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Nutritional Intervention In Heart Failure: An Overview

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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 result inflammation, foremost to oxidative dysfunction in the cardiac ultra-conformation. Oxidative function of the myocardium and how oxidative dysfunction causes pathophysiological remodeling, leading to heart failure (HF), is not well recognized. 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 high-sugar-and-high-fat-induced production of ceramide, advanced glycation end products (AGE) and triamino-methyl-N-oxide (TMAO) can influence individuals to oxidative dysfunction and Ca^{2+}-overloading. The change in the biology may begin with normal cardiac cell remodeling to biological remodeling because of inflammation. An escalation 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 termination of red meat intake and egg, can reason improvement in the oxidative function of the heart, by inhibiting oxidative damage to lipids, proteins and DNA in the cell, ensuing in favorable effects in the early stage of the Six Stages of HF. There is an unmet requisite to conduct cohort studies and randomized, controlled studies to validate the role of the HEART diet in the treatment of HF.

Key words: *Antioxidants, Cardiomyocytes, Heart failure, Myocadium, Oxidative function,*

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I. Introduction

Heart failure (HF) is considered as a present-day epidemic, with about 26 million cases globally [1] resulting in a burden on health care systems; for example, it has been estimated that approximate 2% of the National Health Service (NHS) budget is spent on HF alone [2]. The incidence of HF inclines to upsurge with age due to age-associated variations in the heart's function and structure [3], revealing HF one of the most common reasons for hospitalization in older adults [4]. The 1-year mortality rate among HF patients admitted to hospital has been estimated at about 30% by the latest Annual National HF Audit in England [5]. Furthermore, patients with HF incline to also have a high hospital readmission rate with nearly 25% of patients being readmitted within 30 days [6]. Though maintaining a good quality of life is important for patients' survival and outlook [7], it has been revealed that the quality of life for patients with HF is lower than in any other chronic disease [8].

Malnutrition is common among patients with HF [9], and it foretells worse mortality and hospital readmission outcomes [10, 11]. The occurrence of malnutrition among such a group of patients has been described to be as high as 69% depending on the screening tool being used [12], 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 [13, 14]. Besides, around 5–15% of HF patients have a tendency to suffer from cardiac cachexia [15], defined as 'involuntary progressive weight loss due to the reduction in skeletal muscle mass with or without depletion of adipose tissue' [16]. Cachexia is instigated by immunological and hormonal aberrations, converting the body from an anabolic to a catabolic state by a decline in the activity and levels of anabolic mediators e.g. insulin and growth hormone and an upsurge in activity and levels of

catabolic mediators such as pro-inflammatory cytokines and glucocorticoids [17]. The above alterations lead to a hypermetabolic state [18] and an increase in protein degradation [19], 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 [20-22]. Nevertheless, no nutritional guidelines for the management of HF currently exist. Though systematic overviews have explored the effectiveness 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 [22]. Consequently, this systematic review, being the first of its kind, will emphasize 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 goal is to present the evidence regarding the effectiveness of nutritional interventions, which can potentially help form guidelines for nutritional support in HF patients.

HF is a foremost health care burden and there is a increasing requisite to develop strategies to sustain health and maintain quality of life in persons with HF. The objective of this overview is to critically appraise the components of nutrition interventions and to establish an evidence base for future advances in HF nutrition research and practice.

Nutritional supplementation in heart failure

Chronic heart failure (CHF) is one of foremost health problems in industrialized countries. In spite of therapeutical upgrading, based on drugs and exercise training, it is still described by elevated mortality and morbidity [23]. Data reveal that protein energy malnutrition, clinically obvious principally with sarcopenia, is present in more than 50% of CHF patients and is an self-regulating factor of CHF prognosis. Several pathophysiological mechanisms, predominantly due to the rise in blood hypercatabolic molecules, have been projected to elucidate this phenomenon. Nutritional supplementation with proteins, amino acids, vitamins and antioxidants has all been applied to treat malnutrition. Though, the success and efficiency of these trials are often conflicting and not convincing. Remarkably, data on exercise training show that exercise decreases mortality and increases functional ability, while it also enhances the catabolic state with energy expenditure and nitrogen-providing substrate requirements. Therefore, it is focused that the molecular mechanisms of specific nutritional supplementation integrated with exercise training may improve anabolic pathways. Besides, the association between exercise and the mTOR complex subunit as Deptor and/or correlated signaling proteins, such as AMPK or sestrin, is crucial. As a result, concomitantly with 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 documented comprehensive relevant account as follows:

Clinical Problem

Chronic heart failure (CHF) is one of major health problems of the industrialized countries. It is a complex syndrome where, though the "*primum movens*" is heart disease, it too affects various organs and systems of the human body [24]. In spite of latest therapeutical improvements based on a amalgamation of specific medical approaches/therapies, CHF is still characterized by elevated mortality and morbidity [25]. Remarkably, recently the benefits of cardiac rehabilitation and exercise training have been revealed in patients with heart failure, together with a decline in morbidity and mortality. Though, data also show that even light exercise causes a significant catabolic demolition of muscular proteins [26]. This catabolic effect of exercise is more prominent 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. Surplus nutrients intake reasons over-nutrition that in turn results in the obesity. Nonetheless, the presence of obesity does not essentially recommend that there is no variation in protein metabolism. Indeed, it should be kept in mind that there is a clinical condition, namely sarcopenic obesity, in that the patient is obese; however having all the features of sarcopenia, together with reduced muscle mass and muscle strength. Consequently, the presence of protein metabolism disarrangements should also be pursued in obese patients with CHF.

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. Under-nutrition can occur either due to protein energy wasting or as a consequence of micronutrient deficiencies. It can be a foremost health problem both in children, where it is responsible for incomplete physical and mental development, as well as in adults. Interestingly, under-nutrition is particularly present in elderly people and women. It should be indicated that under-nutrition is an increasing health problem in people aged over 65 years in developed countries, mainly due to physical, psychological and social factors. Indeed, aged people reduce dietary intake because they may have both physical and/or social problems, such as chewing and swallowing difficulties, depression, intestinal-related diseases,

and/or poverty and loneliness. The signs and symptoms of micronutrient deficiencies depend on which micronutrients are lacking. Basically, an inadequate intake of micronutrients includes iodine, vitamins and iron. Clinically, these can cause, respectively, hypothyroidism, hypovitaminosis and hypo-hemoglobinemia (named anemia). Interestingly, anemia is often present in patients with CHF, and it is commonly caused by iron deficiency, although other micronutrients are also needed for hemoglobin synthesis [4]. It is also mandatory to stipulate that iron is important for other vital metabolic processes of cell cycle, including DNA synthesis and matrix metalloprotease activities (MMPs). Further, MMPs play a pivotal 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 recalled that hemoglobin is a heme protein. As such, hypo-hemoglobinemia point out that there is a lack of other heme proteins, together with basic proteins involved in the energy use/production (i.e., cytochrome-c, myoglobin,), in the protection against oxygen free radicals (i.e., catalase, peroxidase) or in inflammatory developments (i.e., cyclooxygenase, NOS) [27]. Under-nutrition is considered protein energy malnutrition as both the micronutrient deficiencies, and an imbalance of protein/energy intake and protein/energy expenditure are present. It contrasts from calorie restriction due to hypoalimentation that has no negative health effects. It is well defined by symptoms like weight loss with normal serum albumin. Remarkably, epidemiological outcomes reflect that protein energy malnutrition is often present in patients with CHF, along with traditional CHF symptoms [28].

These changes results in global metabolic disfunction with protein disarrangements present objectively in CHF patients as a loss of muscular body mass/functions known as sarcopenia that can progress to cachexia [25]. It is fascinating to annotation that protein energy malnutrition links with mortality irrespective of heart disease severity in CHF patients [29]. Nevertheless, 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 [30]. Here, grounded on molecular and pathophysiological evidence, it has been proposed to integrate nutritional supplementation with definite molecules, with exercise training and customary medical therapy to generate a persuasive alliance to treat patients with CHF in the best possible way.

Nutritional supplementation: As previously mentioned, data recommend that CHF-induced hypercatabolic syndrome reasons AA metabolism alterations and the protein disarrangement of both globular and muscular proteins. As a consequence, the exogenous supplementation of food preproteins and/or free AAs could be an effective therapeutical strategy to use with CHF patients. Though, results also reflect that advancement of the metabolic and nutritional status of muscle-depleted CHF patients happens as and when tolerable energy protein intake is combined 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 [31-35]. Besides, recent studies direct that free EAA mixture supplementation upgrades both muscular protein synthesis and the expression of plasma anabolic and anti-inflammatory proteins than nutrition with whey proteins [36-38]. Primarily, food proteins must be digested by pancreatic enzymes and the resultant AAs would then be absorbed by the intestine followed by their introduction into the bloodstream to be transported to cells. As recently revealed in aged and/or diseased patients' pancreas, exocrine efficiency and intestinal metabolism are gradually reduced with consequently changed digestion and the absorption of food constituents. On the other hand, free AAs do not require to be digested, but are speedily absorbed and instantly accessible in the blood for protein syntheses [38-42]. Secondly, from a nutritional point of view, AAs are classified as EAAs, which cannot be synthetized in the body and are therefore needed in the human diet, and non-essential (NEAAs) which can be produced in the body according to the metabolic need, so that their presence in the diet is not strictly necessary. Unfortunately, it should be noted that no dietary proteins have an EAA/NEAA ratio >0.9; while, on the other hand, most proteins have a <0.7 ratio at best.

Remarkably, investigational data display that special EAA mixtures with an EAA/NEAA ratio >1 increase the lifespan [43] and albumin [189], and moreover decrease inflammation in healthy mice [44-46]. This recommends that NEAAs are not indispensable for cell cycle and are synthesized as per metabolic requirements if adequate amounts of EAAs are provided. Indeed, only EAAs have the metabolic features illustrated as follows. Merely EAAs counteract IRS effects by activating glucose transport and protein synthesis [45]. These effects happen because EAA mixtures flowing through the portal vein are the signal for IGF-1 (insulin-like growth factor-1) secretion [47] that is the somatomedin accountable for activating anabolic growth hormones (GH) [21]. 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 [48-50]. Conversely, it has been demonstrated that only EAA mixtures formulated according to human requirements improve energy production and the synthesis of oxygen free radical scavengers via mitochondrial biogenesis [36]. In addition, 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 [36]. Lastly,

EAAs can also influence the insulin effects on adipocytes, enhancing glucose transport and modulating the use of FFAs. Indeed, EAAs and their metabolites have recently been defined as "Metabokine" because they are able to influence local metabolism and systemic physiology [51, not only through direct metabolic influence, but also modifying the gene expression via epigenetic action [51]. Indeed, 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), which is a transcriptional coactivator that regulates the genes involved in mitochondrial biogenesis and the adaptive metabolic response to exercise [52].

In view of all above points, it can be concluded that oral supplementation with special mixtures of free EAAs, in a stoichiometric ratio and formulated as per human metabolic requirements, should be used in CHF patients to contrast protein calorie malnutrition and sarcopenia, muscular wasting and cachexia. Conversely, although the combination of exercise and nutritional support with AAs has solid rational foundations, the relationship itself is very complex. Investigational and clinical data accessible are fairly conflicting and controversial. These mixed results can be partially interpreted by considering the experimental models used as the type of exercise (resistance or force), the diverse nutritional supplementations (food proteins, AA mixtures, ketoacids with or without micronutrients such as vitamins and/or ions), the age of the patients studied, as well as the presence of comorbidities [53]. It should be highlighted 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 converted into other molecules via a series of steps. Each step is assisted by a specific co-factor (i.e., vitamins, ions and others). The result of nutritional metabolic therapeutical methodologies is that nutrition should provide not only one molecule, but all the most vital molecules involved in the anabolic EAA-mediated pathways [54]. This approach has been established in relevant recent clinical study. This exhibited that a specific mixture of EAAs, competent to match human metabolic requirements, has the best influences in 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 [25].

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 [53]. 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 [54]. Finally yet importantntly in this context, it is indispensable to differentiate between being fed with or without nutritional supplementations, and nutrition itself. Being fed means furnishing food and oral supplementation for the maintenance/improvement of the body's overall metabolism. Contrarily, nutrition is the sum of biochemical and physiological complex processes by which a human being digests, absorbs and metabolizes the macro- and micronutrients introduced through ingestion. These findings propose that personalised, 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 Damage and Repair

In spite of 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. However clinicians primarily observed HF as a problem of extreme salt and water retention that was triggered by aberrations of renal blood flow (Cardio-renal model) [23,24], as physicians originated to accomplish careful hemodynamic measurements, it furthermore became obvious 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. Consequently, although the cardiorenal models provided the coherent foundation for the use of diuretics to control the volume status of patients with HF, and the cardiocirculatory model provided the coherent

base for the application of inotropes and intravenous vasodilators to enhance cardiac output, these therapeutic approaches have not prohibited heart failure from developing, nor have they directed to prolonged life for patients with moderate to severe HF.

HF*: *A progressive model

Heart failure may be considered as a progressive disorder that is initiated after an "index event" either damages the heart muscle, with a consequential loss of functioning cardiac myocytes, or instead disturbs the ability of the myocardium to produce force, thus avoiding the heart from contracting consistently. This index event may have an unexpected onset, as in the case of a myocardial infarction, it may have a gradual or deceptive onset, as in the case hemodynamic pressure or volume overloading, or it may be hereditary, as in the case of genetic cardiomyopathies. Irrespective of the nature of the seditious event, the common feature in each of these index events is that they all, in some way, generate a decline in pump functioning of the heart. In maximum occurrences patients will remain asymptomatic or insignificantly symptomatic after the initial decline in pumping capability of the heart or will progress symptoms only after the dysfunction has been present for certain period. Hence, when noticed within this conceptual framework, left ventricular (LV) dysfunction is essential but not adequate for the progress of the syndrome of heart failure.

The portfolio of compensatory mechanisms that have been described include early activation of the adrenergic nervous system and salt- and water-retaining systems in order to preserve cardiac output [29-31], as well as activation of a family of vasodilatory molecules, including natriuretic peptides, prostaglandins (PGE_2 and $PGEI_2$), and nitric oxide, to counteract the excessive vasoconstriction resulting from excessive activation of the adrenergic and renin-angiotensin systems [35,36]. However, our understanding of the family of molecules that may be involved in symptomatic HF [23]. This process is far from complete. The transition to symptomatic heart failure is accompanied by further activation of neurohormonal and cytokine systems, as well as a series of adaptive changes within the myocardium, collectively referred to as "LV remodeling." Although there are further modest declines in the overall pumping capacity of the heart during the transition to symptomatic heart failure, the weight of experimental and clinical evidence suggests that heart failure progression occurs independently of the hemodynamic status of the patient.

Intervention studies and cohort studies of various 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 physiopathological 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 [55]. 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 [56]. 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 [57-60]. 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 [61].

In addition, oxidative stress can induce an energy deficit by influencing the protein function related to metabolism of energy [61]. Oxidative dysfunction may facilitate a pro-fibrotic function, as adaptation, by causing the proliferation of fibroblasts in the heart and matrix metallo-proteinases for extracellular remodeling, which may be the beginning of the hypertrophy of the heart . It seems that the production of ROS in the heart is primarily completed by the mitochondria, xanthine oxidase, NADPH oxidases, and uncoupled nitric oxide synthase (NOS) [56]. The electron transport chain of the mitochondria may cause an overproduction of superoxide anion, contributing to cardiomyocyte damage with an increase in myocardial injury after an acute myocardial infarction [55]. There may be an increase in oxidative stress with an increased expression and activity of NADPH oxidase, due to multiple environmental and biological factors, such as angiotensin II, endothelin-1, mechanical stretch and tumor necrosis factor (TNF)-α [57-60]. The expression of xanthine oxidase and its activity is also increased due to damaging effects of behavioral risk factors such as tobacco intake and alcoholism in the heart exposed to these risk factors.

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 [62]. 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 [63], There may be an uncoupling of the NOS with structural instability, which further increases the generation of ROS, leading to left ventricular (LV) enlargement, dysfunction in the contraction [56], and remodeling of LV [58]. If the cardiac damage continues, it may lead to increased sympathetic activity with decline in parasympathetic activity causing neuro-hormonal dysfunction [62]. Interestingly, the protective factors, such as the HEART diet may prevent the development of HF, if administered in one or the other of the early stages of Six Stages of HF [64-66]. This mechanism is more clearly evident in Figure 1.

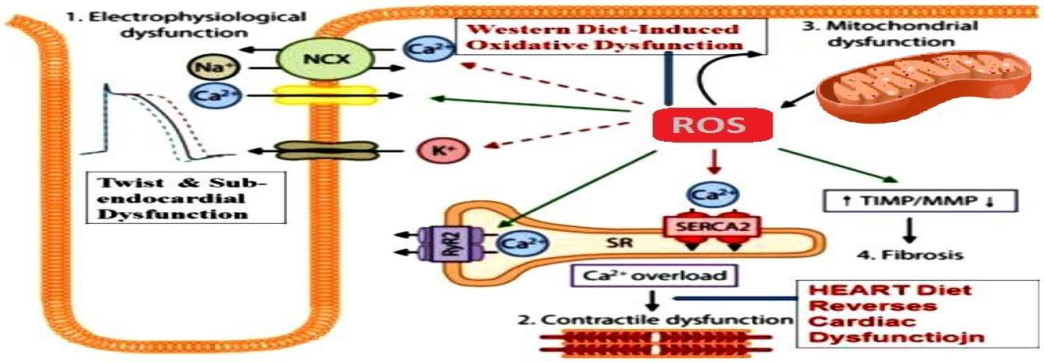

Fig.1: Oxidative dysfunction in the heart due to Western diet, with decrease in antioxidant defenses, causing mitochondrial dysfunction, leading to electrophysiological dysfunction with twist and sub-endocardial dysfunction. Exogenous antioxidants (HEART diet) improve antioxidative function with reduced Ca-overloading and reversal of mitochondrial and electrophysiological dysfunction; Modified from Reference [57].

***Oxidative dysfunction and inflammation as targets for therapeutic antioxidants*:** Preclinical and clinical studies indicate that several therapeutic options are available to treat oxidative stress-associated cardiovascular diseases (CVDs) [67]. Many of the antioxidants, such as dietary content of phytochemicals, and novel polyphenols, have been examined for therapy, in view of the risk factors and inflammatory mediators of HF [59]. Apart from these, new therapeutic methods such as miRNA and nano-medicine are also available for the treatment of CVDs, in particular, HF, which may be tried, during the early stages of the Six Stages of HF.

It seems that an increase in free fatty acids and oxidative dysfunction with reference to variability in biomarkers such as glucose levels, and levels of oxidative stress, predispose individuals to multifold greater inflammation and immune deficiency, leading to cardiac cell apoptosis and heart failure (HF) [68-70]. Decline in immunological responses may result in damage to other body systems contributing in diseases of associated body systems [68-70]. Free radicals are known to damage the cell membranes, causing the development of intracellular Ca2+ overload, activation of proteases and phospholipases, and alterations in mitochondrial gene expression in the cardiac cells, predisposing individuals to cardiomyocyte dysfunction [68-72]. Deficiency of

protective antioxidants may predispose individuals to oxidative damage to proteins, enzymes, fatty acids and DNA [68-72].

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 [73–81]. Apart from endogenous antioxidant defences, several exogenous antioxidants are available that may be administered for the treatment of HF. Since therapy with individual antioxidants in patients with CVDs has only had limited success, there is a need to determine the role of the Mediterranean diet, such as the HEART diet, in the management of HF.

***Effect of heart diet in HF*:** The mechanisms responsible for the beneficial effects of antioxidants or the HEART diet in HF may be a decline in oxidative stress and cardiac inflammation, a reduction in mitochondrial dysfunction, improved Ca2+ homeostasis, increased survival signaling, and an increase in sirtuin 1 activity [56]. It seems that all these mechanisms are heightened in conjunction with excessive oxidative stress due to the intake of a Western type of diet derived primarily by overexpression of nicotinamide adenine dinucleotide phosphate (NADPH)-oxidases (Nox) and an increase in mitochondrial-derived ROS that are major drivers of HF [59]. It is possible that the HEART diet reverses the detrimental effects of oxidative stress, while cellular antioxidants such as vitamin E, C and CoQ10 and detoxifying enzymes neutralize ROS and ameliorate cytotoxic conditions [57]. These enzymes include superoxide dismutase (SOD), catalase, glutathione S-transferase, glutathione peroxidase (GPx), heme oxygenase (HO)-1 and NADPH dehydrogenase quinone 1 (NQO1), which are mostly co-regulated by Sirt1 and nuclear factor erythroid 2-related factor 2 (Nrf2) [58]. Since there is a state of exacerbated oxidative stress and inflammation in HF, the detoxifying system is overwhelmed, as NF-κB overexpression can inhibit Nrf2 nuclear activity, and vice-versa [59]. Inflammation facilitates macrophage recruitment into the myocardium via chemoattractants and also leads to the differentiation of fibroblasts into myofibroblasts, promoting fibrosis [59]. Collectively, these signaling effects lead to cardiomyocyte oxidative dysfunction, cardiac hypertrophy, apoptosis, pro-fibrotic signaling and, at the organ level, reduced functional capacity. It seems that mediating the inflammatory and antioxidant responses and other mechanisms via the HEART diet is of major therapeutic relevance in HF.

There are multiple pathways by which nutritional factors can have adverse or beneficial effects in the development of CVDs [58-62]. It seems that beyond drug therapy, the nutritional status of the patients of HF can also influence the effects of therapy due to cardioprotective factors such as coenzyme Q10 and resveratrol, nutrients in the cardiac tissues [56-58]. Apart from these nutrients, certain factors in the brain, such as the renin–angiotensin–aldosterone system (RAAS), can act as an oxidant, leading to an increase in inflammation in the neurons [58]. Inflammation in the brain as part of neuro-hormonal dysfunction may activate the prefrontal cortex and amygdala, leading to an increase in brain neuropeptide, angiotensinogen II (ANG II). These pro-inflammatory factors can damage the hippocampus, pre-sympathetic neurons in the paraventricular nucleus as well as preganglionic sympathetic neurons.

Since the Mediterranean diet is known to protect brain function by its benefits in depression and dementia, it poses the possibility that the HEART diet, which is an improved Mediterranean-style diet, may provide greater beneficial effect on brain-related mechanisms of HF [71]. There is existing evidence that diets deficient in omega-3 fatty acids [82] and whole grains [82], as well diets with an excess of red meat [83], processed meat 84], and high-glycemic-index foods [85], can predispose individuals to HF.

***Protective 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 reveal a generally poor Western-type diet that may have a negative impact and a Mediterranean-style diet that may have a beneficial effect on pathophysiology and progression of CVDs and HF [86-91]. The Dietary Approaches to Stop Hypertension (DASH) diet, is also a Mediterranean-style diet. Epidemiological studies indicated 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 [51–55,68,69] is beneficial. In dietary trials in patients with CVDs, these diets have been found to have beneficial effects on HF [70,71]. There is evidence that alterations in nutritional status, such as deficiency of fatty acids and amino acids, may predispose individuals to oxidative stress, leading to an increased risk of HF [55–58].

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 [72]. 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-toglutamate 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 [72]. 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 [72–85]. In a previous study, metabolic products of the intestinal microbiom have been found to predispose individuals to atherosclerosis, which is a risk factor of HF [81].There is growing evidence on the role of egg on risk of CVDs, which may be erroneous [83]. 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.

***Epidemiological studies on diet and risk of HF*:** There are limited known large-scale epidemiological studies indicating the role of dietary factors in the pathogenesis of HF [68-71]. 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 [56]. 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 guidelines, 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 [57,76]. 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 [62]. Among 246 patients, 29.8% had hospitalization or death at one year follow-up, which included 44.3% in the subgroup with high-deficiency and 25.1% in the rest of them. The distribution of survival revealed significant differences (log rank, $p = 0.0065$). It is possible to conclude from this study that the quality of dietary intakes of the patients with HF may be crucial in determining outcomes [65]. In another 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 [68]. There was a significant 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. Interestingly, the consumption of SFA and PUFAs was positively co-related with 1-year all-cause mortality in CHF patients [72]. It is possible that decreasing dietary saturated fat with an increase in PUFA consumption should be the strategy in these subjects. Recently, Hristova et al. re-emphasized the role of nutritional modulators among patients with CHF, because these patients may suffer from weight loss as well as cachexia, which is associated with deficiency of antioxidant vitamins, such as magnesium, potassium, and vitamin D, as well as fiber and flavonoids, apart from general malnutrition. Hristova et al., as well as Fedacko et al., reported the risk factors and inflammatory mediators of HF among 116 patients from India, in which only little attention was paid to nutritional risk factors in HF [86,87].

Although dietary intakes were not reported in this paper, personal communication revealed that these patients were consuming a significantly lower quantity of vegetables, fruits, nuts and legumes. However, beyond these factors, several studies have demonstrated that following an injury to the cardiomyocyte during a disease, an intense inflammatory response occurs that predisposes individuals to further damage and the progression of cardiac dilatation and dysfunction [86,87]. The cell debris, such as extracellular ATP, released during tissue injury induces conformational changes in the components of the inflammation in cardiac tissue, which may worsen if there is deficiency of antioxidant nutrients in the tissue. The harmful 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-associated 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 [86,87]. These biochemical mechanisms develop in an attempt to utilize various nutrients present in cardiomyocytes such as vitamin C, E and beta carotene as well as possibly flavanols, which are potential antioxidants for the protection against enormous oxidative stress developed in HF patients [86,87]. The increase 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, which may hasten morbidity and mortality in patients with HF [86,87]. Many clinical practice guidelines support a low-sodium diet and the restriction of fluids among patients with HF, and research findings indicate that a low-sodium diet may have adverse effects on myocardial metabolism, leading to arrhythmias [88]. Therefore, there is an unmet need to determine 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.

In a cohort study, 1140 hospitalizations for HF were made during a mean of 13 years. After multivariable adjustment (energy intake, demographics, lifestyle factors, prevalent cardiovascular disease,

diabetes, hypertension), HF risk was higher with a greater intake of eggs (1.23) and high-fat dairy (1.08) and HF risk was lower with greater whole-grain intake (0.93) [78]. These associations remained significant independent of intakes of the five other food categories, which were not associated with HF. It is possible that consumption of whole-grain was positively associated with a decreased risk of HF, whereas egg consumption and dairy products with high-fat showed higher HF risk [78].

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 prevent and treat HF?

In the USA, as well as in other Western countries, dietary patterns of patients with HF reveal a generally poor Western-type diet that may have a negative impact and a Mediterranean-style diet that may have a beneficial effect on pathophysiology and progression of CVDs and HF [89-91]. The Dietary Approaches to Stop Hypertension (DASH) diet, is also a Mediterranean-style diet. Epidemiological studies indicated 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 [68,69] is beneficial. In dietary trials in patients with CVDs, these diets have been found to have beneficial effects on HF [92].

There is evidence that alterations in nutritional status, such as deficiency of fatty acids and amino acids, may predispose individuals to oxidative stress, leading to an increased risk of HF [93]. 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 [93]. 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-toglutamate 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 [93]. 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 [94-101]. In a previous study, metabolic products of the intestinal microbiom have been found to predispose individuals to atherosclerosis, which is a risk factor of HF.There is growing evidence on the role of egg on risk of CVDs, which may be erroneous [99]. 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.

II. Conclusions:

It is possible that increased intake of certain nutrients and foods, such as saturated fat, trans fat, sugar, red meat and preserved meat, has adverse effects, whereas glutamine and MUFA, PUFA, flavonoids and polyphenolics, omega-3 fatty acids, and other phytochemicals appear to have beneficial effects. Increased intake of unhealthy foods and nutrients may result in oxidative damage to proteins, enzymes, fatty acids and DNA in the biochemical composition, molecular structure, and function of different subcellular organelles of the heart, with oxidative myocardial dysfunction, pathological subcellular remodeling causing HF. The subcellular remodeling may be physiological or pathological and may be intimately involved in the transition of cardiac hypertrophy to HF depending on the optimal availability of useful or unhealthy food and nutrients, antioxidants, fatty acids and amino acids in the tissues. It is proposed that adherence or non-adherence to the HEART diet may allow us to classify HF into six stages, based on STE findings showing dysfunctional twist and sub-endocardial dysfunction. These findings may be useful 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 possible that apart from hypertrophy of cardiomyocytes, new generation of cardiomyocytes predominates over the death of these cells and contributes significantly to organ growth during adulthood and in physiological remodeling. The growth of cardiac cells may be under the influence of protective 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 change the composition of cardiac cell membrane fatty acids of phospholipid and reduce the onset of new HF; according to such studies, it also delays the progression of existing HF. This beneficial effect of

PUFA, in particular, in conjunction with MUFA, flavonoids and other nutrients, may be associated with a decrease 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.

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