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REVIEW ARTICLE

Effects of Antioxidant-rich Indo-Mediterranean Foods on Pre-heart Failure: Results from the Meta-analysis of Randomized Controlled Trials.

Ram B. Singh^{1*}, Toru Takahashi², Ghizal Fatima³, Rie Horiuchi⁴, Jan Fedacko⁵, Zuzana Huzova⁶ and Daniel Gurin⁷

¹Halberg Hospital and Research Institute, Civil Lines, Moradabad, India,

²Graduate School of Human Environmental Medicine, Fukuoka University, Fukuoka, Japan,

³Era Medical College, Lucknow, India,

⁴Mukogawa Women's University, Nishinomiya, Hyogo Prefecture, Japan,

⁵Department of Medicine, Faculty of Medicine, PJ Safaric University, Kosice, Slovakia

⁶Department of Biology, Trnava university, Trnava, Slovakia

⁷Department of Biology, Faculty of Medicine, Trnava University, Trnava, Slovakia

Abstract:

Background:

The role of different diets and nutrients in the pathogenesis of cardiac dysfunction is controversial. However, it is well known that the Western diet has pro-inflammatory systemic effects, whereas Mediterranean-style diets have anti-inflammatory effects in all body systems. This study aimed to examine the effects of functional foods, omega-3 fatty acids and flavonoid-rich diets in patients with a high risk of Cardiovascular Diseases (CVDs) with reference to Heart Failure (HF).

Methods:

This meta-analysis included data from three randomized, controlled single-blind trials, published earlier, on the role of Indo-Mediterranean style foods and nutrients in the prevention of CVDs, including HF. The intervention and control groups were compared for behavioural risk factors, food intakes, fatty acid intake and on the ratio of Polyunsaturated Fatty Acid (PUFA)/flavonoid intake, respectively, in the two groups (n=1446 vs n=1320). The diagnostic criteria for Pre-Heart Failure (PHF) and HF were electrocardiographic abnormalities and radiological increase in the heart size.

Results:

Effects of Indo-Mediterranean style foods on parameters like PHF, HF, and cardiac arrhythmias were significantly lower in the intervention group as compared to the control group. At baseline, all parameters of HF showed no significant differences between intervention and control groups. However, after a follow up of two years, left ventricular strain (Odds Ratio 0.57, confidence interval 0.50-0.65, P<0.01), left ventricular hypertrophy (OD 0.69, CI 0.64-0.75, P<0.01), as well as, NYHA class II-IV HF (OR 0.59, CI 0.50-0.68, P<0.05) were significantly lower in the intervention group as compared to the control group. The incidence of cardiac arrhythmias was also significantly lower in the intervention group as compared to the control group (OR 0.49; CI 0.42-0.56, P<0.01). The intake of omega-3 fatty acids and flavonoids was significantly higher and the ratios of Omega-6/Omega-3 fatty acids, as well as PUFA/flavonoids were significantly lower in the intervention group A, compared to control group B, indicating that increased intake of omega-3 fatty acids and flavonoids may have provided beneficial effects in the electro-mechanical functions of the heart.

Conclusion:

Our results suggest that adherence to the intake of Indo-Mediterranean style diets can markedly reduce the incidence of PHF and HF as well as cardiac arrhythmias. The cardioprotective effects of diets rich in flavonoids and long-chain omega-3 fatty acids (PUFA) are most likely associated with their potent antioxidant and anti-inflammatory actions.

Keywords: Indo-Mediterranean style foods, Cardiovascular benefits, Omega-3 PUFA, Flavonoids, Functional foods, Phytochemicals.

Article History

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1. INTRODUCTION

Pre-Heart Failure (PHF) may be defined as a state of myocardial dysfunction, which subsequently promotes high risk for developing complete heart failure [1 - 3]. It is similar to pre-diabetes or pre-hypertension for developing diabetes mellitus and hypertension, respectively. PHF is characterised with changes in cardiac muscles that are known as remodelling and fibrosis, which may help to keep the blood pumping, but the ventricular walls may eventually weaken and are not able to pump adequate blood to the circulatory system, resulting in chronic heart failure [1 - 3]. The heart may have high filling pressure with symptoms of dyspnoea and other congestive heart failure symptoms. In this process, aldosterone and cortisol predict medium-term left ventricular remodelling in an attempt to prevent cardiac failure [4, 5]. In the pathophysiology of cardiomyocyte dysfunction, and in the conversion process of physiological remodelling to pathological remodelling and PHF leading to complete HF, behavioural risk factors play an important role [6 - 13]. Dhalla *et al.* demonstrated subcellular remodelling and alterations in sarcoplasmic reticulum as important biomarkers, which could be identified early by speckle tracking echocardiography [14 - 18]. In view of the rapid increase of HF and health care burden in the developed and developing countries, and unmet needs in the early diagnosis and treatment, it is imperative to find out new risk factors and methods for the identification of HF in the early stage of PHF [16 - 18]. Recently, cohort studies and case control studies have demonstrated that Western style diets rich in sugar and sugar-loaded drinks, accompanied by physical inactivity and obesity, are paramount behavioural risk factors involved in causing HF [10 - 13]. It is well known that obesity and Western diets cause oxidative stress and inflammation-induced atherosclerosis, whereas Mediterranean style diets are inherently antioxidant and anti-inflammatory in nature. This study determined the role of nutritional factors as unmet needs in the pathogenesis and management of HF.

2. SUBJECTS AND METHODS

This study has analysed data of subjects who were previously recruited in randomized and controlled trials published earlier [19 - 21]. The experiments performed in India, *i.e.*, Infarct Survival Study included a total number of 406 patients ($n = 204$ vs $n = 202$), and the Indian Experiment of Infarct Survival 4, included 360 patients ($n = 122$ vs $n = 118$; vs $n = 120$), with acute myocardial infarction [19, 20]. Apart from these trials, high-risk patients included in the Indo-Mediterranean Diet-Heart Study ($n = 499$ vs. $n = 501$) were also included in this meta-analysis [21]. All the patients of intervention diet, group A ($n = 1446$) and control diet group B ($n = 1320$) included in these randomized controlled trials, received a functional food-rich diet compared to low-fat control diet, advised by the National Cholesterol Education Program (NCEP) [22]. Food and nutrient intake of the subjects was assessed with the help of Indian Food Composition Tables [23].

The intervention diet included Indo-Mediterranean foods such as grams, beans, kidney beans, red beans, green beans and black beans along with vegetables such as onion, garlic, gourds, ladyfingers, tomatoes and green leafy vegetables as well as Indian spices, cumin, coriander, turmeric, fenugreek and green chilies to taste. All intervention groups received mustard oil (rich in w-3 fatty acids) and tea and cocoa (rich in flavonoids), along with low-fat diets. The diet also included Mediterranean types of foods such as oranges, apple, grapes, nuts, fish and chicken for non-vegetarians. In both groups, two-thirds of patients were vegetarian and the remaining one third ate two to five eggs, and one to two portions of meat per week. All participants consumed milk with a modest amount of whole butter, clarified butter (Indian ghee), and trans-fatty acids (*e.g.*, vegetable ghee made from partly hydrogenated oils). Vegetarian participants consumed more milk, vegetables, ghee, peanut oil, mustard oil, soya bean oil and clarified butter than non-vegetarians. The patients in both groups were advised to consume food substitutes that would provide a dietary intake similar to that recommended by the National Cholesterol Education Program (NCEP) [22] in the Step I prudent diet. This diet is characterized by less than 30% of energy from total fat, less than 10% from saturated fat, and less than 300 mg of cholesterol per day. The intervention groups were also encouraged to eat 400-500 g of whole grains; legumes, pulses and wheat bread daily, as well as mustard or soybean oil, in three to four servings per day, which is consistent with the recommendations from the Indian Consensus Group. The aim of the intervention diets was to provide plenty of phytochemicals, antioxidant flavonoids, and alpha-linolenic acid (the major w-3 fatty acid in these foods).

2.1. Data Collection

The Indian Food-composition Tables were used to calculate 24-h nutrient intakes for all patients [23]. The intakes of polyphenolics and flavonoids (Quercetin, kaempferol, isoflavon, resveratrol and epigallocatechin) were calculated based on food composition tables from different sources [24 - 26]. The ratio of intake of flavonoids with Polyunsaturated Fatty Acids (PUFA) was also calculated, because there is controversy on the adverse effects of PUFA [27 - 36]. All participants were instructed to complete weekly records of food intake, and also record occupational, household, and leisure-time physical activities for 1-4 weeks, then at 12-week intervals, to assess dietary adherence and physical activity [23].

2.2. Criteria of Diagnosis

The criteria for the diagnosis of risk factors were: hypertension, diabetes, tobacco and alcohol use, sedentary behavior, mental stress, based on WHO criteria as reported previously [19 - 21]. Short sleep was considered when total sleep per 24 hours was less than 6 hours/night. Mental stress was considered in the presence of any office work or family-related stress, leading to an excess of thinking and difficulty in sleep for more than one week. The criteria for the diagnosis of protective factors; good sleep, moderate physical activity, moderate alcohol consumption, meditation and prayer, yoga postures, intermittent fasting, circadian restricted feeding, low caloric diet, mastication during eating, listening to music,

* Address correspondence to this author at the Halberg Hospital and Research Institute, Civil Lines, Moradabad-10(UP)244001, India; Tel. 91 9997794102; E-mail: rbs@tsimsoum.net

intellectual work and good sleep were based on previous publications [6, 10, 13].

2.3. Total Indo-Mediterranean Diet Score

The Indo-Mediterranean foods included whole grains; grams, beans, kidney beans, millets, grapes, apple, guava, star-goose berry, blueberries, soy products, walnuts, almonds, flax seeds, fish/chicken (white meats), curd/yogurt, olive oil, and mustard oil, bitter gourd, onion, garlic, ginger, leafy vegetables, tomato, tea, cocoa and red wine, as well as spices like turmeric, cumin, coriander, peppers as functional foods [16 - 34]. These foods are known to be rich in vitamins, minerals flavonoids, omega-3 fatty acids, fiber, alpha linolenic acid, as well as essential and nonessential amino acids [16 - 34]. The Western diet or pro-atherogenic foods included sugar, sweetened products, cola drinks, biscuits, white chocolates, cakes, refined cereals; corn flakes, clarified butter, butter, trans fat, omega-6 fat, red meat and processed meat, eggs and salt.

The conformity of the Indo-Mediterranean food intake was examined with a 10 unit scale. The scale relies on food diversity with 8-10 dietary components that capture the essence of functional foods in the traditional Indo-Mediterranean style diets. Vegetables, fruits and nuts, whole grains/legumes; (Bengal gram, kidney beans, millets, peas, other beans) carrots, gourds, green leafy vegetables, yogurt and curd, spices and mustard oil that are presumed to be beneficial for health. However, Western-type foods, such as red meat, processed foods, and eggs and butter, clarified butter, omega-6 rich oils, trans-fatty acids, sugar, salt, refined foods, are presumed to have adverse health effects. We assigned values of 0 or 1 to each of the above-indicated components, using the sex-specific medians in the studied population as cut-offs. A value of 0 was assigned to people whose consumption was below the median values of components, with a presumably beneficial effect and a value of 1 to people with consumption equal to or above the median. In contrast, we assigned a value of 1 to people with below the median consumption of components without a beneficial effect and a value of 0 to those whose consumption of these components was above the corresponding median. Thus, the total diet score can take values from 0 (minimal conformity to the Indo-Mediterranean style diet) to 9 (maximal conformity to the Indo-Mediterranean food rich diet). Multiplication of given value with 100 gave the % adherence with advised diet.

The criteria of diagnosis of PHF were based on the radiological increase in heart size or electrocardiographic increase in heart size or both with or without electrocardiographic strain. This condition was also considered as left ventricular hypertrophy. The criteria for the diagnosis of chronic HF were increase in heart size along with cardinal clinical manifestations such as an increase in liver size, ingorged jugular veins, edema on both feet and dyspnea on exertion [10]. Left ventricular strain was diagnosed in the presence of electrocardiographic ST-segment and T-wave flattening or inversion in conjunction with or without an increase in heart size.

Follow Up: In both groups, completed diaries were checked by the dietician on every visit with the help of a

questionnaire that used household measures, food portions and food models, to estimate the caloric value of food portions and to reinforce dietary adherence. All patients with diabetes mellitus, angina pectoris, a history of myocardial infarction, or hypertension who visited the physician frequently received more frequent dietary advice during the 2 years of follow up than those who did not.

2.4. Statistical Data Analyses

We used Student’s T-test for comparison of continuous variables and Chi-square test for ordinal variables. The prevalence is given in percent and continuous variables as mean ±S.D. Odds ratios and 95% confidence intervals were calculated by dividing percentages of events into two groups. Only P-values <0.0 5 with the two-tailed test were considered significant.

3. RESULTS

The combined results of data obtained from all three trials are summarized in Tables 1-6. Mean age, mean body weight, and body mass index (BMI, Kg/M²) and blood pressures were comparable at the entry to evaluate the differences in two groups (Table 1).

Table 1. Clinical characteristics of subjects in the Indo-Mediterranean style diet group and Standard diet group

Characteristics	Indo-Mediterranean Style Diet (n=1,446)	Standard Diet (n=1,320)
Mean-age years (Standard deviation)	49.52 ± 19.5	50.0±17.6
Mean body mass index (Weight/Height ²) Kg/M ²	24.1±3.4	24.7± 3.8

Values are expressed as mean± (Standard deviation).

Table 2 shows the behavioral risk factors in the intervention and control groups. The prevalence of behavioral risk factors showed no significant difference in the intervention and control group at baseline. However, one-fourth of the subjects in both groups had some protective behaviors. After a follow up of two years, there was a significant increase in the frequency of some of the protective factors in the intervention group as compared to the control diet group, as given in Table 2 and Fig. (1).

The consumption of fruits and vegetables, whole grains, fish, almonds and walnuts, tea and mustard oil was significantly greater among subjects eating Indo-Mediterranean style diets as compared to the control low-fat diet (Table 3). The consumption of refined foods such as bread and biscuits, sugar, white rice and fatty foods, namely butter and clarified butter was significantly lower in the intervention diet group A, compared to standard diet group B. The functional food score for adherence to the intervention diet also showed a markedly increasing trend among intervention group subjects in both sexes. The trends for food intakes and functional food scores were significantly different in the intervention group (Table 3).

Table 4 shows the intake of fatty acids and flavonoids in the two groups at baseline and after 2 years of follow up. The intake of saturated fat was significantly lower, but that of

omega-3 fat and omega-6/omega-3 fatty acid ratios, the intake was significantly lower in the intervention group A, compared

to the control group B. The PUFA/flavonoid intake in the diet was also significantly lower in the intervention group as compared to the control group (Table 4).

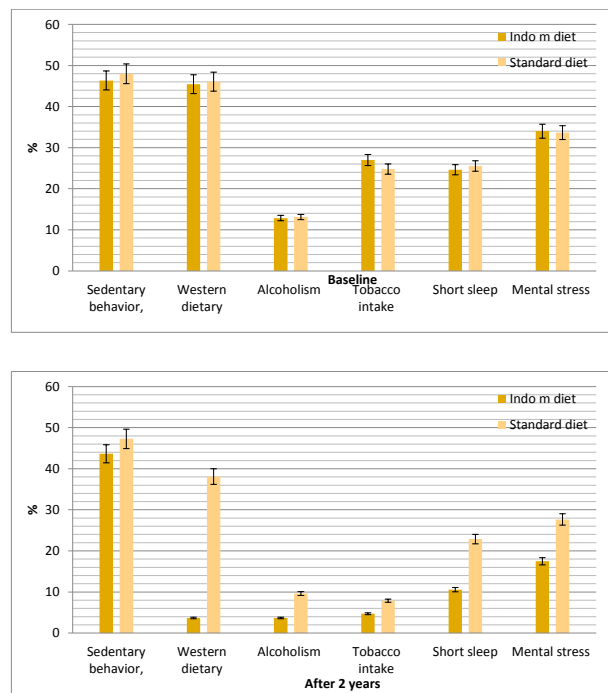


Fig. (1). Behavioral risk factors in the Indo-Mediterranean diet group and control group.

Table 2. Behavioral factors in the Indo-Mediterranean style diet and Standard diet group.

Behavior Assessment	Baseline		After 2 Years Follow Up	
	Indo-Mediterranean Diet (n=1,446)	Standard Diet (n=1320)	Indo-Mediterranean Diet (n=1,446)	Standard Diet (n=1,320)
Risk factors	Number (%)	Number (%)	Number (%)	Number (%)
Sedentary behavior,	670(46.33)	633(47.95)	631(43.63)	624(47.27)
Western dietary pattern (>salt, sugar and fat)	657(45.44)	608(46.06)	53(3.66)**	503(38.10)
Alcoholism (>10 drinks/week)	186(12.86)	173(13.11)	54(3.67)**	127(9.62)
Tobacco smoking (1 unit or more/week)	390(26.97)	327(24.77)	68(4.70)*	104(7.88)
Short sleep(<6 hours/day)	356(24.62)	337(25.53)	153(10.58)**	302(22.87)
Mental stress (Office or family problems)	492(34.02)	444(33.64)	253(17.49)**	365(27.65)
Protective factors				
Moderate physical activity	311(21.51)	290(21.97)	357(24.68)	312(23.63)
Meditation and prayer	319(22.04)	278(21.06)	337(23.30)	285(21.59)
Yoga postures (> once/week)	51(3.53)	41(3.11)	68(4.70)*	43(32.57)
Intermittent fasting (>once/week)	36(2.49)	32(2.42)	58(4.01)	37(2.80)
Circadian restricted eating (Eating once daily)	16(1.11)	20(1.52)	32(2.21)	18(1.36)
Low caloric diet (<1,500 K Cal/day)	16(1.11)	23(1.74)	28(1.93)	21(1.59)
Mastication(Cheewing >15/bite)	308(21.30)	249(18.86)	355(24.55)**	252(19.09)
Music (Listening or playing >once/week)	117(8.09)	110(8.33)	145(10.02)	117(8.86)
Intellectual work(reading writing >1 h daily)	677(46.82)	621(47.05)	650(44.95)	612(46.36)
Moderate alcohol intake, 6 to 10 drinks/week	44(3.04)	42(3.18)	56(5.86)	35(2.65)
Good sleep (6-8 h/day)	135(9.34)	135(10.22)	177(12.24)	142(10.75)

P-values were obtained by comparison of the intervention and control group after follow up of 2-years by Chi-square test. Values represent the number (%).

Table 3. Effects of Indo-Mediterranean style diet and control diet in the two groups.

-	Indo-Mediterranean Style Diet Group (n=1,446)	Standard Diet Group (n=1,320)		
		After 2 years	4-7 days	After 2 years
Foods and nutrients (g/day)	4-7 days	After 2 years	4-7 days	After 2 years
Fruits and vegetables (g/ day)	504.6±47.67**	571±97.8**	258.2±28.2	219.7±28.8
Potato, radish,	60.7±8.9	116±15.7**	71.0±22.5	157.7±44.6
Whole grains (g/day)	80.5±6.6**	95.0±8.9**	52.5±4.6	45.6±5.6
Almonds and walnuts (g/day)	85.7±7.8**	93.8±7.5**	5.2±2.2	7.5±3.4
Fish(g/day)	54.6±8.7**	24.2±6.2**	21.5±4.2	11.5±4.5
Chicken and eggs (g/Day)	-	12.5±4.6*	78.5±8.2	68.7±12.6
Mustard or soybean oil (g/day)	17.7±4.9*	32.6±6.6**	11.6±4.4	5.7±3.9
Butter or clarified butter(g/day)	2.5±0.6*	3.3±0.71*	10.5±2.6	12.6±3.5
Skim milk (ml day-1)	162.7±22.8	156±24.5*	152.4±14.4	167.6±19.2
Wheat chapatti (g/day)	5.7±2.6**	32.3±7.7	51.2±8.7	56.7±9.8
Bread, biscuits (g/day)	9.9±3.1*	24.5±7.4**	232.2±23.2	214.4±28.2
White rice (g/day)	25.6±2.4	30.6±5.5	30.2±3.1	35.6±4.8
Honey or raisins(g/day)	2.7±1.1	6.2±2.2*	1.3±0.41	1.5±0.31
Sugar(g/day)	11.5±4.6*	13.8±5.4*	25.8±7.5	31.7±9.7
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Salt(g/day);3-6g/day,black tea g/day Total Adherence score (%)	68.4± 16.6	64.7± 15.4*	54.1± 21.4	52.2± 25.6

P-values, mean± SD were obtained by comparison of intervention and control groups during 1 week and after 2 years.*=P<0.05,**P<0.01.

Table 4. Fatty acid consumption and flavonoids intake in the Indo-Mediterranean style diet group and standard diet group.

-	Before Entry	At Entry		After 2 Years	
		All patients (n=1,446)	Indo-Mediterranean (n=1,446)	Standard (n=1,320)	Indo-Mediterranean (n=1,446)
Fatty acid KJ/day					
Saturated	10.1± 2.43	7.1± 1.34*	9.2± 2.55	7.2± 0.24*	10.8± 0.36
Monounsaturated	9.4± 2.48	9.6± 2.42*	7.7± 2.36	8.0± 2.15	10.4±3.22
Polyunsaturated	6.91±	8.0± 2.04*	7.23± 2.42	8.8± 2.33*	7.11± 2.25
w-6	1.72)	6.2± 1.34	7.1± 2.31	7.1± 2.45	6.8± 2.23
w-3	6.6± 1.36	1.8± 0.24**	0.31±0.095	1.7±0.33**	0.31±0.095
w-6/w-3 ratio	0.31± 0.08	3.4±0.76**	22.9±2.4	4.2±0.76**	21.9±4.3
Main dietary oil	Pea nut	Mustard	Sunflower	Mustard	Sunflower, Pea nut
Flavonoids, g/day	0.72±0.05	1.85±0.066*	0.65±0.12	1.88±0.067*	0.66±0.13
PUFA/Flavonoid	9.59±2.13	4.32±0.67*	11.12±2.34	4.68±0.88*	10.77±2.33

Values are mean± Standard deviation **=p<0.01, (modified from Singh *et al*, 2012).

Table 5. Effects of the Indo-Mediterranean style diet on heart failure in patients with a high risk of heart diseases.

Data Collected	At Entry (n=1,446)		After Treatment (n=1,320)		Odds Ratio 95% (Confidence Interval)
	Intervention	Control	Intervention	Control	
Left ventricular strain	307(21.0)	325(22.5)	64(4.9)**	114(8.6)	0.57(0.50-0.65)
Left ventricular hypertrophy	86(5.9)	59(4.1)	92(6.9)**	133(10.0)	0.69(0.64-0.75)
NYHA Class II,III,IV heart failure	41(2.8)	39(2.7)	48(3.6)*	80(6.1)	0.59(0.50-0.68)
Ventricular ectopics,8/min	126(8.7)	98(6.8)	50(3.8)**	102(7.7)	0.49(0.42-0.56)
Ventricular ectopics 3 in row	68(4.7)	72(4.9)	11(0.8)*	27(2.0)	0.40(0.37-0.46)

*P <0.05, **P<0.01 by Chi-square test, values represent the number of subjects and percentages shown in parenthesis.>

Effects of Indo-Mediterranean style foods on parameters of PHF and HF and arrhythmias are given in Table 5. At baseline, all the parameters of HF showed no significant differences between the intervention and control group. However, after a follow up of two years, left ventricular strain (Odds Ratio 0.57(confidence interval 0.50-0.65, P<0.01), left ventricular

hypertrophy (OD 0.69,CI 0.64-0.75,P<0.01), as well as, NYHA class II-IV HF(OR 0.59, CI 0.50-0.68,P<0.05) were significantly lower in the intervention group as compared to the control group. Incidences of cardiac arrhythmias were also significantly lower in the intervention group as compared to the control group (OR 0.49;CI 0.42-0.56, P<0.01) (Table 5).

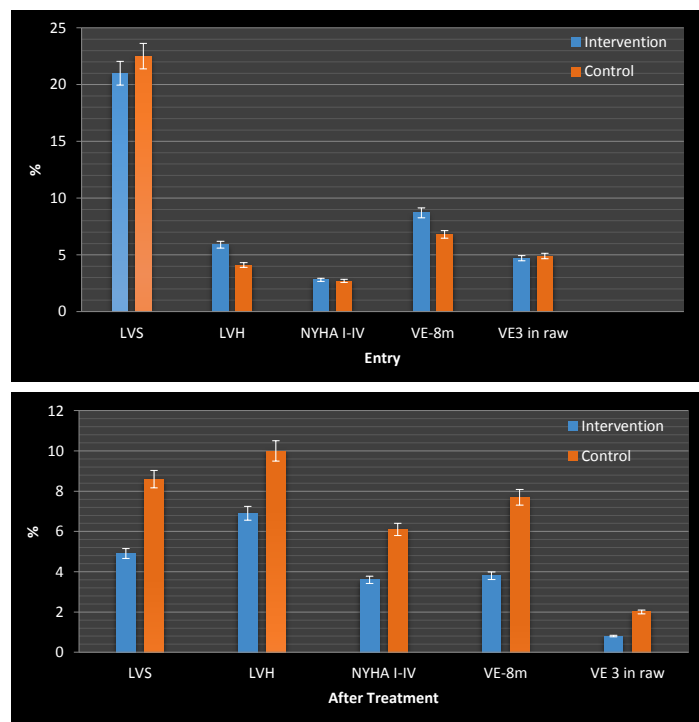


Fig. (2). Effects of the Indo-Mediterranean style diet on Pre-Heart Failure (PHF) and Heart Failure (HF), in patients with a high risk of heart diseases at entry and after treatment. LVS=Left Ventricular Strain, LVH=Left Ventricular Hypertrophy, VE= Ventricular Ectopics, NYHA= New York Heart Association.

4. DISCUSSION

The results of this study showed that PHF and HF were significantly lower in the intervention diet group, receiving Indo-Mediterranean style foods containing excess amount of whole grains, vegetables, nuts and fruits, in conjunction with mustard oil as compared to the control diet group B, which received low-fat diet advised by the NCEP Step-1 diet (Tables 4 and 5). Left ventricular strain (Odds Ratio 0.57, confidence interval 0.50-0.65, $P < 0.01$), left ventricular hypertrophy (OR 0.69, CI 0.64-0.75, $P < 0.01$), as well as, NYHA Class I-IV HF (OR 0.59, CI 0.50-0.68, $P < 0.05$) revealed significant reduction in these parameters within 2 years of follow up period in the intervention group as compared to the control group. Incidences of cardiac arrhythmias were also markedly lower in the intervention group in comparison with the control group (OR 0.49; CI 0.42-0.56, $P < 0.01$) (Table 5, Fig. 2). Collectively, these observations indicate that Indo-Mediterranean style foods with food diversity and desirable nutrient profile induce cardiovascular protection against HF and arrhythmias that are important outcomes against mortality and morbidity in these patients (Fig. 2). It is possible that the reduced risk of PHF, HF, and arrhythmias in the intervention group is due to decreased intake of Western type foods containing larger amounts of salt, sugar, trans fat, and higher glycemic index of these foods with a lower cardioprotective nutrient profile (Tables 3 & 4). The adverse cardiovascular effects of Western type diets may also be due to their high glycemic index and high trans fat accompanied by lower PUFA and flavonoids as well as higher omega-6/omega 3 fatty acids ratio, which pose pro-inflammatory and atherogenic effects [36 - 40].

The diets producing high Glycemic Index (GI) and

Glycemic Load (GL) are the indicators of the propensity of refined sweetened and salted products associated with high blood glucose concentration and diabetes, hypertension, and increased risks of coronary artery disease and HF [10 - 13]. The Swedish Mammography Cohort, a prospective observational study included 36,019 women, aged 48-83 years, without baseline HF, diabetes, or myocardial infarction [12]. After a follow-up of 9 years, 639 of 36,019 women died due to HF ($n = 54$) or were hospitalized for HF for the first time ($n = 585$). The authors suggested an association between dietary GL and HF, however, the values did not reach statistical significance [12]. In another cohort study, comprising 42,400 men, aged 45-79 years, the follow-up period was 12 years [37]. A total of 4,113 events due to HF were identified during the mean follow up period of 11.7 years. A positive correlation was found between sweetened beverage consumption and the risk of HF after adjustment for other risk factors (P -value for trend < 0.001). Those subjects who took two or more servings of sweetened beverages per day had a statistically significant higher risk of developing HF (23%, 95% CI 1.12 to 1.35) as compared to men who were non-consumers [36]. The findings of experimental studies also showed that a high-fructose diet worsens eccentric left ventricular hypertrophy in experimental volume overload and adrenomedullin, whereas antioxidant diets may protect against insulin resistance and myocardial hypertrophy [37 - 40].

Overwhelming evidence indicates that the Indo-Mediterranean type diet, Mediterranean style diet, and Dietary Approaches to Stop Hypertension (DASH), have consistently been associated with decreased HF incidence and severity [13, 19 - 21, 41]. It seems that food diversity in these diets, characterized by fruits, vegetables, legumes and whole grains,

and probiotics confer beneficial effects. On the other hand, red and processed meats, and refined carbohydrate products appear to be harmful, while the role of fish, dairy products and poultry remains controversial. The limited observational and interventional evidence from human studies suggests that the plant-based dietary products high in antioxidants, micronutrients, nitrate and fiber, but low in saturated and trans-fat and Na, may decrease the incidence and severity of HF [41]. Apart from plant-based diets, PUFA rich diets have also been found protective against CVDs [32 - 34]. Our study also shows that the consumption of mustard oil as well as PUFA, specially ω -3 fatty acids and flavonoids was significantly higher among patients in the intervention group as compared to control subjects (Tables 3 and 4). The ratio of PUFA/flavonoids in the diets before entry to study was significantly greater in the intervention group as compared to the control group. However, after treatment, there was a significant decline in this ratio due to a higher intake of flavonoids in the intervention group (Table 4). It is possible that eating diets rich in flavonoids along with PUFA may be highly protective against CVDs, including HF [13 - 15, 32 - 34]. In an epidemiological study, blood fatty acid levels of 2,480 men, aged 42 and 60 years of age, were examined [29]. After 22 years, 1,143 men died due to non-communicable diseases, including CVDs. The risk of premature death due to CVDs was 43% lower in the group with the highest level, when compared to the group with the lowest level of linoleic acid [29]. The composition of dietary fatty acids *e.g.*, saturated *versus* unsaturated, with and without adequate flavonoids, may have important consequences for the development of CVD, including arrhythmias [32 - 35]. It is known that excess of saturated and presence of *trans*-fats have an adversely high risk of CVDs, including HF [32, 42 - 45]. Several epidemiological studies have indicated that both ω -3 and ω -6 PUFA have beneficial effects against CVDs [33, 34, 42 - 45]. Interestingly, the proportion of dietary calories derived from fat is higher in Greenland and Mediterranean countries and relatively low in Japan, whereas all three countries show decreased mortality due to CVDs. These variations may partially be explained due to increased intake of fish, vegetables and soybean by the Japanese, high fish diet in Greenland, and high intake of olive oil and nuts by Mediterranean countries [34, 42 - 45]. The Cardiovascular Health Study also reported that increased circulating long-chain ω -3 fatty acids may be responsible for the lower incidence of congestive HF in older adults [46].

It seems that all studies do not support that the Mediterranean diet is protective against HF. The traditional Mediterranean diet intake among 24,008 Germans was not significantly associated with lower HF risk, but low meat, high fish and moderate alcohol intake were inversely associated with HF risk in this non-Mediterranean population [47]. The consumption of whole grain in our study was 2.5-fold greater in the intervention group as compared to the control group (Table 3). This finding is similar to other studies [48 - 50]. In the Physicians' Health Study I, among 21,376 participants, cereal consumption was assessed in relation to 1018 incident cases of HF during a follow-up of 19.6 years [48]. The hazard ratios (95% confidence intervals) for HF for increasing quantity of cereals intake, were 1, 0.92 (0.78-1.09), 0.79 (0.67-0.93), and 0.71 (0.60-0.85), respectively, ($P < .001$ for trend), adjusting for age, smoking, alcohol consumption, vegetable consumption, use of multivitamins, exercise, and history of

atrial fibrillation, valvular heart disease, and left ventricular hypertrophy [48]. However, the association was limited to the intake of whole-grain cereals ($P < .001$ for trend) but not refined cereals ($P = 0.70$ for trend).

In a cohort of 14,153 African-American and white adults aged 45 to 64 years, the relationship between HF and food intake (whole grains, fruits/vegetables, fish, nuts, high-fat dairy, eggs, red meat) during a follow-up of average 13 years was examined [49]. There were 1,140 cases of HF hospitalizations and the risk of HF was lower with the greater whole-grain intake (0.93 [0.87, 0.99]), but HF risk was higher with greater intake of eggs (1.23 [1.08, 1.41]), and high-fat dairy products (1.08 [1.01, 1.16]). These associations remained significant, independent of the intakes of the five other food categories, which were not associated with HF. In another cohort study, among 4,478 subjects, 179 cases of HF reported during a follow up of 13 years [50]. In subjects younger than 75 years, highest DASH concordance was associated with a lower risk of incident HF compared with those in the lowest quintile (hazard ratio=0.4, 95% CI=0.2, 0.9 *vs* all participants hazard ratio=1.0, 95% CI=0.2, 0.9) after adjusting for demographics, energy consumption, and known cardiovascular confounders [50]. The findings support the hypothesis that the DASH diet is beneficial in the prevention of HF among subjects < 75 years subgroup.

In our meta-analysis, the consumption of almonds, walnuts and peanuts was significantly higher in the intervention group as compared to the control group (Table 3). The Physicians' Health Study I, including 20,976 participants, examined the association of nut consumption with risks of HF [51]. After an average follow-up of 19.6 years, 1,093 new cases of HF occurred, but nut consumption was not associated with the risk of developing HF in this cohort. Although this study does not provide evidence for an association between nut consumption and incident HF in US male physicians, however, our data cannot rule out possible benefits of nut consumption on subtypes of HF as well as on the risk of CVDs. Our study also found that increased intake of fish and a lower intake of meats and eggs were significantly greater in the intervention diet as compared to control group diets (Table 3). Cohort studies indicate that fish consumption is inversely associated, whereas the intake of meat, processed meat and egg is positively associated with HF [52 - 56].

Potential mechanisms for beneficial effects of Indo-Mediterranean style diets include decline in blood glucose, lesser oxidative stress, reduction in homocysteine and inflammation, along with higher antioxidant defense and NO bioavailability, as well as promotion of healthy gut microbiome population due to increased content of flavonoids and fiber, and probiotics in these diets [57 - 66]. Indo-Mediterranean style diets may also decrease sympathetic activity and an increase in vagal activity, resulting in increased heart rate variability [30, 50, 60 - 62]. These are the important mechanisms in the pathogenesis of HF. In our previous studies, we noted a decrease in antioxidant vitamins E and C and nitrite and CoQ10 and an increase in biomarkers of oxidative stress, and such findings have been reported among HF patients as compared to healthy subjects [40, 42]. It was observed that serum concentrations of vitamins E and C, nitrite and CoQ10 were significantly lower among HF patients as compared to healthy subjects. The concentrations of TBARS, MDA and

diene conjugates, as well as cytokines, were significantly higher and vitamins E and C and nitrite and CoQ10 were lower among patients with class III and IV heart failure, compared to patients with class II heart failure [13]. Perhaps, Indo-Mediterranean diets may also increase stem cell survival [67]. A randomised, double-blinded, placebo-controlled, crossover trial was conducted for 8 weeks in metabolically healthy men and women (n=74) [68]. The purpose of the study was to determine whether an increased intake of Alpha-Linolenic Acid (ALA) can alter the fatty acid composition of serum phospholipids and erythrocytes in enrolled subjects with quercetin supplementation. The subjects received a combination of 3.3 g/day of ALA with either 190 mg/day quercetin or placebo (ALA + placebo). Both interventions significantly increased serum phospholipid ALA, whereas quercetin +ALA slightly decreased DHA. The results showed that serum phospholipids and erythrocyte levels remained unaltered by quercetin supplementation in both sexes with an increment of ALA (3.3 to 3.6 g/day) [68]. Linoleic acid may also reduce mortality [69].

It seems that proteins and amino acids, carbohydrates, lipids, fatty acids and vegetable secondary metabolites differently act on mesenchymal cells bearing on the modulation of gene expression and controlling the fate of cell lineages. The literature analysis shows that the major effect of nutrients on mesenchymal cells is the stimulation of transcription factors which modulate the cells toward proliferation or differentiation [67].

5. LIMITATIONS

One important limitation of our study is that other protective nutrients like essential and nonessential amino acids, probiotics and other antioxidant vitamins were not considered in our analysis. Antioxidant activity and total phenolics, vitamins, minerals, in selected fruits, vegetables, pulses, grain products and spices have been reported in several studies, but we could not consider all of them [60 - 63]. Indian foods appear to be inherently rich in phenolics and flavonoids, which are known in 85 foods comprising cereals, pulses, nuts, oilseeds, vegetables, fruits and beverages [60 - 62]. Total phenolics were measured biochemically and flavonoids were measured as a sum of quercetin, kaempferol, luteolin and pelargonidin, which we could not measure in this analysis.

High flavonoid content (> 100 mg/100 gm) are present in tea, coffee, apple, guava, Terminalia bark, fenugreek seeds, mustard seeds, cinnamon, red chili powder, cloves and turmeric. Medium levels (50-100 mg) are found in Indian gooseberry, omum, cumin, cardamom, betel leaf and brandy. Small but significant amounts were also present in food-items of large consumption such as kidney beans, soya beans, grapes, ginger, coriander powder, millets, onions, and brinjal [60 - 62]. In a further study, antioxidant activity is presented as the range of values for each of the food groups [63]. The foods studied had ample amounts of polyphenolic compounds and antioxidant activity, although they belonged to different food groups [63]. A significant correlation was observed between antioxidant activity (DPPH and FRAP) and polyphenolic compounds in most of the Indian foods. Commonly used domestic methods of cooking and processing may not affect the activity of phenolic compounds of the foods studied in general.

CONCLUSION

In summary, our data demonstrate that a higher intake of vegetables, fruits, whole grain, fish and nuts, in conjunction with mustard oil is associated with a lower risk of HF as well as PHF. Decreased intake of refined foods, sweetened foods and beverage consumption, as well as lower intake of meats and eggs, are also associated with a relatively lower risk of HF. Taken together, our findings may have implications for HF prevention strategies, possibly due to the anti-inflammatory effects of Indo-Mediterranean style diets due to increased content of flavonoids and PUFA. Further randomized, placebo-controlled, double-blinded trials are warranted to confirm these findings and identify specific foods and nutrients that are responsible for cardiovascular protection.

CONSENT FOR PUBLICATION

Informed consent was obtained from each subject when they were enrolled.

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CONFLICT OF INTEREST

The author has stated all possible conflicts of interest and all the sources work.

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