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ARYA Atherosclerosis

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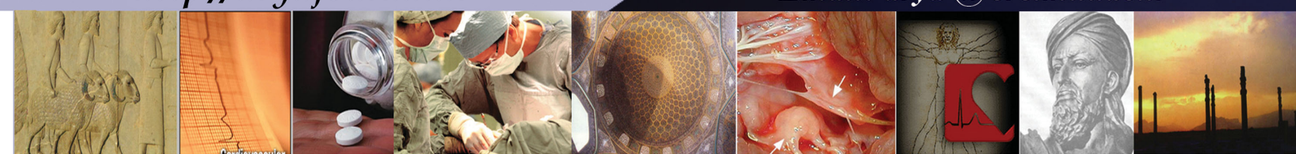

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Subclinical left ventricular systolic dysfunction in patients with metabolic syndrome: A case–control study using two-dimensional speckle tracking echocardiography

Alireza Moaref[(1)], Majid Faraji[(1)], Maryam Tahamtan[(1)]

Original Article

Abstract

BACKGROUND: The dramatic increase in the prevalence of metabolic syndrome is associated with more increased cardiovascular morbidity and mortality in this group. Some recent studies suggested that metabolic syndrome is associated with increased risk of subclinical left ventricular (LV) systolic dysfunction. In the present cross-sectional case–control study, the utility of two-dimensional speckle tracking echocardiography (STE) was examined to detect early LV systolic dysfunction in this population.

METHODS: A total of 75 clinically asymptomatic subjects with left ventricular ejection fraction (LVEF) ≥ 55%, 39 without metabolic syndrome and 36 with metabolic syndrome, matched for gender and age, were enrolled in this case–control study. Metabolic syndrome was diagnosed using the National Cholesterol Education Program/Adult Treatment Panel III criteria. LV systolic function was assessed by STE-derived global and segmental longitudinal strain (ε_{LL}).

RESULTS: Global ε_{LL} was significantly lower in patients with metabolic syndrome compared with normal population (−18.41 ± 2.20% vs. −21.2 ± 2.1%, P < 0.001). Segmental ε_{LL} was significantly lower in patients with metabolic syndrome in comparison to control group except for basal anteroseptal (−19.95 ± 2.90% vs. −21.15 ± 3.30%, P = 0.106), basal anterolateral (−17.5 ± 5.0% vs. −18.3 ± 4.1%, P = 0.437), and basal inferolateral segments (−18.1 ± 6.3% vs. −18.9 ± 4.1%, P = 0.526).

CONCLUSION: STE-derived longitudinal LV strain (ε_{LL}), a marker of subclinical cardiovascular disease, is impaired in asymptomatic individuals with metabolic syndrome and normal LVEF.

Keywords: Metabolic Syndrome, Two-dimensional Echocardiography, Systole, Ventricular Dysfunction, Asymptomatic Disease

Date of submission: 06 Oct 2015, ***Date of acceptance:*** 21 Sep 2016

Introduction

Metabolic syndrome is the concurrence of multiple metabolic abnormalities associated with the development and progression of atherosclerosis,[1] and generally, is diagnosed by the presence of three or more of the following conditions: obesity, insulin resistance, glucose intolerance, dyslipidemia, and hypertension.[2] The dramatically increasing prevalence of the metabolic syndrome, associated with the substantial increase in obesity and diabetes, is, therefore, an important public health concern.[3]

The most conventional tool in echocardiographically quantifying systolic left ventricular (LV) function is the ejection fraction (EF). However, measurement of EF is a simplistic approach, closely correlated to the radial component of myocardial deformation and thus limited by the need for the geometric assumption. As a consequence, subtle changes in myocardial systolic function may be neglected in high-risk subclinical patients with metabolic syndrome when they are only assessed by EF in clinical practice. Novel quantitative techniques such as speckle-tracking echocardiography (STE) and tissue-Doppler imaging (TDI) can reliably measure LV strain which has a more sensitive diagnostic potential.[4-6]

Up to now, a few echocardiography-based studies has focused on subclinical cardiovascular disease in patients with metabolic syndrome using several parameters including more reproducible newer ones such as Tei index and TDI.[7,8] Recently, LV myocardial strain has also been assessed by STE to determine the subclinical systolic effects of metabolic syndrome.[9]

1- Cardiovascular Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
Correspondence to: Maryam Tahamtan, Email: mtahamtan@sums.ac.ir

The purpose of this study was to evaluate the use of STE to assess LV myocardial strain as a marker of LV systolic dysfunction in asymptomatic population with metabolic syndrome and left ventricular ejection fraction (LVEF) ≥ 55% to fortifying data to introduce a non-invasive accurate tool for screening of subclinical LV systolic dysfunction in patients with metabolic syndrome.

Materials and Methods

This case–control study was approved and performed in accordance with the regulations of the University's Institutional Review Board (Shiraz University of Medical Sciences, Shiraz, Iran) enrolling outpatient individuals aged between 35 and 55 with metabolic syndrome who were referred to the Shiraz Healthy Heart House* from April 2014 to December 2014. The patients were labeled to be affected by metabolic syndrome according to the updated National Cholesterol Education Program/Adult Treatment Panel III (NCEP ATP III) criteria for Asians. The subjects had to meet at least 3 of the following components: waist circumference ≥80 cm in women and ≥ 90 cm in men, fasting triglycerides > 150 mg/dl (≥ 1.7 mmol/l) or specific medication, high-density lipoprotein cholesterol < 40 mg/dl (< 1.03 mmol/l) for men or < 50 mg/dl (< 1.29 mmol/l) for women or specific medication, blood pressure ≥ 130/85 mmHg or current use of antihypertensive medications, or fasting plasma glucose ≥ 100 mg/dl (≥ 5.6 mmol/l) or previously diagnosed Type 2 diabetes.[10] Blood pressure was obtained from the upper arm of the patient who stopped smoking ½ hour before, seated quietly in a chair with back support, with both feet flat on the floor for at least 5 minutes prior to measurement using a calibrated Beurer® Sphygmomanometer. Waist circumference was measured midway between the lower limit of the rib and iliac crest with the subject standing using a flexible tape.

Concomitantly, age and sex-matched individuals were selected from normal population to participate in the control group. The overt ischemic heart disease was excluded in all participants according to current symptoms, previous history of coronary artery disease, presence or absence of pathologic Q waves in at least 2 adjacent leads on resting 12-lead electrocardiogram (EKG) and LVEF < 55%. The patients with bundle branch block in EKG, valvular heart disease, congenital heart disease, cardiomyopathies, and chronic kidney disease were also excluded from the study.

To reach the study power of 80% and the effect size of 76% for the longitudinal LV strain (ε_{LL}) according to the same previous study,[9] the sample volume was estimated to be at least 35 participants in each group. The random digit dialing method was used for sampling, and the excluded individuals were substituted by others who met the eligibility inclusion criteria. The two groups were matched for age and gender.

All participants underwent a two-dimensional (2D) transthoracic echocardiography including TDI and STE using a vivid E9 system and all echocardiographic measurements were performed by one echocardiologist according to the latest recommendations of the American Society of Echocardiography.[11] The LVEF was calculated by Simpson's biplane method, and the ε_{LL} (%) was calculated as the change in regional length relative to the length at end-diastole; $\varepsilon_{LL} = (L_t - L_0) \times 100/L_0$, in which L_t is the length at time t and L_0 is the length of the segment at the beginning of the QRS complex. On 2D echocardiography, global ε_{LL} describes the relative length change of the LV myocardium between end-diastole and end-systole. After optimizing image quality, maximizing frame rate and minimizing foreshortening, peak mid-wall segmental and global ε_{LL} measurement was taken in the three standard apical views and averaged by automated function imaging application and demonstrated in Bull's eye (Figure 1).

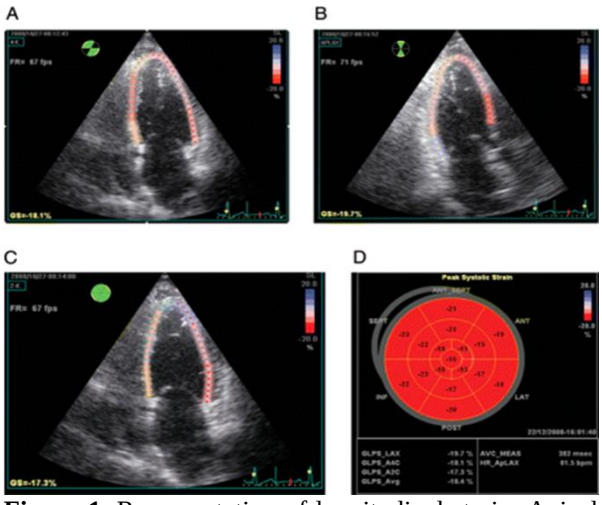

Figure 1. Representation of longitudinal strain. Apical (a), 4-chamber, (b) 3-chamber, (c) 2-chamber views and (d) Bull's-eye map showing segmental ε_{LL}

Using Kolmogorov–Smirnov test, the normal pattern of data distribution in measured

parameters was confirmed and therefore for comparison of data in case and control groups, the independent sample t-test and chi-square test were used for continuous and categorical variables, respectively. All continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as number (n) and percentage (%). All collected data were analyzed by SPSS software (version 18.0, SPSS Inc., Chicago, IL, USA), and a $P < 0.050$ was considered statistically significant.

Results

A total of 75 eligibility criteria met individuals participated in the study from which 36 patients had metabolic syndrome and concomitantly, 39 age and gender-matched individuals from the normal population were examined echocardiographically in the control group.

The mean age of people in case and control groups was 40 ± 8 and 38.7 ± 8.9, respectively ($P = 0.509$). For patients with metabolic syndrome, the distribution of gender was equal and 19 participants (48.7%) in control group were male in comparison with 20 (51.3%) females. Therefore, no statistically significant difference was present between case and control groups regarding age and gender. The clinical and demographic characteristics of participants are summarized in table 1.

Global ε_{LL} was significantly lower in patients with metabolic syndrome compared with normal population ($P < 0.001$) (Table 2) providing an effect size of 90%. In individuals with metabolic syndrome, although global ε_{LL} was slightly higher in women, there was no statistically significant difference between men and women (−17.88 ± 1.80 vs. −18.9 ± 2.5; $P = 0.157$). Segmental ε_{LL} was significantly lower in patients with metabolic syndrome in comparison to control group except for basal anteroseptal, basal anterolateral and basal inferolateral segments ($P = 0.106$, 0.437 and 0.526, respectively).

Discussion

In this cross-sectional, case–control study, the subclinical LV systolic dysfunction was focused which then revealing metabolic syndrome, as defined by NCEP ATP III criteria for Asians, was associated with reduced myocardial systolic function as indicated by an impaired global and segmental ε_{LL} in a sample of participants with metabolic syndrome signifying the need for a sensitive screening tool for asymptomatic LV systolic dysfunction and probably other subclinical aspects of cardiovascular disease in patients with metabolic syndrome according to its evolving prevalence and the hazardous potential of each of its components which in turn translated to a greater risk of cardiovascular disease.[12,13] The results of this study are in concordance with such previous ones. For instance, Wang et al. showed that regional LV myocardial systolic function using strain and strain-rate imaging in patients with metabolic syndrome with normal LVEF was partly impaired and were negatively correlated with blood pressure, waist circumference, fasting plasma glucose and uric acid.[14] Strain and strain-rate imaging were also used in a study on Chinese participants with metabolic syndrome revealing TDI as a sensitive and feasible method to detect subclinical abnormalities in such population;[8] however, strain measured by using TDI has some limitations such as poor reproducibility, angle dependency, and signal noise.[15]

Table 1. The clinical and demographic characteristics of individuals with metabolic syndrome and control group

Variables	With metabolic syndrome (n = 36)	Without metabolic syndrome (n = 39)	P
Age (year) (mean ± SD)	40.00 ± 8.00	38.70 ± 8.90	0.509
BMI (kg/m^2) (mean ± SD)	33.20 ± 3.60	26.60 ± 4.00	< 0.001
Waist circumference (cm) (mean ± SD)	96.31 ± 10.45	80.40 ± 9.67	< 0.001
Fasting TGs (mg/dl) (mean ± SD)	156.00 ± 16.98	92.87 ± 13.00	< 0.001
HDL-cholesterol (mg/dl) (mean ± SD)	46.80 ± 5.00	52.82 ± 6.40	< 0.001
Blood pressure (mmHg) (mean ± SD)	140.00 ± 13.00	132.00 ± 11.50	0.006
Fasting plasma glucose (mg/dl) (mean ± SD)	111.00 ± 15.84	94.00 ± 13.70	< 0.001
Any lipid-lowering medication [Yes (%)]	15 (41.7)	6 (15.4)	0.022
Previously diagnosed Type 2 diabetes [Yes (%)]	10 (27.8)	6 (15.4)	0.304
Gender (Female) [n (%)]	18 (50.0)	20 (51.3)	0.905
Any antihypertensive medication [Yes (%)]	14 (38.9)	7 (17.9)	0.077

The independent t-test and chi-square test were used for comparison of continuous and categorical variables, respectively. $P < 0.050$ was considered statistically significant. BMI: Body mass index; HDL: High-density lipoprotein; TG: Triglycerides; SD: Standard deviation

Table 2. The mean value of global and segmental longitudinal left ventricular (LV) strain (ε_{LL}) in individuals with metabolic syndrome and control group

Variables		With metabolic syndrome (n = 36)	Without metabolic syndrome (n = 39)	P
Segmental ε_{LL} (%)	Anteroseptal			
	Apical	−19.22 ± 4.5	−24.38 ± 4.9	< 0.001
	Mid	−17.69 ± 2.5	−19.15 ± 3.2	0.037
	Base	−19.95 ± 2.9	−21.15 ± 3.3	0.106
	Anterolateral			
	Apical	−16.50 ± 4.7	−23.70 ± 3.1	< 0.001
	Mid	−16.90 ± 4.0	−20.10 ± 3.4	< 0.001
	Base	−17.50 ± 5.0	−18.30 ± 4.1	0.437
	Inferoseptal			
	Mid	−18.00 ± 3.1	−19.80 ± 2.2	0.006
	Base	−15.50 ± 3.5	−17.50 ± 2.5	0.006
	Inferolateral			
	Mid	−17.30 ± 4.4	−20.10 ± 3.5	0.004
	Base	−18.10 ± 6.3	−18.90 ± 4.1	0.526
	Anterior			
	Apical	−16.70 ± 5.7	−20.70 ± 3.9	< 0.001
	Mid	−16.70 ± 5.7	−20.70 ± 3.9	< 0.001
	Base	−16.00 ± 7.1	−19.00 ± 4.4	0.030
	Inferior			
	Apical	−19.70 ± 3.9	−25.10 ± 3.9	< 0.001
	Mid	−19.80 ± 4.0	−21.60 ± 3.2	0.030
	Base	−18.40 ± 4.2	−20.50 ± 3.7	0.021
	Apical cap	−22.10 ± 3.1	−24.40 ± 2.2	0.002
Global ε_{LL} (%)		−18.41 ± 2.2	−21.20 ± 2.1	< 0.001

The independent t-test was used for comparison of all variables between groups. P < 0.050 was considered statistically significant.

Considering the limitations of TDI-derived strain and the fact that more general conclusion can be drawn from studies on populations in whom metabolic syndrome is more prevalent, in a multi-ethnic study using STE which was superior to our study regarding its larger sample size, focus on both circumferential and longitudinal LV myocardial strain and also providing data on reproducibility of parameters, individuals with metabolic syndrome had lower circumferential and longitudinal myocardial shortening as indicated by less negative ε_{CC} and ε_{LL} than those without metabolic syndrome even after adjusting for age, ethnicity, LV mass and LVEF and it was significantly correlated with magnetic resonance imaging (MRI) findings.[9]

In addition to reduced values of global ε_{LL}, our study also depicted significantly reduced STE-derived segmental ε_{LL} in patients with metabolic syndrome except for basal anteroseptal, basal anterolateral and basal inferolateral segments which may be attributable to mid-wall ε_{LL} being inherently highest in the apex and lowest in the base[16] contributing to less statistically significance of compared basal strains between two groups. ε_{LL} is an angle-independent parameter with the established prognostic value[11] for which the same vendor and the same software were used for measurement in all examinations to eliminate the vendor- and software dependency of this valuable parameter.

Although this study is the only study assessing both global and segmental longitudinal STE-derived strain in subclinical metabolic syndrome, it has some limitations including use of ε_{LL} as the single STE-derived parameter due to lack of equipped modalities. In addition, most of the enrolled patients were middle-aged and therefore, the results cannot be generalized to extremes of age groups in adult population. These results would be confirmed by further similar studies worldwide enrolling increased number of subjects whose limited number is one of the other shortages of this study which curtail our ability to draw definitive conclusions for a screening program.

Conclusion

Based on our study, the STE-derived global longitudinal LV strain is reduced in asymptomatic patients with metabolic syndrome and LVEF ≥ 55%. Less value of longitudinal LV strain is also evident in most of LV myocardial segments. Consequently,

LV myocardial longitudinal strain assessed by STE is an early marker of LV systolic dysfunction in asymptomatic population with metabolic syndrome.

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Conflict of Interests

Authors have no conflict of interests.

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The prevalence of hypertension and its relationship with demographic factors, biochemical, and anthropometric indicators: A population-based study

Mohammad Khajedaluee[(1)], Tahereh Hassannia[(2)], Abdolrahim Rezaee[(3)], Maryam Ziadi[(4)], Maliheh Dadgarmoghaddam[(5)]

Original Article

Abstract

BACKGROUND: Hypertension (HTN) is an important public health challenge worldwide. The prevalence of HTN varies across countries. It is necessary to obtain valid information about the prevalence of chronic condition like HTN and its predictors in different societies. Hence, this study was conducted to assess the prevalence of HTN and associated factors in Mashhad, Iran, 2015.

METHODS: This cross-sectional study was performed on 2974 adults residing in Mashhad in 2015. Multistage random sampling was used. A checklist was fulfilled for each subject, and a blood sample was taken for measuring fasting blood sugar, total cholesterol, triglycerides, hemoglobin, serum creatinine, high-density lipoproteins, and low-density lipoproteins. The height and weight of participants and their blood pressure were measured according to protocols.

RESULTS: The prevalence of HTN in this population was 22% (25.9% in male and 20% in female). Most interestingly, smoking and drug abuse were more prevalent in men (14.9% and 3.8%), but the sedentary behavior was more prevalent in women (51%). Interestingly, by increasing the age, the frequency of optimum, normal and high normal type was decreased and the frequency of HTN, specially sever form were increased. In binary logistic regression model, age [odds ratio (OR): 1.07, 95% confidence interval (CI): 1.06-1.09], gender (Ref:Female) (OR: 1.39, 95% CI: 1.05-1.83), and obesity (OR: 1.09, 95% CI: 1.06-1.12) were the predictors of HTN.

CONCLUSION: The prevalence of HTN among this population was found to be high; which indicates the need for HTN-screening programs, especially for the elderly, male and obese population. Given the close relationship between obesity and various diseases, including HTN, practical solutions, including lifestyle interventions, need to be developed.

Keywords: Hypertension, Prevalence, Adult, Anthropometric Indicators

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Introduction

Hypertension (HTN) has become very common worldwide and can lead to major health outcomes, such as myocardial infarction, stroke, renal failure, and ultimately death. The prevalence of HTN is increasing in developing countries and is one of the leading causes of death and disability.[1] The prevalence of HTN increases with age.[2]

The results of descriptive studies showed that death from ischemic heart disease and stroke increased linearly in those with a systolic blood pressure (SBP) level as low as 115 mmHg and a diastolic BP (DBP) level of 75 mm Hg.[3,4] According to one study, the awareness of HTN among general population varied from 25.2% to 75%.[5] The World Health Organization reported that annually, complications of HTN accounted for 9.4 million deaths worldwide.[6]

Based on a systematic review in Iran, the estimated overall prevalence of HTN among those aged 30-55 years and older than 55 years was reported to be around 23% and 50%, respectively.[6] This prevalence was lower in men than in women and it increased by about 0.5% per each year of increase in the mean age of the subjects.[6] Other studies reported HTN prevalence rates of 21.2-41.8%. Among the Iranian

1- Professor, Department of Community Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
2- Department of Internal Medicine, School of Medicine, Arash Hospital, Tehran University of Medical Sciences, Tehran, Iran
3- Assistant Professor, Inflammation and Inflammatory Diseases Research Center AND Department of Immunology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
4- State Health Center, Mashhad University of Medical Sciences, Mashhad, Iran
5- Assistant Professor, Department of Community Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
Correspondence to: Maliheh Dadgarmoghaddam, Email: dadgarmm@mums.ac.ir

adult population, the prevalence of HTN was higher in females, older age groups, illiterate individuals, poor people, and urban residents.[7-12]

Information on the prevalence of chronic conditions, such as HTN, and its predictors in different societies are needed to aid disease management. This study was conducted to assess the prevalence of HTN and associated factors in Mashhad, Iran, in 2015.

Materials and Methods

This was a cross-sectional study of the adult population (> 16 years) in Mashhad, a metropolitan area in the northeast of Iran in 2015. A sample size of 2700 was required, by considering all the assumption and a 30% attrition rate and finally multiplied by 3 for clustering design. Multi-stage cluster random sampling was used.

In the first stage of the study, the population was divided based on the population covered in each district (central health centers numbers 1, 2, 3 and 5). Then, five clusters (health centers) were selected randomly in each district. To allocate samples at the cluster level, the probability proportional to size (each district) method was used. In the second stage of the study, streets were selected randomly, and interviewers who had taken part in 2-day training workshop on data collection visited the homes of potential participants (they were masters in nursery or midwifery who were coworkers in this research). At each house, using a checklist, the interviewers obtained information on the demographic characteristics and socioeconomic status of the residents (maximum of two different genders from a family). The participants who agreed to take part in the study underwent a physical examination at their nearest health center by a general practitioner who had received training (three sessions) in how to minimize measurement and inter-observer bias.

The exclusion criteria were absent in any step of the study, passengers who are not resident in Mashhad.

In this study, sedentary behavior refers to any sitting or reclining posture and included television viewing, video game playing, computer use, driving automobiles and reading. If the respondent says yes to the question that they were spending more time in this activity daily, we considered them yes.

Obesity refers to a body mass index (BMI) ≥ 30.

Diabetes is defined as a fasting blood sugar (FBS) of > 126 mg/dl.[13]

A cigarette smoker refers to someone who smokes more than one cigarette per day or uses a hookah each day.

Drug abused was asked by a question "have you ever used illegal substances"?

In this study, the 3600 IR Rials was equal to 1 US dollar (exchange rate).

The seven blood pressure (BP) categories were defined as follows: "Optimal" SBP < 120 mmHg and DBP < 80 mmHg); "normal" (SBP 120-129 mmHg and/or DBP 80-84 mmHg); high normal (SBP 130-139 mmHg and/or 85-89 mmHg); Stage 1 HTN (mild) (SBP 140-159 and/or DBP 90-99 mmHg); Stage 2 HTN (moderate) (SBP 160-179 and/or DBP 100-109 mmHg); Stage 3 HTN (severe) (SBP 180-209 and/or DBP 110-119 mmHg); HTN Stage 4 (very severe) (SBP ≥ 210 and/or DBP ≥ 120).[14]

BP readings were obtained from the right arm of each subject, with the subject in a sitting period after a period of relaxation for 5 minutes using a standard mercury sphygmomanometer (Omron M6 Comfort, BP Monitors, Japan). Each subject's heart rate was also measured. The BMI was calculated based on the following formula: weight (kg) divided by the height (m^2). Body weight was measured using an analog scale, with the participants wearing single layer of clothing. Height was measured using a stadiometer. Blood samples were taken at health centers after 12 hours of fasting to determine the lipid profile, FBS, serum creatinine (Cr), and hemoglobin (Hb). All the samples were sent to a dedicated laboratory for analysis.

The study was conducted in accordance with the principles of the Declaration of Helsinki (1996 version) and good practice standard. All subjects signed informed consent forms.

Descriptive statistical measures, including measures of central tendency and dispersion, were used to describe the data. The continues variable presented by mean ± standard deviation (SD) and qualitative variable described by number (percent). The distribution of data was checked by one sample Kolmogorov–Smirnov test, and according to the result of this test, the appropriate test was selected.

Chi-square (nominal variable), Kruskal–Wallis, Mann–Whitney (for quantitative or ordinal variables), and binary logistic regression test is used to estimate the probability of HTN based on independent variables All reported P values are based on two-sided tests and compared to a significance level of 0.05. SPSS software for Windows (version 11.5, SPSS Inc., Chicago, IL, USA) was used for all the analyses.

Table 1. Blood pressure (BP) distribution in males and females

BP	Sex n(%)	Age n(%)		P	Sex n(%)	Age n(%)		P	Total n(%) (n=2974)	P Total comparison in two gender
	Female (n=1930)	<65 1840 (95.4)	≥65 88 (4.6)		Male (n=1044)	<65 922 (88.6)	≥65 119 (11.4)			
Optimal*	1378 (71.4)	1319 (73.6)	22 (25.6)	<0.001	634 (60.7)	581 (64.6)	35 (29.9)	<0.001	2012 (67.7)	<0.001
Normal	152 (7.9)	136 (7.6)	12 (14.0)		132 (12.6)	111 (12.3)	17 (14.5)		284 (9.6)	
High normal	14 (0.7)	12 (0.7)	1 (1.2)		8 (0.8)	7 (0.8)	1 (0.1)		22 (0.7)	
HTN	386 (20.0)	325 (18.0)	51 (59.3)		270 (25.9)	200 (22.2)	65 (49.3)		656 (22.0)	
Mild	222 (11.5)	189 (10.5)	26 (30.2)		171 (16.4)	133 (14.8)	35 (29.9)		393 (13.2)	
Moderate	127 (6.6)	103 (5.7)	22 (25.6)		78 (7.5)	55 (6.1)	21 (17.9)		205 (6.9)	
Sever	31 (1.6)	29 (1.6)	2 (2.3)		16 (1.5)	8 (0.9)	8 (0.6)		47 (1.6)	
Very sever	6 (0.3)	4 (0.2)	1 (1.2)		5 (0.5)	4 (0.4)	1 (0.9)		11 (0.3)	

* n (%). Based on chi-square test
HTN: Hypertension; BP: Blood pressure

Results

The study consisted of 2974 participants (age ranged 16-90). The prevalence of HTN in the study population was 22% (25.9% in males and 20% in females). The overall average age of participants was 43.52 ± 14.69 years old; men had a significantly higher age in comparison with female [46.10 ± 15.75 and 42.12 ± 13.89 (P < 0.001), respectively].

Table 1 shows the BP distribution of males and females. The total distribution was statistically different in both genders (P < 0.001). Moreover, based on the American Heart Association writing committee,[15] elderly was defined as those ≥ 65 years of age and accordingly we compared the distribution of different BP categories in our elderly and non-elderly subjects in table 1, which showed that a significantly greater number of subjects in each gender was known to be < 65-year-old.

According to the new category that consisted of three major groups (optimal, normal and hypertensive), we compared the underlying factors in these groups. As demonstrated in table 2, the following factors were statistically different between the groups: Educational level (P < 0.001), job (P < 0.001), marital status (P < 0.001), drug abuse (P = 0.040), sedentary behavior (P = 0.010), and BMI (P < 0.001).

Table 3 shows the comparison of the mean lipid profile, FBS, serum Cr, urine Cr, and Hb in the three groups according to gender. As can be seen from the table, FBS, cholesterol, triglyceride (TG), low-density lipoprotein (LDL), and serum Cr were higher in the hypertensive group of women. FBS, cholesterol, TG, LDL and, surprisingly, high-density lipoprotein were higher in the hypertensive group of men.

In the binary logistic regression (enter model) of the predictors of HTN in this population, age, gender and obesity were meaningful predictors (Table 4).

The sensitivity of the model was 53%, and its specificity was 81%.

Discussion

The prevalence of HTN in this population was 22% (25.9% in males and 20% in females). Interestingly, smoking and drug abuse were more prevalent in men (14.9% and 3.8%, respectively), but the sedentary behavior was more prevalent in women (51%). A total of 71.4% of women and 60.7% of men had optimal BP.

The urban HEART-2 study, which was conducted in 2011 in Tehran, Iran, reported a prevalence of self-reported HTN of 5.27% in the population (3.83% in men and 6.64% in women) (P < 0.001).[16] To some extent, the difference in the prevalence of HTN in that study compared to that of this study may be explained by the different years of the two studies that certainly affect the prevalence rate.

Furthermore, the findings of the Urban HEART-2 were based on self-report data, which are subject to reporting bias. Increased awareness by the public of their HTN status may also increase the likelihood of reporting.

The higher prevalence of HTN found in this study (25.9% in men and 20%% in women) is similar to that reported in most previous studies[8,17-19] although some discordance with previous reports was observed.[12,20-23] The discordance may be due to the self-report questionnaire design of the study and the fact that women are generally more likely than men to say they are unwell.

Table 2. Comparison of underlying factors in the three groups [optimal blood pressure (BP), normal BP and Hypertension (HTN)]

Variables	Optimal (n = 2011)	Normal BP (n = 307)	HTN (n = 656)	P
Educational level				
Illiterate	172 (45.1)	49 (13.0)	160 (41.9)	< 0.001
Elementary	562 (59.7)	106 (11.3)	273 (29.0)	
Not completed high school	400 (75.3)	53 (10.0)	78 (14.7)	
High school diploma	568 (78.9)	67 (9.4)	85 (11.7)	
College diploma	119 (76.0)	12 (8.0)	25 (16.0)	
License and higher degree	190 (77.7)	18 (7.4)	37 (14.9)	
Job				
Jobless	100 (57.3)	19 (10.8)	56 (31.9)	< 0.001
Employee	177 (58.8)	41 (13.5)	83 (27.7)	
worker	92 (64.4)	20 (14.1)	31 (21.5)	
Free lancer	375 (66.5)	69 (12.3)	120 (21.2)	
Student	121 (91.4)	5 (3.9)	6 (4.7)	
Housewife	1151 (69.4)	154 (9.3)	354 (21.3)	
Marital status				
Single	249 (86.9)	17 (5.8)	21 (7.3)	< 0.001
Married	1686 (66.9)	267 (10.6)	567 (22.5)	
Widow	71 (46.9)	22 (14.3)	58 (38.8)	
Divorced	9 (58.8)	2 (11.8)	5 (29.4)	
Tobacco use				
Yes	158 (63.1)	27 (10.8)	66 (26.1)	0.240
No	1852 (68.0)	280 (10.3)	591 (21.7)	
Drug abuse				
Yes	33 (60.4)	2 (4.2)	19 (35.4)	0.040
No	1974 (67.6)	307 (10.5)	639 (21.9)	
Sedentary behavior				
Yes	909 (66.8)	121 (8.9)	331 (24.3)	0.010
No	1097 (68.0)	184 (11.4)	332 (20.6)	
BMI				
Low	93 (91.7)	1 (1.0)	7 (7.3)	< 0.001
Normal	792 (76.8)	88 (8.5)	152 (14.7)	
Over weight	768 (64.9)	136 (11.5)	279 (23.6)	
Obesity	295 (58.7)	58 (11.5)	150 (29.8)	
Very obesity	72 (46.6)	20 (12.8)	63 (40.6)	
Diabetes				
Yes	111 (44.9)	38 (15.6)	98 (39.5)	< 0.001
No	1869 (68.6)	294 (10.8)	561 (20.6)	

Based on chi-square test. BMI: Body mass index; BP: Blood pressure; HTN: Hypertension

In accordance with other reports, this study showed a significant association between obesity and BP. In a previous study of 3423 adults aged 30-65 years in China, 1929 adults in the Philippines and 7957 adults in the U.S., a high BMI was correlated with increasing rates of HTN.[24] A study in Denmark of 13,577 adolescents aged 15-20 years demonstrated an association between fitness and BMIs with HTN.[25] Another study reported that obesity and being overweight could increase BP via physiological changes, including increased insulin resistance, elevated activity of the renin-angiotensin system in the kidney and increased pressure on peripheral vessels.[26] The results of this study, which showed that BP increased with age, are similar to those of other reports.[11,27] In a survey in the U.K., after adjustment for age, BMI, alcohol and social class, a significantly higher SBP was found in older men and in heavy and moderate smokers than in never smokers, whereas no such differences were seen in DBP.[28]

In the binary logistic regression after adjustment for other variables, smoking was not a meaningful predictor of HTN.

Furthermore, in this study, after adjustment for other variables, sedentary behavior was not a meaningful predictor of HTN. In a dynamic cohort study (SUN Study)[29] of 11,837 Spanish university graduates, with a mean age of 36 years, self-reported total sedentary behavior (i.e., interactive and noninteractive) was directly associated with a higher risk of HTN (hazard ratio: 1.48; 95% confidence interval: 1.01-2.18.[29] In a subtype analyses, the same study reported that interactive sedentary behavior (driving and computer use) but not noninteractive sedentary behavior (television viewing and sleeping) was associated with a higher risk of HTN.[29]

Table 3. Comparison of the lipid profile, fasting blood sugar (FBS), serum creatinine (Cr), urine Cr and hemoglobin (Hb) according to blood pressure (BP) and gender

BP	Female (n = 1930)				Male (n = 1044)			
	Optimal (n = 1378)	Normal (n = 166)	HTN (n = 386)	P	Optimal (n = 634)	Normal (n = 140)	HTN (n = 270)	P
FBS	89.88 ± 23.87	99.50 ±33.40	104.03 ± 36.94	< 0.001	97.97 ± 31.56	106.71 ± 45.54	107.42 ± 43.51	0.002
Cholesterol	175.63 ± 38.24	187.27 ± 39.46	193.52 ± 40.10	< 0.001	176.53 ± 35.97	184.79 ± 40.57	190.41 ± 41.61	< 0.001
TG	123.69 ± 100.51	142.14 ± 79.71	160.34 ± 74.92	< 0.001	148.06 ± 85.10	171.05 ± 100.01	173.56 ± 92.76	0.002
LDL	107.43 ± 26.65	113.11 ± 26.48	114.78 ± 29.88	< 0.001	104.79 ± 26.91	108.00 ± 26.53	110.22 ± 33.79	0.040
HDL	43.53 ± 10.47	47.04 ± 11.64	46.65 ± 12.25	< 0.001	42.38 ± 9.99	44.66 ± 10.13	45.40 ± 13.01	0.001
Serum Cr	1.03 ± 0.21	1.07 ± 0.20	1.10 ± 137.00	< 0.001	1.21 ± 0.22	1.27 ± 0.31	1.25 ± 0.28	0.400
Urine Cr	131.91 ± 71.10	114.81 ± 73.58	108.36 ± 56.07	< 0.001	150.19 ± 75.83	134.37 ± 81.39	129.85 ± 65.28	0.010
Hb	13.32 ± 1.55	13.57 ± 1.57	13.38 ± 1.59	0.310	15.19 ± 1.86	14.79 ± 1.89	14.93 ± 1.55	0.370

Based on Kruskal–Wallis test; Hb: Hemoglobin; Cr: Creatinine; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; BP: Blood pressure; HTN: Hypertension; FBS: Fasting blood sugar; TG: Triglyceride

Table 4. Binary logistic regression (enter model) of the predictors of hypertension (HTN) in this population

Variables	B	SE	Wald	df	Significant	OR	95% CI for OR	
							Lower	Upper
Gender (Ref: F)	0.329	0.142	5.377	1	0.020	1.390	1.052	1.836
Educational level (Ref:Illitrate)			8.686	5	0.122			
Elementary	−0.283	0.177	2.548	1	0.110	0.753	0.532	1.067
Not completed high school	−0.614	0.232	7.038	1	0.008	0.541	0.344	0.852
High school diploma	−0.566	0.234	5.828	1	0.016	0.568	0.359	0.899
College diploma	−0.392	0.353	1.232	1	0.267	0.676	0.338	1.350
License and higher degree	−0.459	0.334	1.882	1	0.170	0.632	0.328	1.217
Marital status (Ref:Single)			4.754	3	0.191			
Married	−0.432	0.369	1.368	1	0.242	0.649	0.315	1.339
Widow	−0.822	0.455	3.261	1	0.071	0.439	0.180	1.073
Divorced	−1.818	1.307	1.933	1	0.164	0.162	0.013	2.105
Ethnicity (Ref: Fars)			5.599	6	0.470			
TURK	0.054	0.265	0.041	1	0.840	1.055	0.628	1.773
Kurd	−0.793	0.484	2.682	1	0.101	0.452	0.175	1.169
Baloch	−18.878	40192.970	< 0.001	1	1.000	< 0.001	< 0.001	< 0.001
Lurs	2.630	1.781	2.181	1	0.140	13.868	0.423	454.593
Turkmens	−18.588	40192.970	0.000	1	1.000	< 0.001	< 0.001	< 0.001
Afghani	0.243	0.311	0.609	1	0.435	1.275	0.693	2.348
Family income	0.000	0.000	0.028	1	0.866	1.000	1.000	1.000
Smoking (Ref:No)	0.071	0.215	0.109	1	0.741	1.074	0.705	1.635
Drug abuse (Ref:No)	0.630	0.401	2.470	1	0.116	1.877	0.856	4.116
Sedantary behavior (Ref: No)	−0.197	0.128	2.383	1	0.123	0.821	0.640	1.055
Obesity	0.090	0.014	44.242	1	< 0.001	1.095	1.066	1.124
Age	0.069	0.006	137.917	1	< 0.001	1.071	1.059	1.084
Constant	−6.278	0.566	122.851	1	< 0.001	0.002		

For doing binary logistic regression, we defined two groups; hypertensive (HTN mild, moderate, severe and very severe) and normal (optimal, normal, high normal). Hosmer and Leme show test: chi-square: 11.905, P = 0.15. HTN: Hypertension; Df: Degrees of freedom; 95% Cl: Confidence interval; SE: Standard error; OR: Odds ratio

The difference in the results of that study compared to the current one may be due to the different populations and dissimilar lifestyles in Iranian and Spanish culture and the differences in the age range of the participants in the studies.

Previous research indicated that the prevalence of HTN was strongly highly associated with social class, as measured by education, occupation or income.[30] However, in this study, neither educational level nor family income was a meaningful predictor of HTN. In common with the findings of the current study, a study conducted in China also found no association between education and BP.[31] In another study in Iran, it was found significant relationships between HTN and education.[32]

The results in this study should be interpreted with caution, as the study contains a number of limitations. First, the design of the study was cross-sectional, which could result in reverse causality. Second, the sample population consisted of urban citizens. Third, we did not assess health care access. Further studies should consider the roles of diet and health care access as risk factors for high BP and HTN.

Conclusion

We hope that this study facilitates a better understanding of the relationship between anthropometric indicators and demographic factors and HTN. Continued and accelerating urbanization are likely to increase the prevalence of HTN.[33] Urgent preventive interventions on a national scale are needed to target HTN, which is highly prevalent. Given the close relationship between obesity and various diseases, including HTN, practical solutions, including lifestyle interventions, need to be developed.

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Conflict of Interests

Authors have no conflict of interests.

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Comparative effects of carbohydrate versus fat restriction on metabolic profiles, biomarkers of inflammation and oxidative stress in overweight patients with Type 2 diabetic and coronary heart disease: A randomized clinical trial

Fariba Raygan[1], Fereshteh Bahmani[2], Ebrahim Kouchaki[3], Esmat Aghadavod[2], Sahar Sharifi[2], Elmira Akbari[4], Akbar Heidari[2], Zatollah Asemi[2]

Original Article

Abstract

BACKGROUND: This study was conducted to establish the comparative effects of carbohydrate versus fat restriction on metabolic indices in Type 2 diabetic (T2D) patients with coronary heart disease (CHD).

METHODS: This randomized, clinical trial was done among 56 overweight persons with T2D and CHD aged 40-85 years old. The patients were randomly allocated to take either a high-carbohydrate (HC) diet (60-65% carbohydrates and 20-25% fats) (n = 28) or a restricted carbohydrate (RC) diet (43-49% carbohydrate and 36-40% fats) (n = 28) for 8 weeks to determine metabolic status.

RESULTS: After 8 weeks of treatment, RC diet decreased fasting plasma glucose (FPG) (−11.5 ± 28.3 vs. +7.0 ± 26.9 mg/dl, P = 0.010) and high-sensitivity C-reactive protein (hs-CRP) (−564.3 ± 1280.1 vs. +286.1 ± 1789.2 ng/ml, P = 0.040) compared with a HC diet. Moreover, compared with a HC diet, RC diet increased total antioxidant capacity (TAC) (+274.8 ± 111.5 vs. +20.2 ± 82.5 mmol/l, P < 0.001) and glutathione (GSH) levels (+51.6 ± 111.5 vs. −32.6 ± 88.5 µmol/l, P = 0.003). No significant alterations between the two groups were found in terms of their effect on other metabolic profiles.

CONCLUSION: RC diet in overweight T2D with CHD had beneficial effects on FPG, hs-CRP, TAC, and GSH values.

Keywords: Carbohydrate Restriction, Metabolic Status, Type 2 Diabetes Mellitus, Coronary Heart Disease, Obesity

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Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease and is estimated to reach 439 million persons worldwide in 2030.[1] Prior studies have exhibited that the prevalence of obesity and T2DM in people with coronary heart disease (CHD) exceeds that of the general population.[2] Different factors have been involved in the progression of T2DM and CHD such as little glycemic control and dyslipidemia.[3,4] In addition, low-grade inflammation resulting from free radicals and reactive oxygen species (ROS) may help to the expansion of metabolic complexity in diabetic vascular disease.[5-7]

However, it remains unknown whether favorable effects of restricted carbohydrate (RC) diets are mediated through changes in metabolic profiles, the inflammatory process, and endothelial dysfunction. Some studies have revealed that carbohydrate limitation has a more favorable effect on aspects of the metabolic syndrome (MeTs) than a low-fat diet.[8,9] In a study by Parillo et al.[10] was observed that high-monounsaturated-fat/low-carbohydrate diet compared with low-monounsaturated-fat/high-carbohydrate (HC) diet decreased postprandial glucose, insulin and triglycerides values among patients with T2DM for 15 days, but unchanged other lipid profiles. Likewise, low-carbohydrate (20%) than low-fat diet significantly improved the inflammatory state in T2DM after 6 months.[11] However, in a study, a HC diet significantly increased insulin and triglycerides concentrations by 8% and 13%, respectively, and lowered high-density lipoprotein (HDL)-cholesterol

1- Department of Cardiology, School of Medicine, Kashan University of Medical Sciences, Kashan, Iran
2- Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran
3- Physiology Research Center AND Department of Neurology, School of Medicine, Kashan University of Medical Sciences, Kashan, Iran
4- Physiology Research Center, Kashan University of Medical Sciences, Kashan, Iran
Correspondence to: Zatollah Asemi, Email: asemi_r@yahoo.com

by 6% compared with the low-carbohydrate diet.[12] In addition, few studies have also shown that acute ingestion of carbohydrate clearly induces ROS, inflammation and oxidative stress.[13,14]

To our knowledge, information on the effects of RC versus HC intake on metabolic status in overweight T2DM persons with CHD is limited. This research, therefore, was done to establish the effects of RC intake and its replacement with unsaturated fats on metabolic parameters in these persons.

Materials and Methods

This treatment was a randomized clinical trial, which was done at the Cardiology Clinic of KUMS, Kashan, Iran, between November 2015 and January 2016. At baseline, people were matched according to age, body mass index (BMI), gender, and the dosage and kind of drugs. Since all people were overweight, both diets were designed to be calorie limited (350-700 kcal less than the computed energy). The macronutrient composition of the HC diet was equal with Iranian usual diets.[15] Indeed, in the RC diet, 15-20% of the energy from carbohydrates was replaced by nonhydrogenated vegetable oils. The protein content of both diets was 14-17% of the total energy. To increase compliance, persons were given a portion list of food groups and solely educated about the goals of each phase as well as the portion list. To take nutrient intakes of people according to 3-day food records, we applied Nutritionist IV software (First Databank, San Bruno, CA). Physical activity was described as metabolic equivalents (METs).[16]

In total, 56 patients were randomly divided into two groups: Group A (HC diet; 15 females and 13 males: n = 28) received 60-65% carbohydrates and 20-25% fats and Group B (RC diet; 15 females and 13 males: n = 28) received 43-49% carbohydrate and 36-40% fats for 8 weeks. Inclusion criteria were overweight patients aged 40-85 years old, BMI ≥ 25, having T2DM and CHD. Diagnosis of T2D and CHD was done based on the American Diabetes Association[17] and the American Heart Association,[18] respectively. Exclusion criteria were consuming antiobesity medications within the last 3 months, having an acute myocardial infarction and/or a cardiac surgery within the last 3 months and a major renal or liver failure.

This intervention was confirmed by the Research Ethics Committee of KUMS (reference number IR.Kaums.REC.1394.96) and was registered in the Iranian registry of clinical trials (http://www.irct.ir: IRCT201601025623N61).

Weight and height were quantified at week 0 and week 8 at the cardiology clinic.

About 10 ml fasting blood samples were collected at week 0 and week 8. Fasting plasma glucose (FPG) and lipid parameters were established with enzymatic kits (Pars Azmun, Tehran, Iran). Insulin values were quantified using enzyme-linked immunosorbent assay (ELISA) kit (DiaMetra, Milano, Italy). Indices of insulin metabolism were calculated according to the existing formulas.[19] High-sensitivity C-reactive protein (hs-CRP) was assessed by the commercial ELISA kit. The nitric oxide (NO) using Griess method,[20] total antioxidant capacity (TAC) by Benzie and Strain[21] method, total glutathione (GSH) using the method of Beutler and Gelbart[22] and malondialdehyde (MDA) were determined by spectrophotometric method.[23]

Based on a prior study,[24] we used 2.5 as standard deviation (SD) and 2.1 as the change in mean (d) of homeostatic model assessment insulin resistance (HOMA-IR). Therefore, we needed 24 persons in each group and assuming 4 dropouts in each group; the final sample size was reached to be 28 people.

To establish the normal distribution of indices, the Kolmogorov–Smirnov was utilized. Results of normally distributed markers as mean ± SDs and non-normally distributed markers as median (Q1, Q3) were reported. The intention-to-treat (ITT) analysis of the primary study endpoint was applied for all of the randomly allocated participants with method of the last-observation-carried-forward method.[25] To establish within-group differences (pre- and post-treatment), we used paired-samples t-tests. Pearson chi-square test was used for comparison of categorical markers. To determine the effects of RC diet intake on metabolic parameters, we applied independent samples Student's t-test. To assess the effects of some confounders, we adjusted all analyses using ANCOVA test.

Results

In the RC group, 4 people and in the HC group, 4 people were withdrawn (Figure 1). However, all 56 people were contained in the final analysis using ITT principle.

Mean age, familial history, height, and weight, BMI, and METs at week 0 and week 8 were not alteration between the two groups (Table 1).

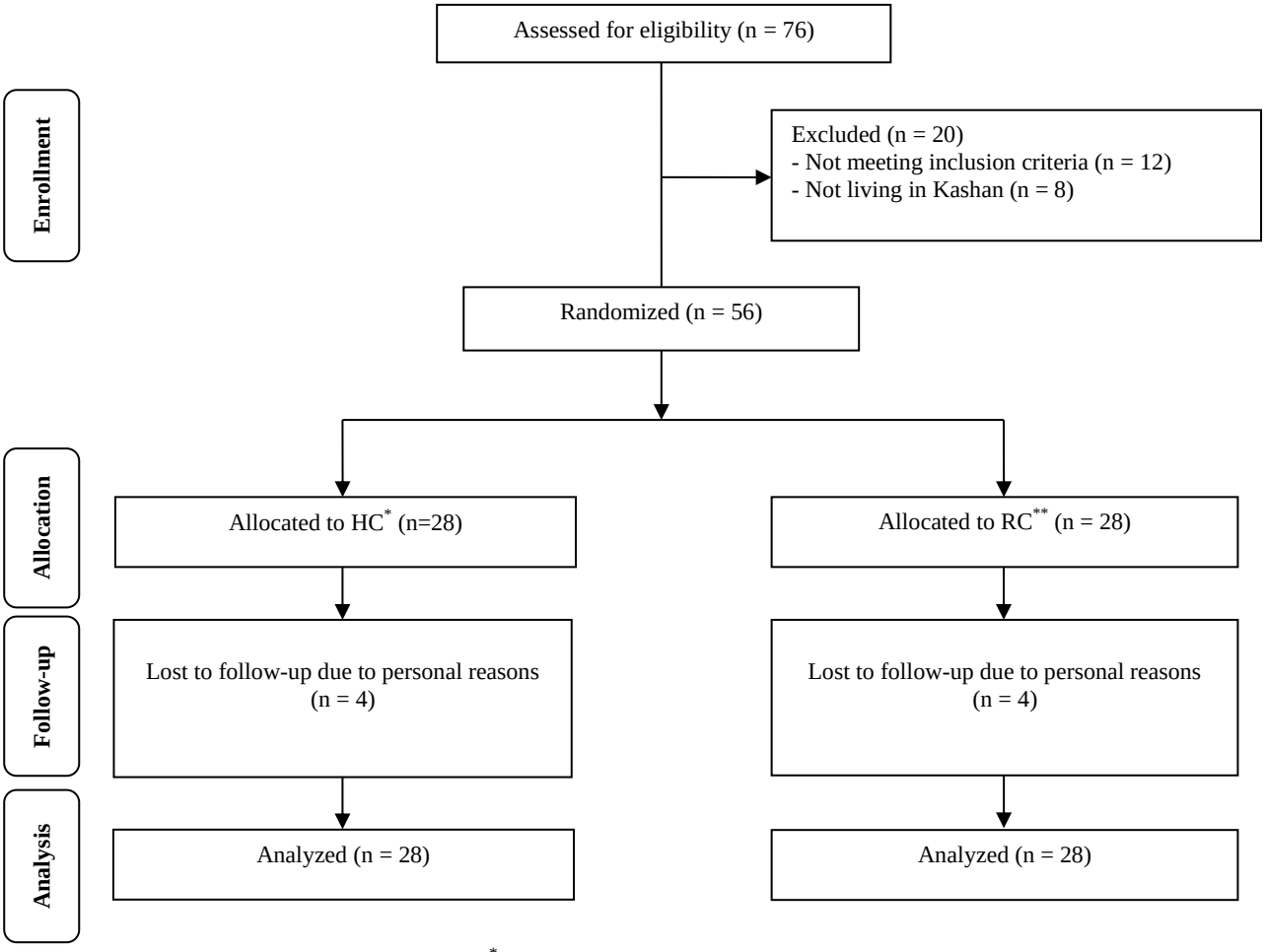

Figure 1. Summary of patient flow diagram. * High-carbohydrate diet: Energy-restricted diet that contained 60-65% of energy from carbohydrates, 20-25% from fats, and 14-18% from proteins. ** Restricted carbohydrate diet: Energy-restricted diet that contained 43-49% of energy from carbohydrates, 36-40% from fats, and 14-18% from proteins
HC: High-carbohydrate; RC: Restricted carbohydrate

Based on the 3-day records, no significant alteration was seen between the two groups in terms of macro- and micronutrients (Table 2).

RC diet decreased FPG (−11.5 ± 28.3 vs. +7.0 ± 26.9 mg/dl, P = 0.010) and hs-CRP (−564.3 ± 1280.1 vs. +286.1 ± 1789.2 ng/ml, P = 0.040) compared with a HC diet (Table 3). In addition, compared with a HC diet, RC diet increased TAC (+274.8 ± 111.5 vs. +20.2 ± 82.5 mmol/l, P < 0.001) and GSH levels (+51.6 ± 111.5 vs. −32.6 ± 88.5 µmol/l, P = 0.003). Within-group changes revealed a significant decrease of FPG (P = 0.040), serum hs-CRP (P = 0.020), and a significant increase of plasma TAC (P < 0.001), and GSH levels (P = 0.020) in the RC diet.

When we controlled the analysis for baseline values of biochemical indicators, age, BMI at week 0, METs change and familial history, findings unaltered (Table 4).

Discussion

We illustrated that RC diet for 8 weeks among overweight diabetic persons with CHD had useful effects on FPG, hs-CRP, plasma TAC, and GSH values; however, it did not influence other metabolic profiles. We did not randomize participants based on their plasma MDA levels because all participants were T2DM and CHD. Random assignment to two groups was done after stratification according to age, BMI, gender, and the dosage and kind of medications and random assignment were done by the use of computer-generated random numbers.

T2DM patients are susceptible to metabolic complications.[26,27] We found that RC diet compared with HC diet in overweight persons with T2DM and CHD for 8 weeks decreased FPG levels, but unaltered insulin metabolism and lipid profiles.

Table 1. General characteristics of study participants

Characteristics	HC diet* (n = 28)	RC diet** (n = 28)	P***
Familial history (%)	10 (35.7)	10 (35.7)	> 0.999†
Smoking (%)	2 (7.1)	2 (7.1)	> 0.999†
Aspirin 80 mg (%)	28 (100)	28 (100)	> 0.999†
Statin (%)	28 (100)	28 (100)	> 0.999†
Insulin therapy (%)	6 (21.4)	5 (17.9)	0.730†
Antidiabetic drugs (%)			
Monotherpy	16 (72.7)	16 (69.6)	
Combination therapy	6 (27.3)	7 (30.4)	0.810†
Hypertension (%)	19 (67.9)	20 (71.4)	0.770†
ACEI/ARB drugs (%)	28 (100)	28 (100)	> 0.999†
Blocker drugs (%)			
β-blocker	26 (92.9)	27 (96.4)	
Calcium channel blocker	2 (7.1)	1 (3.6)	0.550†
Duration of DM (year)	6.3 ± 5.0	6.6 ± 4.8	0.850
Duration of CHD (year)	8.2 ± 4.7	8.8 ± 4.0	0.620
HbA1c (mmol/mol)	56.5 ± 4.7	54.9 ± 6.9	0.300
SBP at study baseline (mmHg)	135.7 ± 7.9	133.2 ± 13.3	0.370
SBP at end-of-trial (mmHg)	136.2 ± 8.0	133.5 ± 13.8	0.360
SBP change (mmHg)	0.5 ± 1.4	0.3 ± 1.1	0.680
DBP at study baseline (mmHg)	84.1 ± 8.4	85.2 ± 8.0	0.620
DBP at end-of-trial (mmHg)	84.3 ± 8.5	85.1 ± 7.8	0.750
DBP change (mmHg)	0.2 ± 1.2	−0.1 ± 1.1	0.200
Age (year)	65.2 ± 11.6	61.1 ± 9.9	0.1500
MET-h/day change	−0.3 ± 0.8	−0.3 ± 0.9	0.850
Height (cm)	156.8 ± 15.9	157.6 ± 11.2	0.820
Weight at study baseline	79.0 ± 14.8	77.6 ± 11.7	0.690
Weight at end-of-trial	76.8 ± 14.3	75.5 ± 11.9	0.700
Weight change (kg)	−2.2 ± 2.1	−2.1 ± 1.7	0.880
BMI at study baseline	32.2 ± 4.4	31.2 ± 3.5	0.360
BMI at end-of-trial	31.3 ± 4.4	30.4 ± 3.6	0.360
BMI change (kg/m^2)	−0.9 ± 0.8	−0.9 ± 0.7	0.960
MET-h/day at study baseline	26.4 ± 2.0	27.0 ± 1.7	0.210
MET-h/day at end-of-trial	26.1 ± 2.1	26.7 ± 1.7	0.250

Data are means ± SDs. * HC diet: Energy-restricted diet that contained 60-65% of energy from carbohydrates, 20-25% from fats, and 14-18% from proteins. ** RC diet: Energy-restricted diet that contained 43-49% of energy from carbohydrates, 36-40% from fats, and 14-18% from proteins. *** Obtained from independent samples student's t-test. † Obtained from Pearson chi-square test. BMI: Body mass index; ACEI: Angiontensin converting enzymes inhibitors; ARB: Aldosterone receptor blockers; CHD: Coronary heart disease; DBP: Diastolic blood pressure; METs: Metabolic equivalents; HbA1c: Hemoglobin A1c; DM: Diabetes mellitus; SBP: Systolic blood pressure; SD: Standard deviation; HC: High-carbohydrate; RC: Restricted carbohydrate

In a study by Ballard et al.[28] was seen that carbohydrate limited diets for 6 weeks decreased insulin, HOMA-IR and triglycerides values, but unchanged FPG and other lipid fractions. A meta-analysis study has shown that changes in values of hemoglobin A1c, FPG, total- and low-density lipoprotein-cholesterol did not differ significantly between the HC and low-carbohydrate groups.[12] However, the HC diet significantly increased insulin and triglycerides concentrations by 8% and 13%, respectively, and lowered HDL-cholesterol by 6% compared with the low-carbohydrate diet.[12] A significant improvement of lipid profiles was seen following the consumption of a carbohydrate-restricted diet among patients with MetS.[29]

This study demonstrated that compared with an HC diet, adherence to RC diet for 8 weeks decreased serum hs-CRP and increased plasma TAC and GSH concentrations, while it did not affect plasma NO and MDA in overweight diabetic patients with CHD. In line with our study, in a parallel randomized clinical trial, Forsythe et al.[30] demonstrated that a very-low-carbohydrate diet (12% of energy from carbohydrate) led to a greater reduction in some inflammatory markers compared to a low-fat diet among overweight men and women with atherogenic dyslipidemia. In addition, in another study among insulin-resistant patients, moderate carbohydrate restriction for 12 weeks resulted in lower inflammatory marker concentrations compared to fat restriction.[31]

Table 2. Dietary intakes of study participants throughout the study

Dietary intakes	HC diet* (n = 28)	RC diet** (n = 28)	P***
Energy (kcal/day)	1679.0 ± 78.0	1652.0 ± 72.0	0.200
Carbohydrates (g/day)	265.7 ± 16.9	200.0 ± 9.2	< 0.001
MUFAs (g/day)	15.9 ± 0.1	26.7 ± 1.3	< 0.001
Fat (g/day)	46.5 (46.5, 46.9)	73.0 (70.1, 74.6)	< 0.001†
SFAs (g/day)	16.6 (16.6, 16.9)	23.1 (22.0, 23.5)	< 0.001†
PUFAs (g/day)	9.8 (9.7, 9.8)	18.6 (17.2, 18.7)	< 0.001†
Protein (g/day)	57.1 (57.1, 62.1)	60.9 (57.2, 62.0)	0.100†
Cholesterol (mg/day)	111.3 (0.8)	133.2 (8.5)	< 0.001†

Values are means ± SDs for normally distributed variables and median (Q1,Q3) for non-normally distributed variables. * HC diet: Energy-restricted diet that contained 60-65% of energy from carbohydrates, 20-25% from fats, and 14-18% from proteins. ** RC diet: Energy-restricted diet that contained 43-49% of energy from carbohydrates, 36-40% from fats, and 14-18% from proteins. *** Obtained from independent samples student's t-test. † Obtained from Mann-Whitney test. MUFAs: Monounsaturated fatty acids; PUFAs: Polyunsaturated fatty acids; SFAs: Saturated fatty acids; SD: Standard deviation; HC: High-carbohydrate; RC: Restricted carbohydrate

Barbosa et al.[32] also indicated that low energy and carbohydrate intake for 2 months were associated with higher TAC levels in apparently healthy adults. Moreover, the energy intake limitation by 2000 kJ among obese persons decreased oxidative stress.[33]

Table 3. Effect of a restricted carbohydrate (RC) diet on metabolic profiles, biomarkers of inflammation and oxidative stress at baseline and 8 weeks after the intervention in patients with overweight type 2 diabetes mellitus (T2DM) and coronary heart disease (CHD)

Variables	HC diet* (n = 28)				RC diet** (n = 28)				P†
	Baseline	End-of-trial	Change	P***	Baseline	End-of-trial	Change	P***	
FPG (mg/dl)	124.1 ± 41.9	131.1 ± 48.9	7.0 ± 26.9	0.170	134.3 ± 54.9	122.7 ± 52.6	−11.5 ± 28.3	0.040	0.010
Insulin (µIU/ml)	15.1 ± 7.3	13.9 ± 5.9	−1.2 ± 4.5	0.160	12.5 ± 4.8	11.3 ± 4.9	−1.2 ± 3.0	0.050	0.930
HOMA-IR	4.5 ± 2.1	4.2 ± 2.1	−0.3 ± 1.2	0.180	4.1 ± 2.0	3.7 ± 2.0	−0.4 ± 1.0	0.050	0.800
HOMA-B	45.1 ± 30.0	40.9 ± 24.1	−4.2 ± 16.4	0.180	33.8 ± 17.9	30.4 ± 16.9	−3.4 ± 10.1	0.080	0.820
QUICKI	0.31 ± 0.02	0.31 ± 0.02	0.001 ± 0.01	0.370	0.31 ± 0.02	0.32 ± 0.02	0.01 ± 0.01	0.120	0.430
Triglycerides (mg/dl)	130.5 ± 42.6	144.7 ± 82.7	14.2 ± 81.3	0.360	119.8 ± 45.5	126.5 ± 44.0	6.7 ± 31.8	0.270	0.650
VLDL−cholesterol (mg/dl)	26.1 ± 8.5	28.9 ± 16.5	2.8 ± 16.2	0.360	24.0 ± 9.1	25.3 ± 8.8	1.3 ± 9.3	0.270	0.650
Total cholesterol (mg/dl)	154.7 ± 32.4	155.1 ± 42.9	0.5 ± 28.8	0.920	145.1 ± 30.7	148.1 ± 30.8	3.0 ± 35.0	0.650	0.760
LDL-cholesterol (mg/dl)	77.5 ± 26.7	76.2 ± 36.4	−1.2 ± 27.0	0.810	83.4 ± 28.1	84.0 ± 25.4	0.7 ± 31.2	0.910	0.810
HDL-cholesterol (mg/dl)	51.0 ± 10.0	49.9 ± 9.3	−1.1 ± 7.6	0.440	37.8 ± 7.5	38.8 ± 7.0	1.0 ± 7.2	0.450	0.280
Total-/HDL-cholesterol	3.1 ± 0.8	3.1 ± 0.7	0.0 ± 0.7	0.760	3.9 ± 1.0	3.9 ± 0.8	0.0 ± 0.8	0.640	0.580
hs-CRP (ng/ml)	2348.0 ± 1925.3	2634.1 ± 1897.0	286.1 ± 1789.2	0.400	2346.4 ± 1730.7	1782.1 ± 1254.5	−564.3 ± 1280.1	0.020	0.040
NO (µmol/l)	42.1 ± 9.9	45.0 ± 8.8	2.9 ± 9.2	0.100	55.7 ± 6.0	57.0 ± 7.3	1.3 ± 4.8	0.150	0.420
TAC (mmol/l)	862.0 ± 169.4	882.2 ± 178.4	20.2 ± 82.5	0.200	943.2 ± 154.3	1218.0 ± 160.9	274.8 ± 111.5	< 0.001	< 0.001
GSH (µmol/l)	403.5 ± 100.6	370.9 ± 57.8	−32.6 ± 88.5	0.060	419.0 ± 105.5	470.6 ± 90.9	51.6 ± 111.5	0.020	0.003
MDA (µmol/l)	3.1 ± 0.7	3.1 ± 0.5	0.0 ± 0.7	0.920	2.5 ± 0.6	2.7 ± 0.4	0.2 ± 0.4	0.020	0.240

All values are means ± SDs. * HC diet: Energy-restricted diet that contained 60-65% of energy from carbohydrates, 20-25% from fats, and 14-18% from proteins. ** RC diet: Energy-restricted diet that contained 43-49% of energy from carbohydrates, 36-40% from fats, and 14-18% from proteins. *** P values represent paired-samples t-test. † P values represent independent samples student's t-test. CHD: Coronary heart disease; FPG: Fasting plasma glucose; GSH: Total glutathione; HOMA-IR: Homeostasis model of assessment-estimated insulin resistance; HOMA-B: Homeostasis model of assessment-estimated B cell function; hs-CRP: High-sensitivity C-reactive protein; RC: Moderately restricted carbohydrate; MDA: Malondialdehyde; NO: Nitric oxide; QUICKI: Quantitative insulin sensitivity check index; TAC: Total antioxidant capacity; T2DM: Type 2 diabetes mellitus; SD: Standard deviation; HC: High-carbohydrate; RC: Restricted carbohydrate; VLDL: Very-low-density lipoprotein; LDL: Low-density lipoprotein; HDL: High-density lipoprotein

Table 4. Adjusted changes in metabolic variables in patients with overweight type 2 diabetes mellitus (T2DM) and coronary heart disease (CHD)

Variables	HC diet* (n = 28)	RC diet** (n = 28)	P***
FPG (mg/dl)	6.900 ± 5.100	−11.300 ± 5.100	0.010
Insulin (µIU/ml)	−0.600 ± 0.700	−1.700 ± 0.700	0.250
HOMA-IR	−0.200 ± 0.200	−0.500 ± 0.200	0.350
HOMA-B	−2.100 ± 2.200	−5.500 ± 2.200	0.310
QUICKI	0.004 ± 0.002	0.006 ± 0.002	0.060
Triglycerides (mg/dl)	14.000 ± 11.400	6.900 ± 11.400	0.660
VLDL-cholesterol (mg/dl)	2.800 ± 2.300	1.400 ± 2.300	0.660
Total cholesterol (mg/dl)	2.800 ± 6.000	0.700 ± 6.000	0.800
LDL-cholesterol (mg/dl)	−1.300 ± 5.200	0.700 ± 5.200	0.770
HDL-cholesterol (mg/dl)	1.600 ± 1.400	−1.700 ± 1.400	0.150
Total-/HDL-cholesterol ratio	−0.100 ± 0.100	0.100 ± 0.100	0.210
hs-CRP (ng/ml)	232.100 ± 260.000	−514.300 ± 260.000	0.040
NO (µmol/l)	0.300 ± 1.500	3.900 ± 1.500	0.140
TAC (mmol/l)	9.400 ± 18.100	285.600 ± 18.100	< 0.001
GSH (µmol/l)	−41.300 ± 13.400	60.300 ± 13.400	< 0.001
MDA (µmol/l)	0.200 ± 0.100	0.003 ± 0.100	0.130

All values are means ± standard error. Values are adjusted for baseline values, age, BMI at baseline, METs change and familial history. * HC diet: Energy-restricted diet that contained 60-65% of energy from carbohydrates, 20-25% from fats, and 14-18% from proteins. ** RC diet: Energy-restricted diet that contained 43-49% of energy from carbohydrates, 36-40% from fats, and 14-18% from proteins. *** Obtained from ANCOVA. FPG: Fasting plasma glucose; GSH: Total glutathione; HOMA-IR: Homeostasis model of assessment-estimated insulin resistance; HOMA-B: Homeostasis model of assessment- estimated B-cell function; hs-CRP: High-sensitivity C-reactive protein; MDA: Malondialdehyde; METs: Metabolic equivalents; NO: Nitric oxide; QUICKI: Quantitative insulin sensitivity check index; TAC: Total antioxidant capacity; HC: High-carbohydrate; VLDL: Very-low-density lipoprotein; LDL: Low-density lipoprotein; HDL: High-density lipoprotein

However, consumption of an RC diet compared with an HC diet did not affect any significant effect on inflammatory biomarkers among women with MetS for 6 weeks.[15] In another study by Rankin and Turpyn.,[34] low carbohydrate diet compared with HC diet increased CRP during weight loss among overweight women for 4 weeks. The previous studies have shown that acute ingestion of carbohydrate clearly induces ROS, inflammation and oxidative stress.[13,14] Decreased total saturated fatty acids, palmitoleic acid levels, down-regulation of nuclear factor-kappa B and cyclooxygenase-2 expression following the consumption of an RC diet may result in its anti-inflammatory and anti-oxidative effects.[30,35] It must be considered that consumption of the MRC diet significantly decreased serum hs-CRP (564.3 ng/ml), and increased plasma TAC (274.8 mmol/l), and GSH (51.6 µmol/l) concentrations in this study.

One strength of our study was an assessment of metabolic status and its randomized design. One of our limitations was no examine the compliance to the RC and HC eating plan. In addition, the current 8-week diet intervention in a group of among 56 overweight diabetic patients with CHD could be viewed as short in duration and small in sample size in comparison to larger clinical trials. In our study, persons were overweight patients with T2D and CHD aged 40-85 years old. We believe that adherence to the same diets in different age ranges may have different outcomes. Therefore, this should be taken into account in the explanation of our findings.

Conclusion

RC diet for 8 weeks among overweight diabetic patients with CHD had useful effects on some metabolic indices. This offers an RC diet with high unsaturated and low saturated fat may allow the advantageous remedial potential for overweight persons with T2DM and CHD handling.

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Conflict of Interests

Authors have no conflict of interests.

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The outbreak fingolimod cardiovascular side effects in relapsing-remitting multiple sclerosis patient: A longitudinal study in an Iranian population

Morteza Abdar[(1)], Payam Ebrahimifar[(2)], Masoud Etemadifar[(3)]

Original Article

Abstract

BACKGROUND: Fingolimod (FTY-720) has shown efficacy in relapsing multiple sclerosis (MS), while some side effects of this drug have been recognized that the most important is cardiovascular side effects. The aim of this study was to evaluate the cardiovascular side effects of FTY-720. However, the effect of fingolimod on cardiac has not been well recognized. This study was designed to evaluate the cardiovascular side effects of fingolimod in relapsing-remitting multiple sclerosis (RRMS) patient in an Iranian population.

METHODS: This prospective clinical trial study was performed on 200 RRMS patients. The patients received a single daily oral dose of fingolimod 0.5 mg. During the first 6 hours after the first fingolimod dose, the patients' vital signs and electrocardiographic traces were continuously monitored. Moreover, the patients followed up over 6 months after receiving fingolimod.

RESULTS: The results showed that pulse rate ($P < 0.001$), systolic blood pressure (BP) ($P < 0.001$), and diastolic BP ($P < 0.001$) were decreased significantly during 6 hours after receiving the first dose of fingolimod. The most reduction in vital sign was observed in 3 hours. Arrhythmia, bradycardia, and dizziness were the other complications of fingolimod, which were detected in our study.

CONCLUSION: All the side effects such as hypotension and bradycardia were happened in first 3 hours after receiving the fingolimod. Indeed, we advise clinicians to monitor the patients for first 6 hours after initiation of fingolimod to decrease worse side effects.

Keywords: Fingolimod, Cardiovascular, Side Effect, Multiple Sclerosis

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Introduction

Multiple sclerosis (MS) is considered as a chronic autoimmune disease with increasing prevalence and incidence,[1,2] which led to a significant expansion in the range of therapeutic options.[3] Therapeutic strategies direct immune modulation and control of inflammatory processes. First-line drugs for MS are interferon beta-1 and glatiramer acetate which have moderate efficacy and frequent side-effects. These features of first line drugs limited long-term adherence consequently restrict their efficacy compared with second-line therapies as fingolimod and natalizumab.[4,5]

Fingolimod (also known as FTY-720) has shown efficacy in relapsing MS,[6,7] which is an oral sphingosine-1-phosphate (S1P) receptor modulator that blocks lymph node egress of lymphocytes expressing the homing receptor CC-chemokine receptor 7 that may include autoreactive T and B-cell subsets, and patients become gradually lymphopenic after a few days of treatment.[8]

However, fingolimod has some side effects such as affecting on cardiac which is associated with a decrease in heart rate (HR) and slowing of atrioventricular (AV) conduction. This is a recognized pharmacological effect of fingolimod, mediated by modulation of S1PR subtype 1 (S1P1) on atrial myocytes, which is similar to vagal stimulation. The effect is typically transient, owing to the internalization/desensitization of S1P1,[9] leading to functional antagonism rather than agonism. However, the effect of fingolimod on cardiac has not been well recognized. Therefore, this study was designed to evaluate cardiovascular side effects of fingolimod in relapsing-remitting multiple sclerosis (RRMS) patient.

1- Professor, Department of Cardiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
2- Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
3- Professor, Department of Neurology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Payam Ebrahimifar, Email: payame1383@yahoo.com

Materials and Methods

This prospective clinical trial study was conducted in Neurology Department of Isfahan Alzahra Hospital, Center of Iran from August 2014 to December 2015. Inclusion criteria consisted of patient referred to neurology department of Alzahra Hospital with a diagnosis of RRMS with age > 18-year-old, expanded disability status scale (EDSS) between 0.5 and 6.5 and having indication to receive fingolimod. Exclusion criteria consisted of patients with other immune system diseases in addition to MS, concurrent malignancy, active infection, use of any drug potentially affecting cardiac rhythm or function within the 4 weeks preceding study entry, uncontrolled diabetes, macular edema and advanced diabetic retinopathy, previous cardiac disease or abnormal electrocardiographic (ECG) findings, having contraindications for receiving fingolimod [(1) History of myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack in the last 6 months, (2) heart failure functional Class 3 or 4, (3) Mobitz Type II-3rd degree atrioventricular block (AVB)–sick sinus syndrome, (4) baseline QTc interval ≥ 500 ms, and (5) taking Class Ia or Class III antiarrhythmic drugs].

A total of 215 patients with an RRMS, who had been diagnosed by neurologist and based on inclusion and exclusion criteria were included in the study. We consecutively enrolled patients with RRMS whose neurologists had advised them to start treatment with a single daily oral dose of fingolimod 0.5 mg. 15 patients excluded due to having contraindications for receiving fingolimod (two patients), uncontrolled diabetes (four patients), loss to follow-up (four patients), other immune system diseases (one patient), abnormal ECG (one patient), and previous cardiac disease (three patients).

Finally, 200 patients completed the study. The study received ethics approval from the Ethics Committee of Isfahan University of Medical Sciences (394, 246), and all participants gave written informed consent.

During the first 6 hours after the first fingolimod dose, the patients' vital signs and ECG traces were continuously monitored to detect any decrease in HR or the prolongation of any ECG interval; the monitoring period was extended in the case of patients who developed significant bradycardia or PQ prolongation. Patients' vital signs and ECG traces were measured each hour for 6 hours after receiving first fingolimod dose.

Since the incidence of bradycardia could make heart palpitations for patients, about feeling heart palpitations in patients were asked and recorded. According to some reports mentioned that fingolimod consumption has been associated with the development chest pain; therefore, existence of angina within 6 hours was asked from patients.

In the absence of significant changes in blood pressure (BP), pulse rate (PR) and symptoms, the subsequent doses will continue outside clinics daily. The patient was admitted to visit and receive medication monthly, and BP and HR were recorded. Due to constant changes, particularly an increase in BP may occur several months after starting medication, the patients will be re-examined at 3 and 6 months. The study flowchart is presented in figure 1.

Data were analyzed and reported only for patients who completed the trial. Statistical analysis of data was performed using SPSS software (version 22, IBM Corporation, Armonk, NY, USA) software. The analysis was performed using descriptive statistics such as mean and standard deviation and analytical statistics such as t-test and chi-square tests. Repeated measurement ANOVA was used to explore the interaction effects of time on PR, systolic blood pressure (SBP), and diastolic blood pressure (DBP). Statistical significance was set at 0.05.

Results

About 15 patients were dropped out, and finally, 200 patients completed the study. The mean age of patients were 32.19 ± 6.44 years and 147 (73.5%) patients were female. Moreover, the mean score of EDSS of patients were 2.58 ± 1.19. As seen the mean of PR before starting fingolimod for patients was 81.60 ± 7.92 per minutes. While the fingolimod was started for patients, the mean of PR decreased, which were 80.40 ± 7.56, 77.60 ± 6.34, 69.30 ± 8.62, 63.60 ± 7.27, 63.00 ± 7.35, 65.87 ± 6.21, and 69.19 ± 5.27/minutes in half, 1-6 hours after receiving fingolimod for each hour, respectively. The peak of reduction in PR was at 4 hours after receiving fingolimod. Moreover by following the patients after 3 and 6 months after receiving the first dose of fingolimod, the mean of PR was 81.34 ± 9.40 and 80.94 ± 9.37 per minutes. 1-6 hours after receiving fingolimod, patients mean of PR was altered significantly from baseline ($P < 0.001$). After 3 and 6 months follow-up, patients PR measuring revealed statistically significant difference from baseline ($P < 0.001$) (Table 1 and Figure 2).

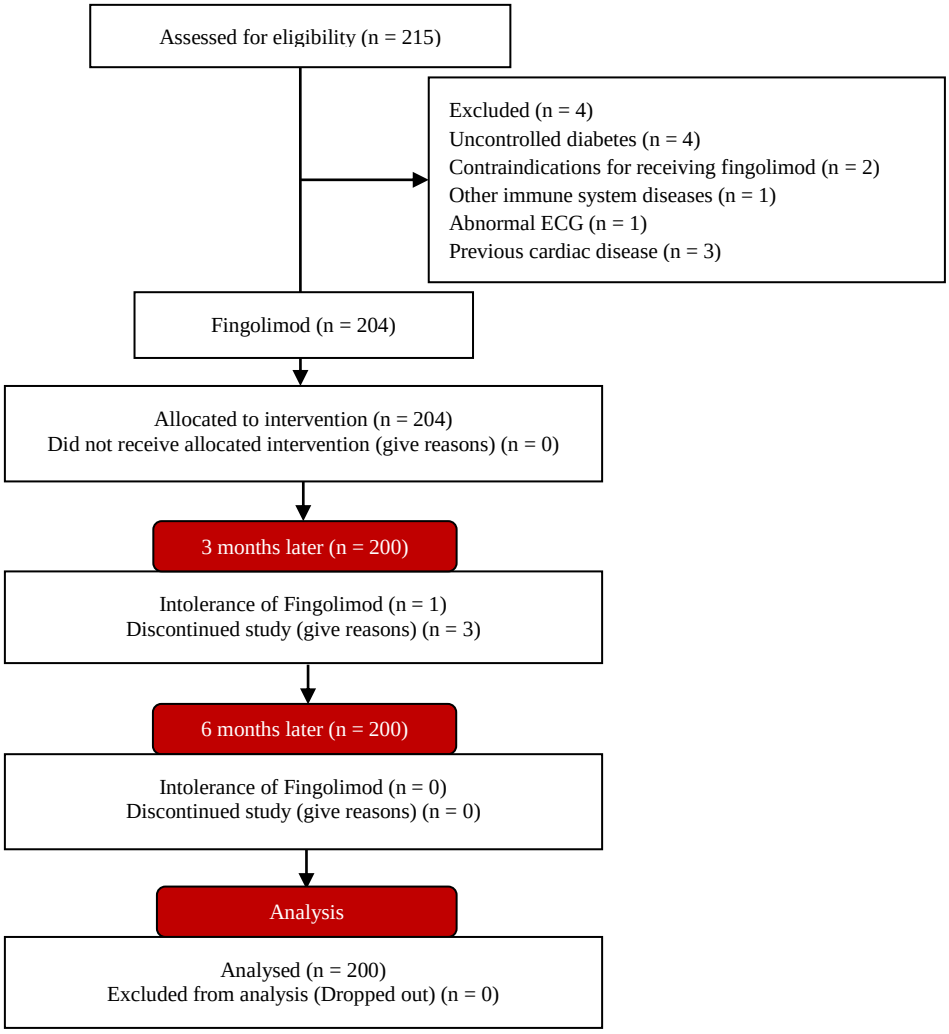

Figure 1. Study flowchart

Table 1. Pulse rate (PR) changes in patients receiving fingolimod during 6 months of follow-up confidence interval (CI 95%)

PR	Mean ± SD	P
Base	81.60 ± 7.92	< 0.001
After half hour	80.40 ± 7.56	
After 1 hour	77.63 ± 6.34	
After 2 hours	69.30 ± 8.62	
After 3 hours	63.61 ± 7.27	
After 4 hours	63.00 ± 7.35	
After 5 hours	65.87 ± 6.21	
After 6 hours	69.19 ± 5.27	
After 3 months	81.34 ± 9.40	
After 6 months	80.94 ± 9.38	

PR: Pulse rate; SD: Standard deviation

Furthermore, the mean of SBP before starting fingolimod for patients, was 120.27 ± 9.85 mmHg. While the fingolimod was started for patients, the mean of SBP decreased, which were 119.65 ± 9.59, 117.77 ± 10.58, 112.10 ± 11.44, 108.45 ± 10.89, 109.70 ± 10.24, 112.32 ± 9.63 and 114.22 ± 8.91 mmHg in half, 1-6 hours after receiving fingolimod for each hour, respectively.

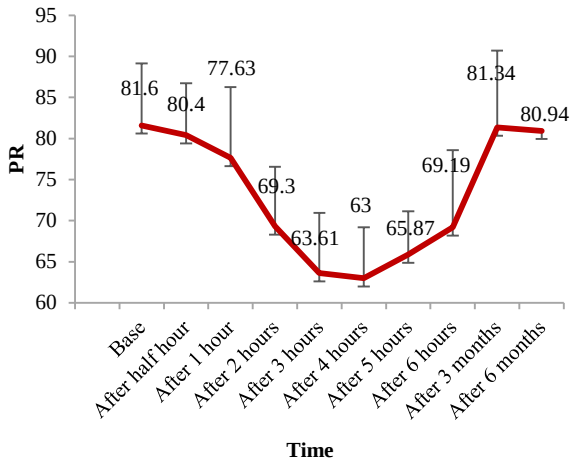

Figure 2. Pulse rate changes in patients receiving fingolimod during 6 months of follow-up
PR: Pulse rate

The peak of reduction in SBP was at 3 hours after receiving fingolimod. Moreover by following the patients after 3 and 6 months after receiving the first dose of fingolimod, the mean of SBP was 122.35 ± 9.58 and 122.72 ± 9.15 mmHg. 1-6 hours after receiving fingolimod, patients mean of SBP was altered significantly from baseline (P < 0.001). After 3 and 6 months follow-up, patients SBP measuring revealed statistically significant difference from baseline (P < 0.001) (Table 2 and Figure 3).

Table 2. Systolic blood pressure (SBP) changes in patients receiving fingolimod during 6 months of follow-up confidence interval (CI 95%)

SBP	Mean ± SD	P
Base	120.27 ± 9.85	< 0.001
After half hour	119.65 ± 9.59	
After 1 hour	117.77 ± 10.58	
After 2 hours	112.10 ± 11.44	
After 3 hours	108.45 ± 10.89	
After 4 hours	109.70 ± 10.24	
After 5 hours	112.32 ± 9.63	
After 6 hours	114.22 ± 8.91	
After 3 months	122.35 ± 9.58	
After 6 months	122.72 ± 9.15	

SBP: Systolic blood pressure; SD: Standard deviation

As obtained, the mean of DBP before starting fingolimod for patients, was 70.45 ± 6.69 mmHg. While the fingolimod was started for patients, the mean of DBP decreased, which were 69.48 ± 7.12, 68.59 ± 6.34, 65.83 ± 5.80, 64.04 ± 5.34, 64.37 ± 5.11, 65.02 ± 5.57 and 66.92 ± 4.33 mmHg in half, 1-6 hours after receiving fingolimod for each hour, respectively.

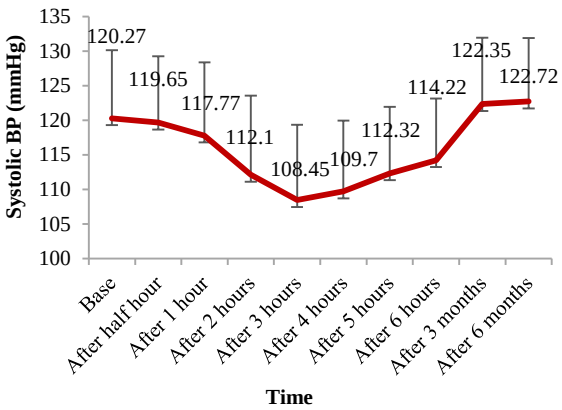

Figure 3. Systolic blood pressure changes in patients receiving fingolimod during 6 months of follow-up
BP: Blood pressure

The peak of reduction in DBP was at 3 hours after receiving fingolimod. Moreover by following the patients after 3 and 6 months after receiving the first dose of fingolimod, the mean of DBP was 70.92 ± 7.52 and 71.62 ± 7.71 mmHg (P < 0.001). 1-6 hours after receiving fingolimod, patients mean of DBP was altered significantly from baseline (P < 0.001). After 3 and 6 months follow-up, patients DBP measuring revealed statistically significant difference from baseline (P < 0.001) (Table 3 and Figure 4).

Table 3. Diastolic blood pressure (DBP) changes in patients receiving fingolimod during 6 months of follow-up confidence interval (CI 95%)

DBP	Mean ± SD	P
Base	70.45 ± 6.69	< 0.001
After half hour	69.48 ± 7.12	
After 1 hour	68.59 ± 6.34	
After 2 hours	65.83 ± 5.80	
After 3 hours	64.04 ± 5.34	
After 4 hours	64.37 ± 5.11	
After 5 hours	65.02 ± 5.57	
After 6 hours	66.92 ± 4.33	
After 3 months	70.92 ± 7.52	
After 6 months	71.62 ± 7.71	

DBP: Diastolic blood pressure; SD: Standard deviation

The most complications rate of fingolimod was bradycardia, which was seen more at 4 hours after receiving the first dose (72 patients (36%) (P < 0.001), moreover, dizziness was the second complications which were seen more at 2 and 3 hours after drug was administrated (35 patients 17.5%) (P < 0.001) (Table 4).

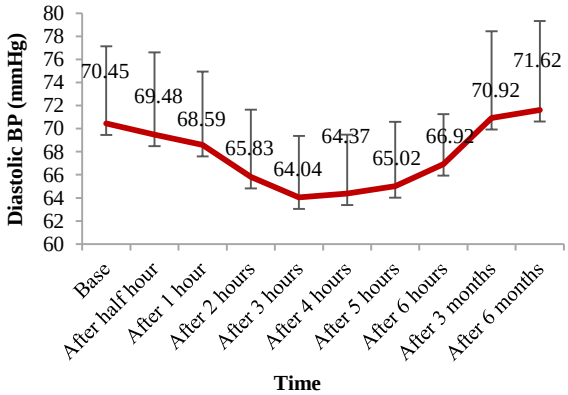

Figure 4. Diastolic blood pressure changes in patients receiving fingolimod during 6 months of follow-up
BP: Blood pressure

Discussion

Our results showed that the first dose of fingolimod was associated with a transient, mostly asymptomatic, decrease in HR, which was in

consistent with previous studies.[6,7,10,11] A larger maximal change in HR was observed at 4 hours after receiving fingolimod. On the other hand, the maximal change in SBP and DBP was measured as a change from baseline 3 hours post-dose of fingolimod. Although the occurrence of bradycardia was rare in the overall study population, more cases of bradycardia were observed during the first 4 hours of treatment.

Table 4. Complications in patients receiving fingolimod during 6 hours of follow-up

Complications	Time (hours)	n (%)	P
Headache	After 1	0	0.998
	After 2	1 (0.5)	
	After 3	2 (1.0)	
	After 4	0	
	After 5	0	
	After 6	0	
Dizziness	After 1	8 (4.0)	< 0.001
	After 2	18 (9.0)	
	After 3	35 (17.5)	
	After 4	35 (17.5)	
	After 5	24 (12.0)	
	After 6	19 (9.5)	
Chest pain	After 1	0	0.998
	After 2	1 (0.5)	
	After 3	2 (1.0)	
	After 4	0	
	After 5	0	
	After 6	0	
Bradycardia	After 1	26 (13.0)	< 0.001
	After 2	45 (22.5)	
	After 3	59 (29.5)	
	After 4	72 (36.0)	
	After 5	64 (32.0)	
	After 6	42 (21.0)	

The overall incidence of AVBs following treatment initiation was low. Mobitz Type I second-degree AVBs and 2:1 AVBs occurred in 6% of patients in the first 6 hours post-dose, which were new-onset AVBs post-dose. Consistent with previous findings, conduction abnormalities were asymptomatic and no patients developed a Mobitz Type II second-degree AVB or complete AVB.

The study findings confirm that cardiac effects following the first dose of fingolimod are transient, which observed in the first 6 hours post-dose; this is consistent with previous studies.[6,7,11] Fingolimod is an oral S1P receptor modulator that blocks lymph node egress of lymphocytes expressing the homing receptor C-C chemokine receptor type 7 that patients become gradually lymphopenic after a few days of treatment.[8] However, S1P receptors are expressed by other cells like cardiac myocytes[12] and glial cells (astrocytes and oligodendrocytes)[13,14] and may promote physiological changes and activation of downstream signaling yet to be fully clarified.

All super-agonist of the pleiotropic S1P receptor (S1P1-3) in heart are stimulated using S1P which leads to activation of (Gi, Gq, and G12/13) but only S1P1 and S1P3 receptors are activated using fingolimod, which leads to activation of Gi.[12,15] Thus, the underlying mechanism of bradycardia is due to the activation of inwardly rectifying Gà1-protein-regualted potassium channel (IKACh) channels in atrial myocytes and endothelial cells). The function of acetylcholine-regulated KACh is stimulated by S1P. S1PR regulates HR through binding to its receptors on the surface of atrial myocytes.[16] This inhibited cardiac pacemaker activity is similar to the vagally-mediated cardiac effects through the same G protein-gated potassium channel with different pathway fingolimod induces dephosphorylation of cTnI in ventricular myocytes.

Fragoso et al.[17] evaluated cardiovascular complications in RRMS patients during the first dose of fingolimod due to transitory effects in S1P receptors expressed in the cardiac myocytes. They showed that the severe bradycardia happened in 6.7% (12/180) and AVB in 1.7% (3/180) which is within the frequency found in other studies.[6,7]

Symptomatic bradycardia, which occurs in about 0.5% of cases is most often self-limiting.[18] Rarely, the occurrence of fatal bradyarrhythmia using fingolimod has also been reported.[12] These effects have also been observed in healthy volunteers.[15] The decrease in mean nadir HR is up to 10 bpm after first does without incremental decrease in HR after day 2 of the drug.[5]

Fingolimod has been shown to have nonsignificant effects on circadian rhythm, oxygen exchange, airflow, and hemodynamic variables as cardiac output and systemic vascular resistance during 14 days treatments in healthy volunteers.[19,20] Benign AVB (Type I or Wenckebach) has reported using fingolimod.[21] An approximate,[22-24] MS increase in PR-interval has been reported using fingolimod, without any change on QRS or QT intervals despite slowing AV conduction, the incidence of Mobitz Type II AVB and 2:1 AVB is respectively. Conduction abnormalities showed to regress during the time and in therapeutic doses, higher degrees of the block were not seen.[24]

Limitation: Our study had no control group, and the duration of the study was relatively short

compared with other studies. However, the aim of this study was to investigate early dosing with fingolimod, with a specific focus on HR and rhythm disturbances and BP during treatment initiation. Owing to small and uneven group sizes, inferential statistical testing was not performed.

Conclusion

Beneficial effects of fingolimod could be higher than its cardiovascular complications through administration of this agent under close observation regarding its side-effects on the cardiovascular system. Moreover, all the side effects such as hypotension and bradycardia were happened in first 3 hours after receiving the fingolimod. Indeed, we advise clinicians to monitor the patients for first 6 hours after initiation of fingolimod to decrease worse side effects.

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Conflict of Interests

Authors have no conflict of interests.

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Review of studies on the fat mass and obesity-associated (FTO) gene interactions with environmental factors affecting on obesity and its impact on lifestyle interventions

Naser Kalantari[(1)], Saeid Doaei[(2)], Nastaran Keshavarz-Mohammadi[(3)], Maryam Gholamalizadeh[(4)], Naeimeh Pazan[(5)]

Review Article

Abstract

BACKGROUND: The prevalence of obesity is influenced by environmental and genetic factors. Recently, it has been reported that an interaction between genotype and environmental factors can affect each other's effects on the phenotype. The purpose of this study is to evaluate the recent studies on the fat mass and obesity-associated (FTO) gene interactions with environmental factors affecting on obesity and the impact of these interactions on the success level of the lifestyle intervention.

METHODS: All articles published in English from June 1990 to June 2015 were studied.

RESULTS: In most studies, the role of the FTO risk alleles for obesity is significantly intensified through reduced physical activity and high calorie diet. Furthermore, the results of studies about the effect of FTO on the success level of lifestyle interventions have been contradictory. Some studies show that FTO genotype influences on the success of lifestyle interventions, while other studies did not report it.

CONCLUSION: The results of these studies generally indicate that the effect of the FTO gene on obesity may be influenced by environmental factors and lifestyle. In the other hand, the FTO genotype can affect the success of lifestyle interventions in the prevention and treatment of obesity. Future studies are crucial to elucidate relationships between FTO gene and lifestyle.

Keywords: Fat Mass and Obesity-Associated Gene, Life Style, Obesity

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Introduction

Overweight and obesity are defined as abnormal and excessive fat accumulation that may impair health.[1] Obesity has a huge negative impact on socioeconomic indicators of health. From health point of view, obesity underlies a large number of diseases, including coronary heart disease, Type 2 diabetes, cancer, hypertension, dyslipidemia, and stroke.[2] From the economic dimension, obesity has a direct negative consequences (costs associated with prevention, diagnosis, and treatment of obesity) and indirect consequences (costs associated with diseases and death caused by obesity).[3-5]

Obesity statistics are worriedly increasing in the worldwide. More than one-third of the adult population (34.9%) and 16.9% of 2-19 years Americans are obese.[6] Obese adolescents (12 to 19) were reached from 5% to 21% from 1980 to 2012.[7] The prevalence of obesity in Iranian men and women has been reported 27.3% and 13.7%, respectively.[8]

The role of various factors in the formation and progression of obesity has been proven. Genetics, behavioral and environmental factors are the most important factors that have been associated with obesity.[9] Most studies reported that unhealthy lifestyle including low physical activity and poor nutrition are the main cause of occurring obesity,[10-13] and therefore, strategies to combat obesity are to change lifestyle.[14-23]

On the other hand, it is seen in various studies of that people who do not have a healthy lifestyle

1- Associate Professor, Department of Community Nutrition, School of Nutrition and Food Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2- Students Research Committee, National Nutrition and Food Technology Research Institute AND Department of Community Nutrition, School of Nutrition Sciences and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3- Associate Professor, Department of Public Health, School of Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran
4- PhD Student, Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
5- Department of Veterinary Medicine, School of Veterinary Medicine, Shahid Bahonar University of Kerman, Kerman, Iran
Correspondence to: Saeid Doaei, Email: sdoaei@sbmu.ac.ir

are unaffected with obesity or even with lifestyle changes; the success rate in reducing obesity is not always satisfactory.[24] Here, the role of genetics in obesity is highlighted. Therefore, lack of a suitable conclusion of lifestyle interventions to reduce the prevalence of obesity in the desired level and also the results of recent studies in the field of nutritional genomics create uncertainties in the context of importance of lifestyle in occurring obesity and/or decrease in the imagined role of the lifestyle in obesity.

After many different studies on the interactions between genomics and diet and its relationship with hyperlipidemia and hypertension,[25-29] recent studies in the field of nutritional genomics have demonstrated that genetic background plays an important role not only in the chance of occurring obesity but also in people's responsiveness to the lifestyle intervention.[30-38] Several genes have been studied in relation to obesity, which one of the most important genes is fat mass and obesity-associated protein (FTO). FTO gene expression is associated with regulation of food intake and energy balance.[39] Furthermore, Single nucleotide polymorphisms (SNPs) in the FTO gene that almost 45% of them are in white,[40] causes to increase in food intake and the desire for high-calorie foods and then increase the risk of obesity (1.67 times more than others).[41] Although the mechanism of this effect is not still understood well, it has also been found that the link of FTO gene with obesity is related to age and most influence of these genes can be seen in the 7-20 years.[42] Furthermore, recent studies have been shown that the success of lifestyle interventions (such as changes in physical activity and intake of micronutrients) may be affected by obesity-related genes.[43-47] The results of various studies in this field have been inconsistent[48,49] that may be due to lack of considering to various aspects of this relationship. Hence, this study aimed to assess the FTO gene interactions with environmental factors affecting on obesity and its impact on lifestyle interventions using the lessons learned in previous studies and by taking into account the various aspects of the relationship.

Considering that so far (according to researchers' information) a study has not been carried out on a comprehensive review of interactions of FTO gene with environmental factors and the impact of FTO genotype on obesity successful interventions in obesity context, so the aim of this study was to review the studies on this field.

Materials and Methods

PubMed and ScienceDirect databases were used for gathering articles published in related fields. Appropriate keywords including FTO, lifestyle intervention, diet, physical activity, and obesity (alone and together) were used to collect the papers. All articles published in English from June 1990 to June 2015 were studied. Of the 277 articles, 162 articles were excluded because of failing to address the role of the FTO gene in obesity, and 90 articles for lack of sufficient information on the impact of the interaction of genes with the environment on the consequences of obesity and 25 articles were included. Of these studies, 14 studies were on the relationship between the FTO gene and obesity, 7 studies were about the interaction of the FTO gene with lifestyle factors and 4 were related to the FTO genotype influence on the success of prevention and treatment interventions of obesity.

Results

FTO gene and obesity: For the first time, FTO gene was identified in animal models as an effective gene on programmed cell death. Mice with mutations in this gene have joined fingers (fused toes), and they have larger thymus than other mice.[49-52]

FTO gene encodes a dependent oxygenase related to 2-exoglotarate that has a role in DNA demethylation.[53] This gene is located on chromosome 16 of region 12.2. Duplication of this gene region causes mental retardation, obesity, and other disorders.[54] FTO gene is expressed in all tissues of the body although its highest expression is in the brain and hypothalamus.[55]

The relationship of FTO with obesity in childhood and adolescence is confirmed through SNPs. The most important SNPs include: rs7202116, rs9930506, rs1421085, rs3751812, rs9939609, and rs17817449. There is no agreement on the mechanisms of FTO impact on obesity yet. Studies have shown that variations in the FTO play a key role in the regulation of food intake and energy expenditure. People with alleles A and AA than the carriers TT allele in rs9939609 polymorphism had 1231 kilojoules higher calorie intake.[56] In other studies, it was observed a positive relationship between the FTO gene mRNA levels in subcutaneous fat tissue with body mass index (BMI).[30,57-59] Furthermore, those who carry allele associated with obesity in FTO had lower fat cell lipolysis, indicating a possible role of FTO in fat metabolism in the body.[60] In another study that the

FTO gene expression was suppressed in mice, decrease in ratio of white adipose tissue (WAT) to brown adipose tissue (BAT) was reported. This finding means that the FTO deficiency may be involved in the conversion of WAT to BAT. In these mice, energy intake and energy consumption also increased significantly.[61]

Interactions of environmental factors and FTO genotype: Six of seven studies about the interaction of the FTO gene with lifestyle factors (i.e. diet and physical activity) reported that improvements of these factors might reduce the effects of FTO polymorphisms on body weight and body composition; while one study showed that these factors do not have a role in the interaction between FTO gene and obesity. The summary of these studies is presented in table 1.

FTO genotype influences on the success of lifestyle interventions on obesity: Three of four studies on the influence of FTO genotype on the success of lifestyle interventions did not find a significantly association between FTO gene polymorphisms with success rate of the interventions, while one study showed that dietary intervention is most useful in subjects with FTO risk allele. The summary of these studies is presented in table 2.

Discussion

Based on this review of studies focusing on the interactions between FTO genotype with lifestyle and obesity, there is some evidence that suggest FTO polymorphisms interact with the effects of environmental factors. Also, the success of lifestyle interventions to reduce obesity might be influenced by FTO genotype.

Andreasen et al.[45] were evaluated the effect of rs9939609 polymorphism in the FTO on obesity and diabetes at different levels of physical activity in 3856 patients with diabetes and 4861 healthy subjects. Information on physical activity and data related to genotype were collected by questionnaire and TaqMan allelic discrimination, respectively. The minor allele of rs9939609 (allele A) was associated with occurring diabetes and obesity. However, when the results were adjusted for BMI, no association was observed between this allele and diabetes. Furthermore, there was a correlation between genotype rs9939609 and physical activity. Sedentary subjects who were carriers of the A allele, compared with patients with homozygous T allele had higher BMI at a rate of 1.95 kg/m^2. These results suggest that low physical activity would accelerate the effect of rs9939609 in FTO on accumulation of fat in the body.

Rampersaud et al.[62] studied a possible link between increased physical activity and reduce the harmful effects of gene polymorphisms in the FTO. 704 adults were selected from the Heredity and Phenotype Intervention Heart Study. Information was collected on the physical activity of the study subjects and was evaluated the 92 SNP using whole blood samples and the method of Gene Chip Human Mapping and Genotyping Analysis Software (GTYPE) GTYPE (Affymetrix company). The study results showed that 27 SNP in the FTO gene were associated with BMI ($P = 0.040$ to < 0.001) and rs1861868 and rs147719 polymorphisms in those had low activities physical are associated with higher BMI after adjustments for age, gender. This relationship was not seen in people whose physical activity rated above average. The results demonstrated that physical activity can adjust the effect of the FTO gene on obesity.

Scott et al.[63] were examined FTO genotype effects as well as its interaction with physical activity and energy intake. 1980 children 1-5 years old and 949 adolescents 11-18 years old were selected from GENESIS study and evaluated for the phenotypes associated with obesity and existence of rs17817449 polymorphism in the FTO gene using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. Adolescents were classified into two categories (active and inactive) based on self-report of physical activity. In adolescents, FTO genotype was associated with weight ($P = 0.001$) and BMI ($P = 0.007$). Furthermore, there was a significant correlation between physical activity interaction and SNP with BMI among men ($P = 0.016$). The amount of BMI in inactive boy adolescents who had the GG genotype was 3 kg/m^2 higher than carriers of T allele ($P = 0.008$). Totally, the results of this study showed that physical activity can improve the FTO genotype effects.[63]

Hubacek et al.[64] investigated the mediating role of diet and physical activity in influence of their FTO gene variation. Existing diversity (G > T in rs17817449 polymorphism in the first intron) in 6024 adults 45-69 years old were evaluated. The subjects were selected from among the participants in the health, alcohol and psychosocial factors. In Eastern Europe project, their DNA was extracted from blood samples through the salting out method and existence of SNP was evaluated using PCR-RFLP method.

Table 1. The review of the fat mass and obesity-associated (FTO) gene interactions with lifestyle factors and its impact on obesity

Writer	The aim of study	The subjects of study	Methodology	The main findings	The related diversity in FTO gene	Environmental factors
Andreasen et al.[45]	The effect of rs9939609 in the FTO gene on obesity and at different levels of physical activity	3856 patients with diabetes and 4861 healthy people	Physical activity by questionnaire and genotype by using Taqman allelic discrimination	Low physical activity accelerates the rs9939609 effect on the accumulation of fat in the body	rs9939609	Physical activity
Rampersaud et al.[62]	Possible association between increased physical activity and reduce the harmful effects of FTO gene polymorphisms	704 adults	Affymetrix Gene Chip Human Mapping 500 K array set and software GTYPE	Physical activity can adjust the FTO gene effects on obesity.	rs1861868 and rs147719	Physical activity
Scott et al.[63]	FTO genotype effects as well as its interaction with physical activity and energy intake	1980 children 1-5 years and 949 adolescents 11-18	PCR-RFLP and self-report of physical activity	Physical activity can adjust the FTO genotype effect	rs17817449	Physical activity
Hubacek et al.[64]	Checking the intermediary role of dietary intake and physical activity on the effects of the FTO gene polymorphism	6024 adults 45-69 years old	PCR-RFLP, food frequency questionnaire and physical activity questionnaire	Physical activity and diet have no meditation role in effects of FTO polymorphism on obesity but may play such a role in change of the BMR.	rs17817449	Physical activity and food intake
Ahmad et al.[65]	Checking the effect of diet modification and physical activity on the effects of FTO gene polymorphism	21675 healthy white women	Illumina's infinium HD bead chips	Lifestyle factors adjust the influence of FTO genotype on obesity, but will not be able to remove the full effects.	rs8050136	Diet and physical activity
Kilpelainen et al.[66]	Is physical activity able to mitigate the impact of FTO on the risk of obesity or not	218, 166 adults and 19,268 children	Meta-analysis	The effect of FTO risk alleles can be adjusted by 27% through physical activity	rs9939609	Physical activity
Ruiz et al.[67]	Does physical activity moderate FTO polymorphism effect on the amount of body fat or not	752 healthy adolescents	Illumina and accelerometer	Adolescents who have a good level of physical activity may overcome the adverse effects of rs9939609 polymorphism	rs9939609	Physical activity

PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism; FTO: Fat mass and obesity-associated; BMR: Basal metabolic rate; HD: High-density

Table 2. A review of studies on the effect of the fat mass and obesity-associated (FTO) genotype on the success of lifestyle interventions on obesity

Writer	The purpose of the study	Subjects	Duration of intervention	Main findings	The variation in the FTO gene	Environmental intervention
Haupt et al.[68]	The relationship between the FTO genotype with fat distribution and body weight changes in a lifestyle intervention	In 1466 the Germans	9 months	Despite the effect on body weight and fat distribution, rs8050136polymorphism had no effect on the success of lifestyle interventions	rs8050136	1. Diet with the aim of losing weight, reducing fat intake and increasing fiber intake 2. Physical activity 3. Nutritional Counseling
Lappalainen et al.[69]	Effects of long-term intervention on weight change considering rs9939609 polymorphism in the FTO gene and its effect on body weight and BMI	522 individuals 40-65 years with a BMI above 25	4 years	rs9939609 Polymorphism in the FTO gene had no effect on the success of lifestyle interventions to reduce obesity	rs9939609	Diet and physical activity
Razquin et al.[70]	The effect of the polymorphism rs9939609 (T/A) in the FTO gene on weight loss after a Mediterranean diet in people at risk for cardiovascular disease	776 individuals 65-80 years old	3 years	Appling dietary intervention is most useful in people with FTO risk allele	rs9939609	Mediterranean diet
Dlouha et al.[71]	The effect of rs17818902 polymorphism in the FTO gene on obesity lifestyle intervention	107 female adults with overweight	10 weeks	Change in BMI and other anthropometric parameters have no correlation with FTO gene variant	rs17818902	Reducing calories and increasing physical activity

FTO: Fat mass and obesity-associated; BMI: Body mass index

Diet was defined by a 140 items food frequency questionnaire and intake of total calories, fat, protein, carbohydrates, and alcohol were achieved using McCance and Widdowson's food composition. Basal metabolic rate (BMR) was estimated through Schofield formula. FTO variation was significantly correlated with BMI (BMI in carriers of genes GG, GT, and TT were 28.7, 28.2 and 27.8 and BMR were 1603, 1588 and 1576 kcal/day, respectively). However, there was no significant correlation between this SNP with energy intake, physical activity and energy intake of each macronutrient. Adjusting results with regard to physical activity and diet did not reduce the effect of FTO polymorphism. In general, the results of this study showed that physical activity and diet have no mediating role in the effects of FTO polymorphism on obesity, but change in the BMR may play such a role to some extent.

Ahmad et al.[65] investigated the effect of diet and physical activity effects on the link of FTO with obesity. Polymorphism rs8050136 in the FTO was assessed using the Illumina's Infinium high-density (HD) Bead Chips method. Physical activity, caloric intake and the anthropometric data were also collected through self-report and related questionnaire from 21,675 healthy white women participated in the study of Women's Genome Health Study. The results showed that the risk allele A in women who are inactive and receive a higher energy resulted in greater effect on people's BMI [odds ratio 13.9, 95% confidence interval (CI): 73.1-27.1 per-allele risk]. Totally, the results of this study showed that lifestyle factors adjust influence the genetic risk factors for obesity in the FTO gene although it is not able to completely eliminate its effects.

Kilpelainen et al.[66] designed a meta-analysis by 45 studies on adults (n = 218,166) and 9 studies on children (n = 19,268) to survey whether physical activity could moderate the effect of FTO on the risk of obesity or not. All studies included information related to the varieties of rs9939609 in FTO. In all studies, the study subjects were divided into two categories: active and inactive. Overall, 25% of adults and 13% of children were classified as inactive. The results showed that in adults, rs9939609 minor allele increases the risk of obesity by as much as 1.23 times [95% confidence interval (CI): 1.26-1.20], whereas physical activity neutralizes this effect. Such an effect was not seen in children and adolescents. At last, the results suggest that FTO risk alleles associated with risk of obesity can be adjusted by 27% by physical activity.

Ruiz et al.[67] examined whether physical activity moderates FTO polymorphism effect on the amount of body fat. 752 healthy adolescents participated in this cross-sectional study. FTO genotype was determined on polymorphism of rs9939609 by the method of illumina. Physical activities were measured using accelerometers. People carry accelerometer at all wake times except water activities for 7 days. Those who had used accelerometer less than 3 days were excluded. Weight, height, waist and subcutaneous fat (in triceps and subscapular) were evaluated, and BMI and percentage of body fat were calculated. The results showed that there was a significant relationship among the A allele of FTO polymorphism with BMI (0.42 per risk allele) and percentage of body fat (1.03% per allele risk) and waist (0.85 per risk allele). Moreover, a significant association was found between physical activity and body fat estimates (P = 0.020, 0.060 and 0.100, for BMI, body fat percentage and waist, respectively). The effect of rs9939609 polymorphism in FTO on the parameters of obesity in adolescents who had higher physical activity (that is 60 minutes a day, moderate to vigorous physical activity) was much lower than others (0.17 vs. 0.65 for BMI, 0.40% vs. 1.70% for body fat percentage and 0.60 vs. 1.15 cm for waist per allele risk). At last, the results of this study showed that teens who have an appropriate level of physical activity may overcome on the adverse effects of rs9939609 FTO polymorphism on occurring obesity. Table 1 shows summary of findings of the studies on the interactions between FTO gene and lifestyle factors.

Haupt et al.[68] investigated the relationship between the FTO gene with fat distribution, insulin resistance, and body weight changes after a lifestyle intervention. In this study, 1466 German people at risk for Type 2 diabetes were evaluated for the presence of polymorphism rs8050136 in intron 1 of FTO gene. The oral glucose tolerance test was taken. Also, to evaluate body fat mass, magnetic resonance imaging was performed in 298 people of them. The prepared kit for the isolation of DNA from blood samples was used for evaluating the subjects' genotype. By using Taqman analysis, people were analyzed for the presence of polymorphisms. Also, 208 of the subjects participated in the lifestyle intervention program and were re-evaluated after 9 months follow-up. A cross-sectional analysis was reported that related polymorphism is associated with the increased BMI, body fat and lean body mass (P < 0.001). After the

lifestyle intervention, this polymorphism was not associated with intervention effects on body weight and lifestyle. So despite effect on body weight and fat distribution, this polymorphism has no impact on the success of lifestyle interventions.

Lappalainen et al.[69] surveyed the effect of long-term intervention of changing weight on the effects of rs9939609 polymorphism in the FTO gene on body weight and BMI as part of the Finnish Diabetes Prevention Study. 522 individuals 40 to 65 years with a BMI over 25 and defect in glucose tolerance participated in the study and were divided into intervention and control groups. The rs9939609 genotype was determined in 502 patients. At the beginning of study, BMI of individuals that had allele A was significantly higher than others (P = 0.006). After adjustment for gender, this relationship was observed only in women. After 4 years, individuals with the allele A had the highest BMI among the study subjects. The amount of weight loss in the intervention group was more than the control group, but the studied allele had no impact on the effectiveness of the intervention. As a whole, the results of this study showed that polymorphisms rs9939609 in the FTO gene had no effect on the success of lifestyle interventions to reduce obesity.

Razquin et al.[70] evaluated the effect of polymorphism rs9939609 (T/A) in the FTO gene on the effect of Mediterranean diet in weight loss in people who are at the risk of cardiovascular disease. 776 subjects 65 to 80 years old participated in the study. They were divided into three groups: two intervention groups who received Mediterranean diet and the control group that was recommended to consume low-fat diet. Dietary intake was assessed by semi-quantitative food frequency questionnaire at baseline and after 2 years of intervention. Individuals' Genotype was determined by reverse transcription-PCR and after that Taqman allelic differentiation. The results showed that people with homozygous alleles A had the highest BMI among whole participants. After 3 years of intervention, they showed the lowest weight gain regardless of diet intervention (P = 0.022). In addition, the corresponding result in people carrying allele A was significant in the group receiving Mediterranean diet, but this relationship was not seen in the control group (P = 0.018). In general, the relationship between the polymorphism rs9939609 in the FTO gene and body weight were confirmed and more importantly it was showed that at the beginning of the study the A allele was associated with patients' higher weight, after 3 years intervention, the lowest weight gain was accounted. Therefore, in this study applying a dietary intervention was most useful in patients with FTO risk allele.

Dlouha et al.[71] investigate the role of polymorphism rs17818902 in the FTO gene in impacts of lifestyle interventions on obesity. In this study, 107 overweight females (BMI < 27) were studied. The intervention consisted of 10 weeks low-calorie diet (based on age) and physical activity (aerobic exercise 4 times/week, each time: 60 minutes). Genetic polymorphisms were studied using PCR and restriction enzymes on blood samples. The results showed that the change in BMI and other anthropometric (such as percentage of body fat, body water percentage, waist-to-hip ratio) and biochemical (lipid and blood sugar) indicators hove no relationship with the rs17818902 FTO gene variant.

In general, the studies on the effect of FTO on the success of lifestyle interventions represent the FTO genotype influence on the success of lifestyle interventions, while other studies did not report it. This difference in the results may be due to differences in lifestyle interventions, different target groups (for example in terms of age group), surveying various polymorphisms in various studies and due to ignore other genetic factors that influence on obesity (such as the impact of lifestyle interventions on IRX3 gene expression mediating FTO gene polymorphisms).[45]

Conclusion

The results of the studies on the FTO interaction with environmental factors show that the impact of FTO genotype on obesity may be affected by lifestyle. In most studies, the role of FTO polymorphisms in increased risk of obesity is significantly intensified by reduced physical activity and high calorie diet.

In the other hand, the results of the studies on the effect of FTO gene on the success of lifestyle interventions have been controversial. Future studies are crucial to further elucidate relationships between FTO gene and lifestyle interventions.

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Conflict of Interests

Authors have no conflict of interests.

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Huge mass in right side of the heart: A rare case report

Reza Ghasemi[(1)], Fahimeh Ghanei-Motlagh[(2)], Susan Nazari[(3)], Mohsen Yaghubi[(4)]

Case Report

Abstract

BACKGROUND: The presence of primary intracardiac tumors are scarce, and most of them are myxomas. We reported, in this paper, a case with huge mass in the right side of the heart.

CASE REPORT: A 45-year-old man, with a complaint of bilateral lower limbs edema and exertional dyspnea, was admitted to intensive cardiac care unit. Cardiac auscultation revealed soft grade systolic murmur without any evidence of "tumor plop." Echocardiography showed a huge mobile mass in right side of the heart that suggested myxoma. Our patient underwent cardiac surgery with excision of 13 cm mass. Histopathological study was confirmed the diagnosis of mass type.

CONCLUSION: In this case report, it shows that in the differential diagnosis of right-sided heart failure, the right sided myxoma must be considered. The preferable approach in patient with cardiac myxomas is surgical excision to alleviate symptoms, early identification, and removal.

Keywords: Myxoma, Cardiac Surgery, Echocardiography, Case Report

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Introduction

In humans, the incidence of cardiac tumors is 0.2% of all tumors.[1] The pathologic category for these tumors includes primary and secondary or metastatic. Secondary tumors are 20-40 times more common than another, but the incidence of primary intracardiac tumors is rare. Approximately, 75% are benign, and half of them are myxomas, which have an incidence of 0.0017% in the general population. Based on histologic evaluations, these are real tumors, derived from multipotent mesenchymal cells of the subendocardium.[2,3]

In cardiac chambers, commonly, myxoma can arise in the left atrium (75%) and are almost always presents with sign and symptoms of mitral valve disorders, but they may present in other sites, such as the right side of the heart (5-18%).[4]

We present a man with huge myxoma in right side of the heart that filling right atrium (RA) and right ventricle (RV), without any significant hemodynamic compromise.

Case Report

A 45-year-old man weighing 50 kg was admitted to intensive cardiac care unit with a complaint of bilateral lower limbs edema and exertional dyspnea. He was in Class 3 functional class. He had not any history of hospitalization. There was also no mentioned family medical history of cardiac disease. He reported worsening of symptoms in the last week before admission. On admission, he was in stable condition and blood pressure was 107/89 mmHg, heart rate was regular and 99 beat per minute, respiratory rate was 26 breath/min, and he was afebrile. Oxygen saturation, at rest, with finger pulse oximeter in index finger was 97%.

In the primary physical examination, we found Grade 2^+ of lower limbs edema (Figure 1), and cardiac auscultation revealed soft Grade 2/6 systolic murmur at the both, right and left sternal border without any evidence of diastolic murmur and "tumor plop" in the apex. Laboratory findings shown a mild hypochromic microcytic anemia (hemoglobin = 10.9 g/dl, hematocrit = 34.9%, mean corpuscular volume = 71.96 fl, and mean corpuscular hemoglobin = 22.47 p.g). Chest X-ray (in posteroanterior view) revealed increased cardiothoracic ratio. Aortic arch was normal, main pulmonary artery was seen flat and right descending pulmonary artery was increased (Figure 2).

1- Assistant Professor, Department of Cardiology, Dey 9th Hospital, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran
2- Department of Obstetrics and Gynecology, Qaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
3- Department of Obstetrics and Gynecology, Dey 9th Hospital, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran
4- Department of Cardiac Anesthesiology, School of Medicine, Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran
Correspondence to: Mohsen Yaghubi, Email: n.m.yaghubi@gmail.com

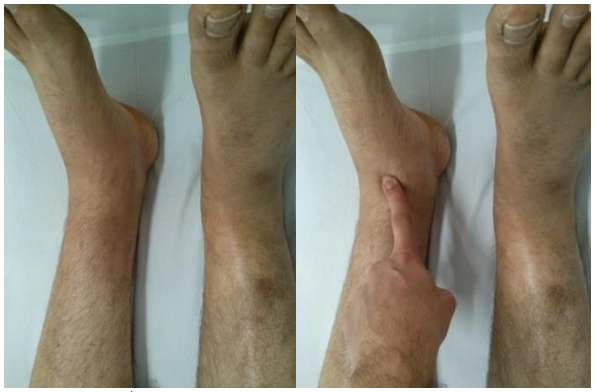


Figure 1. 2^{+} grade of lower limbs edema

In electrocardiogram, there was no sign of abnormal conductive pathways. Cardiac rhythm was sinus tachycardia (Figure 3).

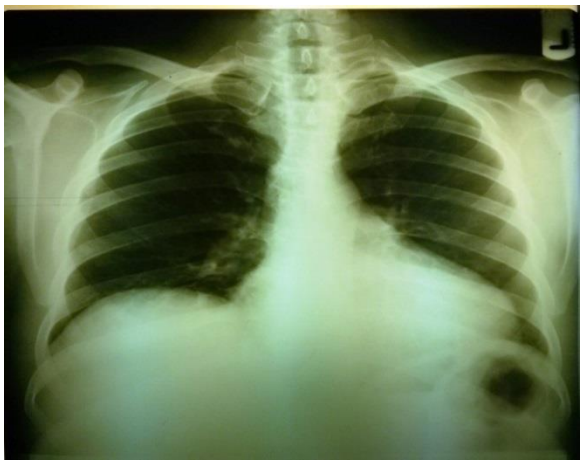


Figure 2. Antro-posterior chest X-ray

The patient referred to echocardiographic study unit; transthoracic echocardiography showed a giant mobile mass in right side of the heart (11.4 × 4.2 cm) attached to the intratrial septum. Inferior vena cava was plethoric and tricuspid valve (TV), function was disturbed by this giant mass. RV function was reduced (Tricuspid annular plane systolic excursion = 0.85 cm) (Figure 4).

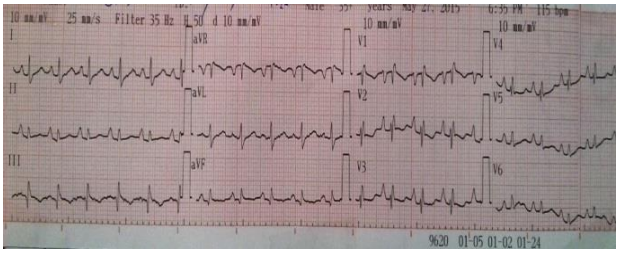
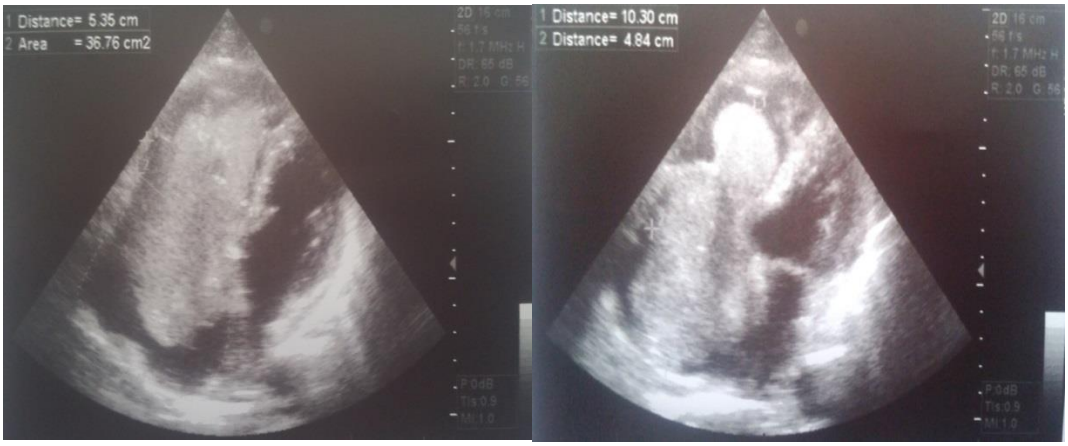


Figure 3. An electrocardiogram (ECG) of the patient (before cardiac surgery) manifested that his cardiac rhythm was sinus tachycardia and precordial leads shown incomplete right bundle branch block. According to this ECG, the patient had a left atrium abnormality

The patient was scheduled for open heart surgery. General anesthesia was performed to median sternotomy. Mild hypothermia strategy (33.0° C) was stablished under cardiopulmonary bypass.

During an anoxic arrest, single aortic cross-clamping performed, and then, the tumor was completely excised through a right longitudinal atriotomy. The mass referred to histopathological analysis. Based on the microscopic evaluation, myxoid matrix rich in mucopolysaccharides, and polygonal cells appeared as a star and nest shape without atypical features, compatible with non-malignant myxoma.

During cardiac surgery and after tumor removal, saline test was performed by cardiac surgeon. According to this test, the surgeon concluded that inappropriate function of TV was due to mass.



a **b**

Figure 4. (a and b) Apical four chambers view (an echocardiography before cardiac surgery), showing hypermobile huge mass in right side of the heart

After 1 month of discharge, our patient readmitted to the cardiac care unit complaining of palpitations. In electrocardiogram, cardiac rhythm was atrial flutter (Figure 5).

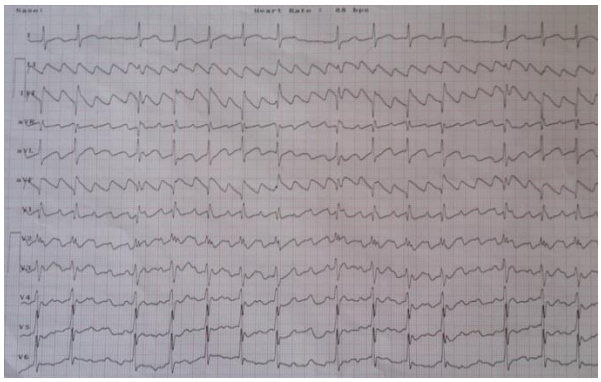


Figure 5. An electrocardiogram after cardiac surgery demonstrate atrial flutter

Echocardiography of patient, as shown in figure 6, indicated that RV and RA, were severely dilated RV systolic function was severely impaired. TV, had leaflet malcoaptation (2 cm), with severe free low-pressure regurgitation [tricuspid regurgitation (TR)], and mild pulmonary insufficiency.

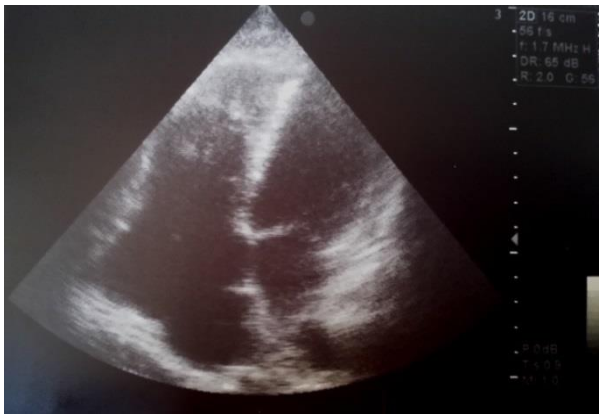


Figure 6. Transthoracic echocardiography four chambers view, shows mal coaptation, with severe free low-pressure tricuspid regurgitation

Because of hemodynamic instability, cardiac rhythm converted to normal sinus rhythm by synchronized shock.

Because of severe low-pressure TR, the patient was candidate for TV repair (TVR), TVR surgery postponed to 6 months after myxoma excision. In this time, the patient has been closely monitored and controlled by medication.

Discussion

Myxoma is the most common primary cardiac mass with rare incidence and usually benign.[5] More than 75% of myxomas are located in the left atrium, whereas right sided myxomas are scarce (15-20%). 3-4% of right-sided myxomas are located in RV or pulmonary artery being extremely rare.[6]

RA myxoma has a lower incidence that reported for a long time in several series of autopsy cases.[1] Although only about 30% of affected patients are men,[2,7] we reported a 45-year-old man suffering from a giant myxoma in right side of his heart.

In our patient like another case report,[1] the myxoma originated in the left of RA and attached to the intratrial septum in some case reports that right atrial myxomas exude in the fossa ovalis or base of the interatrial septum.[8,9]

Nevertheless, transthoracic echocardiography cannot be recognized tumors smaller than 5 cm diameter, but still, it remains the gold standard method for diagnose the site and assessing the extent of myxomas and indicating their recurrence, with a sensitivity of up to 100%.[7] In this report, our patient had a 13 × 9 × 3 cm, with an irregular and smooth surface tumor. In Samanidis et al. article, the mean diameter of the myxoma tumors that were evaluated in a 19 years' period was 5.1 ± 1.8 cm.[9] Therefore, our case had the largest myxoma in the right side of the heart, which heretofore reported.

In some case report, the most common manifestation of right side myxoma is dyspnea that occurring in 80% of affected patients.[1,4,5] Our patient also compliant of dyspnea on exertion. dyspnea in our patient may not be due to huge myxoma itself, it may be caused by enlargement and increased size of RV due to hemodynamic changing in right ventricular function.[10]

Right side myxoma could be yielding other symptoms such as Raynaud's phenomenon and syncope. Our patient had not any of these symptoms, despite the presence of huge myxoma in right side of the heart.

Conclusion

This case report suggests that in differential diagnosis of right-sided heart failure, the right-sided myxoma must be considered. Since surgical excision is reported to alleviate symptoms associated with cardiac myxomas, early identification and removal is preferable.

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management, and cardiac surgeon, cardiac anesthesiologist and perfusionist in Imam Reza Hospital, Mashhad, Iran.

Conflict of Interests

Authors have no conflict of interests.

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Presentation of new classification of perceived risk factors and etiologies of cardiovascular diseases

Saeid Komasi[(1)], Mozhgan Saeidi[(2)]

Letter to Editor

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To the Editor

Recently, a new classification of perceived risk factors of cardiovascular diseases (CVDs) has been suggested through assessment of a large number of cardiac rehabilitation patients. Based on this classification, Komasi and Saeidi divided the perceived risk factors and etiologies related to CVDs in five groups.[1] Here, the details of this classification are explained, and this issue is discussed that this new classification belongs as a subgroup to which model of health field.

Based on self-regulatory model, patients form cognitive representations related to symptoms and treatment based on their perception of information derivate from their last longtime experiences, social environment, and present experiences. The representations of disease can affect on patients' coping strategies and health behaviors.[2] Based on this model, the disease perception has five dimensions: identification, cause (patient's beliefs about the causes of disease), timeline, consequences, and control ability/curability.[3] The second dimension of this model consists of perceived cause of disease that it assesses the perceived risk factors and causes in patients' viewpoints.

Despite introduced components and instrument such as Illness Perceptions Questionnaire that they related to disease perception, recently a new classification has been presented for the perceived causes among cardiac patients.[1] At first, according to this classification, perceived risk factors were divided into four groups titled biological, environmental, behavioral, and psychological factors.[4,5] Then, one classification as titled physiological factors is added to others.[1,6] According to results of two studies[1,5] which assessed 1676 persons totally, 2.7%-4.3% of patients believe that biological risk factors as cause of their disease. In addition, 3.8%-4.4%, 31.7%-42%, 36.3%-39.2%, and 11.4% of patients present the environmental, behavioral, psychological, and physiological risk factors as cause of their disease, respectively.

According to this classification, perceived biological risk factors conclude of genetics and family history, age, gender, and ethnicity. The environmental risk factors include fume and toxin agents, dust, non-hygienic water, and passive smoking. The physiological risk factors consist of hypertension, diabetes, hyperlipidemia, and obesity. The behavioral risk factors include inappropriate nutrition, cigarette smoking and substance abuse, and heavy physical activity. The psychological risk factors include stress, grief and depression, anger and hostility, and partner's misbehavior.[1,6]

It seems that this classification can promote the dimension of etiological perception related CVDs in format of self-regulation and it assesses the perceived risk factors of disease. Future studies about this new classification can indicate its efficacy and advantage in evaluation of beliefs and attitudes among cardiac patients about etiologies of disease.

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1- Cardiac Rehabilitation Center, Imam Ali Hospital AND Clinical Research Development Center, Imam Reza Hospital AND Department of Psychology, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran
2- PhD Candidate, Cardiac Rehabilitation Center AND Department of Psychology, School of Medicine, Imam Ali Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran
Correspondence to: Mozhgan Saeidi, Email: m_saeidi20@yahoo.com

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Myocardial bridging of the posterolateral branches of the right coronary artery

Arash Gholoobi[(1)]

Images in Clinical Medicine

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A 57-year-old male patient presented with typical exertional angina and dyspnea during usual physical activities. He had a history of hypertension. On cardiac examination, he had a load ejection-type systolic murmur which was radiating to both carotid arteries. Transthoracic echocardiography revealed severe calcified aortic stenosis and severe concentric left ventricular hypertrophy. He underwent coronary angiography to define his coronary anatomy before aortic valve replacement. The left anterior descending (LAD) artery had non-significant stenosis after the first diagonal branch, and the left circumflex (LCx) artery was normal. The right coronary artery (RCA) injection demonstrated myocardial bridging of a long segment of the posterolateral branches with complete luminal obliteration during systole (Figures 1 and 2). He underwent surgical aortic valve replacement without right posterolateral myotomy or bypass graft surgery. Beta-blocker was prescribed following surgery to reduce the potential risk of ischemia and arrhythmia.

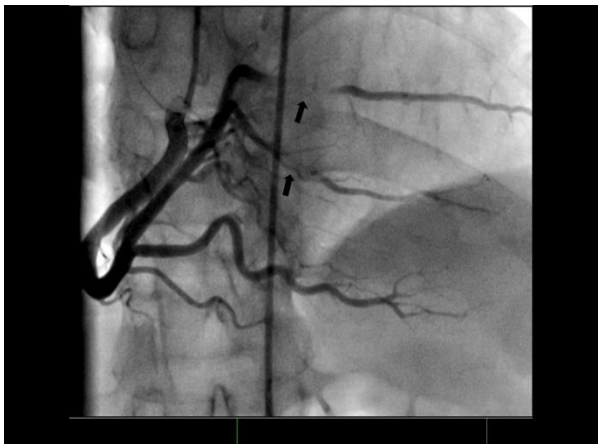

Figure 1. Right coronary angiography in the antero-posterior projection with cranial angulation demonstrates complete luminal obliteration of a long segment of the two postero-lateral branches during systole (arrows)

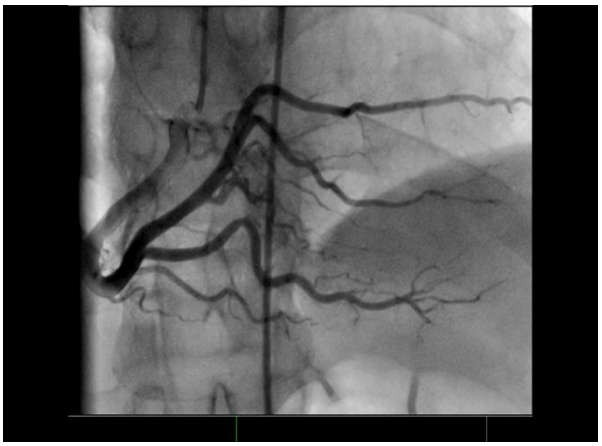

Figure 2. Right coronary angiography in the left anterior oblique projection with cranial angulation demonstrates normal postero-lateral branches during diastole.

Myocardial bridging is a coronary anomaly defined as a segment of an epicardial coronary artery that goes intramurally through the myocardium and is usually confined to the midportion of the LAD artery.[1] Rarely, it has been reported in the main body of the LCx artery or RCA or their branches.[2,3] Multi arterial involvement has been reported as well.[4] To our knowledge, myocardial bridging of the posterolateral branches of the RCA has not been reported so far except for one.[5]

The typical angiographic finding is compression of the involved segment of an epicardial coronary artery during systole. The presence of an aortic outflow tract obstruction enhances the angiographic manifestation due to increased systolic tension which probably had such effect in this patient as well. Myocardial bridging is a benign condition in most instances but has been associated with angina, arrhythmia, coronary vasospasm, and even sudden cardiac death.[1] Medication is considered first-line therapy. In subjects refractory to medication, surgical myotomy is associated with reversal of local myocardial ischemia. However, the risk associated with surgery should carefully be weighed against the

1- Assistant Professor, Atherosclerosis Prevention Research Center, Imam Reza Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
Correspondence to: Arash Gholoobi, Email: gholoobia@mums.ac.ir

usually uneventful long-term course. A few patients refractory to medication have been treated with coronary stents, and the rate of restenosis has been too high to generally recommend this approach.[6]

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Conflict of Interests

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