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Review

High Exogenous Antioxidant, Restorative Treatment for Prevention of Heart Failure: The Heart Diet

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Abstract:

Heart failure (HF) has become a public health problem, but exact pathophysiology is still unknown. Western diet characterised with high sugar, high fat, red meat and processed meat, eggs, fried foods and sweetened beverages, may cause oxidative stress and inflammation, leading to oxidative dysfunction and adverse effects on cardiac-ultra-structure. However, only little is known about oxidative function of the of the myocardium and how oxidative dysfunction predispose Ca-overloading resulting in to physio-pathological remodelling leading to HF. Antioxidants such as flavonoids and polyphenolics, omega-3 fatty acids, vitamins, minerals as well as essential and nonessential amino acids that are rich in Indo-Mediterranean type of diets, may have protective roles in maintaining oxidative functions of the heart. The cardiac cells use fatty acids and glucose for the metabolic functions depending upon physiological and metabolic requirements. Apart from glucotoxicity, lipotoxicity is also damaging to cardiac cells which worsen in presence of deficiency of endogenous antioxidants and lower exogenous antioxidants in the diet. There is increased production of ceramide, advanced glycation end products (AGE) and triamino-methyl-N-oxide (TMAO) due to high sugar and high fat diets, leading to oxidative dysfunction and Ca-overloading. The biological changes may begin with physiological remodelling to pathological remodelling due to oxidative damages. High fat diet in combination with inducible nitric oxide synthase (NOSi) via N-arginine methyl ester has been found to preserve ejection fraction in a mouse model of HF. It is possible that increased supplementation of High Exogenous Antioxidant Restorative Treatment (HEART) diet; polyphenolics and flavonoids, vitamins, minerals, arginine, with omega-3 fatty acids, and cessation of red meat and egg may further improve the oxidative function of cardiac cells, resulting in the prevention and improvement in the earliest of the Six Stages of HF. Cohort studies and randomised, controlled trials would be necessary for demonstration of the role of HEART diet in the management of HF.

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Keywords: Western diet; oxidative stress; cardiomyocyte; micronutrients; dietary fat

In the ancient scripture Bhagavad Gita (3000 BCE) in India, Sattvic diets were advised for health, happiness, peace and longevity.

In Sanskrit:

Aayuh satvabalarogyam, sukhpreetiviverchanah,

Rasyah snigdhah sthirah hradyah aharah satvikpriyah [1].

Translation in English

The sattvic foods are full of juice, good in taste and increase longevity, wisdom, power, health, happiness, peace and love.

The Sattvic diets are rich in fresh, nutrient-dense foods, including fruits, vegetables, sprouted whole grains, fresh fruit juices, legumes, nuts, seeds, honey, and herbal teas. It is clear that Sattvic diet is capable of achieving oxidative function of the body including heart.

Oxidative stress and oxidative function are considered important physio-pathological pathway in the development and progression of heart failure(HF) [1]. Oxidative stress is defined as the imbalance between the production of reactive oxygen species (ROS) and the endogenous antioxidant defense system. Under physiological conditions, small quantities of ROS are produced intracellularly, which function in cell signaling, and can be readily reduced by the antioxidant defense system. However, under pathophysiological conditions, the production of ROS exceeds the buffering capacity of the antioxidant defense system, resulting in cell damage, protein and lipid peroxidation, DNA damage, irreversible cell damage and cell death, indicating loss in cardiac cells [1]. This physiopathology can be seen in the heart showing increase in high sensitive troponin during progression of HF [1,2]. Over the last decades several studies have tried to target oxidative stress with the aim to improve outcome in patients with HF, with very limited success. The reasons as to why these studies failed to demonstrate any beneficial effects remain unclear. However, one plausible explanation might be that currently employed strategies, which target oxidative stress by exogenous inhibition of ROS production or supplementation of exogenous antioxidants, are not effective enough, while bolstering the endogenous antioxidant capacity might be a far more potent avenue for therapeutic intervention [1,2]. This review, provides an overview of oxidative stress and oxidative function in the pathophysiology of HF and the strategies utilized to date to target this pathway. We provide novel insights into modulation of endogenous antioxidants, possibly via High Exogenous, Antioxidant Restorative Treatment (HEART) diet, which may lead to novel therapeutic strategies for possible improved outcome in patients with HF.

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 [3].

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The intracellular oxidative homeostasis in the cardiac cells is closely regulated by the production 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 hstroponin T, in cardiac cells causing abnormalities in global longitudinal strain [4]. 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 [1,2]. Oxidative stress and ROS directly cause inflammation and impair the electrophysiology and the contractile machinery of cardiomyocytes by modifying proteins central to excitation–contraction coupling, including L-type calcium channels, sodium channels, potassium channels, and the sodium–calcium exchanger [1-5]. 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 function of proteins involved in energy metabolism [5]. Oxidative dysfunction may have a pro-fibrotic function, by inducing proliferation of cardiac fibroblast and matrix metallo-proteinases resulting in extracellular remodeling, which may be beginning of the hypertrophy of the heart.

It seems that the production of ROS in the heart is primarily completed by the mitochondria, NADPH oxidases, xanthine oxidase, and uncoupled nitric oxide synthase (NOS)[1]. The electron transport chain of the mitochondria may cause overproduction of superoxide anion, contributing to cardiomyocyte damage with increase in myocardial injury after an acute myocardial infarction [1]. There may be an increase in oxidative stress due to an increased expression and activity of NADPH oxidase, due to multiple environmental and biological factors, such as angiotensin II, endothelin-1, mechanical stretch and tumour necrosis factor (TNF)-α [1-5]. 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 [3-6]. If there is a deficiency of endogenous antioxidants such as super-oxide-dismutase SOD), glutathione-peroxidase(GPS) and catalase or coenzyme Q10, it may cause worsening of cardiac function resulting in to sub-endocardial damage, which may be second stage of HF [6,7], There may be uncoupling of the NOS with structural instability, which further increases the generation of ROS, leading to left ventricular (LV) dilatation, contractile dysfunction [1], and LV remodeling [1,2]. If the cardiac damage continues, it may lead to increased sympathetic activity with decline in parasympathetic activity causing neuro-hormonal dysfunction [1-6]. Interestingly, the protective factors, such as HEART diet may prevent the development of HF, if administered in one or the other of the early stages of Six Stages of HF given in table 1 [7-10]. This is evident from Figure 1.

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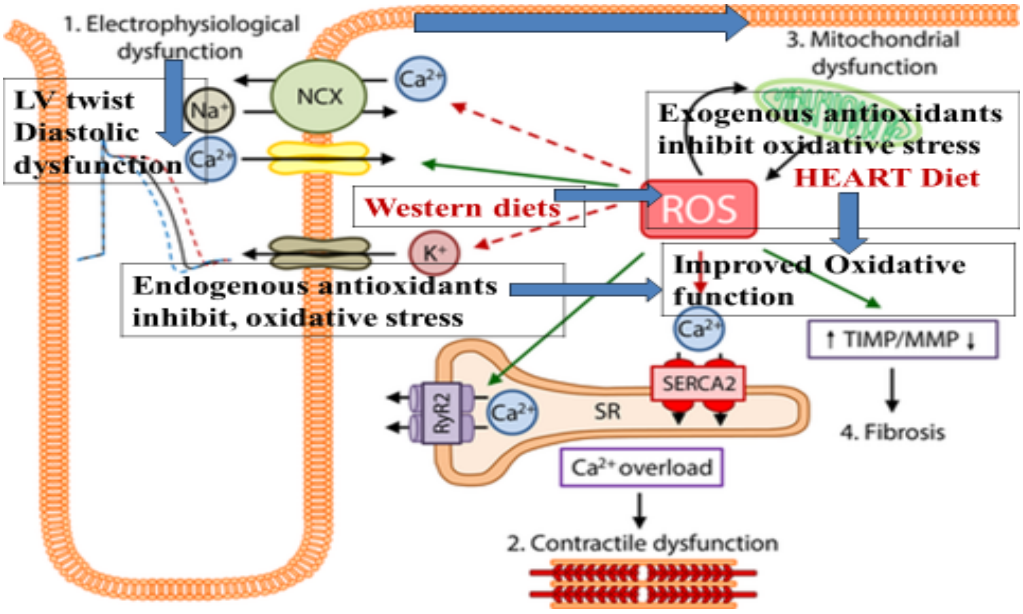

Figure 1. Oxidative dysfunction in the heart due to western diet, with decrease in antioxidant defenses, causing mitochondrial dysfunction, leading to electrophysiological dysfunction with twist and diastolic dysfunction. Exogenous antioxidants (HEART Diet) improve oxidative function with reduced Ca overloading and reversal of mitochondrial and electrophysiological dysfunction. (Modified from reference 1)

Left Ventricular Twist as Function of the Heart.

R Lower was the first to report the twisting motion of the left ventricle in 1669, as “the wringing of a linen cloth to squeeze out the water” which continue to intrigue the experts in their quest to understand cardiac function [11-13]. Apart from speckle tracking echocardiography (STE), magnetic resonance imaging (MRI) may be used to examine LV twist [13, 14].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 clockwise and counter-clockwise 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 storage of potential energy. A further recoil of twist deformation may cause release of restoring forces, which contributes to diastolic relaxation of the LV with early diastolic filling [14]. Interestingly, systolic function was not entirely normal despite the normal ejection fraction (EF). There may be decline in left ventricular systolic long-axis at earlier stages followed by evidence of more extensive, subtle defects. On exercise, with reduced augmentation of long-axis function, impaired systolic twist, reduced global strain, electromechanical dys-synchrony, will reduce myocardial systolic reserve [14-16]. The twist function may alter during oxidative myocardial dysfunction, which may be early marker of HF.

The physiology of twist mechanics indicate that left ventricle twists in systole stors potential energy and untwists (recoils) in diastole release the energy [15]. It seems that twist aids left ventricular ejection and untwist aids relaxation and ventricular filling. Therefore, rotation and torsion are important in cardiac mechanics. Torsion or twist of the LV is the wringing motion of the ventricle around its long axis induced

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by contracting myofibers in the LV wall [11]. During initial isovolumic contraction, the apex and the base both rotate in a counterclockwise direction, when viewed from apex to base. However, in the normal heart, the base rotates clockwise during systole and the apex rotates counterclockwise, producing a wringing motion. The cardiologists are not able to understand utility of twist function in clinical practice which may be due to the

limitations in measuring rotation and twist in routine clinical practice [16,17]. It seems that three-dimensional STE, should be used to avoid the effect of the through plane motion. However, it seems that measuring twist would further our understanding of cardiac mechanics, such as identification of hyper-rotation indicating sub-endocardial dysfunction, 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 [16-20]. It seems that the physician need to have a closer look to understand the physio-pathogenesis of oxidative myocardial function and cardiac dysfunction; in particular LV twist and decline in myocardial strain [6]. There is an unmet need to use rotation and twist, as well as reversible diastole dysfunction in the diastole, via STE, as new markers of cardiac function, in presence of oxidative dysfunction of the myocardium [18-20]. These six stages of oxidative myocardial dysfunction, proposed by us, may be used to begin therapy, possibly for primordial prevention of HF Table 1.

Table 1. Clinical and echocardiographic features of Six Stages of Heart Failure with oxidative dysfunction.

Stages (HT on HF)	Manifestations	2D Echocardio graphic	2D Speckle Tracking Echo	3D Speckle Tracking Echo
Stage A	Mild to moderate Oxidative dysfunction, neuro-humoral dysfunction begins.	Increasing filling pressure with abnormal relaxation	Dysfunctional untwist rate LA strain reduced.	Dysfunctional Untwist Rate, LA strain reduced.
Stage B	Moderate oxidative dysfunction, hyper-rotation. Sub-endocardial dysfunction.	Dysfunction of systole	Dysfunctional untwist rate and Increased diastolic pressure. LA strain decreased	Dysfunctional untwist rate and Increased diastolic pressure. LA strain decreased
Stage C, PHF	Asymptomatic Physio-Pathological remodeling+	EF % normal >53%	Normal GLS -20--23% ≥ −27.0% area strain	Normal GLS -17 -21% Normal AS -31--36 %
Stage D, PHF and HFpEF	Pathological remodeling disease without symptoms of HF but elevated Natriuretic peptide, dyspnea on exertion	EF% ≥50 % Systolic LV dysfunction.	EF% 40- 49 % Impaired GLS -16-20 % Impaired GCS,GRS Impaired early diastolic SR, right ventricular LS,	Impaired GLS-16-20% Impaired AS -27-31%

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			and global RV longitudinal SR	
Stage E, HFmrEF	Structural heart disease with symptoms of HF	EF%40-49% Grade 1,diastolic dysfunction	Reduced GLS-12-16% Reduced GCS, GRS, Treat with ACE,ARB.ARNI	GLS ≤ -16% AS ≤-27 %
Stage F, HFrEF	Refractory class III HF	EF%<40%	All above GLS<-12% Treated with ARNI	GLS <-13% AS < -27 %

GLS = Global longitudinal strain, GCS = Global circumferential strain, GRS-=Global radial strain, LV =left ventricle , SR = strain rate, ARNI -=Angiotensin Receptor Neprilysin Inhibitor, mr EF= mild reduction in EF, r-reduction in EF, LA=left atrial (modified from following references. 17,18)

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]. Many of the antioxidants, such as dietary supplements, as well as more novel antioxidants have been studied, in view of the risk factors and inflammatory mediators of HF [21,22]. In addition, novel therapeutic strategies using miRNA and nano-medicine are also being developed to treat various CVDs, in particular HF, which may be tried, during the early stages of the Six Stages of HF (Table 1). It seems that increase in free fatty acids and oxidative dysfunction with reference to variability in biomarkers such as, in glucose levels, and levels of oxidative stress, predispose multifold greater inflammation and immune deficiency leading to cardiac cell apoptosis and heart failure (HF) [23-25]. Decline in immunological responses may result in to damage to other body systems contributing in diseases of associated body systems [23-25]. Free radicals are known to damage the cell membranes causing development of intracellular Ca^{2+} overload, activation of proteases and phospholipases, and alterations in mitochondrial gene expression in the cardiac cells, predisposing cardiomyocyte dysfunction [23-27]. Experimental and epidemiological studies have also demonstrated that Western-type diets characterized with high sugar and refined carbohydrates with high glycemic index, as well as high fat diet; red meat and preserved meat, may predispose increased risk of HF [28-36].

Figure 2.

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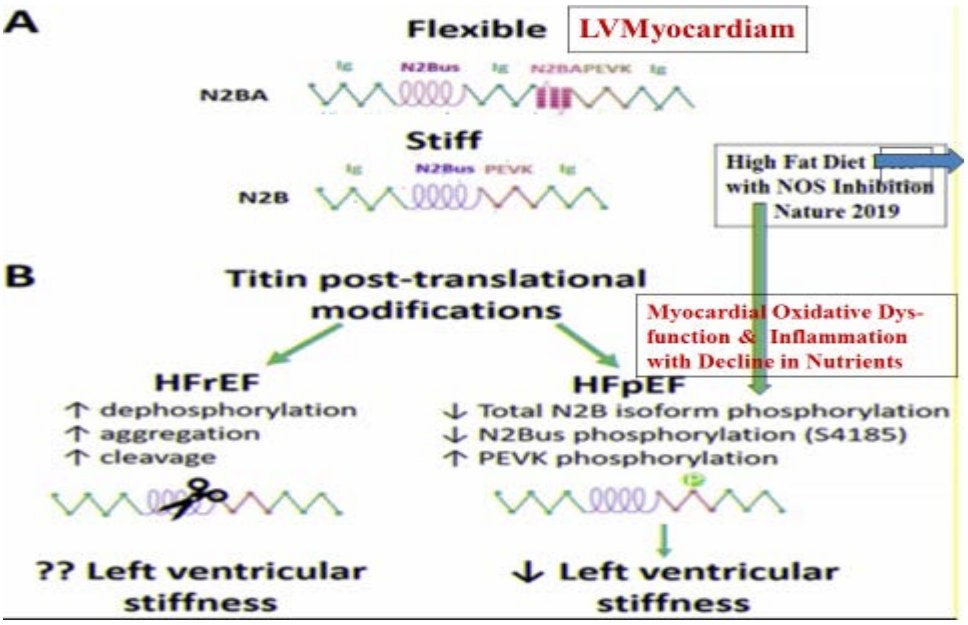

Figure 2. Myocardial oxidative dysfunction due to high fat diet causing NOS inhibition leading to heart failure with preserved ejection fraction (HFpEF). (Adapted from reference 23).

Simmonds SJ, Cuijpers I, Heymans S, Jones EAV. Cellular and Molecular Differences between HFpEF and HFrEF: A Step Ahead in an Improved Pathological Understanding. Cells. 2020;9: 242. 10.3390/cells9010242.

Apart from endogenous antioxidant defenses, 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 limited success, there is need to find out the role of Mediterranean diet, such as the HEART diet in the management of HF, Table 2.

Table 2. Antioxidant defenses 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

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Alpha-lipoic acid	Lycopine
Melatonin	Beta-cryptixanthin
Uric acid, cholesterol	**Minerals**
Metal binding proteins	Magnesium
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

There are multiple pathways by which nutritional factors can have adverse or beneficial effects in the development of CVDs [24-28]. It seems that beyond drug therapy, 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 [24-26]. Apart from these nutrients, certain factors in the brain such as renin-angiotensin-aldosterone- system (RAAS) in the brain can act as oxidant leading to increase in inflammation in the neurons [27,28]. Inflammation in the brain as part of neuro-hormonal dysfunction may activate prefrontal cortex, and amygdala leading to increase in brain neuropeptide, angiotensinogen II (ANG II). These pro-inflammatory factors can damage hippocampus, pre-sympathetic neurons in the paraventricular nucleus as well as preganglionic sympathetic neurons as shown in the Figure 3.

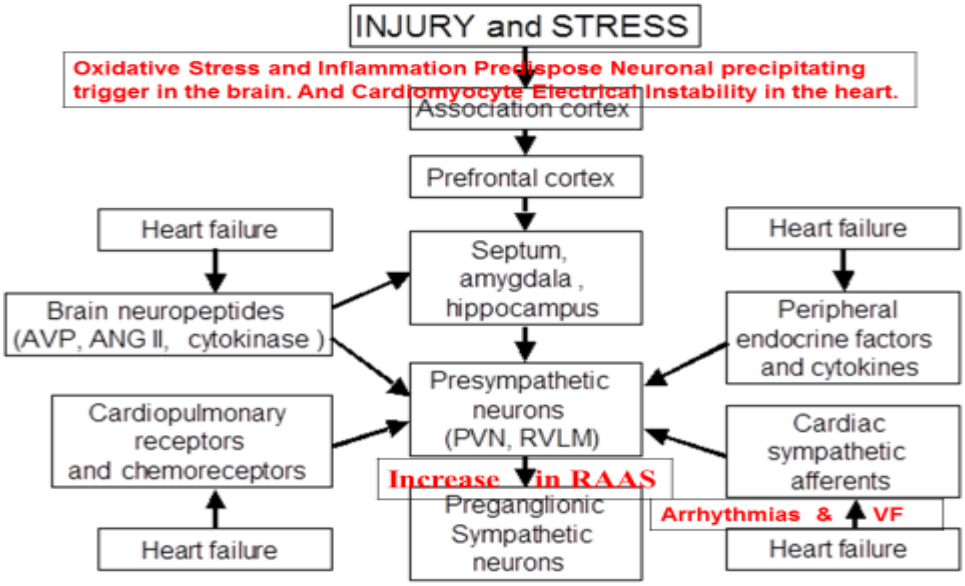

Figure 3. Shown interaction of brain areas with heart failure.

Since Mediterranean diet is known to protect brain function by its benefits in depression and dementia, it poses the possibility that it may provide a beneficial effect on brain related mechanisms of HF [29,30]. There is evidence that dets deficient in omega-3 fatty acids [31], whole grains [32], excess of red meat [33], and processed meat [34], as well as high glycemic infex foods [35] can predispose HF.

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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 [37,38]. 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 decline in ejection fraction, as a mechanism of molecular adaptation [38]. In a previous experimental study, high fat diet to fathers in mice showed adverse effects on offspring [37]. 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 adult female offspring. These genes were related to 13 functional clusters, including cation and ATP binding, cytoskeleton and intracellular transport [37]. Further analysis of 2492 genes differentially expressed, demonstrated the involvement of Ca-MAPK and MnT signaling pathways, apoptosis and the cell cycle. It has also been observed that gut flora metabolism of phosphatidylcholine promotes cardiovascular disease including HF [39].

HF with preserved ejection fraction (HFpEF) is difficult to treat and its exact pathogenesis is unknown. In the pathophysiology of HFpEF, fibrosis and the rigidification of titin are two important factors which predispose high diastolic left ventricular stiffness which may preserve the ejection fraction as a mechanism of adaptation [44-50]. A recent study of a mouse model indicated an alternative path, with implications for new experimental strategies [44]. This experiment showed that concomitant metabolic and hypertensive stress in mice produced by a combination of high fat diet and constitutive nitric oxide (NO) synthase inhibition by $N^{[w]}$-nitro-l-arginine methyl ester (L-NAME) may alter the pathophysiology of HF. The mouse model simulates the numerous systemic and cardiovascular features of human HFpEF [31]. Interestingly, one of the unfolded protein response effectors, the spliced form of X-box binding protein 1 (Xbp1s), was reduced in the myocardium of both experimental and human HFpEF. Treatment with drug or genetic suppression of iNOS, or cardiomyocyte-restricted overexpression of Xbp1s, were able to inhibit the production of HFpEF phenotype, unveiling iNOS-driven dysregulation of IRE1α-Xbp1s as a crucial mechanism of cardiomyocyte dysfunction in HFpEF [42]. It seems that HFpEF may be a nutritional adaptation of the cardiac cells by which they preserve the myocardial function without any reduction in ejection fraction. It is possible that increased supplementation of monounsaturated fatty acids and w-3 fatty acids with flavonoids; resveratrol and cessation of red meat and egg (betaine and choline) may further improve the function of cardiac cells, resulting in the prevention of HFrEF [31,37-43]. The role of choline in the pathogenesis of HF is discussed below.

In all CVDs and diabetes metabolic processes, diet hold promise for the discovery of new pathways that link the primary risk factors to disease processes [37-40]. 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 [39,40]. Dietary supplementation of mice with choline, TMAO or betaine

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predisposed upregulation of several macrophage scavenger receptors linked to pathophysiology of atherosclerosis [39]. However, administration of TMAO or phosphatidylcholine 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 [39]. This discovery indicates a relationship between gut-flora-dependent metabolism of dietary phosphatidylcholine 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 prevention of these diseases. TMAO is produced in the body, in a microbial-mammalian co-metabolic pathway from the digestion of meat-containing food and dietary quaternary amines; phosphatidylcholine, betaine, or L-carnitine [50]. Fish intake has been found protective against CVDs and diabetes but it provides a direct significant source of TMAO. It is possible that adverse effects of TAMO such as oxidative stress and inflammation are neutralized due to 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 [50]. Recent preclinical 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 [50]. In obesity, the relative proportion of Bacteroidetes is decreased compared to lean subjects, and that this proportion increases with weight loss on two types of low-calorie diet [53]. It is possible that obesity has a microbial component, which might have potential novel therapeutic implications [53]. Figure 4.

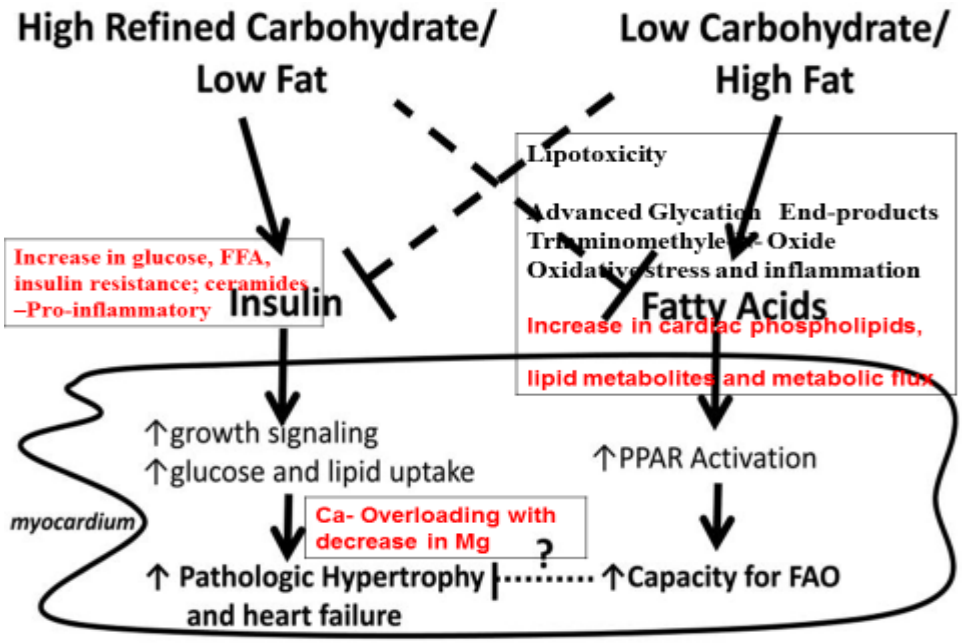

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Figure 4. Effects of high glucose or high saturated fat diets on development of cardiomyocyte and cardiac hypertrophy. (modified from reference 40).

Cardiac inflammation associated with a Western diet is mediated via activation of multiple mechanisms which predispose CVDs including CHF [37-42]. Apart from glucotoxicity, lipotoxicity may be associated with activation of receptor for advanced glycation end products (RAGE) due to increase in advanced glycation end products (AGEs) predisposing to oxidative stress and inflammation [45]. In earlier studies, such actions have largely been ascribed to fat deposition due to Western diet, the accumulation of AGEs and subsequent activation of the RAGE may also represent important mediators of cardiac injury leading to hypertrophy of cardiac cells. This experimental study, included male C57BL6J and *RAGE* knockout mice who were administered, either a standard diet (7% fat) or a Western high fat diet containing 21% fat [45]. Animals receiving a high-fat diet were further randomized to receive the AGE inhibitor alagebrium chloride (1 $mg \cdot kg^{-1} \cdot day^{-1}$) and followed for 16 wks. The group given a Western high fat diet was associated with cardiac hypertrophy, inflammation, mitochondrial-dependent superoxide production, and cardiac AGE accumulation in wild-type mice. Although *RAGE*-KO mice fed a Western diet also became obese and accumulated intra-myocardial lipid, cardiomyocyte hypertrophy, inflammation, and oxidative stress, they were attenuated compared with wild-type mice. Interestingly, mice of both strains receiving alagebrium chloride had reduced levels of inflammation and oxidative stress, in association with a reduction in cardiac advanced glycation end-products and receptors of advanced glycation end-products. It is clear that advanced glycation end- products may represent important mediators of cardiac injury associated with a Western fast-food diet [45]. These data point to the potential utility of AGE-reducing strategies in the prevention and management of cardiac disease.

In view of the growing evidence indicating that dietary fat intake influences the development and progression of HF, there is an unmet need to find out which fat is lipotoxic and which one has lipo-protective effects [44]. Experimental studies in rodents, indicate that in the absence of obesity, substituting refined carbohydrate with fat may attenuate or prevent ventricular expansion and contractile dysfunction in response to hypertension, infarction or cardiomyopathy [44]. However, adding n-3 polyunsaturated fatty acids from marine sources alters cardiac membrane phospholipid fatty acid composition, improves mitochondrial function, decreases the onset of new HF, and slows the progression of established HF [31,51]. Clinical studies generally support high consumption of n-3 polyunsaturated fatty acids, to prevent and treat HF. Dietary omega-3 fatty acids can alter cardiac mitochondrial phospholipid composition and delay Ca^{2+}-induced transition of cell membrane permeability [51]. It is proposed that increased availability of magnesium (Mg^{2+}) may activate Ca-Mg- ATPASE and improve anti-inflammatory effects of these fatty acids. Figure 5.

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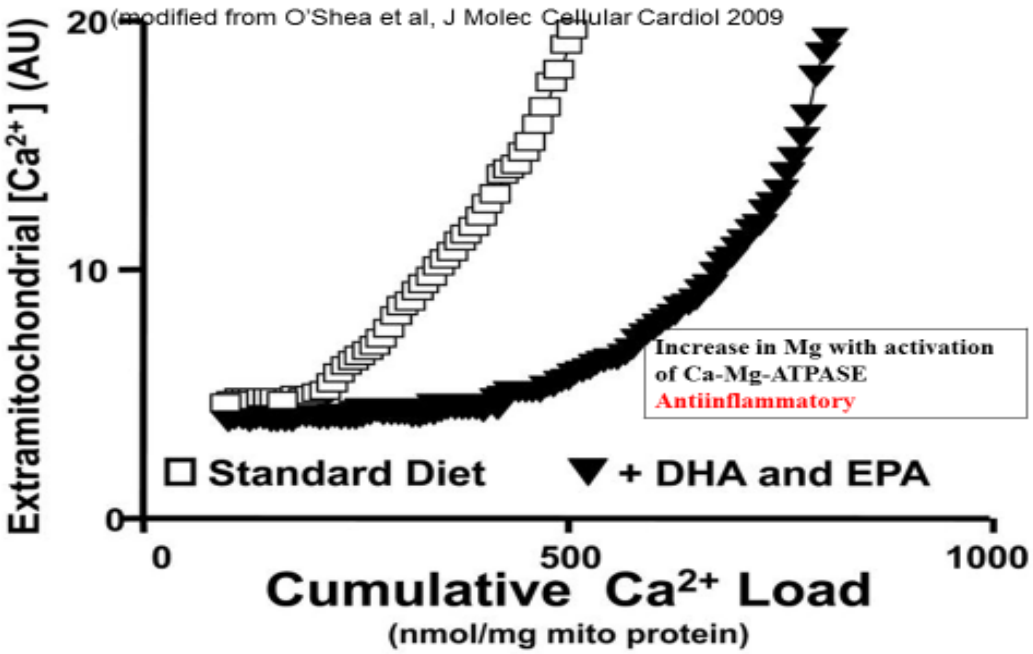

Figure 5.Treatment of a normal rat with DHA+EPA (70:30 ratio; 2.3% of energy intake) for three months delays Ca^{2+}-induced MPTP opening in isolated cardiac mitochondria, as seen in an increase in the capacity for mitochondrial Ca^{2+} uptake.(modified from reference 51, O'Shea et al, J Molec Cellular Cardiol 2009,).

Increased consumption of saturated, monounsaturated or n-6 polyunsaturated fatty acids has also shown beneficial effects in rodent studies [44]. This effect is associated with decline in inflammation and improved resistance to mitochondrial permeability transition. The underlying mechanisms are complex and may be due to cardiac adaptation, in particular when diets rich in saturated fat are administered. A more thorough knowledge is necessary to know the effects of various fatty acids on cardiac phospholipids, lipid metabolites and metabolic flux in the normal and failing heart. It is proposed that the presence of other nutrients such as flavonoids, coenzyme Q10 and w-3 fatty acids decrease the lipotoxic effects of saturated fat and slow the progression of hypertrophy, resulting in HFpEF, rather than HFrEF. It is clear, that alterations in dietary fat intake may have promise in the management of HF. The effects of diet on cardiac cells may depend on various biomarkers that are known to damage cardiomyocytes. Increase in ceramides due to high glucose or fast food diets, high levels of TMAO due to increased intake of red meat (L Carnitine) and egg (phosphatidylcholine) as well as increase in advanced glycation products due to high fat diets are new biomarkers of cardiac hypertrophy [44,47-50].These markers should be prevented by new therapies for prevention of cardiac hypertrophy, may be also HFpEF. Cohort studies and animal experiments are needed to determine the role of healthy diet in terms of saturated, monounsaturated and n-6 polyunsaturated fatty acids intake for this group of vulnerable population. Figure 6.

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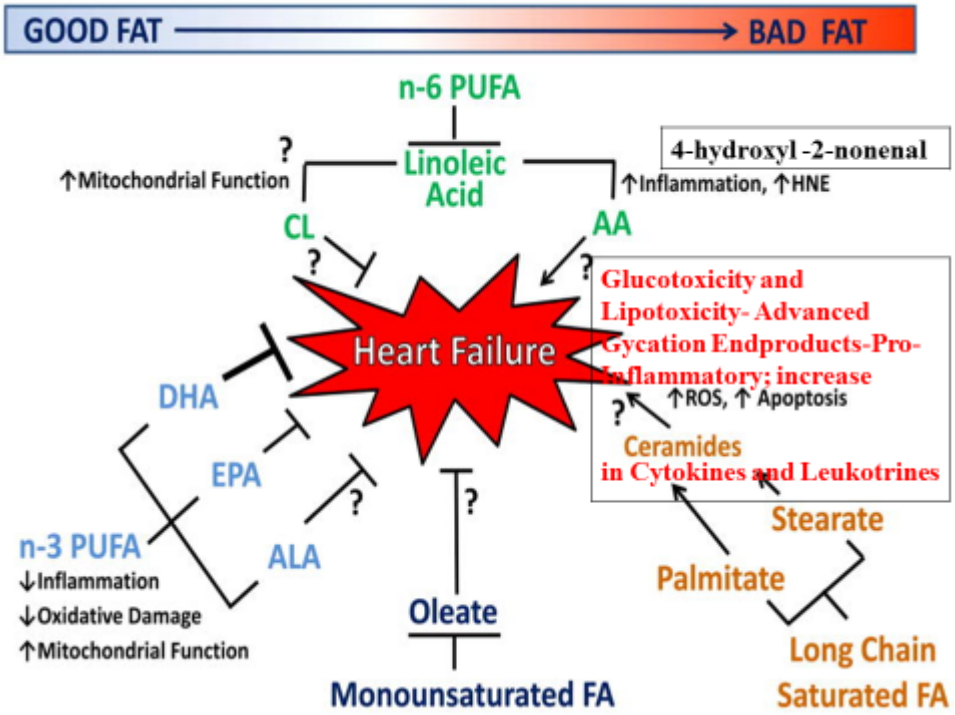

Figure 6. Depiction of the potential underlying mechanisms of how a high fat and high glucose diets predispose the development and progression of HF (modified from reference 40).

Mechanisms of Diet and Obesity in Heart Failure

There is evidence that the Western type diet is a risk factor of obesity, whereas Mediterranean-style diets may have protective effects on obesity and HF [50-52]. Diet-induced obesity in mice and rats can be generated in selected strains using a diet that is relatively high in fat (usually 40% to 50% of total energy intake compared to 10–15% in the typical commercial rodent chows) combined with high sugar (~20% to 30% sucrose). Obesity has complex effects on the heart largely mediated through changes in circulating hormones, impaired vascular function and altered autonomic regulation of the cardiovascular system [53]. Therefore, experimental studies that investigate high fat/low carbohydrate intake should be evaluated with caution, as diet-induced obesity is frequently a confounding factor [53]. In the absence of obesity, replacing carbohydrate with fat in the diet may attenuate or prevent the development and progression of HF in response to hypertension or myocardial infarction indicating that sugar may have more adverse effects than saturated fat. Thus, feeding of 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. Studies with obesity resulting from high fat feeding show either no adverse effects on the heart [53], or mild LVH and contractile dysfunction associated with hypertension and elevated leptin [53-55]. Classic studies in transgenic mice and leptin-deficient Zucker fatty rats demonstrated that when myocardial fatty acid uptake and/or esterification is elevated to supra-physiological levels it can result in accumulation of intracellular triglycerides and lipid intermediates associated with cardiac contractile dysfunction, cardiomyocyte hypertrophy, apoptosis, and HF[56,57].The clinical value of these observations in terms of dietary fat intake and the development and progression of HF in humans is limited, as the underlying causes of lipotoxicity in these genetic models are not directly relevant to conditions in the healthy or failing human heart [56-58].

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Epidemiological Studies on Diet and Risk of Heart Failure

There are limited known large scale epidemiological studies indicating role of dietary factors in the pathogenesis of HF [50,59-61].The dietary quality of persons with HF was examined in the NHANES 1999–2006, among 574 patients, mean age 70 years, with 52% women [50].The intake of mean sodium was 2,719 mg, with 34% consuming less than 2,000 mg per day. The intake of potassium was, mean 2,367 mg/day, without consideration for type of diuretic used or renal disease status. The intake of other nutrients as per guidelines were low for some nutrients; 13% for calcium, 10% for magnesium, 2% for fish oils, and 4% for fiber but high (13%) for saturated fat [50,27]. 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 [59]. Among 246 patients, 29.8% of patients had hospitalization or death during the one year follow up, including 44.3% in the high-deficiency group and 25.1% in the no/moderate group. The difference in survival distribution was significant (log rank, P=0.0065). It is possible to conclude from this study that diet quality of patients with HF plays an important role in outcomes [59]. In another study, among the 118 patients, 54% were men, median age 66 year, median ejection fraction 45% (30%-60%), and etiology of CAD was present in 49% of patients [62]. The association with 1-year mortality was significant for both polyunsaturated fatty acids (PUFA; adjusted hazard ratio (HR), 0.67, for intake as percentage of daily energy and saturated fatty acids (SFA; adjusted HR, 1.15; for intake as percentage of daily energy. Median of intake as a percentage of daily energy was 5.3% for PUFAs and 8.2% for SFAs. The consumption of PUFAs and SFAs was independently associated with 1-year all-cause mortality in patients with chronic HF [62]. It is possible that decreasing dietary saturated fat and increasing PUFA intake may be advisable in this population.

Recently, Hristova et al. have 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, magnesium, potassium, 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 [21,22]. Although dietary intakes were not reported in this paper, personal communication revealed that these patients were consuming significantly lower quantity of vegetables, fruits, nuts and legumes (<400g/day)[22]. However, beyond these factors, several studies have demonstrated that following an injury to the cardiomyocyte during a disease, an intense inflammatory response occurs which predisposes further damage and progression of cardiac dilatation and dysfunction [21,22]. 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 [21,22]. The harmful biomarkers in failing cardiac cells are; cryopyrin (NLRP3 encodes cryopyrin, which belongs to an emerging family of danger sensors, called NLRs =NOD-like receptors, that are sensor proteins) and the apoptosis-associated speck-like protein containing a CARD (C-terminal caspase-recruitment domain) (ASC), adaptor proteins which trigger activation of caspase-1, and effector proteins which are pro-inflammatory [21,22]. 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 protection against enormous oxidative stress developed in HF patients [21,22]. The increase in homocysteine related to oxidative stress, is antagonized by vitamins B6, B12 and folic acid. L-carnitine, coenzyme Q_{10}. 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 [21,22]. Many clinical practice guidelines support a low-sodium diet and restriction of fluids among patients with HF, research findings indicate that a low-sodium diet

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may have adverse effects on myocardial metabolism leading to arrhythmias [63]. Therefore, there is an unmet need to find out if a Mediterranean type of foods or Indo-Mediterranean-style diets rich in whole grains, vegetables, fruits, nuts, olive oil, and spices which are rich in all the micronutrients, may be protective against CHF [32,33].

In a cohort study, 1,140 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 greater intake of eggs (1.23) and high-fat dairy (1.08) and HF risk was lower with greater whole-grain intake (0.93) [32]. These associations remained significant independent of intakes of the five other food categories, which were not associated with HF. It is possible that whole-grain intake was associated with lower HF risk, whereas intake of eggs and high-fat dairy were associated with greater risk of HF [32]. The Physicians' Health Study (1982–2008) studied 21,120 apparently healthy men (mean age 54.6 years) for approximately 26 years [33]. There was a positive and graded relation between red meat consumption and HF [hazard ratio (95% CI) of 1.0, 1.02 (0.85–1.22), 1.08 (0.90–1.30), 1.17 (0.97–1.41), and 1.24 (1.03–1.48) from the lowest to the highest quintile of red meat, respectively (p for trend 0.007) [33]. This association was observed for HF with (p for trend 0. 035) and without (p for trend 0.038) antecedent myocardial infarction [33,9]. In a prospective cohort study of 15 362 participants from the Physicians' Health Study, frequency of fried food intake was assessed by a food frequency questionnaire (1997-2001) [64]. After an average follow-up of 9.6 ± 2.4 years, a total of 632 new HF cases occurred in this cohort. Compared to subjects who reported fried food consumption of <1 per week, HRs (95% CI) for HF were 1.24 (1.04 to 1.48), 1.28 (1.00 to 1.63), and 2.03 (1.37 to 3.02) for fried food intake of 1 to 3/week, 4 to 6/week, and 7+/week, respectively, after adjustment for age, energy intake, alcohol use, exercise, smoking, and overall diet score (P linear trend, 0.0002) [64]. The results were similar for intake of fried foods at home or away from home and among subjects with higher dietary score or HF without antecedent myocardial infarction. The results are consistent with a positive association of fried food intake frequency with incident HF in male physicians [64].

This study [65] included 16,068 subjects (mean age 64.0 ± 9.1 years, 58.7% women, 33.6% black participants, 34.0% residents of the stroke belt). After a follow-up of median of 8.7 years, 363 subjects had hospitalizations for incident HF [65]. Highest adherence to the Southern dietary pattern; refined foods, fried foods, red meat and processed meat, sweetened foods, was associated with a 72% higher risk of HF after adjusting for age, sex, and race and for other potential confounders (education, income, region of residence, total energy intake, smoking, physical activity, and sodium intake; hazard ratio: 1.72; 95% confidence interval: 1.20 to 2.46; p = 0.005) [65]. However, the highest quartile of adherence to the plant-based dietary pattern, compared with the lowest quartile, was associated with a 41% lower risk of HF in multivariable-adjusted models (hazard ratio: 0.59; 95% confidence interval: 0.41 to 0.86; p = 0.004). Figure 7.

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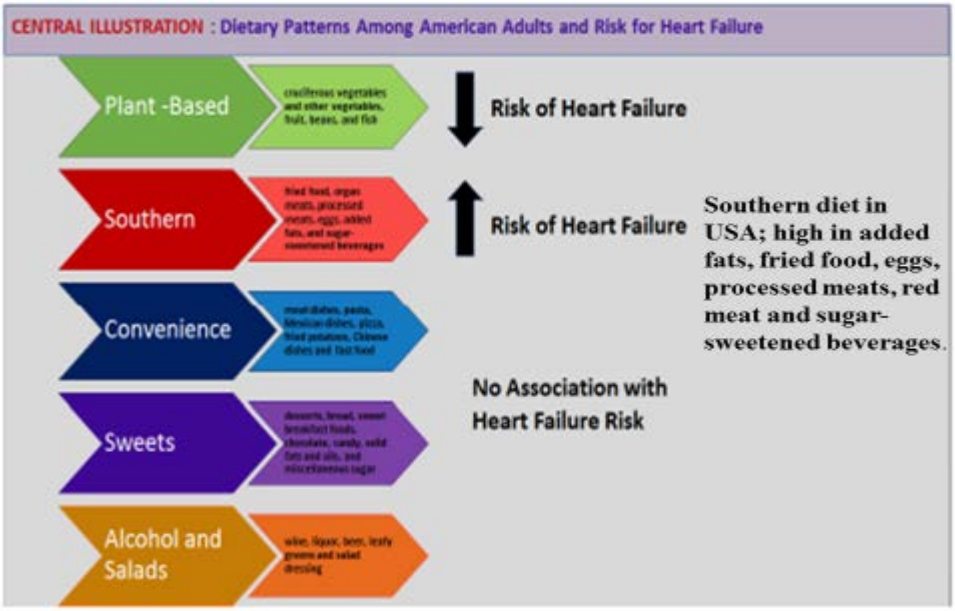

Figure 7. Dietary patterns among American adults and risk for heart failure. (modified from reference 65).

However, the association was attenuated and no longer statistically significant after further adjusting for body mass index in kg/m^2, waist circumference, hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, and chronic kidney disease. No statistically significant associations were observed with incident HF with reduced or preserved ejection fraction hospitalizations and the dietary patterns [65]. No associations were observed with the other 3 dietary patterns. It is possible that adherence to a plant-based dietary pattern was inversely associated with incident HF risk, whereas the Southern dietary pattern was positively associated with incident HF risk [65,42].

This study [66] included 2441 men aged 42 to 60 years at the baseline examinations in 1984 to 1989 in the Kuopio Ischemic Heart Disease Risk Factor Study. The risk of HF according to protein intake was estimated by Cox proportional hazard ratios. After follow up of mean 22.2 years, 334 incident HF cases occurred. Higher intake of total protein indicated a trend toward increased risk of HF (multivariable-adjusted hazard ratio in the highest versus lowest quartile =1.33; 95% confidence interval: 0.95-1.85; P-trend=0.05) [66]. The associations between specific types and sources of protein with incident HF were consistent with this overall finding although, all associations did not reach statistical significance. The hazard ratio in the highest versus lowest quartile was 1.43 (95% confidence interval: 1.00-2.03; P-trend=0.07) for total animal protein and 1.17 (95% confidence interval: 0.72-1.91; P-trend=0.35) for total plant protein. It is possible that higher consumption of protein was marginally associated with increased risk of HF.

A meta-analysis involving 39 studies, including nearly 2 million subjects and 85,053 cases with CAD, 25,103 with stroke, 7,536 with HF, and 147,124 CVD cases were assessed [67]. The summary analysis from 14 studies revealed that intake of up to six eggs per week is inversely associated with CVD events, when compared to no consumption (for four eggs per week, SRR = 0.95 (95% CI: 0.90; 1.00)); a decreased risk of CVD incidence was observed for consumption of up to one egg per day (SRR = 0.94 (95% CI: 0.89; 0.99)).For CAD incidence and mortality, the summary analysis from 16 studies revealed a decreased risk up to two eggs per week ((SRR = 0.96 (95% CI: 0.91; 1.00)). No associations were retrieved with risk of stroke. The summary analysis for risk of HF, from four studies showed that intake of one egg per day was associated with

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increased risk raising for higher intakes compared to no consumption (for 1 egg per day, SRR = 1.15 (95% CI:1.02; 1.30)) [67]. After considering GRADE criteria for strength of the evidence, it was rated low for all outcomes but stroke, for which it was moderate (yet referring to no risk). There is no conclusive evidence on the role of egg in risk of CVD, despite the fact that higher quality studies are warranted to obtain stronger evidence for a possible protection of CVD associated with moderate weekly egg consumption compared to no intake. It seems that future studies may strengthen the evidence for increased risk of HF associated with high regular egg consumption [67]. There is no mention that taking designers egg containing w-3 fatty acids and tea flavonoids may be protective against CVDs including HF. Figure 8.

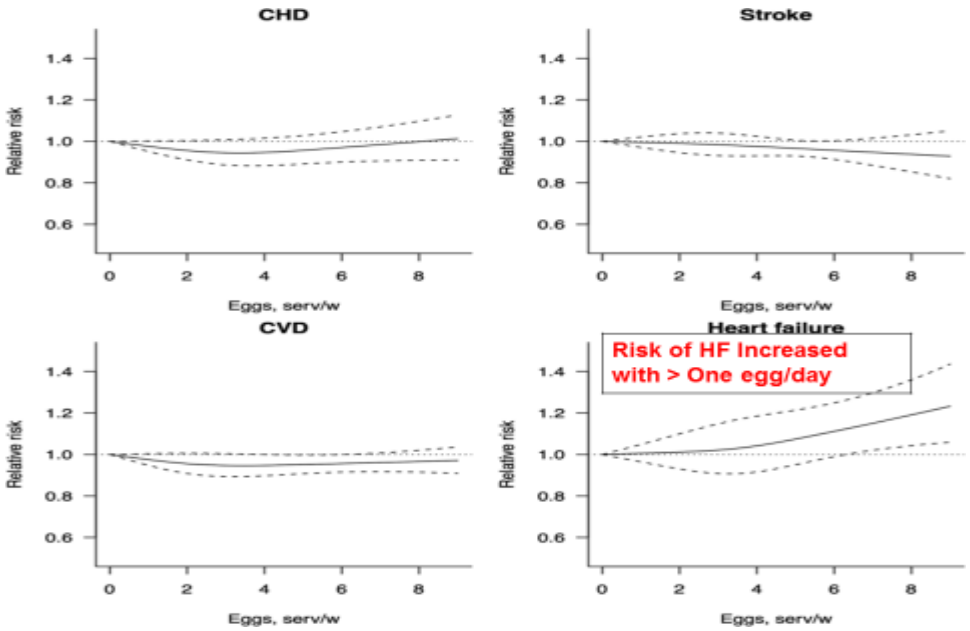

Figure 5: Egg intake and risk of cardiovascular diseases (modified from reference 67).

Role of Dietary Patterns in the Prevention of Heart Failure

In the USA as well as in other Western countries, dietary patterns of patients with HF reveals a generally poor Western-type diet that may have a negative impact and a Mediterranean-style diet may have a beneficial effect on pathophysiology and progression of CVDs and HF [50-52]. (The role of Mediterranean-type of diets or Indo-Mediterranean-style diets in the prevention of HF would be discussed in detail in the second volume of this book). The Dietary Approaches to Stop Hypertension (DASH) diet, is also a Mediterranean-style diet. Population-based studies indicated that the incidence of HF is significantly lower in people who adhere to 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 oxidative stress, predisposing 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 follow up of 10 years,

glutamate was associated with a 29% increased risk of HF and glutamine-to-glutamate ratio with a 20% decreased risk. Glutamine-to-glutamate ratio was also inversely associated with HF risk (OR per 1-SD increment: 0.80; when comparing extreme quartiles. Higher glutamate concentrations were associated with a worse cardiometabolic risk profile, whereas a higher glutamine-to-glutamate ratio was associated with an improvement in the risk profile. No associations between the concentrations of these metabolites and AF were observed. It is possible that high plasma glutamate concentrations possibly resulting from alterations in the glutamate-glutamine cycle may contribute to the development of HF in individuals at high 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 in the management of HF. There is new evidence from experimental and clinical studies to elucidate the mechanisms of cardiac hypertrophy and HF [72-83]. In aprevious study, metabolic products of the intestinal microbiom may predispose atherosclerosis which is a risk factor HF [81].There is growing evidence on the role of egg on risk of CVD" is erroneous;[83]. Cardiac imaging via speckle tracking echocardiography and MRI may be useful in finding out the role of nutritional factors and biomarkers in the pathogenesis of HF.

Conclusion: It is possible that increased intake of some of the nutrients and foods, such as saturated fat, trans fat, sugar, red meat and preserved meat have adverse effects, whereas glutamine and MUFA, PUFA, flavonoids and polyphenolics, omega-3 fatty acids, appear to have beneficial effects. Increased intake of unhealthy foods and nutrients, may result in changes 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 optimal availability of useful or unhealthy, food and nutrients; antioxidants, fatty acids and amino acids in the tissues. It is possible that apart from hypertrophy of cardiomyocytes, new generation of cardiomyocytes predominates over death of these cells and contributes significantly to organ growth during adulthood and in physiological remodelling. The growth of cardiac cells may be under the influence of protective nutrients. On the other hand, it is becoming increasingly clear from clinical and animal studies that relatively low intake of n-3 PUFA from marine sources (approximately 0.4 to 2% of energy intake) alters cardiac membrane phospholipid fatty acid composition, decreases the onset of new HF, and slows the progression of established HF. This beneficial effect of PUFA, in particular, in conjunction with MUFA, flavonoids and other nutrients may be associated with 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..

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