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ARYA Atherosclerosis

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Serial Issue: 42 *Volume 10, Issue 5, September 2014* *Print ISSN: 1735-3955*
Online ISSN: 2251-6638

Original Article(s)

Review Article(s)

Case Report(s)

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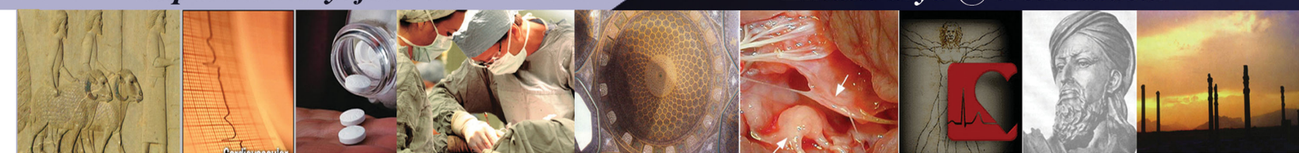

ARYA Atherosclerosis

Official Journal of the Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences

Publisher: Isfahan University of Medical Sciences,
Email: publications@mui.ac.ir

Copy Edit, Layout Edit, Design and Print: Farzanegan Radandish Co.
Tel: +98-311-2241953
+98-311-2241876
Email: f.radandish@gmail.com

Circulation: 500
Distribution: International
Language: English
Interval: Bimonthly
Print ISSN: 1735-3955, **Online ISSN:** 2251-6638

Address: ARYA Journal Office, Isfahan Cardiovascular Research Institute, Seddigheh Tahereh Research Complex, Khorram Ave. Isfahan, Iran
PO. Box: 81465-1148 Tel: +98-311-3377883 Fax: +98-311-3373435
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2. Bonow RO, Mann DL, Zipes DP, Libby P. Braunwald's Heart Disease E-Book: A Textbook of Cardiovascular Medicine. 7th ed. Philadelphia, PA: Elsevier Health Sciences; 2007. p. 1976, 1981, 1982.

3. Gaston M. The psychological care of patients following a myocardial infarction [Online]. 2003; Available from: URL: http://www.nursingtimes.net/the-psychologicalcare-of-patients-following-a-myocardialinfarction/199464.article/

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- **Original Articles** are scientific reports of the results of original clinical research. The text is limited to 3000 words (excluding abstracts and references), with a structured abstract, a maximum of 5 tables and figures (total), and up to 40 references.
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Surgical outcomes of heart valves replacement: A study of tertiary specialied cardiac center

Niloufar Samiei[(1)], Mohammad Reza Hakimi[(2)], Yalda Mirmesdagh[(3)], Mohammad Mehdi Peighambari[(4)], Alireza Alizadeh-Ghavidel[(5)], Saeid Hosseini[(5)]

Original Article

Abstract

BACKGROUND: Heart valve disease is a significant and increasing global problem in the developing world. The aim of this study is to evaluate the incidence of postoperative complications and mortality in patients who underwent heart valve replacement.

METHODS: In this prospective study, 320 adult cases (186 females and 134 males, mean age of: 45.7 ± 15.0) with valvular heart diseases who underwent heart valve replacement at our center, from June 2011 to January 2012 were enrolled. All the required demographic, echocardiographic, and electrocardiogram data were studied. The incidence of intraoperative and early postoperative complications and mortality were evaluated.

RESULTS: Among total, 96.3% of the cases underwent elective surgery. Mitral valve replacement surgery was occurred the most in 58.8% of the cases. In 11.3% of the cases, bioprosthetic valves and in 88.8% of the patients prosthetic valves were required. Early postoperative complications were occurred in 85 patients (26.6%), including: valve-related events: 7 cases, postoperative arrhythmia: 24 patients, worsening function of the repaired valve: 16 cases and general complications: 38 patients. Mortality was occurred in 25 patients (7.8%), 10 cases due to cardiac problems versus 15 patients due to non-cardiac problems. There were significant correlations between age, simultaneous valve repair and replacement, the anatomic site of the valve and the incidence of postoperative complications. Age, history of diabetes mellitus (DM), hypertension (HTN), and high grade of functional capacity were reported the significant causes of postoperative mortality.

CONCLUSION: Age, DM, HTN, functional capacity and multivalve disease are significant predictors of post-valvular surgery morbidity and mortality.

Keywords: Heart Valve Diseases, Cardiac Surgery, Heart Valves

Date of submission: 9 Jan 2013, ***Date of acceptance:*** 20 Apr 2013

Introduction

Valvular heart disease (VHD) is one of the most important cardiovascular diseases which its prevalence differs regarding age; gender and different societies.[1] There are various etiologies of VHD including rheumatic, degenerative, traumatic, congenital, and infectious heart diseases. VHD remains common in developing countries, because the increase in prevalence of rheumatic heart diseases.[2] Rheumatic heart disease is caused by infection with group A beta-hemolytic streptococcus bacteria, and it occurs when the patient does not receive proper medical treatment. The prevalence of VHD has been also increased during the past years in industrialized countries due to increase in prevalence of degenerative valve diseases.[3] Surgery performs a main role in order to treat the patients with VHDs, which lead to less

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mortality and better quality-of-life. Heart valve replacement is the second most common type of heart surgery after coronary artery bypass graft surgery.[4] Different postoperative complications are associated with this procedure. In past studies, the rate of mortality following heart valve replacement was reported from 4.3% to 14%.[1] There are different rates of prevalence and incidence of VHDs between industrialized and developing countries and limited number of studies have been conducted regarding VHDs in Iran as a developing country, therefore, we conducted this study in order to determine the rates of postoperative complications and mortality in patients underwent heart valve replacement surgery in one of the tertiary center in our country.

Materials and Methods

After approval of the study protocol was granted by the Institutional Review Board, this prospective cross-sectional study was conducted at Rajaie Cardiovascular Medical and Research Center, Tehran, Iran, from June 2011 to January 2012. This paper represents the results of the dissertation. There were 436 cases that underwent heart valve replacement surgery during this time interval; however 116 patients were excluded from this study due to exclusion criteria including concomitant coronary artery bypass graft surgery or other cardiac operations and simultaneous repair of complex congenital heart defects. Therefore, 320 adult cases (186 female and 134 male patients) with a mean age of: 45.7 ± 15.0 were enrolled in this study. The data gathering forms were designed based on scoring system for reporting mortality and morbidity after cardiac valve interventions, European association for cardio-thoracic surgery.[5] All the required data, including present and history of the patients, echocardiographic data and preoperative and postoperative electrocardiogram parameters were studied. The incidence of intraoperative and early postoperative (in hospital) complications including; valve-related events (paravalvular leakage, thrombosis, endocarditis, and mismatch), worsening function of simultaneously repaired valve, arrhythmia and general complications [cerebrovascular accident (CVA), deep vein thrombosis, re-exploration due to massive bleeding and tamponade, myocardial ischemia]; and mortality were also evaluated for all the cases. Statistical analyses were performed with SPSS for Windows (version 15, SPSS Inc., Chicago, IL, USA). Differences were analyzed with Student's t-test for the values of a scaling term and Pearson's chi-square test for nominal values. $P < 0.05$ was considered to be statistically significant.

Results

Among 320 adult cases, 186 (58.1%) were females and 134 (41.9%) were males with a mean age of: 45.7 ± 15.0 years (minimum: 14 years, maximum: 83 years). Preoperative demographic data were analyzed, and the mean value of body mass index (BMI) among cases was 24.8 kg/m^2, and 43.1% of the patients had normal BMI (range from 18.5 to 25.0 kg/m^2). Fifty-five patients (17.2%) had a history of hypertension (HTN), 20 cases (6.3%) had a history of diabetes mellitus (DM), 16 patients (5%) suffered from CVA, and 6 patients (1.9%) suffered from chronic renal failure before surgery. Among total, 205 patients (64%) had a history of cardiac interventions and percutaneous trans-venous mitral commissurotomy was the most frequent intervention (45 cases). Regarding New York Heart Association Functional Classification (FC), 92 cases (28.8%) were in FC I, 119 patients (37.2%) were in FC II, 95 cases (29.7%) were in FC III and 14 patients (4.4%) were in FC IV. The preoperative echocardiography revealed that 94 cases (29.4%) had normal left ventricular (LV) systolic function, 144 cases (45%) had mild [ejection fraction (EF) ≥ 45-50%], 57 cases (17.8%) had moderate (35% < EF < 45%) and 25 cases (7.8%) had severe (EF ≤ 35%) LV dysfunction based on the preoperative echocardiography reports. Regarding right ventricular (RV) systolic function, 78 cases (24.4%) had normal RV function, however, 83 cases had mild [17 mm ≤ tricuspid annular plane systolic excursion (TAPSE) < 20 mm and S velocity ≥ 9 cm/s], 129 cases had moderate TAPSE (≥ 15-17 mm or S velocity > 7-9 cm/s) and 30 cases had severe TAPSE (< 15mm or S velocity ≤ 7 cm/s) RV dysfunction. About 125 cases (39.1%) had a history of one time cardiac surgery, while 14 cases (4.4%) had ≥ 2 times history of cardiac operations. Elective surgery was performed for 308 cases (96.3%), while 12 patients (3.7%) required emergent valve replacement. The frequencies of different procedures regarding the types of the operated valves have been demonstrated in table 1. Regarding the number of the operated valves for 69 patients (21.6%), 2 valves were replaced and in 5 cases (1.6%) 3 valves were replaced. Biologic valves were used in 36 cases (11.2%) while metallic valves were used in 284 patients (88.8%). Postoperative complications were occurred in 85 patients (26.6%), including: valve-related events (7 cases), arrhythmia

(24 cases), worsening function of the repaired valve (16 cases) and general complications (38 cases). The relationships between the incidence of postoperative complications and different factors including demographic data and type of the repaired valves have been demonstrated in tables 2 and 3. Mortality was occurred in 25 patients (7.8%) before discharge due to cardiac problems:10 cases (3.1%) including arrhythmia: 6 patients (1.9%), heart failure and cardiogenic shock: 4 cases (1.3%) and non-cardiac problems: 15 cases (4.7%) including bleeding due to coagulopathy: 6 patients (1.9%), CVA or encephalopathy: 2 cases (0.6%), respiratory failure: 3 cases (0.9%), septicemia: 3 cases (0.9%) and multi-organ failure: 1 (0.3%). The relationships between the incidence of postoperative mortality and different factors including demographic data and type of the repaired valve have been demonstrated in tables 4 and 5.

Table 1. The frequencies of different valve replacement procedures

Operated valve	Frequency	Percent
MVR	120	37.5
AVR	72	22.5
PVR	44	13.8
TVR	10	3.1
MVR-AVR	56	17.5
MVR-TVR	7	2.2
MVR-AVR-TVR	5	1.6
AVR-PVR	1	0.3
AVR-TVR	2	0.6
PVR-TVR	3	0.9
Total	320	100

MVR: Mitral valve replacement; AVR: Aortic valve replacement; PVR: Pulmonary valve replacement; TVR: Tricuspid valve replacement

Table 2. The relationship between the incidence of postoperative complications and demographic data

Evaluated factors	Valve related events n (%)	P	Worsening function of repaired valve n (%)	P	Arrhythmia n (%)	P	General events n (%)	P
Gender								
Male	2 (3.4)	0.471	5 (8.5)	0.377	6 (10.1)	0.081	16 (27.1)	0.976
Female	5 (5.0)		11 (11.0)		18 (18.0)		22 (22.0)	
Age								
< 25	3 (20.0)		2 (13.3)		1 (6.7)		3 (20.0)	
25-45	8 (21.6)		2 (5.4)		8 (21.6)		11 (29.7)	
45-65	18 (21.4)	< 0.001	9 (10.7)	0.254	11 (13.1)	0.180	17 (20.2)	0.063
65-75	1 (5.9)		3 (50.0)		4 (23.5)		6 (35.3)	
> 75	1 (16.7)		-		-		1 (16.7)	
Systolic function/dysfunction								
Normal	3 (6.1)		12 (24.5)		15 (30.6)		8 (16.3)	
Mild	3 (4.2)	0.463	3 (4.2)	0.365	2 (2.8)	0.632	21 (29.6)	0.632
Moderate	-		1 (3.6)		6 (21.4)		9 (32.1)	
Severe	1 (9.1)		-		1 (9.1)		-	
Type of prosthetic valve								
Biologic	-	0.341	3 (18.7)	0.330	1 (6.2)	0.254	4 (25.0)	0.880
Metallic	7 (4.9)		13 (9.1)		23 (16.1)		34 (23.8)	
History of cardiac OP								
No	4 (4.4)		9 (10.0)		13 (14.4)		18 (20.0)	
1 time	3 (5.1)	0.840	5 (8.5)	0.250	10 (16.9)	0.944	16 (27.1)	0.100
≥ 2 times	-		2 (20.0)		1 (10.0)		4 (40.0)	

OP: Operation

Table 3. The relationship between the incidence of postoperative complications and type of the repaired valve

Postoperative complications	Frequency	AVR	MVR	PVR	TVR	MVR-AVR	MVR-AVR-TVR	AVR-TVR	MVR-TVR	PVR-TVR	P
Valve related events	7	1	4	0	0	2	0	0	0	0	0.962
Worsening function of repaired valve	16	2	7	2	0	3	0	1	1	0	0.227
Arrhythmia	24	3	14	0	1	3	1	0	1	1	0.167
General complication	38	7	3	1	3	10	2	1	1	0	0.304

AVR: Aortic valve replacement; MVR: Mitral valve replacement; PVR: Pulmonary valve replacement; TVR: Tricuspid valve replacement

Table 4. The relationship between the incidence of postoperative mortality and demographic data

Evaluated factors	Mortality [n (%)]	P
Gender		
Male	9 (6.71)	0.555
Female	16 (8.60)	
Age (year)		
< 25	1 (2.38)	
25-45	4 (3.84)	
45-65	9 (6.71)	< 0.001
65-75	7 (24.10)	
> 75	4 (36.30)	
Past medical history		
HTN	9 (16.36)	< 0.001
DM	7 (35.00)	< 0.001
CRF	1 (16.66)	0.415
CVA	1 (6.25)	0.473
NYHA FC		
FC I	5 (5.43)	
FC II	7 (5.88)	0.039
FC III	9 (9.47)	
FC IV	4 (28.57)	
Systolic function/dysfunction		
Normal	6 (6.38)	
Mild	11 (7.63)	0.290
Moderate	4 (7.01)	
Severe	4 (16.00)	
History of operation		
No	13 (7.18)	
1 time	11 (8.80)	0.838
≥ 2 times	1 (7.14)	
Priority of the surgery		
Elective	18 (5.84)	< 0.001
Emergent	7 (58.33)	
Number of repaired valve		
1	17 (6.43)	
2	7 (10.14)	0.600
3	1 (20.00)	

HTN: Hypertension; DM: Diabetes mellitus; CRF: Chronic renal failure; CVA: Cerebrovascular accident; NYHA FC: New York Heart Association Functional Classification

Table 5. The relationship between the incidence of postoperative mortality and type of the repaired valve

Operated valves	Mortality [n (%)]	P
AVR	7 (9.7)	
AVR-TVR	1 (50.0)	
MVR	9 (7.5)	
MVR-AVR	4 (7.1)	0.099
MVR-AVR-TVR	1 (20.0)	
MVR-TVR	2 (28.6)	
TVR	1 (10.0)	
Total	25	

AVR: Aortic valve replacement; TVR: Tricuspid valve replacement; MVR: Mitral valve replacement

Discussion

The burden of heart valve disease among adults is enormous in the developing countries. The high prevalence of rheumatic heart disease remains the predominant contributor to heart valve dysfunction, which if uncorrected lead to congestive heart failure and increased morbidity and mortality. Heart valve replacement is the second most common type of heart surgery after coronary artery bypass graft surgery.[4] Geissler et al. declared in their study that 30,000 heart valve replacement surgeries are performed annually due to increase in prevalence of degenerative valve diseases in developed countries.[5] Regarding the increased rate of this type of procedure in this study we evaluated the incidence of complications and mortality following heart valve replacement surgery. Regarding the risk model to predict the incidence of mortality and morbidity after aortic and/or mitral valve replacement or repair in the study of Ambler et al. the significant factors were age, gender, female, BMI > 20 kg/m^2, renal failure, HTN, diabetes, arrhythmia, EF and the number of previous cardiac surgeries.[6] Similar to our study, the incidence of postoperative events were higher in female patients. In contrast to the study of Ambler et al. the incidence of valve-related events was significantly higher in group of patients with age 25-45 years.[6] The mentioned result may be due to more mitral valve replacement requirement in younger adults that essentially accompanies more complications compared with aortic and pulmonary valve replacement. However, there was no significant relation between preoperative LV EF, type of the prosthetic valve, the number of previous cardiac operations and the incidence of postoperative events. In the study of Shahian et al.[7] and O'Brien et al.[8] the incidence of mortality following heart valve replacement surgery was 4.3-14.0%. In our study, this criteria was occurred in 7.8% of the cases. In the study of Shinn et al. mortality rate was reported in 6.9% of cases who underwent heart valve replacement surgery, and the contributor factors were old age, preoperative renal failure, postoperative pulmonary events and stroke.[9] Based on European system for cardiac operative risk evaluation (Euroscore), significant factors for the incidence of mortality and morbidity following heart valve replacement surgery are: old age, female gender, chronic obstructive pulmonary disease, neurologic dysfunction, history of recent cardiac surgery, renal dysfunction, impaired ventricular function, emergency cardiac surgery, and pulmonary HTN. In our study, mortality rate was higher in

female group with no significant difference. The incidence of mortality was significantly more in old age group (age > 75 years) and patients who underwent emergent procedures. There was a statistically significant relation between the incidence of mortality and the history of HTN and diabetes. Also the type of the prosthetic valve, the anatomic site of the repaired valve and the number of repaired valves were reported as the significant factors for the incidence of mortality.[7,8] In contrast, in our study, no significant relation was reported between the incidence of mortality and the mentioned factors. This difference may be due to the different study population in the study by Shahian et al.[7] The cases in the study of Shahian et al. underwent valve replacement surgery in addition to coronary artery bypass grafting.[7]

Conclusion

Based on the results, age, presence of DM, HTN, high grade of functional capacity and multivalve disease are significant predictors of post-valvular replacement morbidity and mortality.

Acknowledgments

We express our thanks to the research department of the Rajaei Cardiovascular Medical and Research Center.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Samiei N, Hakimi MR, Mirmesdagh Y, Peighambari MM, Alizadeh-Ghavidel A, Hosseini S. **Surgical outcomes of heart valves replacement: A study of tertiary specialized cardiac center.** ARYA Atheroscler 2014; 10(5): 233-7.

Carotid intima-media thickness and plasma fibrinogen among subjects with metabolic syndrome: Isfahan cohort study, Iran

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Original Article

Abstract

BACKGROUND: The role of plasma fibrinogen, a key regulator of inflammation processes and increased carotid intima-media thickness (cIMT) to predict metabolic syndrome (MetS) is currently under investigation. We assessed differences in the indicators of cIMT and also plasma fibrinogen level between MetS and non-MetS subjects. We also assessed the role of these two parameters for independently relationship with MetS state.

METHODS: The subjects in this cross-sectional survey were population-based samples of 93 men and women aged ≥ 35 years and over who were selected from the Isfahan cohort study, Isfahan, Iran. Fibrinogen was measured by the clotting assay of Clauss. Ultrasound studies of the carotid artery were performed to measure cIMT. MetS defined based on the National Cholesterol Education Program's Adult Treatment Panel III.

RESULTS: The mean level of plasma fibrinogen was not different in the two groups with and without MetS (240.10 ± 27.80 vs. 242.56 ± 35.82, P = 0.714), but the mean of cIMT was considerably higher in MetS group than in non-MetS group (0.85 ± 0.06 mm vs. 0.66 ± 0.09 mm, P < 0.001). Using a multivariable logistic regression model, high cIMT could effectively predict MetS state with the presence of different components of MetS (odds ratio = 17.544, 95% confidence interval = 2.151-142.860, P = 0.008). The optimal cutoff point of cIMT for discriminating these two clinical states was 0.6 mm yielding a sensitivity of 61.5% and a specificity of 59.6%.

CONCLUSION: Individuals with MetS demonstrated increased cIMT values compared with those without MetS. However, high plasma fibrinogen level may not be associated with MetS state.

Keywords: Metabolic Syndrome, Carotid Intima-Media Thickness, Fibrinogen, Prediction

Date of submission: 24 Mar 2014, ***Date of acceptance:*** 10 May 2014

Introduction

Subclinical atherosclerosis in great vessels is one of the clear identified results of cardio-metabolic abnormalities like metabolic syndrome (MetS). One of the most important atherosclerotic-mediated changes is increased carotid intima-media thickness (cIMT) and hence has been agreed as a well-established surrogate index of coronary and cerebral atherosclerotic events.[1] According to recent evidences, this vascular event can be shown following appearance of MetS and its progression may be also prevented by spontaneous recovery from this syndrome.[2] Even, it has been indicated that MetS is more predictive of cIMT than the sum of the individual components of the syndrome.[3,4] However, while there are some reports that increased cIMT may not be associated with each of MetS components such as insulin resistance.[5] In this

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regard, evidences on associations between MetS and atherosclerosis as well as increased cIMT are eagerly waited for.

The role of plasma fibrinogen, a key regulator of inflammation processes, as a cardiovascular risk factor remains controversial. Some surveys could demonstrate that higher plasma fibrinogen concentrations were associated with a greater incidence of coronary heart disease and its progression.[6-10] Besides, increased age-adjusted plasma level of fibrinogen has been revealed to be associated with a cluster of cardiovascular risk factors and MetS components including obesity, high blood pressure, and dyslipidemia.[11] It is evidenced that some major components of MetS such as central obesity may be linked to elevation in plasma fibrinogen concentration through the mediation of blood pressure, C-reactive protein, as well as via being affected by cigarette smoking.[12] In this context, considering hyperfibrinogenemia as a main component of MetS has been recently recommended.

In the present study, we followed two targets: first, we assessed differences in the indicators of cIMT and also plasma fibrinogen level between MetS and non-MetS subjects. Second, we assessed the role of these two parameters for independently predicting MetS state.

Materials and Methods

The subjects in this cross-sectional survey were population-based samples of 93 men and women aged ≥ 35 years and over (power of study: 80%, α = 5%) who were selected by random sampling from the Isfahan, Iran, cohort study that was performed in 2001 in three central provinces in Iran, including Isfahan, Arak, and Najafabad and enrolled 6504 participants with the aim of detecting the incidence of cardiovascular diseases and its-related major risk factors.[13] The subjects with a history of any cardiovascular or related disorders, pregnant women, breastfeeding mothers, and those subjects with serious systemic illnesses from the study. The protocol of this study was approved by the Research and Ethics Committees of the Isfahan Cardiovascular Research Institute. The individuals enrolled in this study were informed about the aims of the investigation and those who agreed signed informed consent forms. All participants were asked to fast for 8-12 h before attending the first visit in order to obtain demographics information, medical history, to conduct clinical examination and venous blood samples for lab tests. In this regard, venous blood samples were drawn in vacuum tubes containing sodium citrate as an anticoagulant. Blood samples were centrifuged at 2500 rpm for 10 min to obtain plasma. The plasma was separated and stored at −70 °C for 2 weeks until the measurement. Fibrinogen was measured by the clotting assay of Clauss,[14] using a commercially available kit in the same laboratory. Serum total cholesterol was measured by enzymatic methods, and high-density lipoprotein (HDL) cholesterol was measured after heparin-manganese precipitation using the Liebermann–Burchard method using an autoanalyzer (Eppendorf, Hamburg, Germany). Hypercholesterolemia was defined as total cholesterol 240 mg/dl, HDL-cholesterol < 40 mg/dl in men, and < 50 mg/dl in women, triglycerides ≥ 240 mg/dl.[15] Serum glucose was measured by enzymatic methods. Diabetes mellitus was defined as serum glucose of 140 mg/dl or more fasting and/or blood glucose of 200 mg/dl or more non-fasting and/or taking hypoglycemic medication.[15] Measurement of blood pressure and anthropometric parameters were carried out following standard protocols.[16,17] Height in stocking feet and weight in light clothing were measured, and body mass index was calculated as weight (kg)/height (m^2) using Seca Stadiometer (Germany, 2009). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with a standard mercury sphygmomanometer on the right arm of seated participants after a 5-min rest. Hypertension was defined as SBP of 140 mmHg or more and/or DBP of 90 mmHg or more and/or taking antihypertensive medication.[15] MetS was defined based on the presence of three or more components of the defined criteria for MetS by the amended National Cholesterol Education Program's Adult Treatment Panel III (ATP-III).[16] The ATP-III criteria include: (1) fasting triglycerides > 150 mg/dl or lipid medications; (2) SBP > 130 mmHg, DBP > 85 mmHg, or use of antihypertensive medications; (3) fasting plasma glucose > 110 mg/dl or use of diabetes medications; (4) HDL cholesterol < 40 mg/dl (men) or < 50 mg/dl (women); and (5) waist circumference > 102 cm (men) or > 88 cm (women). Using the previous criteria we found 39 patients who were diagnosed to have MetS and 54 patients without MetS. Ultrasound studies of the carotid artery were performed to measure cIMT from the posterior wall of the left common carotid artery about 10 mm proximal from the bifurcation.[17] Incident high cIMT or plaque was defined as those with cIMT ≥ 90th percentile[18] that was estimated 0.75 in the present study by one observation.

Shapiro–Wilk and Kolmogorov–Smirnov test was used to check the normality of data distribution. Bartlett's test was used to check the homogeneity of variances. Differences in sex-specific mean values and proportions of baseline characteristics were compared between people who developed MetS and those who remained free of MetS by using a t-test or chi-square test. Logistic regression models were used to examine the relations of plasma fibrinogen and cIMT with the incidence of MetS. Correlation between the quantitative variables was tested by the Pearson's test. A receiver operating characteristic (ROC) curve was used to identify the best cutoff point of both fibrinogen and cIMT values by which to maximize the sensitivity and specificity of discriminating MetS from non-MetS conditions. For the statistical analysis, statistical software SPSS for Windows (version 19.0, SPSS Inc., Chicago, IL, USA) was used. P-values of 0.05 or less were considered statistically significant. All probability values were two-tailed.

Results

The characteristics of study subjects by MetS status and those without MetS are presented in table 1; 39 subjects (41.9%) had MetS. The two study groups were statistically similar in the average age, history of smoking, and serum level of low-density lipoprotein (LDL); while those with MetS were more female as well as had a higher prevalence of obesity, hypertension, hyperlipidemia, and diabetes mellitus. The mean level of plasma fibrinogen was not different in the two groups with and without MetS (240.10 ± 27.80 vs. 242.56 ± 35.82, P = 0.714), but the mean of cIMT was considerably higher in MetS group than in non-MetS group (0.85 ± 0.06 mm vs. 0.66 ± 0.09 mm, P < 0.001). Applying a linear regression modeling, among different definitive components of MetS, higher waist to hip ratio [β = 0.331, standard error (SE) = 0.138, P = 0.029], serum total cholesterol level (β = 0.002, SE = 0.001, P = 0.021), and high LDL cholesterol level (β = 0.002, SE = 0.001, P = 0.040) were positively associated with cIMT. However, none of the MetS components was associated with the level of plasma fibrinogen.

Considering 0.75 mm as the cut-off for high cIMT showed higher incidence of high cIMT in MetS group compared with non-MetS group (25.6% vs. 1.9%, P < 0.001). No significant association was revealed between plasma level of fibrinogen and cIMT in both MetS group (r = 0.018, P = 0.913) and non-MetS group (r = −0.052, P = 0.714). Using a multivariable logistic regression model (Table 2), it was shown that high cIMT could effectively predict MetS state with the presence of different components of MetS [odds ratio = 17.544, 95% confidence interval (CI) = 2.151-142.860, P = 0.008]. In this context, high level of plasma fibrinogen was not a determinant for MetS status. According to the ROC curve analysis (Figure 1), cIMT measurement had an acceptable value for discriminating MetS from non-MetS states [Area under curve (AUC) = 0.746, 95% CI = 0.644-0.848, P < 0.001]. The optimal cut-off point of cIMT for discriminating these two clinical states (Figure 2) was 0.6 mm yielding a sensitivity of 61.5% and a specificity of 59.6%.

Table 1. Baseline data in two groups with and without metabolic syndrome

Characteristics	Group with MetS (n = 39)	Group without MetS (n = 54)	P
Male gender	15 (38.5)	35 (67.3)	0.006
Hyperlipidemia	35 (89.7)	25 (48.1)	< 0.001
Diabetes mellitus	8 (20.5)	3 (5.8)	0.033
Hypertension	17 (43.6)	7 (13.5)	0.001
Cigarette smoking	7 (17.9)	18 (34.6)	0.078
High intima-media thickness	10 (25.6)	1 (1.9)	0.001
Body mass index (kg/m^2)	32.46 ± 5.52	26.71 ± 5.26	< 0.001
Waist to hip ratio	0.97 ± 0.06	0.89 ± 0.06	< 0.001
Fasting blood sugar (mg/dl)	100.87 ± 44.75	84.88 ± 14.35	0.018
Total cholesterol (mg/dl)	210.56 ± 41.79	193.33 ± 29.55	0.023
Serum triglyceride (mg/dl)	244.36 ± 134.56	119.06 ± 48.25	< 0.001
HDL (mg/dl)	41.41 ± 9.67	47.83 ± 11.77	0.005
LDL (mg/dl)	117.90 ± 24.87	111.67 ± 19.64	0.201
SBP (mmHg)	133.83 ± 19.38	119.62 ± 15.01	< 0.001
DBP (mmHg)	84.10 ± 10.06	76.63 ± 7.90	< 0.001
Plasma fibrinogen	240.10 ± 27.80	242.56 ± 35.82	0.083
Intima-media thickness (mm)	0.85 ± 0.06	0.66 ± 0.09	< 0.001
Age (year)	44.82 ± 6.09	47.31 ± 8.87	0.136

MetS: Metabolic syndrome; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; SBP: Systolic blood pressure
DBP: Diastolic blood pressure

Table 2. Multivariate logistic regression model for determining value of high intima-media thickness and plasma fibrinogen to predict metabolic syndrome

Variables	P	Odds ratio	95% Confidence interval
High intima-media thickness	0.008	17.544	2.151-142.860
Plasma fibrinogen	0.395	0.991	0.970-1.012
Male gender	0.095	0.228	0.040-1.293
Age	0.139	0.906	0.796-1.032
Body mass index	0.028	1.210	1.021-1.435
Hyperlipidemia	< 0.001	35.546	4.889-258.443
Diabetes mellitus	0.670	1.603	0.184-13.991
Hypertension	0.007	15.848	2.093-119.993
Cigarette smoking	0.696	1.462	0.217-9.846

Hosmer–Lemeshow goodness of fit: χ^2 = 20.564; P = 0.008

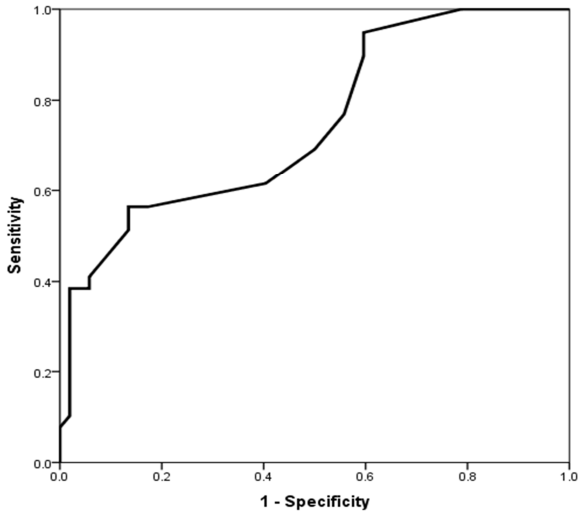

Figure 1. Receiver operating characteristic curves were constructed to investigate the diagnostic power of the intima-media thickness for predicting metabolic syndrome (area under curve = 0.746, 95% confidence interval = 0.644-0.848; P < 0.001)

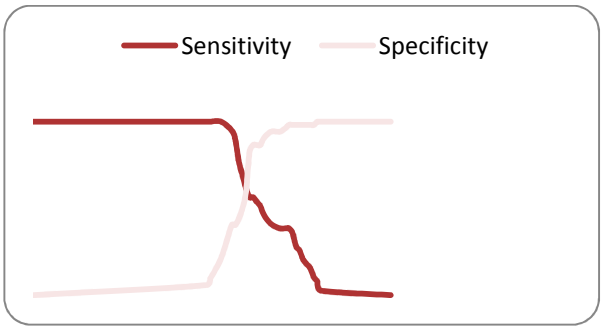

Figure 2. Optimal cutoff value of intima-media thickness for prediction of metabolic syndrome (best cutoff point was 0.6 mm)

Discussion

MetS significantly associated with increased cIMT in our cross-sectional study sourced from Isfahan prospective cohort analysis, and the association between MetS and incident high cIMT was considerably attenuated after controlling or different components of MetS in a multivariate logistic regression model. These findings suggest that the high cIMT can be an integral part of MetS. A variety of studies could show association between MetS and high cIMT. Reinehr et al. showed in subjects with MetS demonstrated increased intima-media thickness (IMT) values compared those without MetS.[4] In another study, MetS strongly predicted incident high cIMT, defined as cIMT > 90th percentile and/or plaque.[19] In this regard, it is now suggested that a combination of different components of MetS may have synergistic effects on existence and progression of carotid plaques resulting increased cIMT. Timoteo et al. could demonstrate that advanced age, male gender, insulin, and HDL cholesterol were independent predictors of cIMT. They showed that in patients without MetS, only age and HDL cholesterol were associated; while, in MetS group, independent predictors were age, male gender, and high serum glucose.[19] Tonstad et al. suggested that the classic lipid and hemostatic risk factors, as well as plasma total homocysteine, were associated with markers of early carotid atherosclerosis from the second decade of life.[20] According to the results of the Framingham study, the introduced Framingham risk factors accounted for 28.6% and 27.5% of the variability in the common carotid artery and internal carotid artery IMT, respectively. Furthermore, age and gender contributed 23.5% to the variability of the common carotid artery IMT and 22.5% to that of the internal carotid artery IMT, with the next most important factor being SBP (1.9%) for the common carotid artery IMT and smoking (1.6%) for the internal carotid artery IMT.[21] In another observation by Shiri et al., obesity, high LDL cholesterol, high triglycerides, hypertension and cardiac arrhythmia were associated with increased IMT in subjects aged 30-44.[22] Oren et al. also showed that

age, body mass index, pulse pressure, sex, and LDL cholesterol level were independent determinants of increased cIMT in young adults.[23] In our survey, higher waist to hip ratio, high serum total cholesterol level, and high LDL cholesterol level were positively associated with cIMT that is consistent with several previous studies.

Regarding the association between MetS state and plasma fibrinogen level, we found no significant association between these two parameters. On the other hand, although relation between inflammatory processes and MetS has been shown in some studies, but association between fibrinogen as an inflammatory index and MetS and its-related components was not meaningful in our study. Imperatore et al. showed that age-adjusted fibrinogen levels correlated significantly with obesity, SBP and DBP, plasma total cholesterol, LDL cholesterol, triglycerides, insulin, and HDL cholesterol inversely.[11] In a study by Ford,[24] participants with the MetS had higher fibrinogen concentrations than those without this syndrome. Besides, the association between fibrinogen level and MetS was only demonstrated in women, not in men in Onat et al. study.[12] On the other hand, MetS was not significantly predicted by fibrinogen levels in women in either multivariable model and thus plasma fibrinogen predicts MetS independently of its components in men, in contradistinction to women. It seems that our paradoxical findings may be affected by different factors such as selecting a population with a narrow range for plasma fibrinogen concentration, a wide range of the patients' age, as well as considering a partial small sample size and therefore achieving a moderate study power. Hence, for more investigation of the association of plasma fibrinogen concentration and MetS state, further studies should be conducted in our population.

Our results are limited to our small size but in this is the first report in Iranian sample, which focused on the relationship of cIMT and fibrinogen and would be provide a view of the procedure in this population.

Conclusion

Our study demonstrate that measuring cIMT can help to predict MetS state, however measuring plasma fibrinogen has no this potential predictive role. In fact, association between MetS and cIMT can be mediated by the presence of some MetS components including waist to hip ratio, high serum total cholesterol level, and high LDL cholesterol level.

Acknowledgments

This study was conducted as thesis. We are thankful to the team of the ICRC, Isfahan Provincial Health Center, Najaf-Abad Health Office and the Arak University of Medical Sciences.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Bayanfar Z, Sadeghi M, Heidari R, Gharipour M, Talaie M, Sedaghat A. **Carotid intima-media thickness and plasma fibrinogen among subjects with metabolic syndrome: Isfahan cohort study.** ARYA Atheroscler 2014; 10(5): 238-43.

Coronary artery disease and plasma apolipoprotein E4 in mild cognitive impairment

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Original Article

Abstract

BACKGROUND: Atherosclerosis and apolipoprotein E4 (APOE4) are known risks for Dementia. We sought to evaluate the relationship between coronary atherosclerosis and APOE4 with mild cognitive impairment (MCI).

METHODS: In a case-control study, subjects with age more than 60 years and recent coronary angiography were evaluated by mini-mental state examination and neuropsychiatry unit cognitive assessment tool (NUCOG) to find the patients with MCI (n = 40) and the controls with normal cognition (n = 40). Coronary angiography records were re-assessed to find the severity of coronary artery disease by the Gensini scores. Plasma levels of APOE4 were measured.

RESULTS: There were no-significant difference between the 2 groups regarding the plasma APOE4 levels (P = 0.706) and the Gensini scores (P = 0.236). Associations between the Gensini scores and the NUCOG scores in the MCI group (r = −0.196, P = 0.225) and the control group (r = 0.189, P = 0.243) were not significant. However, the interaction effect between the Gensini and the NUCOG scores based on allocation to the control or the patient groups showed statistically significant difference ($F_{(1,67)}$ = 4.84, P = 0.031).

CONCLUSION: Although atherosclerosis has been considered as known risk factor for dementia and MCI, this study could not reveal that coronary atherosclerosis-related to declining in cognitive functioning. There was no significant association between plasma APOE4 levels and MCI.

Keywords: Mild Cognitive Impairment, Coronary Artery, Angiography, Apolipoprotein E4

Date of submission: 9 Mar 2014, ***Date of acceptance:*** 7 Jul 2014

Introduction

World population is growing older. In the United States, the proportion of the population over 65 years has increased from 3.1% in 1900 to 13.2% by 2010.[1] The same trend has been observed other developed and in developing countries. In Iran, more than 5 million people are over 60 years, which is 7.26% of the population. It is estimated that more than 10% of the population will be in old age by 2030.[2]

Dementia is one of the most common health problems in the elderly population with estimation of 5-8% prevalence rate in people 65-70-year-old. This rate doubles every 5 years by aging.[3] It is defined as a progressive impairment of cognitive function including difficulties with memory, language, visuospatial skills, praxis, attention, and executive functioning. The deficits would result in significant impairment in personal, social, or occupational functioning.[3] Neuropathological cascades leading to dementia starts decades before the clinical manifestations. Therefore, there is a prolonged transitional time with gradual cognitive decline between the normal state and overt dementia. This period has been named "mild cognitive impairment" (MCI).[3,4]

MCI is characterized by cognitive deterioration that is confirmed by family members and proved in

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neuropsychological tests without influence on activities of daily living. MCI is sub-classified into two forms: amnestic MCI (a-MCI), which includes predominant memory deficit and non-amnestic MCI (na-MCI), which is characterized by deficit in cognitive domains other than memory such as language, visuospatial skills, and executive functioning.[3] MCI affects 12-18% of individuals over 65 years. It will progress to dementia in 10-15% of cases within a year, and this number is increasing each year.[3,5] MCI has an increasing rate by aging.[3] Lower education is another risk factor for MCI.[6] Late-life depression is also hypothesized to increase the risk for cognitive impairment.[3] The other frequently proposed risk factor is lower brain reserve The concept of brain reserve indicates to the effects of brain size and neuron density, which means higher brain reserve may lead to protection against clinical manifestations of MCI despite the presence of neurodegeneration and vice versa.[3] Apolipoprotein E4 (APOE4) polymorphism in some, but not all, studies was found as a risk factor.[7-9] Similarly, vascular risk factors such as hypertension, diabetes, and hyperlipidemia have been reported as possible risk factors for MCI.[10,11] Cross-sectional studies revealed association between MCI and vascular diseases such as stroke, transient ischemic attack, cerebral hemorrhage, and peripheral artery disease.[6]

Ischemic heart diseases (IHD) are among the prevalent illnesses in the elderly population. Currently, the prevalence of IHD is about 21.10% for men and 10.60% for women at age of 60-79 years in the United States.[12] In one study in Iran, the prevalence of coronary artery disease (CAD) was reported 37.50% for women and 22.20% for men up to age 35 years that increased with aging.[13] Some researches have reported a relation between IHD and MCI. In one study, about 37-45% of candidates for coronary artery bypass graft had MCI.[14] In neuroimaging and post-mortem studies of patients who had history of CAD, despite absence of clinical dementia, degenerative changes and amyloid plaques were found in their brains.[15,16] Increased prevalence of silent myocardial infarction was reported in Alzheimer's disease and, to a lesser extent, in MCI.[17] Lima et al. reported that atherosclerosis extent in CAD is associated with severity of cognitive decline.[18] According to the study by Siuda et al., in MCI group with vascular risk factors more intensive dysfunction in learning ability, short-term memory, delayed recall and operational memory were found.[4] In most of these studies, however, IHD were only diagnosed based on the clinical criteria and objective results of coronary angiography were not considered.[14,18]

Diagnosis of MCI has been mainly based on clinical manifestations and neuropsychological evaluations.[3] Many research groups are working on MCI biomarkers for early diagnosis, faster treatment, better prevention, rising prognosis, and planning of rehabilitation programs.[4] Of these biomarkers, neuroimaging parameters, biochemical measures, and genetic markers have repeatedly been used.[15,19,20]

Parameters that indicate to vascular or endothelial health and atherosclerosis may also be considered as cognitive function biomarkers and may point to possibility of MCI.[21] In contrast to use of coronary angiography as an objective, reliable, and valid method for estimation of atherosclerosis in IHD,[22] measurement of cerebral atherosclerosis by cerebral angiography, especially in small sized arteries has not been possible. Coronary angiography parameters involve severity and location of stenosis and efficiency of collateral arteries in the heart.[23] Despite invasiveness, it is a routine procedure. About 1.5 million patients underwent coronary angiography in the United States in 2011 for precise diagnosis of CAD.[22]

In this study, we evaluated the relation of plasma APOE4 level and coronary angiography parameters with cognitive performance in different domains in MCI patients and control individuals. We sought to find if coronary angiography findings could use as an indirect index for possible MCI.

Materials and Methods

This case-control study included subjects above 60 years with elementary or higher education. Subjects should undergo coronary angiography in the recent year. They were selected from patients who admitted to cardiac catheterization units of Sina and Nour Hospitals, Isfahan, Iran, from March 2012 to October 2012. The study design was scientifically and ethically discussed and approved by the deputy of research and technology, Isfahan University of Medical Sciences, Isfahan, Iran. Subjects with a history of major psychiatric disorders, substance misuse, head trauma, serious medical disease, and dementia were excluded. A total of 1625 subjects were screened based on inclusion and exclusion criteria to select 40 cases and 40 controls (Figure 1). The study process was explained for all subjects and written informed consent was obtained.

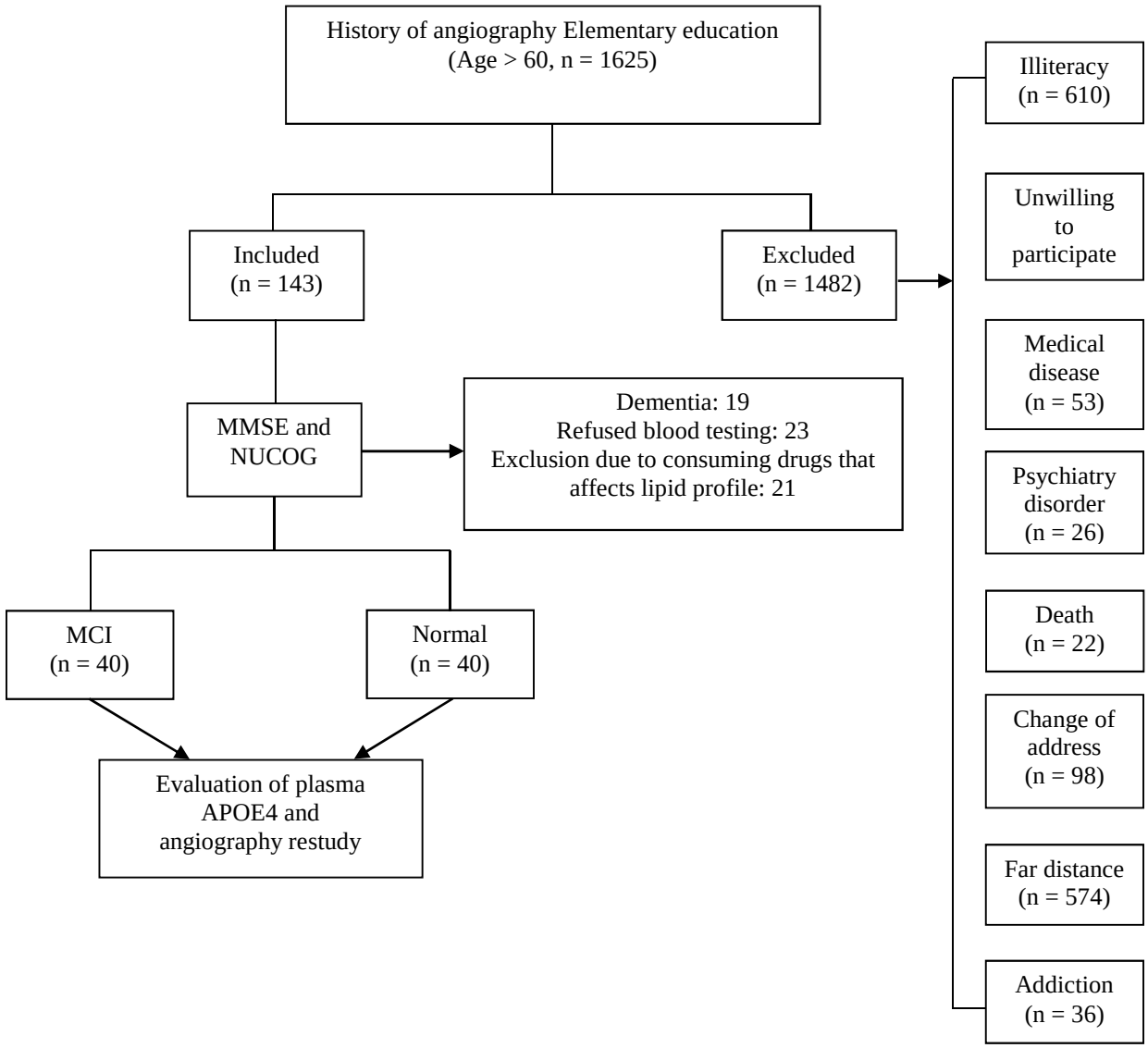

Figure 1. The flow chart of the study
MMSE: Mini-mental state examination; NUCOG: Neuropsychiatry unit cognitive assessment tool; MCI: Mild cognitive impairment

Subjects underwent neuropsychiatric interview considering Peterson`s criteria for MCI.[3] Mini-mental state examination (MMSE) scores from 21 to 26 were utilized for validation of MCI diagnosis. Subjects, with MMSE scores more than 26, were considered normal controls.[24]

We used neuropsychiatry unit cognitive assessment tool (NUCOG) to confirm the diagnosis of MCI and as a dependent variable. The NUCOG provided five distinct cognitive domains including attention, memory, executive function, language, and visuoconstruction.[25] The NUCOG scores more than 86.5, between 75 and 86.5, and lower than 75 were considered normal cognitive state, MCI, and dementia respectively in Iranian population.[26]

In both groups, coronary angiography records were re-assessed by an expert cardiologist (MH). The Gensini score was used as valid and reliable indicator for coronary arteries atherosclerosis. It was calculated by the multiplying severity of stenosis by the segment location by collateral adjustment factor. Increase in the Gensini score means more severity of coronary artery atherosclerosis.[23]

History of cigarette smoking, hyperlipidemia, diabetes, hypertension, and familial history of Alzheimer`s disease were asked. General health questioner was administered for all participants. In physical examination, blood pressure, pulse rate, height, and weight were recorded, and body mass index was calculated. Plasma triglycerides, total cholesterol, fasting blood glucose, and creatinine were measured. Plasma APOE4 level was evaluated by

enzyme-linked immunosorbent assay plate rever kit.[27]

Independent t-test and Chi-square test were used to compare baseline variables. Pearson correlation test was used to find the associations. Analysis of covariance and multivariate analysis of covariance were used to find the effect of Gensini scores and plasma APOE4 level on cognitive state scores. Statistical significance was set at $P < 0.050$.

Results

This study included 40 subjects with MCI (33 men and 7 women) as patient group and 40 subjects with normal cognitive state (29 men and 11 women) as a control group.

Baseline characteristics of subjects were summarized in table 1.

The Gensini scores, plasma APOE4 levels, and NUCOG scores were demonstrated in table 2. There were no significant difference between the two groups regarding the plasma APOE4 levels ($P = 0.706$) and the Gensini scores ($P = 0.236$). Relationships between plasma APOE4 levels and the NUCOG scores in the MCI group ($r = 0.114$, $P = 0.483$) and the control group ($r = 0.127$, $P = 0.435$) were not significant. Association between plasma APOE4 levels and the Gensini scores in the MCI group ($r = -0.110$, $P = 0.500$) and the control group ($r = 0.014$, $P = 0.933$) were not significant.

Increasing Gensini scores accompanied with decreasing NUCOG scores in the MCI group. However, it was not significant ($r = -0.196$, $P = 0.225$). In the control group, the increasing Gensini scores jointed with increasing NUCOG scores but it was not significant ($r = 0.189$, $P = 0.243$). However, the interaction effect between the Gensini and the NUCOG scores based on the allocation to the control or the MCI groups showed statistically significant difference ($F_{(1,67)} = 4.84$, $P = 0.031$) (Figure 2). On the other hand, the interaction effect between the plasma APOE4 levels and the NUCOG scores based on the allocation to the control or the MCI groups did not show statistically significant relationship between the MCI and the control groups ($F_{(1,67)} = 0.32$, $P = 0.575$).

The scores of the NUCOG subscales in its five different cognitive domains were displayed in table 2. The relations between the Gensini scores and each of the five different cognitive domains are shown in table 3.

Table 1. Baseline characteristics and cardiovascular risk factors

Characteristic	MCI (n = 40)	Control (n = 40)	P
Age (year)	65.3 ± 4.1	65.7 ± 4.1	0.627
Education (year)	9.5 ± 3.8	10.2 ± 3.2	0.073
GHQ score	17.0 ± 7.8	18.4 ± 8.5	0.463
BMI (kg/m^2)	25.8 ± 2.9	25.3 ± 2.2	0.428
SBP (mmHg)	127.8 ± 13.7	126.6 ± 12.8	0.675
DBP (mmHg)	78.7 ± 9.1	80.2± 7.7	0.422
Fasting glucose (mg/dl)	124.5 ± 44.6	121 ± 47.4	0.733
Total cholesterol (mg/dl)	163.9 ± 39.6	165.7 ± 50.6	0.858
Triglycerides (mg/dl)	158.5 ± 98.4	143.8 ± 89.1	0.488
Creatinine (mg/dl)	1.3 ± 0.3	1.3 ± 0.4	1.000
Sex			
Male [n (%)]	33 (82.5)	29 (72.5)	0.284
Female [n (%)]	7 (17.5)	11 (27.5)	
Smoker [n (%)]	6 (15.0)	11 (27.5)	0.172
Diabetes [n (%)]	16 (40.0)	15 (37.5)	0.818
Hypertension [n (%)]	22 (55.0)	16 (40.0)	0.179
Hyperlipidemia [n (%)]	16 (40.0)	20 (50.0)	0.369
Family history of dementia [n (%)]	7 (17.5)	6 (15.0)	0.762

Continuous variables are represented as mean ± SD and categorical variables as frequency (percentage) BMI: Body mass index GHQ: General health questioner; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SD: Standard deviation

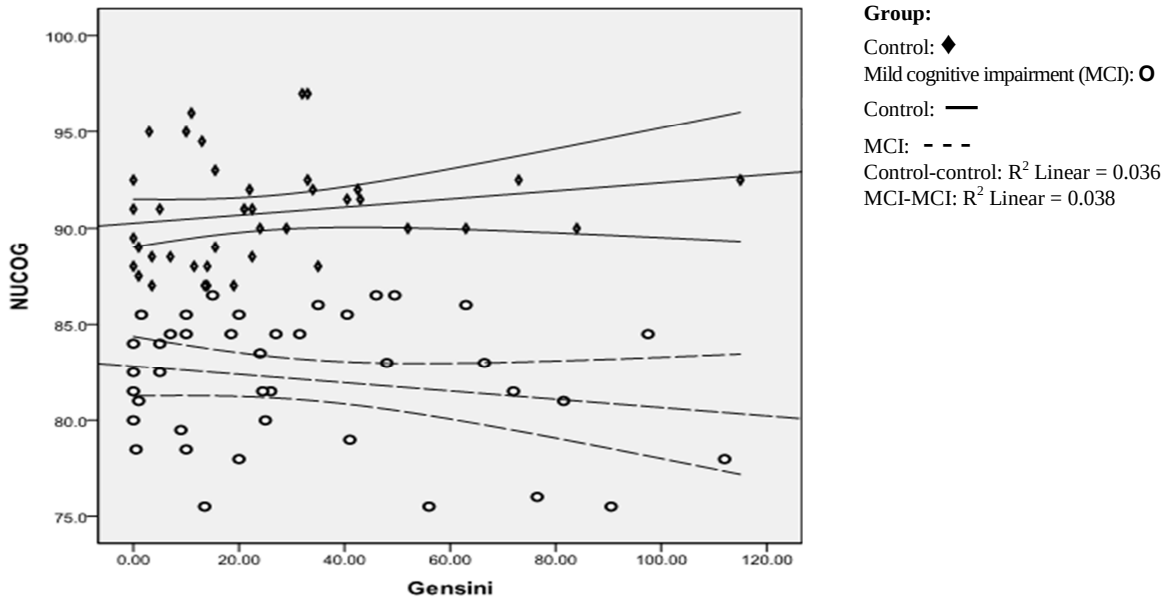

Figure 2. Correlation between the Gensini and the Neuropsychiatry Unit Cognitive Assessment Tool Scores in the mild cognitive impairment and the control groups

Table 2. Neuropsychological performance, Gensini scores and apolipoprotein E4 levels in the mild cognitive impairment and the control groups

Characteristics	MCI (n = 40)	Control (n = 40)	P
Gensini scores	31.9 ± 30.4	24.5 ± 23	0.236
APOE4 level	36.1 ± 40.5	32.3± 48.2	0.706
NUCOG	82.1 ± 3.3	90.7 ±2.7	< 0.001
Attention	13.6 ± 1.4	15.3 ± 1.6	< 0.001
Visuospatial	17.8 ± 1.5	19.2 ± 1	< 0.001
Memory	15.4 ± 1.9	18 ±1.5	< 0.001
Executive function	16 ± 1.9	18.3 ± 1.4	< 0.001
Language	19.2 ± 0.7	19.7 ± 0.3	< 0.001

APOE4: Apolipoprotein E4; NUCOG: Neuropsychiatry unit cognitive assessment tool
MCI: Mild cognitive impairment

Table 3. Correlation between Gensini scores and cognitive domains of Neuropsychiatry Unit Cognitive Assessment Tool in the mild cognitive impairment and the control groups

Cognitive domains	Correlation with Gensini scores in control group	Correlation with Gensini scores in MCI group
Attention	r = -0.090 P = 0.581	r = -0.228 P = 0.157
Visuospatial	r = -0.205 P = 0.204	r = -0.016 P = 0.923
Memory	r = 0.084 P = 0.608	r = 0.067 P = 0.681
Executive function	r = 0.233 P = 0.149	r = -0.176 P = 0.278
Language	r = -0.013 P = 0.936	r = -0.078 P = 0.633

MCI: Mild cognitive impairment

Discussion

We investigated the association between plasma APOE4 levels in the MCI group and cognitively normal controls. We could not find significant relationship between the plasma APOE4 levels and cognitive functioning in the MCI group (r = 0.114, P = 0.483) or the control group

(r = 0.127, P = 0.435). APOE4 allele is a genetic biomarker for dementia, especially of Alzheimer type. However, the extent to which this allele also predicts the development of MCI is unclear.[7] Risacher et al. reported that MCI patients have significantly more APOE4 allele than control subjects (40.70% vs. 24.45%).[8] In the study by Robert et al., there was a significant association of APOE4 carrier status with a-MCI but not na-MCI.[28] In contrast, another study revealed that the frequency of the APOE4 genotype did not differ between individuals with MCI and cognitively normal subjects (12.90% vs. 18.40%).[7] It would be concluded that APOE4 allele may be a risk factor for a-MCI. However, if MCI is considered as a single entity, which contains both a-MCI and na-MCI, this conclusion may not be found. The MCI patients in this study included both types of a-MCI and na-MCI that resulted in decreased power to reveal correlation between APOE4 level and cognitive function.

There were no significant correlations between cognitive performance and other risk factors such as elevated Plasma cholesterol, diabetes, increased blood pressure, and smoking in our study. In some studies, vascular risk factors including elevated Plasma cholesterol in midlife, diabetes, increased diastolic blood pressure, smoking, brain infarcts, and white matter brain lesions, have been suggested as risk factors for MCI.[10,29-31] In contrast, other reports did not confirm the role of vascular risk factors for cognitive impairment in non-demented MCI subjects.[12,32]

We also could not find any significant association between the Gensini scores and cognitive functioning in the MCI group (r = −0.196, P = 0.225) and in the control group (r = 0.189, P = 0.243). However, the interaction effect between the Gensini and the NUCOG scores based on the allocation to the control or the MCI groups showed statistically significant difference ($F_{(1,67)}$ = 4.84, P = 0.031) (Figure 2). There are expanding bodies of evidence pointing CAD up as a specific risk factor for cognitive decline. In the cardiovascular health study cohort, the incidence of dementia was higher in those with prevalent CAD.[33] Several studies have confirmed that CAD has been associated with cognitive impairment[11,14,34,35] reduced hippocampal volume,[35] and increased senile plaque formation in cortical areas of the brain.[16] In cross-sectional study of "age, gene, environment susceptibility-Reykjavik," Vidal et al. evaluated the computed tomography-based coronary artery calcium (CAC) measures, a measure for estimation of severity of atherosclerosis and scores on each cognitive domain. They found that lower scores on specific cognitive domains were strongly related to atherosclerotic burden, estimated by CAC load. However, adjustment for white matter lesions, silent brain infarctions, cerebral micro-bleeds, and brain volumes attenuated the observed association between CAC load and cognitive state, implicating other vascular mechanisms.[36] In a population-based study with 1969 subjects of 70-89 years old, there was a positive association between a history of angiographic coronary stenosis and na-MCI [odds ratio (OR) = 3.21)].[28] Lima et al. reported that atherosclerosis extent in CAD is associated with cognitive decline but not correlated with APOE4 Polymorphism and it's plasma level.[18] However, a few studies did not show the relation between IHD and cognitive impairment. In the study by Rafnsson et al., clinical diagnosis of IHD was neither related to initial cognitive performance nor cognitive decline after 4 years.[37] Similarly, another study found no association between MMSE scores and coronary artery events.[38] Individuals with constitutional tendency for MCI may be predisposed to lower cognitive functioning if confronted with CAD. This may not be the case for subjects who do not have MCI diathesis. Significant association between CAD and psychomotor speed and executive dysfunction was reported.[28] There was also evidence that na-MCI subtype was a more concomitant state with vascular risk factors.[5] In the study by Robert et al., CAD was identified as an independent risk factor for na-MCI, especially in women.[10] Interestingly, our study revealed that patients with higher Gensini scores in MCI group had more problems in executive functioning, although, this was not significant (P = 0.09).

Our study had a few limitations. First, it was a cross-sectional study that limited power for recognizing the risk factors. Second, we did not consider MCI subtypes for better classification of symptoms. Third, we did not consider clinical symptoms of IHD. Fourth, all participants have been treated for IHD, hypertension, hyperlipidemia, and diabetes. These interventions could have positive and negative effects on cognitive performance.

Conclusion

Although atherosclerosis has been considered as known risk factor for dementia and MCI, this study could not reveal that coronary atherosclerosis-related to declining in cognitive functioning. There was not

significant association between plasma APOE4 levels and MCI.

Acknowledgments

The information contained in this article was extracted from the thesis of Dr. Faezeh Zahedian, which was funded by Psychosomatic Research Center, Isfahan University of Medical Sciences (Grant No.: 391065). We thank to all of the staff of who work in the catheterization labs of Nour and Sina hospitals in Isfahan, Iran.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Barekatain M, Zahedian F, Askarpour H, Maracy MR, Hashemi-Jazi M, Aghaye-Ghazvini MR. **Coronary artery disease and plasma apolipoprotein E4 in mild cognitive impairment.** ARYA Atheroscler 2014; 10(5): 244-51.

Short term high dose atorvastatin for the prevention of contrast-induced nephropathy in patients undergoing computed tomography angiography

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Original Article

Abstract

BACKGROUND: Statins are shown effective by some studies in preventing contrast-induced nephropathy (CIN). We evaluated the effectiveness of atorvastatin in the prevention of CIN in computed tomography angiography (CTA) candidates.

METHODS: This study was conducted on patients referring for elective CTA with normal renal function. Patients received atorvastatin (80 mg/day) or placebo from 24 h before to 48 h after administration of the contrast material. Serum creatinine was measured before and 48 h after contrast material injection. CIN was defined as an increase in serum creatinine level of ≥ 0.5 mg/dl or ≥ 25% of the baseline creatinine.

RESULTS: A total of 236 patients completed the study; 115 atorvastatin, 121 placebo, mean age = 58.40 ± 9.80 year, 68.6% male. Serum creatinine increased after contrast material injection in both the atorvastatin (1.00 ± 0.16-1.02 ± 0.15 mg/dl, P = 0.017) and placebo groups (1.03 ± 0.17-1.08 ± 0.18 mg/dl, P < 0.001). Controlling for age, gender, comorbidities, drug history, and baseline serum creatinine level, patients who received atorvastatin experienced less increase in serum creatinine after contrast material injection (beta = 0.127, P = 0.034). However, there was no difference between the atorvastatin and placebo groups in the incidence of CIN (4.3 vs. 5.0%, P = 0.535).

CONCLUSION: In patients undergoing CTA, a short-term treatment with high dose atorvastatin is effective in preventing contrast-induced renal dysfunction, in terms of less increase in serum creatinine level after contrast material injection. Further trials including larger sample of patients and longer follow-ups are warranted.

Keywords: Kidney Diseases, Multidetector Computed Tomography, Contrast Media, Hydroxymethylglutaryl-CoA Reductase Inhibitors, Atorvastatin

Date of submission: 11 Apr 2014, ***Date of acceptance:*** 30 Jun 2014

Introduction

Computed tomography angiography (CTA) is one of the novel, non-invasive, and accurate diagnostic methods for cardiac diseases, including coronary artery and valvular diseases.[1,2] However, CTA has some complications, including contrast-induced nephropathy (CIN).[3] CIN, defined as an impaired kidney function after administration of intravascular contrast agent within 3 days of contrast injection in the absence of another cause, is one of the most common causes of acute renal failure in hospitalized patients.[4] Previous studies in patients undergoing coronary catheterization and angiography show that the incidence of CIN in patients who have no risk factors for CIN is < 2%, but the incidence in patients who are high risk for CIN is increased up to 90%.[5,6] Due to lower dose of contrast material used and characteristics of the patients, the incidence of CIN in patients undergoing CTA is much less frequent (between 2.6% and 15%) than those who undergoing coronary catheterization and angiography.[3,7-9] However, the CIN in CTA patients

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is important as well as this complication increases mortality, costs of medical care, and length of hospitalization.[6,10,11]

Suggested treatment strategies for CIN are limited to supportive cares and dialysis. Therefore, screening for high-risk patients and taking appropriate preventive regimes have an important role in reducing the incidence of CIN. Previous studies proposed some preventive medications for CIN including hydration, sodium bicarbonate, N-acetylcysteine (NAC), calcium channel blockers, diuretics, dopamine, endothelin antagonists, atrial natriuretic peptide, ascorbic acid and hemodialysis, or filtering the blood during and after the administration of contrast material. Among these strategies, the increase in extracellular volume, using intravenous saline or sodium bicarbonate, minimizing the dose of contrast material, the use of non-ionic contrast medium with low osmolarity instead of the high osmotic and ionic agents, and discontinuation of nephrotoxic drugs, and medications including NAC, theophylline, and statins have been shown effective in preventing CIN.[12-15]

In addition to regulating the lipid profile, statins have anti-inflammatory and anti-oxidative effects that can be used in preventing CIN according to its pathophysiology.[16] Recent studies evaluated the efficacy of statins in the prevention of CIN, but the results have been controversial. Meta-analyses on current randomized clinical trial concluded that the short-term treatment of high dose statins prevents CIN, but the quality of data is still unsatisfactory and further studies are required in this regard.[17,18] Studies on the effects of statins in the prevention of CIN are not enough to introduce this method as a standard method for the prophylaxis of CIN. Moreover, most of the previous studies have been performed among the patients undergoing invasive coronary angiography, and very few studies have been done in patients undergoing CTA. Therefore, this study aimed to evaluate the effectiveness of the short-term treatment with high-dose atorvastatin in the prevention of CIN in CTA candidates with normal kidney function.

Materials and Methods

This study was conducted on patients referring for elective CTA from July 2013 to February 2014 to Alzahra Hospital in Isfahan, Iran. Patients with the following characteristics were not included into the study; unstable angina, myocardial infarction, cardiac arrhythmias, heart failure, acute or chronic renal failure, serum creatinine level > 1.5 mg/dl, intravascular administration of contrast material in the past month, known hypersensitivity to statins, and those who were living out of the city and were not able to refer for the follow-up evaluation. The study was approved by the Ethics Committee of the Isfahan University of Medical Sciences and informed consent was obtained from patients before entering the study.

The study was designed as a randomized, double-blind, comparative trial with two parallel arms, including high dose atorvastatin and placebo. Patients were consecutively entered into the study and were assigned an order number. Using the Random Allocation Software (version 1.0., Isfahan, Iran),[19] two study arms of atorvastatin and placebo were randomly distributed to a set of sequential numbers. An independent investigator placed drugs in sequentially numbered, opaque and stapled, drug pockets. Allocation sequence was concealed from the investigators who enrolled patients into the study. Blinding the attending physicians and patients was achieved by administering placebo tablets identical in shape, size, and color to atorvastatin into the placebo arm. A sample of 125 patients in each group would provide us the power of 0.80 in detecting a difference of at least 10% in creatinine change between groups after operation.[20] The trial was registered in clinicaltrials.gov (ID: NCT02114346).

Patients in the atorvastatin group received 80 mg atorvastatin (two tablets of atorvastatin 40 mg, DarooPakhsh Co., Tehran, Iran) and patients in the placebo group received two placebo tablets from 24 h before to 48 h after administration of contrast material. Also, the non-steroidal anti-inflammatory drugs were discontinued from 24 h before to 48 h after the procedure.[21] The CTA was done according to the clinical standards using 64-detector rows CT scanner (Light speed VCT, GE healthcare. USA). In all cases, Iopromide (ULTRAVIST® 320 mg/100 mL, Bayer healthcare Pharmaceuticals, Berlin, Germany) was used as a contrast media. All patients received a total of 100 ml of the contrast material; 15 ml for the test bolus and 85 ml for the imaging (6 ml/s injected with injector device).

Before the operation, all the patients underwent a detailed history and physical examination by a cardiologist. Age, gender, and history of hypertension, diabetes mellitus, and dyslipidemia were recorded, and weight was measured. Cardiopulmonary examination was done for the evaluation of systolic/diastolic blood pressure and heart rate. Serum creatinine was measured before, and 48 h after contrast material injection and the amount of change was considered as the study outcome. CIN was defined as an increase in serum creatinine level of

≥ 0.5 mg/dl or ≥ 25% of the baseline creatinine after 48 h of contrast material injection.[22]

Data were analyzed using the SPSS software for Windows (version 16.0, SPSS Inc., Chicago, IL, USA). Continuous variables were checked if normally distributed in each group. Data are presented as mean ± standard deviation or number (%). The independent sample t-test, Mann–Whitney U-test, and Chi-square test were applied for comparisons between the atorvastatin and placebo groups. Paired t-test and Wilcoxon test were applied for within group comparisons. Furthermore, a linear regression model was conducted with the amount of change in serum creatinine level from baseline to 48 h after CTA as the dependent variable and baseline characteristics and intervention type as predictors. $P < 0.050$ was considered to be indicating a statistical significant difference in all analyses.

Results

During the study period, 350 patients were referred to our center for CTA from which 90 patients were not eligible to participate; 12 unstable angina, 15 serum creatinine > 1.5 mg/dl, 1 possible history of adverse reaction to atorvastatin, and 62 living out of the city and not able to refer for follow-up evaluation. 10 eligible patients were not willing to participate. A total of 250 patients were included into the trial from which 14 patients (4 in the placebo and 10 in atorvastatin groups) did not refer for the measurement of serum creatinine level 48 h after CTA and were excluded from the trial. Finally, 236 patients with a mean age of 58.40 ± 9.80 year (68.6% male) completed the study and were considered for analyses (Figure 1). Demographic data of the patients are summarized in table 1. The two groups were similar in demographic characteristics except the frequency of hypertension (79.3% vs. 64.3%, P = 0.008) and using anti-hypertensive drugs (81.0% vs. 64.3%, P = 0.003), which was higher in the placebo group.

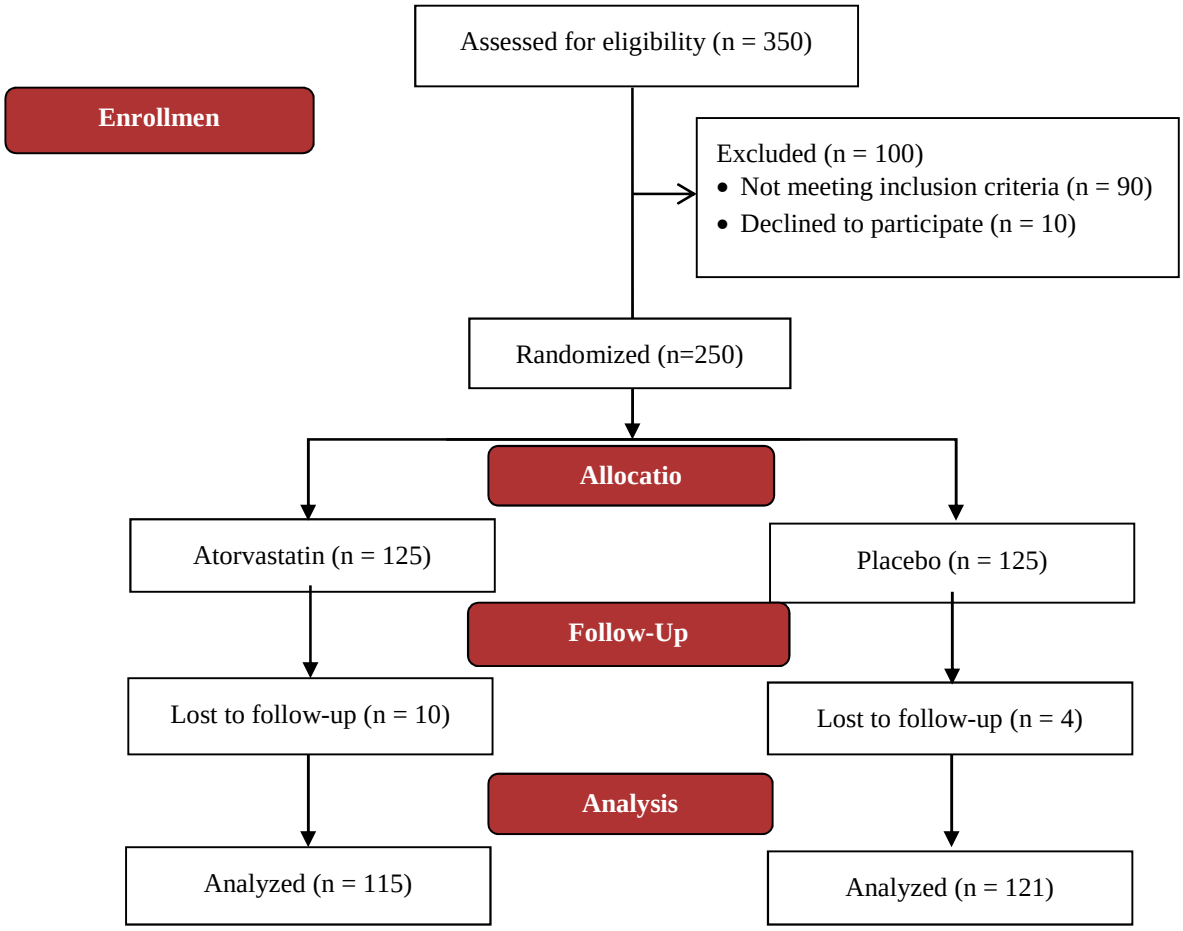

Figure 1. Patients' flow diagram

Table 1. Demographic data of the patients

Demographic data	Atorvastatin (n = 115)	Placebo (n = 121)	P
Male/female (%)	77 (67.0)/38 (33.0)	85 (70.2)/36 (29.8)	0.343†
Comorbidities			
Hypertension	74 (64.3)	96 (79.3)	0.008†
Dyslipidemia	60 (52.2)	74 (61.2)	0.104†
Diabetes	36 (31.3)	48 (39.7)	0.114†
Drug history			
Statins	63 (54.8)	62 (51.2)	0.339†
Antihypertensive	74 (64.3)	98 (81.0)	0.003†
Hypoglycemic	35 (30.4)	45 (37.2)	0.169†
Cardiac examination			
Systolic blood pressure, mmHg	124.10 ± 11.70	122.50 ± 10.90	0.176‡
Diastolic blood pressure, mmHg	79.70 ± 7.00	78.10 ± 6.10	0.071‡
Heart rate, beat/min	73.20 ± 9.50	71.50 ± 11.30	0.096‡
Age	58.10 ± 10.40	58.70 ± 9.30	0.636*

Data are presented as mean ± SD or number (%); * Independent sample t-test; † Chi-square test; ‡ Mann–Whitney U-test; SD: Standard deviation

Table 2. Comparison of study outcomes between the atorvastatin and placebo groups

	Atorvastatin (n = 115)	Placebo (n = 121)	P
Baseline creatinine (mg/dl)	1.00 ± 0.16	1.03 ± 0.17	0.231*
48 h creatinine (mg/dl)	1.02 ± 0.15	1.08 ± 0.18	0.039*
Delta creatinine (mg/dl)	0.02 ± 0.10	0.04 ± 0.09	0.076*
Creatinine change (%)	2.80 ± 10.9	4.70 ± 9.30	0.124*
P†	0.017	< 0.001	
Contrast-induced nephropathy	5 (4.3)	6 (5.0)	0.535‡

Data are presented as mean ± SD or number (%); * Mann–Whitney U-test; † Wilcoxon test; ‡ Chi-square test; SD: Standard deviation

The two groups were similar in baseline serum creatinine (Table 2). A significant change was observed in serum creatinine 48 h after contrast material injection in both the atorvastatin (1.00 ± 0.16-1.02 ± 0.15 mg/dl, P = 0.017) and placebo groups (1.03 ± 0.17-1.08 ± 0.18 mg/dl, P < 0.001). Serum creatinine at 48 h after contrast material injection was significantly higher in the placebo group as compared with the atorvastatin group (P = 0.039). However, the difference between the two groups in the amount of change in serum creatinine after contrast material injection was not statistically significant (P = 0.076). A total of 11 (4.7%) patients experienced CIN, all of them had > 25% increase in serum creatinine. There was no difference between the atorvastatin and placebo groups in this regard (P = 0.535).

Considering some differences between the study groups in baseline characteristics, a linear regression model was conducted controlling for age, gender, comorbidities, drug history, and baseline serum creatinine level. Results showed an association between intervention type (atorvastatin) with the amount of change in serum creatinine level from baseline to 48 h after contrast material injection [R^2 (adjusted) = 0.271 (0.239), beta = 0.127, P = 0.034] (Figure 2). Chronic statin pretreatment has no association in this regard (beta = −0.043, P = 0.633).

Discussion

Various interventions are evaluated for the prevention of CIN. Among the most studied medications, theophylline, NAC, and statins are shown to be effective in this regard,[23,24] with controversy on the efficacy of NAC[25] and statins.[26,27] We evaluated the effectiveness of short-term treatment with high-dose atorvastatin (4 days, 80 mg) in the prevention of CIN in CTA candidates with normal kidney function. Our study results showed that atorvastatin is effective in preventing CIN in terms of less increase in serum creatinine level after contrast material injection. However, it was not effective in reducing the incidence of CIN, a clinically important outcome.

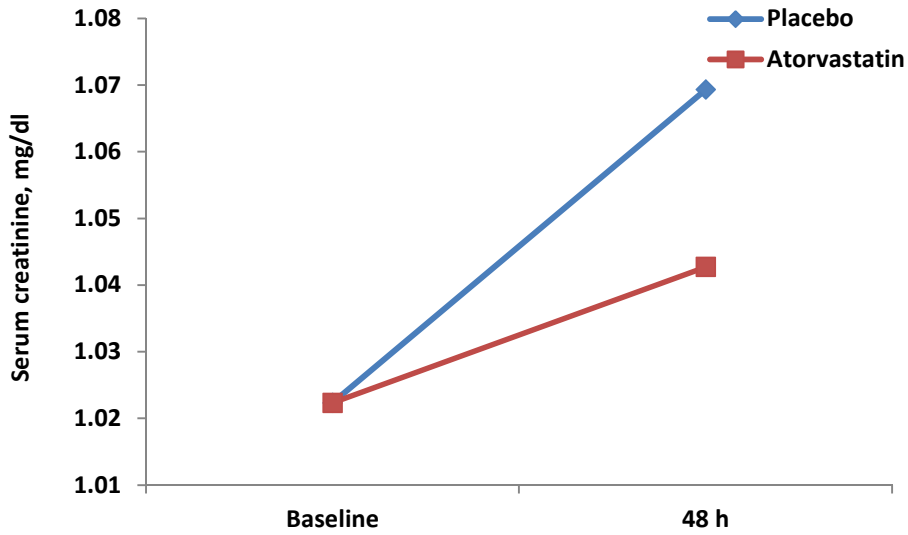

Figure 2. Change in serum creatinine level from baseline to 48 h after contrast material injection in the atorvastatin versus placebo group adjusting for demographic data and baseline characteristics

Beta = 0.127; P = 0.034

The pathophysiology of CIN is not completely clear. It seems that the contrast-induced renal dysfunction is due to a change in renal blood flow accompanied with a reduction in flow of the central part of the kidney and direct tubular epithelial toxicity. Although the meditators behind these changes are not completely identified, alteration in the metabolism of angiotensin, adenosine, endothelin, nitric oxide, and prostaglandins are proposed in this regard.[4,28,29] Statins may counteract to various pathological mechanisms underlying the CIN. These agents can decrease the activity of the angiotensin receptor,[30] decrease synthesis of endothelin and increase the bioavailability of nitric oxide,[31] leading to an increase in renal blood flow and prevention of CIN. Also, statins reduce inflammation,[32] inhibit oxidative stress reactions,[33] and protect kidney from the injuries of complements.[34]

Results of the previous studies have been controversial on the preventive effects of statins against CIN. In a meta-analysis by Zhang et al. on 4 randomized controlled trials including 751 patients, administration of statins was not effective in reducing the incidence of CIN, but it was effective in reducing the serum creatinine level by −0.06 mg/dl (95% CI -0.12-0.00 mg/dl).[18] A recent meta-analysis by Takagi and Umemoto on 7 randomized controlled trials including 1251 patients undergoing angiography showed that a short-term treatment with atorvastatin before angiography can reduce the change in serum creatinine by 0.07 mg/dl and the incidence of CIN by 44%.[17] Another meta-analysis by Zhang et al. was not conclusive due to the limitations of the included studies, albeit a preventive effect against CIN for chronic statin pretreatment is reported.[26] Although we found a protective effect for high dose atorvastatin in change of serum creatinine after contrast material injection, we found no effect for chronic low dose statin pretreatment in this regard. It must be noted that most of the previous studies were conducted on patients undergoing coronary angiography, which according to using a higher dose of contrast material in these patients, have a higher risk of CIN. Furthermore, several of previous trials have been conducted on patients with abnormal renal function. In contrast, we included patients with normal renal function undergoing CTA for whom a lower dose of contrast material is used. Also, various statins have been used in previous studies. It has been shown that atorvastatin is more effective than simvastatin in reducing the oxidative stress.[35,36] The difference among the previous study results can be due to these factors, and further studies, and head-to-head comparative trials are still required before a precise conclusion in this regard.

Our study has some limitations. First, the trial was a single-center study, which may reduce its generalizability. Second, our study sample size was small, and we were not able to show statistical significant effects of the medications in terms of

CIN incidence, which is a clinical important outcome. Finally, we monitored our patients for 48 h. Longer follow-ups can provide more information on the efficacy of preventive measures.

Conclusion

The results of this study showed that, in patients undergoing CTA, a short-term treatment with high dose atorvastatin is effective in preventing contrast-induced renal dysfunction, in terms of less increase in serum creatinine level after contrast material injection. We found no effect for chronic low dose statin pretreatment in this regard. Further trials, including larger sample of patients and longer follow-ups are warranted.

Acknowledgments

This study was supported by the Isfahan University of Medical Sciences as a residency thesis (grant # 392353). We are thankful for the Alzahra Hospital CTA Unit staff for helping us in data gathering and Dr. Ali Gholamrezaei for conducting data analyses and editing this report.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Sanei H, Hajian-Nejad A, Sajjadieh-Kajouei A, Nazemzadeh N, Alizadeh N, Bidram P, et al. **Short term high dose atorvastatin for the prevention of contrast-induced nephropathy in patients undergoing computed tomography angiography.** ARYA Atheroscler 2014; 10(5): 252-8.

Effects of oat and wheat bread consumption on lipid profile, blood sugar, and endothelial function in hypercholesterolemic patients: A randomized controlled clinical trial

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Original Article

Abstract

BACKGROUND: Increased lipid profile after each meal can disturb the endothelial function. The present study assessed the effects of bread supplemented with oat bran on serum lipids and endothelial dysfunction in patients with hypercholesterolemia.

METHODS: This clinical trial was conducted on 60 isolated hypercholesterolemic patients. The subjects were randomly allocated to either intervention (consuming at least five daily servings of oat bread with 6 g beta-glucan) or control (receiving at least five servings of wheat bread). Anthropometric indicators, fasting blood sugar and lipid profiles ere measured at baseline and after 6 weeks (in the end of the intervention). Endothelial function was assessed using flow-mediated dilation (FMD). Within the group and between group differences were investigated using paired t-test and Student's t-test, respectively.

RESULTS: Oat bread consumption could significantly reduce total cholesterol (P = 0.029). A significant increase in baseline and after ischemia brachial artery diameters at the end of the study was seen. However, it did not have a significant effect on FMD (P = 0.825). In the control group, none of the measured indices had changed significantly at the end of the study. Finally, only the mean change of brachial artery diameter after ischemia and baseline brachial artery diameter were significantly higher in the intervention group than in the control group (P = 0.036 and P = 0.012 respectively).

CONCLUSION: Oat bread with beta-glucan could successfully reduce cholesterol levels. Furthermore, in this study oat bread did not reduce FMD more than wheat bread. Since hypercholesterolemia is a proven risk factor for endothelial dysfunction, hypercholesterolemic patients can hence be advised to eat oat bread.

Keywords: Bread, Diet, Flow-Mediated Dilation, Hypercholesterolemia

Date of submission: 30 Mar 2014, ***Date of acceptance:*** 1 May 2014

Introduction

Hypercholesterolemia has been identified as a risk factor for the development of various diseases including cardiovascular diseases, diabetes, and a number of cancers.[1,2] It is also known to increase oxidative stress through decreasing access to vascular nitric oxide (NO). Such conditions will induce a potent proinflammatory state, disturb and change vascular reactivity, and finally endothelial dysfunction.[3,4]

Proper functioning of the endothelium is essential to vascular tone and regulation of blood flow in response to alterations in different organs and tissues' need for blood.[5,6] Endothelial function is affected by several mediators.[7] Hypercholesterolemia is a major risk factor for the

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incidence of endothelial dysfunction.[8,9] Great attention has been paid to the role of dietary fiber in controlling lipid and lipoprotein metabolism.[10] Fibers can reduce total cholesterol (TC) by affecting low-density lipoprotein-cholesterol (LDL-C) via different mechanisms.[11]

Potential hypocholesterolemic effects of different dietary components, for example, beta-glucan, have been recently evaluated.[12] Beta-glucan, a non-starch polysaccharide, is the fiber in barley (especially in its bran), oat, yeast, rye, and mushrooms.[13] Degroot was the first to show that a 3-week course of daily consumption of 300 g bread containing 140 g oat can reduce serum TC in men by 11%. Therefore, the Food and Drug Administration has suggested consuming 3 g/day oat to reduce serum TC.[14] Later studies have also confirmed the efficacy of beta-glucan in serum TC reduction.[15-17]

Since bran is usually separated from wheat, Iranian breads currently lack fiber, vitamins, and minerals. As this deficiency may cause different diseases, supplementing flour with beneficial compounds and hence producing proper, high-quality bread will contribute to public health. Bread is a widely used food item whose production with oat flour will allow for adding useful properties. The present study aimed to assess the effects of bread containing oat bran on serum lipid levels and endothelial dysfunction in patients with hypercholesterolemia.

Materials and Methods

This randomized controlled clinical trial was conducted on 60 patients (age: 20-60 years old) who were receiving statins for hypercholesterolemia. The subjects were selected from hypercholesterolemic participants in out-patient clinics.[18] Considering $\alpha = 5\%$, $\beta = 0.2$, standard deviation (SD) = 6, and d = 4, the sample size was calculated as n = 30 in each group using the following formula:

$$n = \left(\frac{2(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}) \times SD}{d} \right)^2$$

Individuals with diabetes type one or two, hypothyroidism, renal failure, anemia, cholestasis, pancreatic cancer or malignancy, and secondary dyslipidemia were not included. Patients who used antihypertensive drugs or alcohol, smoked, did vigorous regular exercise, had a history of eating disorders, or had weight changes (losing or gaining more than three kilogram weight during the 3 months prior to the study) were not included, either.

TC levels higher than 200 mg/dl or LDL-C levels greater than 160 mg/dl were considered as hypercholestrolemic.[3] Participants were normal in other part of their lipid profile.

Overall, 600 hypercholesterolemic participants of the third phase of Isfahan Healthy Heart Program, Iran, (IHHP) were contacted. Although 100 patients accepted to refer to the center, only 64 were found eligible after base test, medical history, and physical examinations. Moreover, four of these subjects withdrew during the course of study.

A total of 60 subjects out of 100 participants were randomly selected. They were explained about the aims, methods, benefits, and probable hazards of the study and asked to sign a consent form. Non-consenting individuals were excluded and replaced by a new randomly selected person.

Before the intervention, demographic characteristics (age, gender, and marital status) of all participants were recorded. Height, weight, pulse rate, and systolic and diastolic blood pressure (after 20-min rest, in sitting a position) were then measured. All height measurements were performed with one particular measuring tape. A Seca scale was used to measure weight for all subjects. Body mass index (BMI) was calculated as weight divided by height squared. Hip and waist circumference were also measured based on standard protocols.

After completing the questionnaires, 10 ml fasting blood samples were taken to determine serum lipid concentrations [TC, triglyceride, LDL-C, and high-density lipoprotein cholesterol (HDL-C)] and fasting blood sugar (FBS) and were measured using Autoanalyzer.

Endothelial function was assessed with flow-mediated dilation (FMD). FMD is a noninvasive technique where forearm ischemia is induced by inflating a sphygmomanometer cuff to 50-100 mmHg for 5 min. Increased blood flow after the transient ischemia increases NO levels and consequently vasodilation. In this study, a resident of cardiology used ultrasound to measure brachial artery diameter before ischemia (baseline brachial artery diameter) and immediately (< 60 s) after deflation (brachial artery diameter after ischemia). The percentage increase in vessel diameter from baseline conditions to maximum vessel diameter (FMD %) was also calculated as a measure of brachial artery endothelial dysfunction.[19]

The ultrasound system (Vivid Echo, UK) comprised 2D imaging, color Doppler, and electrocardiography. The timing of the images was synchronized with patients' echocardiograms, and all measurements were performed from the internal part of the wall to the internal part of the other wall at the end of the diastole (the peak of R wave). The process of the present study is shown in figure 1.

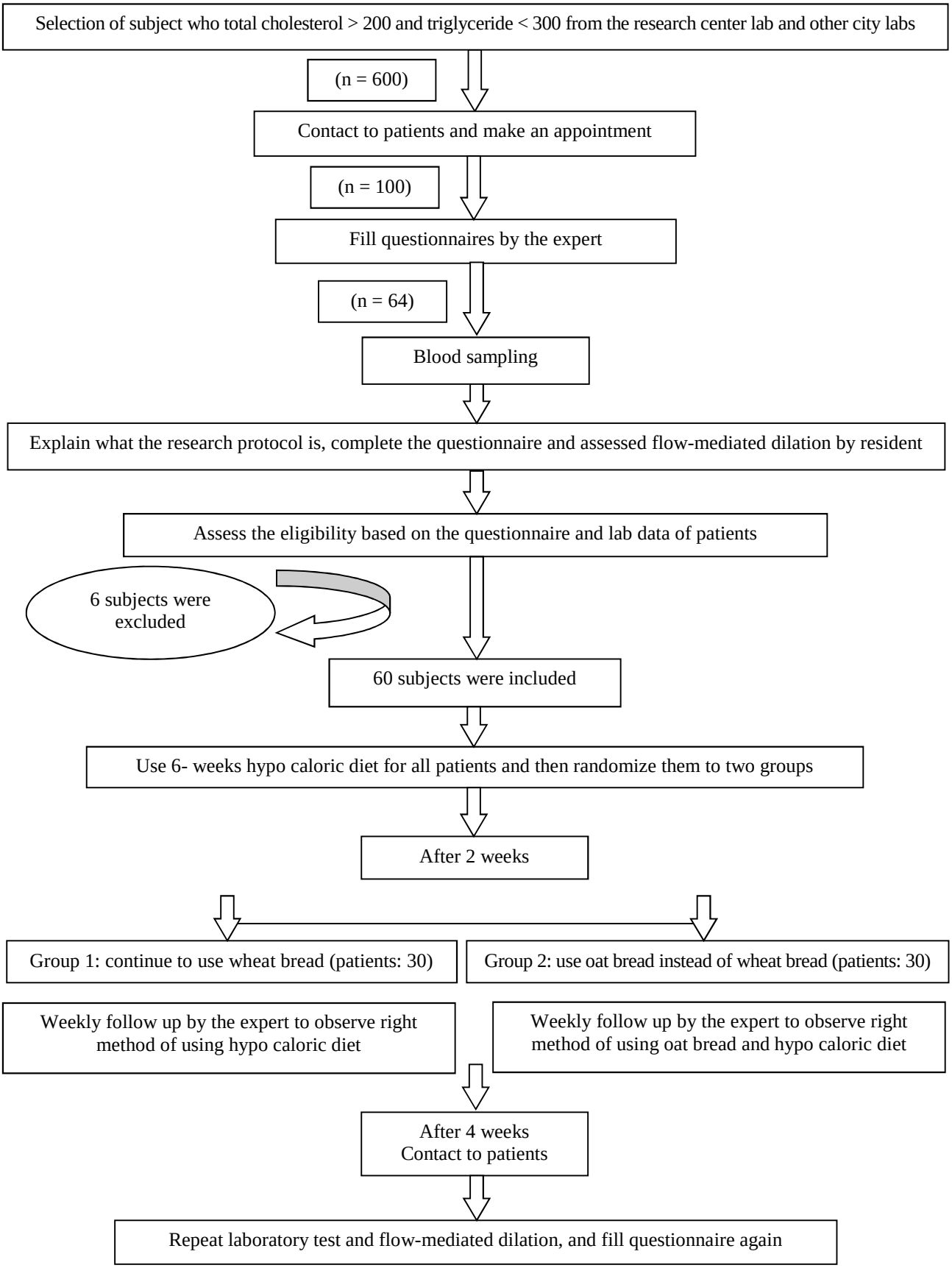

Figure 1. The chart of study process

The 6-week duration of our study was divided into a 2-week weight-maintenance phase followed by a 6-week weight-loss phase. In the first phase, all subjects had the same diet of usual food items in order to maintain their constant body weight by week 2. In the following phase, all subjects were provided with a hypo caloric diet in the calorie range of 1500-2000 for 4 weeks. Energy intake for each was calculated based on maintenance energy needs minus 500-700 kcal/d depending on their BMI. In the next stage, the participants were randomly allocated to two groups of 30 (intervention and control) with computerized random-number generator. In this phase, subjects were randomized to consume one of these diets: the intervention group received the hypocaloric diet containing an experimental bread rich in beta-glucan from oat bran [at least five servings (150 g/day) based on their needs, each serving of which had 6 g beta-glucan], and the control group consumed the hypocaloric diet with control bread rich in wheat fiber [at least five servings (150 g/day) based on their needs, with no beta-glucan]. In both phases, energy needs were predicted using the recommended dietary allowances for energy and the target macronutrient composition for all the subjects was 55% of energy as carbohydrate, 30% of energy as fat (with a focus on unsaturated fats), and 15% of energy as protein. Every week new batches of both experimental and control bread were prepared by a local bakery and then delivered at home to each subject once a week based on their request. For their next use of remaining breads, the participants were taught to deep freeze them at −18 °C. Their adherence to diet was checked weekly by a dietitian through a diary log in which the daily amounts of all consumed foods including bread were recorded. In addition, the participants were instructed to keep a detailed 3-day diet record every week that would be reviewed by a dietitian in the next visit during the 6 weeks protocol.

Both groups were asked to continue their routine levels of physical activity and not to consume fiber supplements, weight loss drugs, herbals medicines, or laxatives. During the 6-week course of the intervention, the participants attended weekly visits with the mentioned resident and nutritionist (who evaluated their daily intake of food items).

Individuals who were not willing or able to continue the study were excluded. At the end of the intervention, all initially measured variables were re-assessed.

Quantitative variables were presented as mean ± SD, while qualitative variables were compared in terms of frequency and relative frequency. Paired t-test was used to compare variables before and after the intervention. Between group, differences were evaluated using Student's t-test. All analyses were performed in SPSS for Windows (version 18.0, SPSS Inc., Chicago, IL, USA) and at a significance level of 0.05.

Results

The mean age of participants was 51.12 ± 9.31 years. Females (n = 39) constituted 65% of the study population. In the beginning of the study, the mean TC and LDL-C levels were 229.48 ± 23.33 and 131.88 ± 24.31 mg/dl, respectively. The mean FMD of all participants was 5.25 ± 2.54% in the beginning of the study and 5.35 ± 2.79% at the end.

Data normality was confirmed with Kolmogorov–Smirnov test and histograms.

The two groups were identical in terms of age, gender, and marital status. They were not significantly different in baseline anthropometric indices, systolic and diastolic blood pressure, heart rate, FBS, and blood lipids. Although there was no significant difference in baseline brachial artery diameter and brachial artery diameter after ischemia between the two groups, FMD was significantly higher in oat bread consumers than in wheat bread users.

At the end of the study oat bread consumption could significantly reduce BMI and TC. It also caused a significant increase in baseline and after ischemia brachial artery diameters. However, it did not have a significant effect on FMD. In the control group (wheat bread consumers), on the other hand, only hip circumference decreased significantly at the end of the study. Compare the final measurements of various indices between the two groups. The mean difference between baseline brachial artery diameter and brachial artery diameter after ischemia was significantly higher in the intervention group than in the control group. Although, this was the only significant difference between the two groups, at the end of the intervention course, FMD had decreased in the intervention group, but increased in the control group ($P > 0.05$) (Table 1).

Discussion

Our findings suggested the efficacy of a 6-week course of oat bread consumption in increasing baseline and after ischemia brachial artery diameters in hypercholesterolemic patients. Significant reductions in TC and BMI were also observed in oat bread consumers. However, this type of bread failed to change FMD. No such changes were seen in wheat bread consumers.

Table 1. The mean of anthropometrics variables in two groups before and after breads consumption

Variable	Bread	Before	After	P
BMI (kg/m^2)	Oat	28.94 ± 3.52	28.68 ± 3.55	0.531
	Wheat	28.99 ± 4.92	28.81 ± 4.85	
Hip circumference (cm)	Oat	105.33 ± 6.44	104.90 ± 6.39	0.631
	Wheat	106.68 ± 10.32	105.98 ± 10.28	
Waist circumference (cm)	Oat	93.42 ± 9.97	93.23 ± 9.53	0.762
	Wheat	97.60 ± 11.67	97.49 ± 11.96	
Systolic blood pressure (mmHg)	Oat	114.83 ± 10.95	112.50 ± 12.16	0.434
	Wheat	115.17 ± 14.65	114.83 ± 13.55	
Diastolic blood pressure (mmHg)	Oat	77.00 ± 9.15	76.33 ± 8.90	0.739
	Wheat	76.33 ± 10.74	75.33 ± 9.37	
Heart rate (beat/min)	Oat	71.37 ± 6.30	71.70 ± 7.07	0.535
	Wheat	72.70 ± 5.93	73.40 ± 6.43	
LDL (mg/dl)	Oat	137.40 ± 24.48	135.57 ± 30.59	0.755
	Wheat	126.37 ± 23.45	128.90 ± 23.82	
HDL (mg/dl)	Oat	52.17 ± 11.92	51.20 ± 10.38	0.306
	Wheat	50.10 ± 11.67	52.30 ± 14.90	
Triglyceride (mg/dl)	Oat	179.67 ± 63.14	177.40 ± 63.49	0.628
	Wheat	172.93 ± 59.40	165.83 ± 74.56	
TC (mg/dl)	Oat	234.90 ± 27.05	227.57 ± 30.88	0.748
	Wheat	224.07 ± 17.76	219.27 ± 33.86	
FBS (mg/dl)	Oat	87.97 ± 8.39	91.10 ± 11.17	0.070
	Wheat	92.30 ± 9.58	89.93 ± 6.71	
Baseline brachial artery diameter (mm)	Oat	3.48 ± 0.68	3.55 ± 0.67	0.050
	Wheat	3.67 ± 0.54	3.66 ± 0.55	
Brachial artery diameter after ischemia (mm)	Oat	4.15 ± 0.65	4.25 ± 0.66	0.014
	Wheat	4.22 ± 0.54	4.24 ± 0.55	
FMD change (%)	Oat	5.99 ± 2.85	5.91 ± 2.73	0.867
	Wheat	4.54 ± 1.99	4.77 ± 2.77	

BMI: Body mass index; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TC: Total cholesterol; FBS: Fasting blood sugar; FMD: Flow-mediated dilation

Several studies have confirmed the benefits of beta-glucan in reducing serum cholesterol. A double-blind, multicenter study on 345 individuals in Canada compared the effects of diets including wheat fiber and four different doses and molecular weights of beta-glucan during a 4-week course. It found that the breakfast having beta-glucans with moderate or high molecular weight could significantly reduce LDL-C.[15] In a clinical trial on 43 male and female hypercholesterolemic patients, Biorklund et al. reported that 5 weeks of drinking soup with 4 g beta-glucagon significantly reduced LDL-C and TC levels.[16] Another clinical trial on 152 female and male patients with high LDL-C levels revealed that the oat (with 3 g beta-glucan) consumers had significantly lower LDL-C and TC levels compared to corn consumers.[17] Similarly, the present research indicated significant cholesterol reductions in patients who used bread containing beta-glucan. Although reduced cholesterol was also observed among wheat bread consumers, this difference was not significant. Since changes in cholesterol levels at the end of the study were not significantly different between the two groups, the reductions seen in both groups could have been partly caused by the hypocaloric diet.

Despite significant reductions in cholesterol levels, FMD did not significantly change in oat bread consumers. As hypercholesterolemia has been suggested to result in endothelial dysfunction, various clinical trials have sought for pharmaceutical and non-pharmaceutical methods to treat this disease. A great deal of research about the effects of medicines on serum lipids and endothelial function has clarified the benefits of cholesterol-lowering drugs on endothelial function.[20-22] Non-pharmaceutical methods have also identified the considerable effects of cholesterol-lowering food items.[23,24] In general, brachial artery has a larger diameter in hypercholesterolemic subjects than in normal individuals. In addition, endothelial dysfunction decreases FMD to levels lower than normal in these patients.[25] The results of the current study regarding baseline brachial artery diameter and

brachial artery diameter after ischemia were similar to those reported by previous studies on hypercholesterolemic individuals.[23-25]

Other studies have suggested improved endothelial function following the treatment of hypercholesterolemia.[20-25] In the present study, however, FMD in oat bread consumers had no significant change despite the reduction in cholesterol and increment of baseline brachial artery diameter and brachial artery diameter after ischemia. The reason might have been an increase in both baseline brachial artery diameter and brachial artery diameter after ischemia or the short period and low dose of oat consumption in the studied population. Nevertheless, the majority of studies in this field have been similar to ours in terms of duration and dose of beta-glucan administration. On the other hand, since our participants were selected from hypercholesterolemic patients in the third phase of IHHP (in 2007), the subjects had already been suffering from hypercholesterolemia for 5 years. Due to such long duration of the disease, the desirable response could have required longer course of treatment or greater dose.

Furthermore, the presence of other risk factors (e.g., BMI > 28 kg/m^2, mean waist circumference > 90 cm) should not be ignored. Knowing that obesity and overweight are effective in the development of endothelial dysfunction, unimproved FMD can be justified by the failure to reduce weight to normal (changes in BMI were too little in oat bread consumers). While we did not assess the number of risk factors such as smoking and immobility, future studies are recommended to assess subjects without other risk factors.

Oat bread consumption could significantly reduce cholesterol levels. Therefore, adding oat flour to bread can be beneficial to treat high cholesterol in hypercholesterolemic patients.

Conclusion

Overall, oat bread could successfully reduce cholesterol levels. However, changes in cholesterol levels were not significantly different between the two groups. Furthermore, in spite of increased baseline brachial artery diameter and brachial artery diameter after ischemia among oat bread consumers, FMD showed no significant change. Since hypercholesterolemia is a proven risk factor for endothelial dysfunction, its long-term treatment may affect FMD. Hypercholesterolemic patients should hence be advised to eat oat bread. Further studies with a longer course of treatment and higher dose of beta-glucan are suggested to assess subjects with a shorter history of the disease.

Acknowledgments

This study was a residency thesis (number 392059) funded by the Research Deputy of School of Medicine, Isfahan University of Medical Sciences, Iran. It has been registered in Iranian Registry of Clinical Trials (IRCT201312073733N3). The authors appreciate the mentioned deputy and Isfahan Cardiovascular Research Center for their kind cooperation in performing ultrasound and blood test.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Momenizadeh A, Heidari R, Sadeghi M, Tabesh F, Ekramzadeh M, Haghighatian Z, et al. **Effects of oat and wheat bread consumption on lipid profile, blood sugar, and endothelial function in hypercholesterolemic patients: A randomized controlled clinical trial.** ARYA Atheroscler 2014; 10(5): 259-65.

Dietary intakes and leptin concentrations

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Review Article

Abstract

BACKGROUND: Leptin, a peptide contained 146 amino-acids, is mostly secreted from adipose tissue and it has a critical role on regulation of body weight, body fat mass, appetite, and food intakes. We tried to review the previous evidence regarding the effects of dietary intakes, including consumption of carbohydrates, fats and protein on concentrations of leptin concentration.

METHODS: We searched in PubMed search engine to January 2013 by using the following key words: dietary intake, diet, dietary fat, high-fat diet, dietary carbohydrate, high carbohydrate diet, dietary protein, high protein diet in combination with leptin, adipokine. Then, we recruited 35 articles to review in the present study.

RESULTS: It seems that beside the amount of fats, type of fatty acids have the key roles on circulating leptin concentration. Energy intake also significantly associated with the hormone. Studies regarding the association between carbohydrate intake and concentration of lepton have been reached to contradictory results. It seems that protein intake can increase the lepton activity.

CONCLUSION: Findings from several studies suggest that a diet display an important role on change the concentration of lepton.

Keywords: Diet, Carbohydrate, Protein, Fat, Leptin

Date of submission: 16 Jun 2013, ***Date of acceptance:*** 9 Oct 2013

Introduction

Leptin, a 16 kDa protein, is a peptide contained 146 amino-acids that are discovered in 1994. Leptin is mostly secreted from adipose tissue, and it has a critical role on regulation of body weight and also body fat mass.[1-3] It markedly regulates energy expenditure, appetite, thermogenesis and food intakes. Leptin caused to increase fatty acids oxidation and decrease triglyceride synthesis and so that it attenuates lipogenic action of insulin and increases insulin sensitivity of muscle and liver. This hormone has the favorable effect on glucose homeostasis.[4-7] Given the key role of leptin on regulation of body weight and prevention of obesity, it seemed that leptin levels were decreased during the elevation of body weight.[8] But according to a large body of evidence, most obese humans have higher circulations of leptin.[9] It has been indicated that obesity might induces state of leptin resistance.[10]

Inactivation of leptin receptors enhance leptin resistance and reduces satiety, and it enhances the risk of obesity.[5] Therefore, treatment of obesity tends to increase leptin action in central nervous system (CNS), which is able to decrease food intake and body fat through the reduction of energy intakes.[1,5,8]

Expression and secretion of leptin is enhanced by estrogen, tumor necrosis factor-α, corticosteroids as well as glucose and insulin. In contrast, T_4, growth hormone, catecholamine, androgens and free fatty acids suppress the expression of this hormone.[11,12] Among these parameters, diet-related factors display the important roles on augmentation and amelioration of this hormone.[13-19]

Among diet-related factors, dietary components including consumption of beverages, fatty acids, proteins and carbohydrates have been shown to have a significant association with concentrations of leptin.[1,15,20-22] However, contradictory results are found in this regard. Based on several evidence diets rich in polyunsaturated fatty acids (PUFA) (ω_3 and ω_6) leads to increase circulating of leptin compared to diet rich in monounsaturated fatty acids (MUFA) and saturated fatty acids (SFA),[20] In contrast, according to some studies consumption of ω_3 fatty acids showed a reduction in leptin gene expression.[23,24] High carbohydrate diet might

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increase leptin sensitivity in some studies.[5,8] Beside percent consumption of carbohydrate, glycemic index and glycemic load of carbohydrate also have been indicated to have a critical role on concentrations of leptin.[16]

In this review article, we tried to review the previous evidence regarding the effects of dietary intakes, including consumption of carbohydrates, fats and protein on concentrations of leptin and also explain about potential underlying mechanism in this regard.

Materials and Methods

To investigate the relationship between dietary intakes and concentrations of leptin, we searched in PubMed search engine from 2000 to January 2013 using the following key words to the topics: dietary intake, diet, dietary fat, high fat diet, dietary carbohydrate, high carbohydrate diet, dietary protein, high protein diet in combination with leptin, adipokine. All 265 articles with design of clinical trial, cohort and cross-sectional studies have been reviewed. 35 articles were recruited in this study, and others were excluded owing to lack of the direct relation with this issue, duplication and lack of full-text articles. Studies that investigated among association between dietary intakes and leptin concentrations are shown in table 1.

Table 1. Studies regarding the association between dietary intakes and concentrations of leptin

Study	Type of study	Numbers/sex	Age (year)/BMI	Design and aim	Duration of study	Results
1	Parallel	55 obese men and women	Age: 25.7 ± 5.4 BMI: 23.0 ± 2.3	Effect of diets with 3 types of fat (olive, rapeseeds, sunflower oil)	2 weeks diet with SFA and 4 intervention diets	Serum levels of leptin effect on diet rich in α-linoleic acids
6	Parallel	18 women and men	Age: 45.3 ± 13.6 BMI: 27.1 ± 2.3	Effect of high carbohydrate low fat on serum level of leptin (35% fat, 45% CHO, 20% protein) compared to (15% fat, 65% CHO, 20% protein)	2 weeks weight maintenance, 2 weeks isocaleric and 12 weeks weight loss diet	No change was found in level of leptin and increase in leptin sensitivity
8	Cross sectional	31 (women and men) cirrhosis patients and 10 controls	Age: 54-57 BMI: 25.7-56.5	Assessing the association between energy intakes and leptin	-	No significant relationship was found
9	Parallel	19 lean and obese women	Age: 21.5 ± 1.9 BMI: 21.6 ± 1.8 Age: 34.6 ± 7.8 BMI: 49.8 ± 6.9	Isocaleric meals: 166 g CHO, 38 g protein and 70 g fat, 36 g protein	-	Significant lower levels of leptin after carbohydrate meals in obese women compared to lean women
16	Parallel	19 women and men	Age: 41 ± 11 BMI: 26.2 ± 2.1	Effect of high protein diet on leptin (50% CHO, 35% fat, 15% protein) compared to (50% CHO, 20% fat, 30% protein)	2 weeks normal diet with weight maintenance 2 weeks isocarelie high protein diet, 12 weeks high protein weight loss diet	Greater status of satiety with no change in plasma leptin after high protein diet
17	Cross sectional	165 healthy overweight and obese women in postmenauposal status	Age: 60.73 ± 6.7 BMI: 30.5 ± 3.9	Assessing the association between habitual dietary intakes and leptin	-	Inverse relationship between consumption of high carbohydrate and fat with hormone
18	Parallel	13 lean and overweight men	Age: 18-27 BMI: 20.8 ± 0.7 30.8 ± 1.7	High carbohydrate, low fat meals (80% CHO, 17% protein, 3% fat)	3 days	No significant difference was found
19	Parallel	200 women	Age: 100 women with ≤ 50 100 women: > 50 BMI: 25.7	Diet rich in fruits, vegetables and fiber with low amount of fat	12 months	Had no effect on leptin

Table 1. Studies regarding the association between dietary intakes and concentrations of leptin (Continue)

Study	Type of study	Numbers/sex	Age (year)/BMI	Design and aim	Duration of study	Results
20	Cross sectional	60 men and women with Type 1 diabetese	Age: 22.8 ± 6.8 BMI: 22.7 ± 2.3	Assessing the association between consumption of SFA and PUFA and lepton	-	Positive relationship with consumption of SFA and lepton in men/ positive and negative association between linolenic acid and arashidonic acids and leptin, respectively
25	Experimental	344 female rats	-	High fat diet in comparison with low fat with complex carbohydrate	20 months	Increase in plasma level of hormone by the high fat diet
26	Cross over	9 men and women	Age: 20-37 BMI: 18-26	High carbohydrate diet with different in glycemic index and fat in 4 groups	8 days	17% greater in diets with high glycemic index
27	Experimental	rats	-	Effect of type of fat in low calorie diet on leptin	10 weeks	60% increase in leptin concentration among fish oil and sunflower oil fed compared to beef tallow fed
28	Cross sectional	211 male and 205 female of Japanese-American in Hawaii and Japanese in Japan	Age: 40-59 BMI: < 25 and ≥ 25	Assessing the association between energy intake and serum leptin concentration	-	Inverse relationship between energy intake and serum level of leptin in obese persons
29	Parallel	44 healthy male	Age: 43 ± 5 BMI: 27.3 ± 3.2	Effect of low calorie diet on plasma leptin	4 days	39.4% decrease in leptin by the energy restricted diet

BMI: Body mass index; PUFA: Polyunsaturated fatty acid; SFA: Saturated fatty acid; CHO: Carbohydrate

Results

Carbohydrate intake and concentrations of leptin: results from studies evaluated the association between adherence to high carbohydrate diet and leptin concentration have been shown to reach contradictory results.[5,6,16,17,30]

Consumption of carbohydrate with high glycemic load may leads to leptin resistance.[6,17] However, consumption of the high amount of fiber and high carbohydrate diet were found to have a decreased concentration of leptin and increase in insulin sensitivity, respectively.[5,8,16] One crossover clinical trial study conducted among 9 healthy individuals indicated that high glycemic index carbohydrate diet increased diurnal rhythm of leptin.[7] Consumption of 80% carbohydrate in 13 lean and overweight men had not shown a significant difference in concentration of leptin. However, oxidation of carbohydrate was substantially lower in obese subjects that may be due to leptin resistance in obese individuals.[17]

One parallel intervention study conducted among 18 men and women individuals suggested that adherence to high carbohydrate diet [65% carbohydrate (CHO), 15% fat, 20% protein] had not significant effect on concentration of leptin in comparison with subjects consumed control diet (45% CHO, 30% fat, 20% protein). This diet enhanced leptin sensitivity.[5] It seems that leptin response implicate after consumption of carbohydrate meals among obese subjects,[8,17] one cross-sectional study conducted among 165 overweight and obese women, in the age range of 50-75 years, showed that significant inverse association between consumption of habitual high carbohydrate and fat intakes and leptin concentration after adjustment for potential confounders ($\beta = -0.11$, $P = 0.04$).[16] Adherence to diet rich in fruits, vegetables and fiber with lower amounts of fat during 12 months had not showed the substantial effect on leptin level in healthy women.[18]

Fats intake and leptin levels: most studies regarding the relationship between high-fat diet and concentration of leptin were found that there is a positive association between intake of higher fats and leptin level.[8,31] Furthermore, type of fats including SFA, MUFA and PUFA play the key roles on augmentation or reduction of circulating leptin concentration.[1,19,21,25] However, contradictory results were observed in this regard.[14,26]

One cross-sectional study conducted among

individuals with type 1 diabetes had shown that men consumed more SFA had more concentration of leptin.[19] Consumption of linoleic acid and arachidonic acids among women had a positive and negative correlation with serum levels of leptin, respectively.[19] In one parallel clinical trial conducted among 55 obese subjects, adherence to diet rich in α-linolenic acid source (rapeseed oil) in 4 weeks led to increase in serum level of leptin compared with individuals who followed the diet rich in MUFA and ω_6 sources (olive oil and sunflower oil, respectively).[1]

High-fat diet substantially enhanced plasma level of leptin in rats.[31] In one parallel intervention study, consumption of the meal with 70 g fat and 36 g protein showed no significant change in postprandial leptin among 19 lean and obese women compared to high carbohydrate diet.[8] In one experimental study rats, fed fish oil and safflower oil energy restricted diet had 62% reduction in leptin levels compared to beef tallow fed.[21] In contrast, energy-restricted diet independent of the type of fats could increase leptin production in rats.[14]

Protein intake and leptin levels: fewer studies examining the effect of high protein diet on leptin concentration.[13,15] It seems that high protein low-calorie diet tend to increase in leptin activity.[15]

Results from one parallel clinical trial conducted among 19 participants (men and women) indicated that adherence to high protein diet (30% protein) in 2 weeks of iso-calorie diet did not enhance the area under curve (AUC) of leptin compared to control diet (15% protein). Furthermore, leptin AUC markedly decreased during 12 weeks energy restricted high protein diet.[15] It seems that higher protein intake could increase leptin sensitivity despite any increase in the hormone concentration.[15] Augmentation of high dietary protein during second trimester of gestation led to significantly increase plasma level of leptin in one experimental study.[13] Results from other experimental investigation found no substantial effect of high protein diet on serum level of leptin.[27]

One intervention study conducted among 17 non-diabetic male suggested that low protein diet (0.6 g/kg) decrease plasma level of leptin that not to be mediated through insulin-related mechanism.[32] In contrast, serum leptin concentration was markedly greater in rats with low protein diet, and food intake enhanced due to augmentation of leptin in one experimental study.[33] Increase of leptin concentration suggested that low protein diet might lead to the state of leptin resistance.[33]

Energy intake and concentration of leptin: it seems that energy restriction reduces concentration of leptin and high energy intake induces state of leptin resistance.[7,34,35] A cross-sectional study conducted among a sample of patients with liver cirrhosis showed that there is an inverse relationship between fasting leptin and resting energy expenditure. Energy intake was found to have no substantial correlation with fasting concentration of leptin [7] Serum level of leptin was substantially negatively correlated with dietary energy intake in obese individuals in one cross-sectional study among a sample of Japanese-American in Hawaii and Japanese in Japan.[34] One intervention study conducted among 44 healthy men suggested that energy restricted diet decreased 39.4% fasting leptin concentration.[35]

Discussion

Findings from several studies suggest that a diet display an important role on change the concentration of leptin.[5,8,15] It seems that beside the amount of fats, type of fatty acids have the key roles on circulating leptin concentration.[1,2] Energy intake also significantly associated with the hormone.[34,35]

Carbohydrate intake has an important role on regulation of leptin level that may be due to change in insulin secretion.[8] It is supported by evidence that carbohydrate meal induces greater postprandial leptin concentrations than fat meal.[28] According to evidence leptin deficiency leads to state of obesity, as well as insulin resistance and glucose tolerance impairment.[29] In the other hand, obese subjects have more concentration of leptin that tends to be the state of leptin resistance.[36] In addition, concentration of leptin implicates in subjects with Types 1 and 2 diabestes.[37,38]

Obesity is one of the important factors in the etiology of metabolic syndrome, diabetes and cardiovascular diseases[39-41] and dietary intakes have the important role on controlling the obesity and chronic diseases.[31] Consumption of high glycemic load of carbohydrates enhance concentration of the hormone.[6] In addition, intake of the high amount of fiber causes to increase the leptin sensitivity and controls the secretion of leptin.[42] It is possible that the leptin response is different in diverse types of carbohydrates. Also, the effect of high carbohydrate intake on leptin concentration may implicate in obese subjects.[8]

Sex and body fat are two most important factors in concentration of leptin that are supported by evidence.[43] Weight loss and starvation also can

decrease circulating of leptin.[44] According to evidence, SFA enhance the risk of obesity that may be mediated through a change in concentration of the hormone. Experimental studies showed that high-fat diets may elevate the leptin concentration.[44,45]

It seems that a diet rich in MUFA and PUFA decrease the concentration of the hormone especially in women compared to SFA.[1] Dietary patterns rich in MUFA and PUFA usually characterized by high amount of fiber sources as well as low glycemic index of carbohydrate that lead to the lower concentration of leptin.[46] Given the important role of estrogen on expression of leptin, it is possible that the type of fatty acids has more effects on women than men.[1]

To the best of our knowledge, fewer evidence is available regarding the impact of high protein diet on leptin concentration. It seems that higher protein intake increases satiety and enhances the leptin concentrations in CNS as well as elevates leptin sensitivity which tends to be weight maintenance.[15] However, different protein sources were found to have diverse effects on health status.[47,48]

Based on studies, individuals who consumed more energy from protein were found to have greater satiety. Increase in dietary protein intakes promotes an inverse energy balance and body fat loss. On the other hand, protein intake tends to increase energy expenditure that may be related to leptin action.[1]

Conclusion

Findings from several studies suggest that a diet display an important role on change the concentration of lepton.

Acknowledgments

Isfahan University of Medical Sciences, Iran supported this paper.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Izadi V, Saraf-Bank S, Azadbakht L. **Dietary intakes and leptin concentrations.** ARYA Atheroscler 2014; 10(5): 266-72.

A rare presentation of patent ductus arteriosus in an adult patient with normal pulmonary hypertension and limb edema

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Case Report

Abstract

BACKGROUND: Patent ductus arteriosus (PDA) at childhood is one of the five major and frequent congenital abnormalities, but it can be rarely seen in adults. Pulmonary hypertension (PHTN) and other presentations such as heart failure and edema are the identified complications of longstanding PDA, but adult case with no permanent heart symptoms and PHTN was rare. We reported a rare case of with an obvious PDA and normal pulmonary pressure.

CASE REPORT: A 61-year-old woman presented with dyspnea (New York Heart Association class 2), chest pain, and lower limb edema. Echocardiogram showed; normal left ventricular chamber size and function, normal size of both atria. Furthermore, an obvious PDA (diameter = 6-7 mm) connecting the aortic arch to the pulmonary artery was reported in echocardiography. No lung congestion and evidence for PHTN was reported by computed tomographic angiography [Pulmonary capillary wedge pressure (PCWP) = 30 mmHg]. The patient was treated with antihypertensive drugs and after 1 and 3 months follow-up, edema and other symptoms were resolved.

CONCLUSION: Finally, we conclude that PDA in adulthood can present with nonspecific cardiovascular symptoms, and it seems that PHTN is not a fixed echocardiographic finding in these patients.

Keywords: Adults, Edema, Patent Ductus Arteriosus eri, Pulmonary Hypertension

Date of submission: 8 Jul 2013, ***Date of acceptance:*** 16 Feb 2014

Introduction

Patent ductus arteriosus (PDA) at childhood is one of the five major and frequent congenital abnormalities that its frequency was reported as 10-14.4% of all congenital defects.[1,2] "PDA normally closes soon after birth, but in some newborns it does not close spontaneously, and there is continuous flow from the aorta to the pulmonary artery (i.e., left-to-right shunting)".[2] Rarely, PDA maybe presented in adulthood but most adult cases reported with pulmonary hypertension (PHTN). PHTN and other presentations such as heart failure and edema are the identified complications of longstanding PDA, but adult case with no permanent heart symptoms and PHTN was rare. We reported a rare case of with an obvious PDA and normal pulmonary pressure.

Case Report

A 61-year-old woman presented with dyspnea (New York Heart Association class 2), chest pain and lower limb edema. In past medical history, she was under treatment for hypertension, hyperlipidemia, and acute coronary syndrome (ACS) and she had a history of hospital admission twice for chest pain and ACS. Despite the hospital admissions, cardiopulmonary assessment was not perfectly performed to diagnose the main cause of her chest pain. At the first visit, initial blood pressure was 110/70 mmHg, heart rate: 68/min, respiratory rate in normal range, and body temperature was 37 °C. She did not have any complaint of productive or dry cough, fever, nocturnal dyspnea or orthopnea.

Her physical examination revealed an obvious systolic machinery murmur, which was best-heard at the second left intercostal space, and the second heart

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sound was physiologically split suggesting an absence of significant PHTN. Pulses and diastolic murmurs were near to normal. Pulmonary rates and wheezing could not find in any of both lungs, but bilateral pretibial pitting edema was obviously seen. Echocardiogram showed; normal left ventricular chamber size and function, normal size of both atria. Furthermore, an obvious PDA (diameter = 6-7 mm) connecting the proximal of descending aorta to the left to the pulmonary artery was reported in echocardiography (Figures 1 and 2).

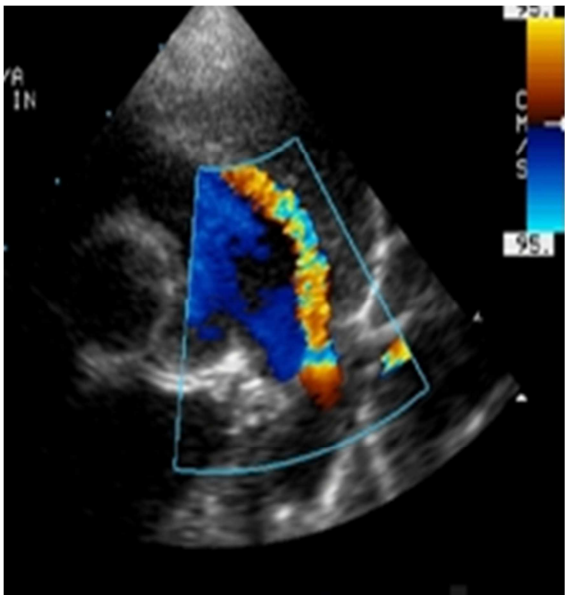

Figure 1. Patent ductus arteriosus (PDA) in Transthoracic echocardiography

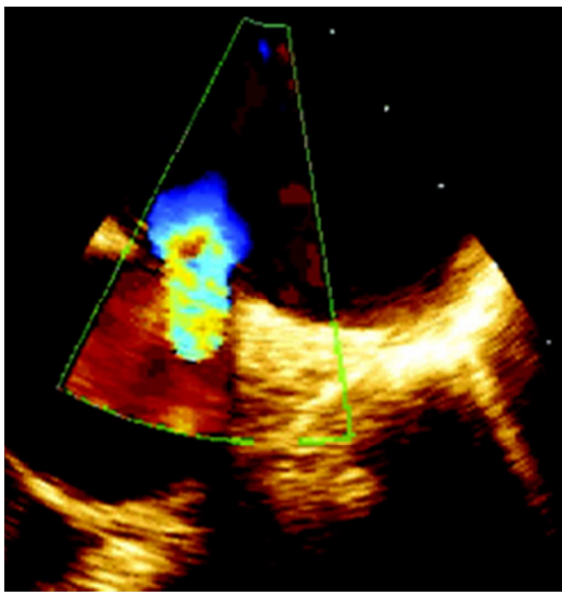

Figure 2: Patent ductus arteriosus (PDA) in Transesophageal echocardiography

For more accurate evaluation, a transthoracic echocardiogram (TTE) was performed, and it showed visualized jet flow at main pulmonary artery, indicating the presence of PDA. TTE also showed mild mitral and tricuspid regurgitation and showed mild diastolic dysfunction but preserved left ventricular function (ejection fraction of the left ventricle = 55%). Patients referred for cardiac catheterization and computed tomographic (CT) angiography. CT angiography was revealed a PDA with 5.5-7 mm luminal width interposed between the roof of left pulmonary artery and descending aorta (both at origins) (Figure 3).

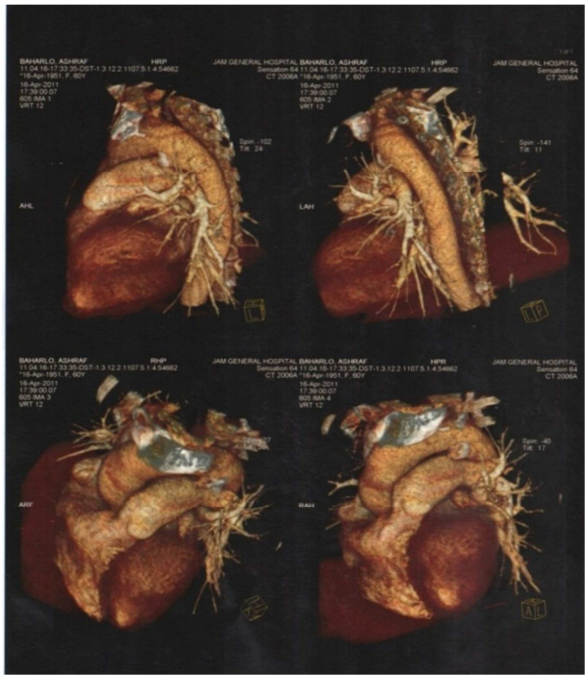

Figure 3. Computed tomographic angiographic findings

No lung congestion and evidence for PHTN was reported by CT angiography (pulmonary capillary wedge pressure: 30 mmHg). Saturation study showed a step up from right pulmonary artery to the right ventricle (72-60 %). Measured pulmonary to systemic blood flow ratio (Qp/Qs) through oxygen saturation was 1.26. Renal dysfunction, thyroid imbalance, and other etiology of edema were ruled out. The patient was treated with aspirin (80 mg/day), Lasix (tablet, 40 mg/day), losartan (tablet, 0.5 twice a day), atorvastatin (tablet, 20 mg/day), nitrocontin (tablet, 2.6 twice a day), and atenolol (tablet, 50 mg daily). After 1 and 3 months follow-up, edema and other symptoms were resolved.

Discussion

Presentation of PDA in adulthood often associated with congestive heart failure, pulmonary arterial

hypertension, atrial fibrillation, recurrent pneumonia, sign of volume overload, endocarditis and also may be silent.[3] We reported a case of adult PDA that present with general symptoms of cardiovascular disorders. Due to the recent improvement in the quality of medical care services, the survival of premature infants increases. On the other hand, PDA is mostly seen in preterm newborns. Therefore, it is expected that the prevalence of incidental PDA in adult's increase. Thus, primary care physicians need to be alert to the clinical situations suggesting a previously undiagnosed PDA.[3]

There are few similar reports in the literature review that most of them had presented with PHTN and heart failure.[4,5] PDA with increase of pulmonary blood flow or pulmonary vascular resistance cause increase of pulmonary pressure and cause PHTN.[6] Occurrence of symptoms such as Eisenmenger syndrome in systemic to pulmonary shunt are related to location, size and also magnitude of the shunt. It was previously reported that if the size of the defect is large (more than 2.5 mm), occurrence of PHTN and Eisenmenger syndrome will increase.[7,8] The normal pulmonary artery pressure in our patient despite a moderate defect could because of the potential ability of pulmonary vascular bed for tolerating longstanding high volume of blood from the childhood.[9]

Surgical treatment is the standard and recommended method for treating these patients but we showed that accurate medical therapy with antihypertensive drugs can help for managing their symptoms although it is not the definite treatment.[10] Recently, percutaneous trans catheter occlusive devices was effectively and safely used in both children and adults and it seems this new interventions can remove the need to surgical ligature in the near feature.[3] Moreover, Moller and Anderson were revealed that: "In patients with ventricular septal defect, atrial septal defect, and PDA, the Kaplan–Meier survival curves followed a normal curve. When these conditions were present with another malformation, the curves were significantly lower than normal, and showed a marked variation."[11] Therefore, it can be a useful clue that pure adult PDA maybe need no further intervention except routine drug therapy but in complicated adult PDA, the treatment protocol may be deferent.

Finally, we conclude that PDA in adulthood can present with nonspecific cardiovascular symptoms, and it seems that PHTN is not a fixed echocardiographic finding in these patients.

Acknowledgments

We would like to thank the patient and her family for their kind cooperation.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Pishgoo B, Saburi A, Khosravi A. **A rare presentation of patent ductus arteriosus in an adult patient with normal pulmonary hypertension and limb edema.** ARYA Atheroscler 2014; 10(5): 273-5.

Complete heart block in a patient with POEMS syndrome: A case report

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Case Report

Abstract

BACKGROUND: Polyneuropathy, organomegaly, endocrinopathy, monoclonal syndrome (POEMS) is a rare paraneoplastic syndrome associated with plasma cell dyscrasia.

CASE REPORT: A 48-year-old man presented with a 1-year history of paresthesia and progressive weakness of extremities. Diagnosis of POEMS syndrome was made for him on the basis of clinical presentation, additional physical findings, typical sclerotic bone lesion, and bone marrow findings. In last admission, he explained episodes of dyspnea and chest pain that associated with frequent premature ventricular contraction in his electrocardiograph. Patient heart monitoring showed some episodes of complete heart block. Infra-His atrioventricular block in electro-physiologic study was detected. He had no history of ischemic heart disease. His cardiopulmonary findings on examination were normal. All results of cardiac biomarkers and serum electrolytes and repeated echocardiography were within normal range. Cong red staining of rectal fat pad biopsy was negative. After pacemaker insertion radiation of sclerotic bone, lesion started for him, but radiotherapy was ineffective, and he expired with respiratory failure. Complete heart block in POEMS syndrome has not been reported previously, and it is the first POEMS case with complete heart block.

CONCLUSION: Complete heart block is a cardiac manifestation of POEMS syndrome.

Keywords: Complete Heart Block, POEM Syndrome, Multiple Meloma

Date of submission: 31 Aug 2013, ***Date of acceptance:*** 16 Feb 2014

Introduction

POEMS syndrome is a rare paraneoplastic syndrome associated with plasma cell dyscrasia. The acronym POEMS refers to several, but not all, of the features of the syndrome: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.[1] There are two points related to this acronym. First, all of the features within the acronym are not required to make the diagnosis.[2] Second, there are some other features such as sclerotic bone lesion, thrombocytosis, erythrocytosis, papilledema, and extravascular volume overload that are not included in the acronym POEMS.[2,3] The diagnosis of POEMS syndrome is confirmed when both of the mandatory major criteria (polyneuropathy and plasma cell gammopathy), and at least one of the minor criteria (sclerotic bone lesions, Castleman disease, organomegaly, edema, endocrinopathy, skin changes, and papilledema) are present.[3] Polyneuropathy and plasma cell dyscrasia are the most common features in patients and seen in all of them.[4] Cardiopulmonary manifestation of POEMS syndrome consist of pulmonary hypertension,[5] cardiomyopathy,[3,6] heart failure,[3] pericarditis,[3] and myocardial infarction.[3,7] Kanda et al. reported five patients with POEMS syndrome and cardiomyopathy. In all patients, diffuse hypokinesia of left ventricular wall motion was seen on echocardiograms. In one case cardiac amyloidosis was diagnosed by Congo red staining of the myocardium biopsy, but the etiology of the cardiomyopathy was not determined in the other four cases.[6] Myocardial infarction in POEMS syndrome has rarely been reported. Manning et al. reported a 27-year-old man with POEMS syndrome and extensive myocardial infarction and ulcerative proctitis. The patient had no significant risk factor for coronary arterial disease.[7] Manning et al.

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hypothesized that an abnormal immunoglobulin (or fragment) is responsible for these findings.[7]

Despite variable manifestation of cardiac disease in POEMS syndrome, complete heart block has not been reported previously. Herein, we present a case of POEMS syndrome with cardiac involvement, characterized by complete heart block.

Case Report

A 48-year-old man presented with numbness and weakness in lower extremities 1 year before admission in our center. Progressive proximal weakness had been developed in 3 weeks, and he was not able to walk and became wheelchair dependent. No abnormalities in urination and bowel habit were detected. In history he has had a history of low back pain since last year that had been diagnosed as a discopathy and medical treatment had been advised. In the physical examination, his muscle strength was 2/5 in proximal lower extremities and 3/5 in proximal of upper extremities. Deep tendon reflexes were decreased. Touch and pain sensation were also impaired, but anal sphincter tone and cranial nerves were normal.

In lab data except elevated cerebrospinal fluid protein (90 mg/dl), there were no other abnormalities. Due to ascending and distal sensory motor polyneuropathy, Guillain-Barre syndrome was diagnosed, and plasmapheresis and intravenous immunoglobulin (IVIG) were administered. About 2 weeks after hospitalization thrombocytosis (1,120,000/µl) was detected in lab data, which was associated with splenomegaly and para aortic lymphadenopathy in abdominopelvic computed tomography (CT) scan. Peripheral adenopathy was not detected. Bone marrow aspiration and biopsy reported normal. Splenectomy was performed, but patient had no symptom relief. Finally, after 2 weeks, he discharged with chronic inflammatory demyelinating polyneuropathy diagnosis and advised receiving IVIG monthly. Despite receiving IVIG monthly, his neurological symptoms were aggravated, and he became bedridden. Plasmapheresis was administered, but it had no effect. About 10 months after symptoms onset he was referred to hematology the ward for evaluation of thrombocytosis. He complained of overt weight loss, low back pain, nasal speech and pedal, and hand edema. He had no cardiac or respiratory symptoms. In physical examination, the patient was quadriplegic and deep tendon reflexes were absent. In ophthalmoscopy bilateral papilledema were present. Other abnormal physical examination findings were clubbing and whitening of nails, pedal and hand edema, bilateral gynecomastia and hypertrichosis. Peripheral lymph nodes were not palpable. The cranial nerves were normal. Table 1 shows the patient lab data. Serum protein electrophoresis was normal, but in serum immunofixation immunoglobulin G (IgG) lambda and IgA lambda biclonal gammaglobuline were seen.

Table 1. Laboratory data

Variable	Reference range	Result
White-cell count (/mm^3)	4500-11000	12500
Differential count (%)		
Neutrophils	55.0-75.0	45
Lymphocytes	22.0-44.0	51.9
Mix	0.0-10.0	3.1
Platelet count (/mm^3)	150000-350000	1019000
Hematocrit (%)	41.0-53.0 (men)	48.0
Hemoglobin (g/dl)	13.5-17.5 (men)	14.5
Mean corpuscular volume	80.0-100.0	89.6
Testosterone (ng/ml)	3.0-12.0	0.4
Albumin (mg/dl)	3.4-5.0	2.9
Creatinine (mg/dl)	0.6-1.5	0.5
BUN (mg/dl)	8.0-25.0	13.0
aPTT (s)	22.1-34.0	28.0
PT (s)	10.3-13.2	14.2
INR	1.00	1.16
TSH (µg/dl)	0.3-50.0	2.4
T4 (µU/ml)	4.0-12.0	5.5
FBS (mg/dl)	< 100	78

BUN: Blood urea nitrogen; aPTT: Particle thromboplastin time; PT: Prothrombin time
INR: International normal ratio; TSH: Thyroxin stimulating hormone; T4: Tetraiodo-thyronine
FBS: Fasting blood sugar

In urine immunofixation, free kappa and lambda light chain were detected. In bone marrow aspiration large clumps of platelets suggestive of severe thrombocytosis and up to 3% highly atypical plasma cells was seen. In bone marrow biopsy, although osteosclerosis was not seen, but infiltrated sheets of poorly differentiated cells were seen (Figure 1). Rectal biopsy was performed. Congo red stain of rectal biopsy was negative. Electromyography and nerve conduction velocity studies revealed axonal and demyelinating polyneuropathy. Multislice CT scan of full spine revealed a sclerotic bone lesion in the body of T5; measuring about 10 mm (Figure 2).

As the patients had most criteria, diagnosis of POEMS syndrome was considered. In last admission, he had explained episodes of chest pain and dyspnea. Results of cardiovascular and pulmonary examination were normal, evaluation of pulmonary thromboembolism was negative, his electrocardiograph (ECG) showed normal sinus rhythm, frequents premature ventricular contractions (PVC) (three geminal PVC), PR interval 160 ms, QRS interval 100 ms, and QTC interval 163 ms. To reduce PVC diltiazem 30 mg twice daily started. After 2 days heart monitoring in cardiac care unit the patient had frequent episodes of transient complete heart block in cardiac rhythm. On echocardiography, normal cardiac function whit no structural abnormality was detected. After discontinuation of diltiazem, electro-physiologic study was done that showed infra-His atrioventricular (AV) block and patient candidate for permanent pace maker. After pace maker insertion, he referred to the radiotherapy ward for irradiation of sclerotic bone lesion. Unfortunately, radiotherapy was ineffective, and his neuropathy progressed and he passed away with respiratory failure.

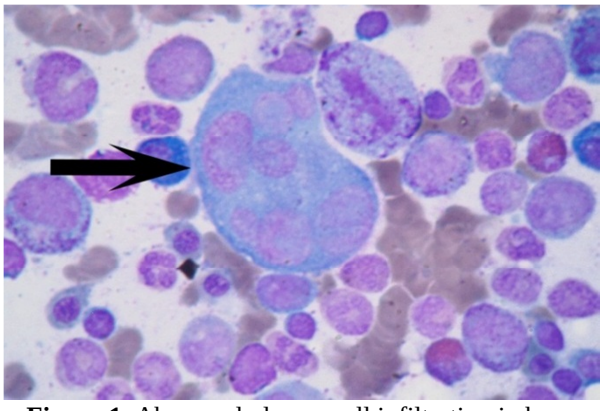

Figure 1. Abnormal plasma cell infiltration in bone marrow aspiration

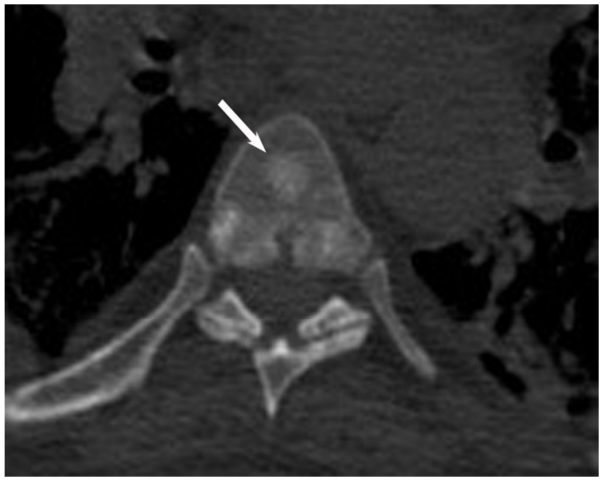

Figure 2. Sclerotic bone lesion in body of T5

Discussion

Complete AV block has a variety of causes. Ischemic heart disease is responsible for about 40% of cases of AV block.[8] Infiltrative disease such as amyloidosis[9] and sarcoidosis[10] are other common causes of AV block. Some drugs such as digitalis, amiodarone, calcium channel blockers (especially diltiazem and verapamil), β-blockers and adenosine can impair AV conduction, leading to AV block.[11] Most patients with AV block who have no obvious cause except these drugs have underlying conductive disease.[11] Drug discontinuation can result in resolution of AV block in some patients but most of them without treatment AV block later recurred. Our patient had no history of coronary and atherosclerotic risk factors for ischemic heart disease; in serial ECG no ST-T changes were seen. An echocardiogram is the most valuable procedure to detecting decreased cardiac function in patients suspected for myocarditis, even when it is subclinical.[12,13] On repeated echocardiography, cardiac function was normal, and no evidence of structural disease was seen. Cardiac biomarkers were normal, and patient had no clinical suspicious for myocarditis. To exclude amyloidosis rectal fat biopsy was taken that was negative for Congo red staining. Results of thyroid function test and serum electrolytes were within normal range. Diltiazem was discontinued. However AV block was not resolved. These indicated that underline conducting system abnormality in the patient existed that was related to primary disease.

Acknowledgments

We would like to thank the patient for permitting the publication of this article.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Ashrafi F, Darakhshandeh A, Nematolahy P, Khosravi A. **Complete heart block in a patient with POEMS syndrome: A case report.** ARYA Atheroscler 2014; 10(5): 276-9.

Investigation of the effect of short-term supplementation with curcuminoids on circulating small dense low-density lipoprotein concentrations in obese dyslipidemic subjects: A randomized double-blind placebo-controlled cross-over trial

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Short Communication

Abstract

BACKGROUND: Small dense low-density lipoprotein (sdLDL) is a sub-fraction of LDL considered to have the most atherogenic properties. The present trial aimed to assess changes in circulating sdLDL concentrations following supplementation with curcuminoids, polyphenolic compounds with diverse potential cardio-protective functions.

METHODS: This study was designed as a randomized double-blind placebo-controlled cross-over trial. A total of 30 obese dyslipidemic subjects were assigned to curcuminoids (1 g/day) or placebo for 4 weeks, followed by a 2-week washout and then treatment with the alternate for another 4 weeks. Serum sdLDL was measured at baseline and weeks 4, 6, and 10 of the trial.

RESULTS: Supplementation with curcuminoids (1 g/day) did not cause any significant alteration in serum sdLDL ($P > 0.05$).

CONCLUSION: Four-week supplementation with curcuminoids was not associated with any significant alteration in circulating sdLDL concentrations.

Keywords: Diferuloylmethane, Curcuma longa L., Turmeric, Cardiovascular Disease, Hypercholesterolemia, Atherosclerosis

Date of submission: 1 Mar 2013, ***Date of acceptance:*** 12 May 2014

Introduction

Overweight and obesity are major public health concerns in both developed and developing world. These conditions are major determinants of chronic diseases such as diabetes, hypertension, and metabolic syndrome.[1,2] In addition, obesity is often accompanied by dyslipidemia and increased susceptibility to atherosclerosis and coronary heart disease (CHD).[3]

There are two major subclasses of low-density lipoprotein (LDL) based on particle properties: large buoyant LDL that predominates in the pattern A profile (particle diameter ≥ 25 nm) and small dense LDL (sdLDL) that is the predominant form in pattern B (particle diameter < 25 nm).[4] Predominance of pattern B and increased formation of sdLDL particles is a recently discovered feature of atherogenic dyslipidemia.[5]

In addition, sdLDL has greater potential for permeation into the arterial wall and sub-endothelial space, lower interaction with LDL receptor, longer plasma half-life, more susceptibility to modification (e.g., glycation) and less resistance to oxidative stress.[6-9] It has been reported that patients with a predominant sdLDL phenotype have a higher risk of developing CHD compared with those with the large buoyant LDL phenotype. Further, circulating concentrations of sdLDL appear to serve as a useful biomarker for the severity of CHD.[5-7]

Curcuminoids are polyphenolic compounds accounting for most of the biological and medicinal effects of Curcuma longa L. (turmeric). During the past three decades, there has been a substantial

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body of research on the pharmacological properties of these phytochemicals leading to the identification of numerous health benefits.[10-20] Among these benefits are cardio-protective functions that are secondary to the interaction of curcuminoids with several types of receptors, enzymes, hormones, inflammatory mediators, and transcription factors.[21-23] Moreover, there has been in-vitro and in-vivo evidence on the modulation of lipoprotein metabolism and lipid profile by curcuminoids.[20] In spite of some findings on the impact of curcuminoids on conventional lipid profile parameters [comprising total cholesterol, LDL-cholesterol (C), triglycerides, and high-density lipoprotein cholesterol (HDL-C)], no study has yet investigated changes in circulating concentrations of sdLDL, as a novel CHD risk factor and the risk marker, following supplementation with curcuminoids. The present study aimed to evaluate this in a group of obese dyslipidemic subjects.

Materials and Methods

This study is a post-hoc analysis performed on the samples obtained from our previous investigation (IRCT2013082914521N1).[19] The original study was conducted at the Ghaem Hospital of Mashhad, Iran, between 21/08/2010 and 20/08/2012. The study population included men and women aged 18-65 years with a body mass index (BMI) > 30 kg/m^2 who were not originally on lipid-lowering therapy. Other inclusion criteria were the presence of either < 2 risk factors (except diabetes mellitus) for CHD + 160 mg/dl < LDL-C < 190 mg/dl, or ≥ 2 CHD risk factors (except diabetes mellitus) and 130 mg/dl < LDL-C < 160 mg/dl. Individuals with BMI ≤ 30 kg/m^2, history of CHD and history of consuming lipid-lowering medications or supplements within the preceding 6 months were excluded. Thirty subjects were randomized to receive curcuminoids (1000 mg/day + 5 mg piperine for absorption enhancement) or matching placebo (5 mg piperine) as their first intervention. The duration of treatment with either curcuminoids or placebo was for 4 weeks and then each subject was assigned to the alternate intervention following a 2-week washout phase. The primary efficacy parameter change in serum sdLDL levels. Thirty subject completed trial and their blood samples were stored for analyses. Among these completers, the samples of 22 subjects were available for sdLDL assay comprising 12 samples in the placebo-curcuminoids arm and 9 samples in the curcuminoids-placebo arm (Figure 1). There was no pre-specified guideline for interim analysis and study discontinuation owing to the well-documented safety of curcuminoids.

Randomization was carried out by alternative allocation of patients to encoded capsules with the first code being chosen randomly. Both curcuminoids (C3 Complex®) and piperine (Bioperine®) were prepared and encapsulated by the Sami Labs Ltd., Bangalore, India and were completely identical in shape, size, and color. The study protocol was approved by the Ethics Committee at the Mashhad University of Medical Sciences (date: May 12, 2012; code: 88313).

Fasted blood samples (after an overnight fast) were collected from each subject at 4 time points, that is, at the start and end of each intervention period. Samples were then centrifuged at 10,000g for 15 min to obtain serum. Sera were kept at −80 °C until analysis. Blood pressure recordings were conducted after rest using a stethoscope and calibrated mercury sphygmomanometer calibrated by the Iranian Institute of Standards and Industrial Research. The appearance of the first sound (Korotkoff phase 1) was defined as systolic blood pressure (SBP) and the disappearance of the sound (Korotkoff phase 5) during cuff deflation was defined diastolic blood pressure (DBP). Measurement of weight was performed with the subjects dressed in light clothing after an overnight fasting using a standard scale with an accuracy of ± 0.1 kg. Measurement of height was performed to an accuracy of ± 0.1 cm. Waist circumference was measured at the midpoint between the lower rib margin and top of the iliac crest. Hip circumference was measured at the widest point over the buttocks. Total body fat percentage were assessed using a calibrated stand-on Bio Impedance Analyzer (BIA) (Tanita-305 Body Fat Analyzer, Tanita Corp., Tokyo, Japan) with a CV of < 1%). In order to minimize the impact of physiological factors on body fat percentage, BIA was used under constant conditions, that is, fasted state and before exercise. Anthropometric parameters including weight, height, BMI, waist and arm circumference and body fat were measured using standard procedures as described previously.[19,24]

The statistical analysis software SAS (version 9.1, SAS Institute Inc., Cary, NC, USA) was used for statistical analysis. A mixed model analysis of variance for 2 × 2 crossover studies was fitted when assumptions for normality were met. A two-sided P-value of < 0.050 was considered to be statistically significant.

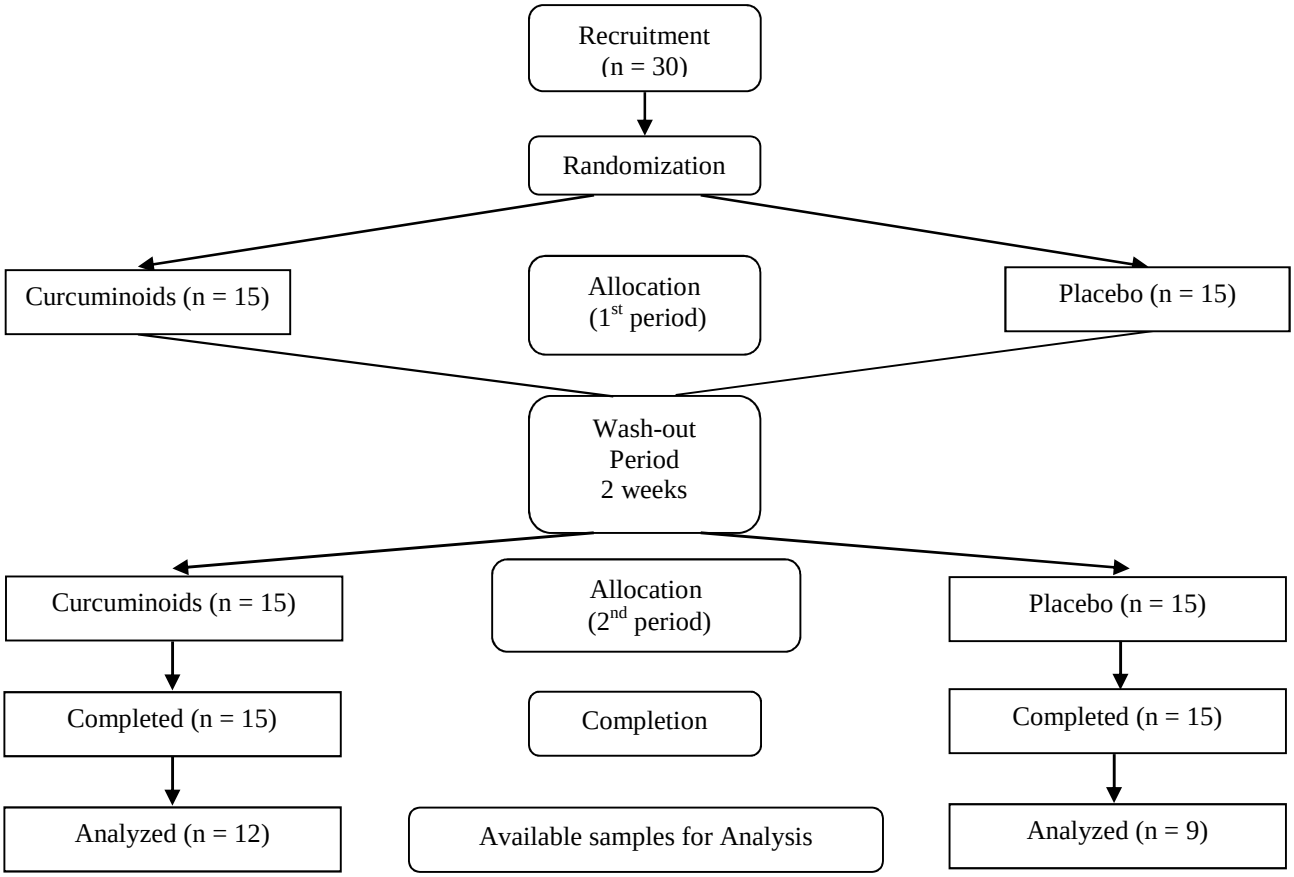

Figure 1. Flow chart of trial

Serum sdLDL was determined using the method described by Hirano et al.[25] Briefly, a precipitation reagent (150 U/ml heparin-sodium salt and 90 mmol/l $MgCl_2$) was added to 0.5 ml of serum sample, mixed and incubated for 10 min at 37 °C. Samples were then placed in an ice bath and left for 15 min, and centrifuged for 15 min at 4 °C. The concentration of sdLDL-apolipoprotein B in the heparin-Mg supernatant was measured by an immunoturbidimetric assay (Biosystems, Spain). The coefficients of variation for inter- and intra-assay were 1.3-1.6% and 1.7-3.7%, respectively.

Results

Demographic characteristics of study population are summarized in table 1. Curcumin-placebo and placebo-curcumin groups were comparable in baseline parameters including age, gender, weight, height, BMI, waist and hip circumference, waist/hip ratio, and SBP and DBP. The only factor with significant baseline difference was fat percentage, which was higher in the curcumin-placebo group (P = 0.019). Baseline sdLDL was also comparable between the study groups (P = 0.472).

Supplementation with curcuminoids (1 g/day) did not cause any significant change in serum sdLDL by the end of the trial (P = 0.820). This effect was found to be robust and not subject to any carry-over, period or sequence effect (P > 0.050). Changes in serum sdLDL in the four assessed intervals are illustrated in figure 2.

Discussion

Findings of the present trial did not indicate any significant effect of 4-week curcuminoids supplementation on circulating levels of sdLDL. Recently, there has been increasing interest in lipoprotein particle size and composition as additional risk factors for atherosclerosis. This is in part due to the observations of normal lipid profile in a considerable fraction of patients with documented CHD. sdLDL particles have been proposed as a sub-fraction of LDL associated with more atherogenic risk, while the larger buoyant LDL particles are much less atherogenic.[26,27] Certain constituents of lipid metabolism, that is, lipoprotein lipase, hepatic lipase, and cholesterol ester transfer protein (CETP) have been shown to contribute to the formation of sdLDL particles.[28,29]

Table 1. Demographic characteristics of study population

Parameter	Curcumin-placebo	Placebo-curcumin	P
Female (%)	89.50	75.00	
Age (year)	38.84 ± 11.12	37.81 ± 12.31	0.797
Height (cm)	158.50 ± 6.36	159.94 ± 9.64	0.601
Weight (kg)	85.57 ± 12.95	83.83 ± 17.43	0.737
BMI (kg/m^2)	33.95 ± 3.81	32.66 ± 4.69	0.373
Waist circumference (cm)	110.34 ± 10.41	106.53 ± 10.43	0.289
Hip circumference (cm)	117.97 ± 9.85	115.07 ± 9.31	0.379
Waist/hip ratio	0.94 ± 0.06	0.93 ± 0.05	0.606
Fat percentage (%)	41.25 ± 5.49	36.48 ± 5.83	0.019
SBP (mmHg)	118.84 ± 13.29	117.62 ± 10.99	0.772
DBP (mmHg)	79.63 ± 10.21	80.44 ± 8.41	0.803

Values are expressed in mean ± SD; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure
SD: Standard deviation

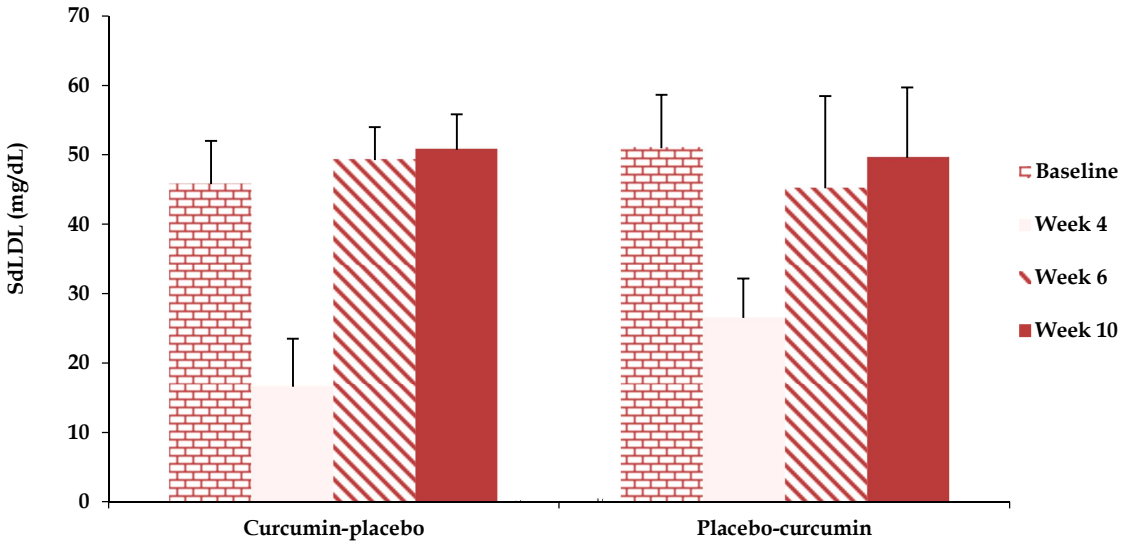

Figure 2. Serum small dense low-density lipoprotein (sdLDL) concentrations (mg/dl) at different time points of trial; Values are expressed as mean ± SEM. There was no effect of curcuminoids on serum sdLDL (P = 0.382, first carry-over effect; P = 0.262, second carry-over effect; P = 0.820, treatment effect);
SEM: Standard error of mean

Different mechanisms have been proposed for the atherogenicity of sdLDL.[27-30] According to Bjornheden et al., sdLDL is more readily taken up by arterial tissue because of easier transendothelial migration of smaller particles.[27] It has been reported that the prevalence of sdLDL is 5-10% in young men and women under 20 years old and around 30% in adult males.[31,32] The sdLDL-C/LDL-C in our trial exceeded these values and conformed to previous findings in obese individuals.[33,34]

Several lines of preclinical evidence have indicated the hypolipidemic effects of curcuminoids in different experimental models, for example, rats, rabbits, hamsters, and mice.[20] These effects were reported to be reductions in circulating levels of total cholesterol, LDL-C, triglycerides and free fatty acids, and increases in HDL-C.[20] Different mechanisms have been proposed for these hypolipidemic actions including inhibition of intestinal cholesterol absorption, inhibition of hepatic lipid biosynthesis, stimulation of bile secretion and modulation of the expression and/or activity of lipoprotein receptors.[20] In spite of these promising findings, hypolipidemic effects of curcuminoids have not been consistently reported in randomized controlled trials.[19,35-39] Taken together, the overall clinical findings on the effect of curcuminoids supplementation on LDL-C levels weighs in favor of lack of efficacy. The present findings on sdLDL are also in line with those previously found on LDL-cholesterol.[19,40]

Increasing evidence has suggested a link between

circulating triglycerides levels, as well as triglycerides content of LDL particles, with CHD risk.[41,42] In a recent report from the same trial, it was shown that curcuminoids supplementation is associated with a significant hypotriglyceridemic effect but not any change in the levels of total and LDL-C.[19] Interestingly, another recent trial by DiSilvestro et al. showed the same finding.[40] The lack of efficacy on the circulating levels of total cholesterol, LDL-C and sdLDL is unlikely to be due to the low-bioavailability of this compound as both of the above-mentioned trials used improved formulations of curcuminoids through co-administration with piperine,[19] or using lipidated form of curcuminoids in combination with absorption enhancing adjuvants.[40] Therefore, it is plausible that the positive cardio-protective and anti-atherogenic properties of curcuminoids are primarily due to an effect on triglyceride levels rather than LDL and its sub-fractions. This issue merits further investigation.

The lack of efficacy of curcuminoids in altering serum levels of sdLDL is unlikely to be attributable to the insufficient administered dose or trial duration as similar trials with the same durations were able to show the efficacy of curcuminoids on other CHD biomarkers, most importantly triglycerides, as mentioned above. There is evidence indicating down-regulation of genes involved in lipogenesis by curcuminoids.[20] Nevertheless, there has been as yet no evidence of the modulatory effect of curcuminoids on hepatic lipase, the main enzyme responsible for the conversion of large and medium LDL particles (LDL-I and LDL-II) to sdLDL. Furthermore, evidence regarding the impact of curcuminoids on activity of CETP is also lacking. CETP is another key enzyme responsible for the remodeling of LDL from large to smaller particles. There has been only one previous study showing the inhibitory effect of curcumin on CETP, but this study was conducted in LDL receptor knockout mice model that cannot be a true representative of clinical conditions.[43]

The main strength of the present study is that it was based on a robust placebo-controlled and cross-over design and conducted in the target population, not under concomitant lipid-lowering therapy. Therefore, many of the confounding factors that may generally affect lipid alterations were eliminated from the present trial. Second, this study is the first one to look at sdLDL changes following curcuminoids therapy. Aside from these strengths, a number of limitations need to be acknowledged for the present trial: First, this study was not primarily aimed to assess the impact of curcuminoids on serum sdLDL. Second, the composition of LDL was not investigated in this study. Recent data have shown that lipid composition of LDL particles plays a significant role in the atherogenicity of particles.[44]

Conclusion

In summary, results obtained from the current trial indicated no significant effect of curcuminoids supplementation on circulating levels of sdLDL. This finding may imply that beneficial cardiovascular effects of curcuminoids are exerted via mechanisms other than affecting LDL sub-fractions. Nevertheless, future studies are encouraged to explore the impact of curcuminoids on serum lipidome as well as triglyceride and fatty acid composition of lipoprotein species.

Acknowledgments

This study was financially supported by a grant (no. 88313) from the Research Council at the Mashhad University of Medical Sciences, Mashhad, Iran. The authors kindly appreciate the assistance of Eng. Saeed Akhlaghi for undertaking statistical analyses.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Moohebati M, Yazdandoust Sh, Sahebkar A, Mazidi M, Sharghi-Shahri Z, Ferns G, et al. **Investigation of the effect of short-term supplementation with curcuminoids on circulating small dense low-density lipoprotein concentrations in obese dyslipidemic subjects: A randomized double-blind placebo-controlled cross-over trial.** ARYA Atheroscler 2013; 10(5): 280-6.