caspase-recruitment domain) (ASC), adaptor proteins that trigger the activation of caspase-1, and effector proteins that are pro-inflammatory. These biochemical mechanisms develop in an effort to employ various nutrients present in cardiomyocytes viz. vitamin C, E and beta carotene as well as possibly flavanols, which are prospective antioxidants for the protection against enormous oxidative stress developed in HF patients [53-55]. The escalation in homocysteine related to oxidative stress is antagonized by vitamins B6, B12 and folic acid. L-carnitine, coenzyme Q10, cysteine, taurine, magnesium and potassium may also decline due to increased requirements during oxidative stress that may accelerate morbidity and mortality in patients with HF [54, 55]. Many clinical practice approaches support a low-sodium diet and the constraint of fluids among patients with HF, and research findings direct that a low-sodium diet may have adversative effects on myocardial metabolism, leading to arrhythmias [55]. Thus, there is an unmet requirement to define if a Mediterranean type of foods or Indo-Mediterranean-style foods rich in vegetables, whole grains, fruits, nuts, olive oil, and spices that are rich in all the micronutrients may be protective against CHF.

Using GRADE criteria for strength, it was rated low for all outcomes. No conclusive evidence was observed on the role of egg in increasing risk of CVD. Higher quality studies are urgently warranted to find stronger evidence for a possible protection from CVD associated with egg intake compared to not eating. It seems that future research is necessary to demonstrate the role of egg intake for increased risk of HF. There is no mention of taking designer egg containing w-3 fatty acids and tea flavonoids being protective against CVDs, including HF.

Pathogenesis how Nutrients and Mediterranean diet can avert and treat HF?

Epidemiological studies directed that the incidence and risk of HF is significantly lower in patients who continue to follow this diet, which emphasizes that lower intake of saturated fat and high consumption of PUFA, complex carbohydrates, fruits, spices and vegetables is advantageous. In dietary trials in patients with CVDs, these diets have been found to have favorable effects on HF [56].

It is documented that variations in nutritional status viz. deficiency of fatty acids and amino acids, may predispose individuals to oxidative stress, leading to an increased risk of HF [55, 56]. Besides, the global obesity epidemic is well established, with increases in obesity prevalence for most countries since the 1980s. Obesity contributes directly to incident cardiovascular risk factors, including dyslipidemia, type 2 diabetes, hypertension,

and sleep disorders. Obesity also leads to the development of cardiovascular disease and cardiovascular disease mortality independently of other cardiovascular risk factors [57, 58]. More recent data highlight abdominal obesity, as determined by waist circumference, as a cardiovascular disease risk marker that is independent of body mass index. There have also been significant advances in imaging modalities for characterizing body composition, including visceral adiposity. Studies that quantify fat depots, including ectopic fat, support excess visceral adiposity as an independent indicator of poor cardiovascular outcomes. Lifestyle modification and subsequent weight loss improve both metabolic syndrome and associated systemic inflammation and endothelial dysfunction. However, clinical trials of medical weight loss have not demonstrated a reduction in coronary artery disease rates. In contrast, prospective studies comparing patients undergoing bariatric surgery with nonsurgical patients with obesity have shown reduced coronary artery disease risk with surgery. The association between glutamate and glutamine in relation to cardiometabolic disorders has been assessed, in the development of atrial fibrillation (AF) and HF among 509 incident cases of AF, 326 with HF and 618 control subjects. After a follow-up of a decade, glutamate was associated with a 29% greater risk of HF and glutamine-to-glutamate ratio with a 20% reduced risk. Interestingly, glutamine-to- glutamate ratio was also inversely associated with risk of HF (OR per 1-SD increment: 0.80, when comparing extreme quartiles). There are no large-scale randomized, controlled intervention trials in patients with HF, to demonstrate the role of the Mediterranean-style diets or the HEART diets in the management of HF. There is also additional evidence from experimental and clinical studies to interpret the mechanisms of cardiac hypertrophy and HF [55, 56]. In a previous study, metabolic products of the intestinal microbiome have been found to predispose individuals to atherosclerosis, which is a risk factor of HF. Recent findings are inconsistent regarding the possible relationship between egg consumption and CVD mortality and morbidity. Dietary guidance should focus on improving the overall quality of the diet to promote cardiovascular health [59-62]. There is growing evidence on the role of egg on risk of CVDs, which may be erroneous. Cardiac imaging through speckle tracking echocardiography and MRI may be advantageous in defining the role of certain nutritional factors and biomarkers in the prevention, pathogenesis and remedy of HF [59-62].

II. Conclusions And Future Perspectives

It is conclusively proposed that adherence or non-adherence to the HEART diet may allow relevant experts to classify HF into six stages, based on STE findings showing dysfunctional twist and sub-endocardial dysfunction. These findings may be advantageous in the early diagnosis of HF in its early stages of A, B and C, which may be reversed via increased adherence to the HEART diet. It is conceivable that apart from hypertrophy of cardiomyocytes, new cohort of cardiomyocytes predominates over the death of these cells and likely to contribute significantly to organ growth during adulthood and in physiological restoration. The growth of cardiac cells may be under the influence of defensive nutrients such as peptides, fatty acids and flavonoids. Clinical and preclinical studies indicate that lower intake of n-3 PUFA (approximately 0.4 to 2% of energy intake) may alter the profile of cardiac cell membrane fatty acids of phospholipid and lessen the onset of new HF; according to such studies, it also delays the progression of prevailing HF. This beneficial effect of PUFA, in particular, in conjunction with MUFA, flavonoids and other nutrients, may be connected with a diminution in oxidative dysfunction and inflammation as well as in improved resistance to mitochondrial permeability transition and prevention of HFrEF. There is an unmet need to conduct large clinical trials with an appropriately optimal HEART diet in established HF or in the primary prevention of HF to establish its role in the management of CHF. Educational nutrition interventions positively affect patient clinical outcomes. Although clinical practice guidelines support a low-sodium diet and fluid restriction, research findings have revealed that a low-sodium diet may be harmful. Future research should examine the role of macronutrients, food quality, and energy balance in HF nutrition. Today, oxidative stress remains and attractive target towards cardiovascular prevention as well as therapy. Nevertheless, a profounder considerate of its basis, and of its pivotal role in vascular pathology, is essential prior to new trials are endeavored.

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