Heart Diet in Prevention of Heart Failure

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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. 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 heart failure (HF).

Western diet cardiomyocyte oxidative stress bioactive agents dietary fat cardiac failure

1. Oxidative Dysfunction in Heart Failure

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 [1]. 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 [2]. 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 heart failure (HF) [3][4]. 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 [1][2][3][4][5]. Oxidative stress may also cause alteration in the activity of the sarcoplasmic reticulum Ca^{2+}-adenosine triphosphatase (SERCA) as well as reduce myofilament calcium sensitivity [5]. In addition, oxidative stress can induce an energy deficit by influencing the protein function related to metabolism of energy [5]. 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 [3][4].

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) [3]. 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 [3]. 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 [1][2][3][4][5]. 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 [1][2][5][6]. 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 [6][7], 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 [3], and remodeling of LV [3][4]. If the cardiac damage continues, it may lead to increased sympathetic activity with decline in parasympathetic activity causing neuro-hormonal dysfunction [1][2][3][4][5][6].

2. Left Ventricular Twist as Function of the Heart

Richard Lower FRCP (1631–1691) was the first to publish the twisting motion of the LV, in 1669, as “the wringing of a linen cloth to squeeze out the water”, which continues to intrigue the experts in their quest to understand cardiac function [8][9][10]. Apart from speckle tracking echocardiography (STE), magnetic resonance imaging (MRI) may be used to examine LV twist [10][11]. It appears to be crucial to examine twist function to understand the oxidative function of the heart, which would require quantification of the LV twist. The cardiac twist or torsion represents the mean longitudinal gradient of the net difference in the clockwise and counterclockwise rotation of the apex and base of the LV, as viewed from the apex of the left ventricle. The LV twist deforms the sub-endocardial fiber matrix, resulting in the storage of potential energy. A further deformation in the recoil of twist may cause the release of restoring forces, which contributes to diastolic relaxation of the LV with early diastolic filling [11]. Interestingly, systolic function may not be entirely normal, despite the normal ejection fraction (EF). There may be a decline in the left ventricular systolic long-axis at earlier stages, followed by evidence of more greater, subtle defects. On physical training, with decreased augmentation of function in the long-axis, impairment in systolic twist, decreased global strain, and electromechanical dys-synchrony will reduce the myocardial systolic reserve [11][12][13]. The twist function may alter during oxidative myocardial dysfunction, which may be an early marker of HF.

The physiology of twist mechanics indicate that LV twists in systole store optimal energy and, during the recoils (untwists) in diastole, cause energy release [12]. It seems that left ventricular ejection is aided by twist and untwist, which is helpful for the relaxation and filling of the ventricle. Thus, twist or torsion and rotation are crucial in cardiac contraction mechanics. Torsion or twist is accompanied by the wringing motion of the heart in its long axis produced by contraction of the myofibers in the wall of LV [8]. The apex and the base of the heart, during initial isovolumic contraction, both rotate in a counterclockwise method, if observed from apex to base. However, in the normal heart, the base of the heart has clockwise rotation during systole and the apex of the heart has counterclockwise rotation, causing a wringing movement. The cardiologists are not able to understand the utility of the twist function in clinical practice, which may be due to the problems in the measurement of cardiac rotation and torsion in the clinic [13][14]. It seems that three-dimensional STE may be an alternative method to assess the twist function, during plane motion. However, it seems that the measurement of the twist function would enhance the knowledge of physiological mechanics of the heart, such as the early diagnosis of abnormality in the rotation, indicating sub-endocardial dysfunction, the second stage of the six stages of HF, that may occur due to behavioral risk factors such as tobacco and Western diet. These risk factors may be also helpful in exploring the secrets of the diastole (a Rosetta stone), which could be a new concept in diastolic function and diastolic HF, via STE, in the light of neuro-humoral dysfunction [13][14][15][16][17]. It seems that the physician needs to have a closer look to understand the physio-pathogenesis of oxidative myocardial function and cardiac dysfunction, in particular, the LV twist and decline in myocardial strain [6]. There is an unmet need to use rotation and twist, as well as reversible sub-endocardial and diastole dysfunction in the diastole, via STE, as new markers of cardiac function, in the presence of oxidative dysfunction of the myocardium [15][16][17].

3. 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) [1][3][4]. 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 [4][18][19]. 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) [20][21][22]. Decline in immunological responses may result in damage to other body systems contributing in diseases of associated body systems [20][21][22]. Free radicals are known to damage the cell membranes, causing the development of intracellular Ca^{2+} overload, activation of proteases and phospholipases, and alterations in mitochondrial gene expression in the cardiac cells, predisposing individuals to cardiomyocyte dysfunction [20][21][22][23][24]. Deficiency of protective antioxidants may predispose individuals to oxidative damage to proteins, enzymes, fatty acids and DNA [25][26][27]. 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 [25][26][27][28][29][30][31][32][33].

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, **Table 1**.

Table 1. Antioxidant defences and antioxidants available in the HEART diet.

Indogenous Antioxidants	Exogenous Antioxidants from HEART Diet
Enzymes	Vitamins
Superoxide dismutase (SOD)	Vitamin C, ascorbic acid, ascorbate
Glutathion peroxidase (GPS)	Vitaminss, E, tocopherol, tocotrienol
Glutathion reductase	Vitamin A, vitamin D
Glutathion-S-transferase	Polyphenolics and favonoids
Paraoxanase	Quercitin, resveratrol
Thioredoxin reductase	Catechins; Flavonols, Flavanols
Heme- oxygenase	Curcumin
Aldehyde dehydrogenase	Anthrocyanins
8-Oxyguanine glycoselase	Phenolic acid
Catalase (Iron dependent)	Isoflavons/Genestein
Non-enzyme antioxidant	Carotinoids
Bilirubin	Alpha-carotine, beta-carotine
Coenzyme Q10	Zeaxanthin
L-carnitine	Lutein
Alpha-lipoic acid	Lycopine
Melatonin	Beta-cryptixanthin
Uric acid, cholesterol	Minerals
Metal binding proteins	Magnesium

Indogenous Antioxidants	Exogenous Antioxidants from HEART Diet
Metallothioneine	Selinium, cromium
Lactoferrin	Zinc, copper
Transferrin	Fiber in the diet; oligosaccharides, polysaccharides
Ferritin	Fatty acids; Omega-3 and Monounsaturated
Ceruloplasmin (Cu dependent)	Amino acids; L-theanine, arginine, L-tryptophan

4. Effects of HEART Diet in Heart Failure

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 Ca^{2+} homeostasis, increased survival signaling, and an increase in sirtuin 1 activity [3]. 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 [3][4]. 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 [3][4]. 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) [3][4]. 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 [4]. Inflammation facilitates macrophage recruitment into the myocardium via chemoattractants and also leads to the differentiation of fibroblasts into myofibroblasts, promoting fibrosis [4]. 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 [21][22][23][24][25]. 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 [21][22][23]. 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 [24][25]. 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

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provide greater benefit, or ketosis, brain-related mechanisms of HF [26][27]. There is existing evidence that diets deficient in omega-3 fatty acids [28] and whole grains [29], as well as diets with an excess of red meat [30], processed meat [31], and high-glycemic-index foods [32], can predispose individuals to HF.

5. Dietary Fat and Risk of Heart Failure

Recent and previous experiments published in *Nature* confirm the role of nutrition in the pathogenesis of CVDs and diabetes as well as in HF [34][35]. Experimental studies confirm that high dietary total and saturated fat and high glucose intake have an adverse effect on cardiac cell function, and high fat intake along with arginine may be associated with increased risk of HFpEF, in an attempt to prevent a decline in the ejection fraction, as a mechanism of molecular adaptation [35]. Such diets may begin their adverse effects by causing twist dysfunction (Stage 1 HF) and later on sub-endocardial dysfunction (Stage 2 of HF) due to oxidative damage of proteins, enzymes, fatty acids and DNA. In a previous experimental study, a high-fat diet given to fathers in mice showed adverse effects on offspring [34]. The findings revealed that a chronic high-fat diet administered to fathers programs β-cell dysfunction in female rat offspring and induces obesity-impaired glucose tolerance [IGT], insulin resistance that worsened with time, relative to controls. Administration of this diet was associated with alteration in the expression of 642 pancreatic islet genes in the offspring of female adults. These genes were related to 13 functional clusters, such as ATP binding, cation, intracellular transport and cytoskeeton [34]. Further analysis of 2492 genes with variable expression, showed the participation of pathways related to Ca-MAPK and MnT signaling, apoptosis and the cell cycle. It has also been observed that the gut flora metabolism of phosphatidylcholine promotes CVDs, including HF [36].

In all CVDs and diabetes metabolic processes, diet holds promise for the discovery of new pathways that link the primary risk factors to disease processes [34][35][36][37]. There is evidence that metabolites of the dietary lipid phosphatidylcholine, betaine, choline and trimethylamine *N*-oxide (TMAO) may have a major role in the pathophysiology of CVDs [36][37]. Dietary supplementation of mice with choline, TMAO or betaine predisposed individuals to the upregulation of several macrophage scavenger receptors linked to the pathophysiology of atherosclerosis [36]. However, administration of TMAO or its precursors increased the process of atherosclerosis. Experimental studies in germ-free mice showed a critical role for dietary choline and gut flora in TMAO production, which augmented cholesterol accumulation in the macrophage cholesterol, leading to foam cell formation. In the atherosclerosis-prone mice experiment, suppression of intestinal microflora was associated with inhibition of dietary-choline-enhanced atherosclerosis. There are variations in the gene-controlled expression of flavin monooxygenases, an enzymatic source of TMAO, segregated with atherosclerosis in mice with hyperlipidemia [36]. This discovery indicates a relation of gut-flora-dependent metabolic function of phosphatidylcholine in the foods and pathophysiology of CVDs. It is possible that new biomarkers may be developed for making an early diagnosis of CVDs and diabetes, which may be useful in developing new therapeutic approaches for the prevention of HF. TMAO is produced in the body, in a co-metabolic pathway, concerned with microbial-mammalian, from the digestion of foods with meats having dietary quaternary amines, such as betaine, phosphatidylcholine and L-carnitine [38]. Intake of fish has been found to be protective against

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CVDs and diabetes, but fish provides a large and significant source of TMAO. It is possible that adverse effects of TAMO, such as oxidative stress and inflammation, are neutralized due to the presence of omega-3 fatty acids and peptides in the fish, leading to overall benefits. There may be discrepancies and inconsistencies in the recent investigations, and the role of TMAO has been questioned in some diseases, because its precursor L-carnitine has been found to be beneficial in CVDs [38]. Recent experimental and epidemiological studies on the effects of TMAO indicate that it may have beneficial effects in the presence of a diet, which is protective for the microbiome [38]. In obesity, the relative proportion of Bacteroidetes is decreased compared to lean subjects, and that this proportion increases with loss of weight on two types of low-energy diet [39]. It is possible that obesity has a microbial part, which might have important therapeutic potentials [39].

Western-diet-induced inflammation of the heart may mediate the activation of multiple mechanisms that predispose individuals to CVDs, including CHF [34][35][36][37][40][41]. Apart from glucotoxicity, lipotoxicity may be associated with the activation of the receptor for advanced glycation end products (RAGE) due to an increase in advanced glycation end products (AGEs) predisposing individuals to oxidative stress and inflammation [42]. In earlier studies, such actions have largely been ascribed to fat deposition due to Western diet and the accumulation of AGEs. Subsequently, there is RAGE activation, which can represent necessary mediators of cardiac cell injury leading to the hypertrophy of cardiac cells.

It seems that greater consumption of oleic acid or n-6 fat has also been found to provide improvement in cardiac hypertrophy [43]. This finding may indicate a decrease in oxidative stress and inflammation and better resistance to transition in mitochondrial permeability. It seems that the related mechanisms are complex, which could be on account of adaptation of the heart, in a situation, on saturated fat diets. There is an unmet need to have complete understanding of the effects of different types of dietary fats on phospholipids in the cell membrane of cardiac cells, metabolites of lipids and metabolic functions in the failing as well as in the normal heart. It is likely that existing nutrients such as w-3 fatty acids, flavonoids, and coenzyme Q10 may inhibit the lipotoxicity caused by saturated fat and delay the progression of cardiac hypertrophy, by improving twist function and sub-endocardial function, which may cause HFpEF in place of HFrEF. It seems that changes in fat consumption could be crucial in the management of HF. The influence of the HEART diet or Western type of diet on cardiac cells could be dependent on pro-inflammatory biomarkers that can damage cardiomyocytes. High-glucose or fast-food diets induce an increase in ceramides and high levels of TMAO on account of greater consumption of red meat (L Carnitine) and egg (phosphatidylcholine) as well as a rise in AGE products, caused by increased saturated fat in the diets that are new biomarkers of dilatation of the heart [38][43][44][45][46]. These oxidants should be duly inhibited by new therapies for the prevention of cardiac hypertrophy, which may also produce HFpEF.

6. Mechanisms of Diet and Obesity in Heart Failure

There is evidence that the Western type of diet is a risk factor of obesity, whereas Mediterranean-style diets may have protective effects on obesity and HF [38][47][48]. It is possible to create diet-induced obesity in animal experiments, in selected strains, by use of a diet that is rich in fat (about 40% to 50% of energy, verses 10–15%) in conjunction with sugar (~20% to 30% sucrose). It appears that obesity may have complex influences on the

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cardiac ultrastructure, mediator metabolism, circulating hormones, impairment in diastolic function and changes in the autonomic regulation of the heart and vessels [39]. Therefore, experimental research that determines the effects of high-fat/low-carbohydrate intake should be examined with caution, because obesity induced by diet may have confounders [39]. If the obesity is absent, then substituting carbohydrate with fat in the diet may inhibit or decrease the progression of HF. This benefit occurs by preserving twist function and/or sub-endocardial function, which develops in response to hypertension or myocardial infarction, indicating that sugar may have more adverse effects than saturated fat. Thus, feeding a high-fat/low-carbohydrate diet to normal healthy rats and mice generally has no adverse effects on the heart if there is not concomitant obesity. In some of the experiments with obesity, produced via high-fat feeding, there are often no pathological changes on the heart [39], or there may be mild LVH and dysfunction in the contraction with hypertension and increase in leptin [39][49][50].

7. 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 Mediterranean-style diet that may have a beneficial effect on pathophysiology and progression of CVDs and HF [38][47][48]. 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 [39][47][48][49][50][51][52] is beneficial. In dietary trials in patients with CVDs, these diets have been found to have beneficial effects on HF [53][54].

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 [50][55][56][57]. 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 [58]. 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 [58]. 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 [58][59][60][61][62][63][64][65][66][67][68][69][70][71]. In a previous research, metabolic products of the intestinal microbiom have been found to predispose individuals to atherosclerosis, which is a risk factor of HF [67].There is growing evidence on the role of egg on risk

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of LVDs, which may be enormous [69]. 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.

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