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ARYA Atherosclerosis

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Original Article(s)

Resistin and prooxidant-antioxidant balance: Markers to discriminate acute coronary syndrome from stable angina
Ali Pourmoghaddas, Armin Elahifar, Faramarz Darabi, Ahmad Movahedian, Afshin Amirpour, Nizal Sarrafzadegan.....46-54

The psychometric properties of the Hypertensive Treatment Adherence Scale
Mahlagha Dehghan, Nahid Dehghan-Nayeri, Sedigheh Iranmanesh ...55-71

Knowledge production in Iranian cardiovascular research centers: A way to reduce the burden of disease
Asghar Ebadifar, Monir Barabaran-Eftekhari, Katayoun Falahat, Masoumeh Eltemasi, Zahra Sobhani, Elham Ghalenoei, Elham Habibi, Nizal Sarrafzadegan, Shahin Akhondzadehi, Reza Malekzadeh 72-78

Accuracy of the amount of trans-fatty acids in traffic light labelling of traditional sweets distributed in Isfahan, Iran
Neda Ghazavi, Ebrahim Rahimi, Zahra Esfandiari, Amir Shakerian ...79-84

Comparison of survival rate and complications of percutaneous coronary intervention, coronary artery bypass graft, and medical treatment in patients with left main and/or three vessel diseases
Alireza Khosravi, Mehrbod Vakhshoori, Vahid Sharif, Farshad Roghani-Dehkordi, Jamshid Najafian, Asieh Mansouri.....85-93

Enzymatic antioxidant system and endothelial function in patients with metabolic syndrome
Fariba Sakhaei, Mahtab Keshvari, Sedigheh Asgary, Leila Salehizadeh, Ali Rastgar, Seyyed Ziaedin Samsam-Shariat 94-101

Case Report(s)

Large pericardial mesothelial cyst coexisting with hypertrophic obstructive cardiomyopathy
Anita Sadeghpour, Alireza Alizadeh-Ghavidel, Kambiz Mozaffari, Hamidreza Pouraliakbar, Behshid Ghadrdoost, Mohaddeseh Behjati...102-104

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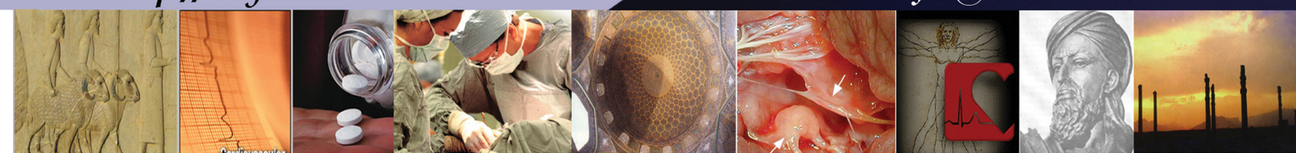

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Qualitative Research	3500	7,000,000	2,000,000
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* All the words of the article containing the references; each table is considered as 300 words.
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Table of Contents

Original Article(s)

1. Resistin and prooxidant-antioxidant balance: Markers to discriminate acute coronary syndrome from stable angina
Ali Pourmoghaddas, Armin Elahifar, Faramarz Darabi, Ahmad Movahedian, Afshin Amirpour, Nizal Sarrafzadegan ……46-54

2. The psychometric properties of the Hypertensive Treatment Adherence Scale
Mahlagha Dehghan, Nahid Dehghan-Nayeri, Sedigheh Iranmanesh ……55-71

3. Knowledge production in Iranian cardiovascular research centers: A way to reduce the burden of disease
Asghar Ebadifar, Monir Barabaran-Eftekhari, Katayoun Falahat, Masoumeh Eltemasi, Zahra Sobhani, Elham Ghalenoei, Elham Habibi, Nizal Sarrafzadegan, Shahin Akhondzadehi, Reza Malekzadeh ……72-78

4. Accuracy of the amount of trans-fatty acids in traffic light labelling of traditional sweets distributed in Isfahan, Iran
Neda Ghazavi, Ebrahim Rahimi, Zahra Esfandiari, Amir Shakerian ……79-84

5. Comparison of survival rate and complications of percutaneous coronary intervention, coronary artery bypass graft, and medical treatment in patients with left main and/or three vessel diseases
Alireza Khosravi, Mehrbod Vakhshoori, Vahid Sharif, Farshad Roghani-Dehkordi, Jamshid Najafian, Asieh Mansouri.....85-93

6. Enzymatic antioxidant system and endothelial function in patients with metabolic syndrome
Fariba Sakhaei, Mahtab Keshvari, Sedigheh Asgary, Leila Salehizadeh, Ali Rastgar, Seyyed Ziaedin Samsam-Shariat ……94-101

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Resistin and prooxidant-antioxidant balance: Markers to discriminate acute coronary syndrome from stable angina

Ali Pourmoghaddas[1], Armin Elahifar[2], Faramarz Darabi[3], Ahmad Movahedian[4], Afshin Amirpour[5], Nizal Sarrafzadegan[2],[6]

Original Article

Abstract

BACKGROUND: Resistin and oxidative stress may play a role in the pathogenesis of coronary heart disease (CHD) including acute coronary syndrome (ACS). The aim of this study was to investigate the role of serum resistin and prooxidant-antioxidant balance (PAB) in ACS occurrence in order to differentiate it from stable angina. Moreover, we aimed to determine the correlation between resistin and PAB in patients with ACS and its difference from patients with stable CHD.

METHODS: This cross-sectional, descriptive study was conducted on 50 patients with ACS and 50 patients with stable CHD who underwent coronary angiography (CAG). Serum resistin level was measured using enzyme-linked immunosorbent assay (ELISA). PAB and other variables were analyzed using standard methods.

RESULTS: A significant increase in serum resistin and PAB was observed in patients with ACS (2.55 ± 0.13 ng/ml and 123.5 ± 5.58 HK unit, respectively) compared to patients with stable CHD (1.53 ± 0.12 ng/ml and 95.9 ± 2.7 HK unit, respectively) (P < 0.001). In addition, a significant positive correlation was seen between serum resistin and PAB in patients with ACS (r = 0.39; P = 0.005), but this correlation was not found in patients with stable CHD (r = 0.21; P = 0.140). Resistin (r = 0.52; P < 0.001) and PAB (r = 0.55; P < 0.001) were significantly associated with high-sensitivity C-reactive protein (hs-CRP) in patients with ACS, but this association was not found in patients with stable CHD (resistin: r = 0.24; P = 0.090; PAB: r = -0.02: P = 0.910).

CONCLUSION: High serum resistin or PAB levels, and their association with the occurrence of ACS, can be used as a robust discriminating factor to differentiate ACS from stable CHD.

Keywords: Acute Coronary Syndrome; Resistin; Antioxidants

Date of submission: 28 Dec. 2018, ***Date of acceptance:*** 12 Oct. 2019

Introduction

Cardiovascular disease (CVD) is among the main causes of mortality and disability, and is becoming the worldwide leading cause of death in 2020. It is believed that oxidative stress due to increased formation of reactive oxygen species (ROS) leads to the manifestation of CVD. However, we consider all factors that increase the reactivation of oxygen species and their derivatives, such as peroxynitrite and lipid peroxides, as risk factors of CVD. The most critical event in CVD is the acute coronary syndrome (or unstable CVD) which occurs due to thrombus formation within the lumen of coronary arteries at the site of ruptured or eroded atherosclerotic plaques.[1,2]

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Acute coronary syndrome (ACS) represents a complex phenotype involving the interplay between endothelial dysfunction, pro-inflammatory, and pro-thrombotic components, and is influenced by genetic and environmental factors. Symptoms range from stable angina to myocardial infarction (MI) due to coronary artery occlusion by vulnerable plaques. Recent studies have supported the role of oxidative stress and inflammation as significant risk factors for CVD.[2]

The activation of ROS and their derivatives leads to the depletion of antioxidant capacity of tissues, structural damage, and loss of high-energy phosphates in the myocardium. However, increased chemical reactions or inadequate antioxidant defense system results in oxidative stress.[2]

The imbalance between antioxidant defense and the production of pro-oxidants causes endothelial dysfunction which results in atherogenesis and plaque destabilization.[1,3-5]

From the molecular aspect, atherosclerosis is an inflammatory condition. Inflammation leads to both formation and rupture of plaque, which leads to acute ischemic CVDs including ACS.

ROS are thought to play a role in the pathophysiology of CVDs.[6,7] Prooxidant-antioxidant balance (PAB), which is an indicator of oxidative stress, is considered as a cardiovascular risk predictor that estimates the extent of oxidative stress. However, studies have shown that PAB values are associated with CHD.[8]

In fact, coronary artery inflammation and its associated oxidative stress, due to the accumulation of lipids, leads to the formation of arterial lesions called atheroma. Furthermore, a high level of lipid in the plasma activates the endothelium and increases the adhesion of immune cells to the endothelium, which results in endothelial dysfunction. Ultimately, chemotactic factors are released from ruptured atherosclerotic lesions, resulting in platelet aggregation and thrombosis of the coronary artery and ACS.[9,10]

Moreover, ACS itself activates the systemic inflammatory cascade to protect the body against injury caused by ischemia. Homeostatic imbalance of adipokines interfere with the rate of production and secretion of other cytokines during the ACS-activated inflammation.

Recent studies have focused on diagnosing markers of oxidative stress and prognostic factors of ACS. Although several researchers have demonstrated the association between various cytokines and CHD, the impact of ACS-activated inflammation on adipokines remains unknown in ACS patients.

Moreover, the epicardial adipose tissue (EAT) covers the surface of the heart. The adipokines secreted from EAT can be divided into anti-atherogenic (such as adiponectin) and proatherogenic adipokines (such as resistin and leptin). Resistin is the adipocytokine that worsens glucose tolerance and induces insulin resistance.[11,12] Follow-up studies have explained the role of resistin in inflammatory processes, insulin resistance, and atherosclerosis, but there remains questions in this regard.[13]

Resistin is exclusively expressed in peripheral blood monocytes and macrophages of atheromas. It is expressed in human peripheral blood mononuclear cells and involved in inflammatory reactions.[14,15]

Human resistin is also expressed and secreted exclusively from macrophages and bone marrow cells in atheromas, which affect endothelial function and induce vascular smooth muscle cell proliferation.[16,17] Lipopolysaccharide, interleukin-1, IL-6, and tumor necrosis factor-α can enhance the resistin mRNA expression in human peripheral blood monocytes.[18] Furthermore, recombinant human resistin can promote human endothelial cell activity by enhancing endothelin-1 release, expressions of vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and monocyte chemoattractant protein-1.[19,20] It has been reported that resistin, secreted by macrophages infiltrating the atheroma, affects endothelial function and stimulates vascular smooth muscle cells migration.[17] Therefore, resistin plays a role in the development of atherosclerosis. Resistin is an adipocytokine and functions as a link between inflammation, metabolic disorder, and atherosclerosis. In humans, resistin is primarily a product of macrophages.[21,22] Resistin is highly expressed in human peripheral blood mononuclear cells and is involved in inflammatory reactions.[23] Resistin secreted by macrophages infiltrating the atheromas affects endothelial function and stimulates vascular smooth muscle cells migration.[13,17]

In chronic inflammatory conditions such as diabetes, obesity, and atherosclerotic CVD, proatherogenic imbalance is observed; this means the serum contains higher adiponectin levels and lower resistin and leptin levels. Therefore, it seems that ACS-activated inflammation must be categorized as an acute inflammation rather than a chronic inflammation.[24]

It has been hypothesized that resistin serum

level and PAB can predict ACS in patients with CHD. Several studies have reported the significant association between resistin serum level and ACS. In the present study, we assessed the possible association of resistin with high-sensitivity C-reactive protein (hs-CRP) as a marker of inflammation and other CVD risk factors.

Materials and Methods

In this cross-sectional descriptive study was conducted on 100 patients [50 patients with ACS and 50 patients with stable coronary artery disease (CAD)] aged between 44 and 86 years who underwent diagnostic coronary angiography (CAG) in Chamran Hospital in Isfahan, Iran, from May 2015 to January 2016. The subjects were selected from among patients who referred to the department of cardiology with a complaint of chest pain. The diagnosis was made according to the result of angiography, electrocardiogram, serum troponin level, and clinical findings. They were all admitted to the hospital between May 2015 and March 2016. Patients with inflammatory diseases (such as rheumatoid arthritis, lupus, vasculitis, pulmonary fibrosis, and retroperitoneal fibrosis), malignant diseases, impaired liver function, renal failure, uncontrolled diabetes, severe heart failure, and history of trauma and surgery were excluded from the study.

CAG was performed for all subjects through the femoral artery approach. Informed consent was obtained from all patients before enrollment. The study protocol was approved by the Ethical Committee of Isfahan University of Medical Sciences (Project number: 395890) according to the principles of the Declaration of Helsinki.

Characteristics of patients and sample collection: Based on the definition, stenosis in more than 75% of any major coronary arteries or more than 50% of the left main coronary artery cross-sectional area is considered a significant CAD.[25,26]

All data including age, gender, serum creatinine, lipid profile [total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG)], body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), tobacco use, medication history, hypertension (HTN; defined as systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg in two consecutive times or consumption of antihypertensive drugs), diabetes mellitus (DM; defined as a fasting blood glucose ≥ 126 mg/dl and hemoglobin A1C ≥ 6.5%, or use of hypoglycemic medication), and other risk factors of CHD were recorded.

Before angiography, venous blood samples were obtained from patients and placed in a serum separator tube. We let the tube stand for at least 20 minutes at room temperature. Then, the tube was centrifuged at 3000 G for 10 minutes and the obtained serum was liquated and stored at -80 °C until assayed.

Then, CAG was performed in all subjects through the radial or femoral artery approach. Two experienced cardiologists, who were unaware of the patient's clinical history and biochemical results, evaluated all angiograms.

Serum levels of blood sugar (BS), TG, TC, HDL-C, and LDL-C were measured via enzymatic methods by using commercial kits (Pars-Azmoon, Tehran, Iran) and an automated analyzer (Hitachi, Japan) according to the manufacturer's recommendations.

Using an immunoturbidimetric method and a commercial kit (Pars-Azmoon, Tehran, Iran) according to the manufacturer's recommendations, hs-CRP was measured. Cases with an elevated level of hs-CRP (above 3.0 mg/l) were also excluded to avoid the bias effect of an existing inflammation.

Resistin analysis using enzyme-linked immunosorbent assay: Enzyme-linked immunosorbent assay (ELISA) technique was used to evaluate serum resistin levels. This was measured with an enzyme immunoassay kit (Hangzhou East Biopharm Co. Ltd, China) according to the manufacturer's instructions. Subsequently, the standard curve was calculated using a linear regression equation, and the results were extracted for the samples.

Prooxidant-antioxidant balance assay: PAB assay was applied based on the method proposed by Pasterkamp et al.[27] In brief, the standard solutions were prepared from 0 to 100% by mixing 250 µM hydrogen peroxide with 3 mM uric acid in 10 mM NaOH. The TMB (3,3',5,5'-Tetramethylbenzidine) solution was prepared by dissolving a tablet of TMB in 10 ml substrate buffer (0.05 M acetate buffer; pH: 4.5). TMB cation was prepared by adding 18 µl of freshly-pure chloramine-T solution (10 mM) to 1 ml of the TMB solution. The TMB cation was incubated for 20 minutes at 37 °C and 1.25 units of peroxidase were added to 9 ml of the TMB solution (working solution).

In each well of a 96-well plate, 10 µl of each sample, standard or blank, was mixed with 200 µl of

working solution and incubated in a dark place at 37 °C for 12 minutes. Then, 100 µl of HCl (2N) was added to each well, and HCl was measured in an ELISA reader at 450 nm. A standard curve was provided for the values relative to the standard samples. The percentage of hydrogen peroxide in the standard solution was defined as arbitrary Hamidi-Koliakos (HK) units. The values of the PAB are expressed in arbitrary HK units. Based on the values obtained from the abovementioned standard curve, the values of the unknown samples were calculated.

Continuous normally distributed variables are presented as mean ± standard deviation (SD), and non-normally distributed variables are presented as median [interquartile range (IQR)]. Normality assumption was checked using Kolmogorov–Smirnov test. Two-tailed student's t-test was used to compare serum resistin level and the other variables between the two groups. To investigate the associations between serum resistin level and other variables, paired t-test and one sample sign test were used for normally and non-normally distributed variables, respectively. P-values of less than 0.05 were considered statistically significant. The statistical analyses were performed using SPSS software (Version 22, IBM Corporation, Armonk, NY, USA). The receiver operating characteristic (ROC) curve was used for illustrating the ability of PAB and resistin serum level in predicting the occurrence of ACS.

Continuous variables were compared between ACS and stable CAD groups using independent t-test. The Pearson correlation analysis was used to investigate the correlations between serum miR-21, visfatin, and other related variables.

Results

After primary evaluations, 50 patients were included in each of the groups (ACD and stable CHD). The mean ± standard error (SE) age of the participants was 63 ± 1.74 and 62 ± 1.26 years in the ACS and stable CHD groups, respectively (age range: 45-85). Clinical characteristics data of all subjects are summarized in table 1. The demographic characteristics of age, BMI, and blood pressure were not significantly different between the ACS and stable CHD groups. There were no significant differences in other cardiovascular risk factors, including cigarette smoking, LDL-C, TC, total TG, creatinine, and history of diabetes. The levels of serum HDL-C were significantly lower in the ACS group than the stable CHD group. Rates of current smoking were similar between the two groups ($P > 0.050$) (Table 1).

According to the data analysis, levels of serum inflammatory markers (hs-CRP) were significantly higher in the ACS group (2.1 ± 0.051 mg/l) than the stable CHD group (1.68 ± 0.052 mg/l) ($P < 0.001$).

The result of ELISA analyses showed that the mean serum resistin levels were significantly higher in patients with ACS (2.55 ± 0.13 ng/ml) than those with stable CHD (1.53 ± 0.12 ng/ml) ($P < 0.001$) (Figure 1a).

The result of PAB assay showed that the mean serum PAB value was significantly higher in patients with ACS (123.5 ± 5.58 HK unit) than in those with stable CHD (95.9 ± 2.7 HK unit) ($P < 0.001$) (Figure 1b). These results indicate that the PAB level was significantly elevated in the ACS group compared to the stable CHD group.

Table 1. Summary of data analysis in the acute coronary syndrome and stable coronary heart disease groups

Characteristics	Patients with ACS (n = 50)	Patients with stable CHD (n = 50)	P
Male gender [n (%)]	31 (19)	30 (20)	0.840
Age (year)	63.26 ± 1.74	62.32 ± 1.26	0.670
Systolic blood pressure (mm Hg)	133.75 ± 2.88	128.21 ± 1.91	0.115
Diastolic blood pressure (mm Hg)	81.23 ± 1.32	79.31 ± 0.74	0.207
BMI (kg/m^2)	24.48 ± 0.35	24.11 ± 0.31	0.413
Serum creatinine (mg/dl)	1.06 ± 0.029	1.01 ± 0.027	0.203
TC (mg/dl)	196.10 ± 3.87	195.70 ± 3.88	0.930
LDL-C (mg/dl)	128.38 ± 3.67	122.96 ± 3.98	0.280
HDL-C (mg/dl)	35.58 ± 5.02	40.60 ± 3.20	0.008
TG (mg/dl)	161.20 ± 6.02	160.32 ± 3.72	0.940
Glucose (mg/dl)	120.00 ± 2.34	124.70 ± 1.62	0.112
Hemoglobin A1c (%)	6.09 ± 0.088	6.23 ± 0.061	0.177

Normally distributed data are presented as mean ± [Standard error (SE)] or number (%). Two-tailed student's t-test was used to compare variables between the two groups. P-value < 0.050 was considered as a statistically significant association. ACS: Acute coronary syndrome; CHD: Coronary heart disease; BMI: Body mass index; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol; TG: Triglycerid

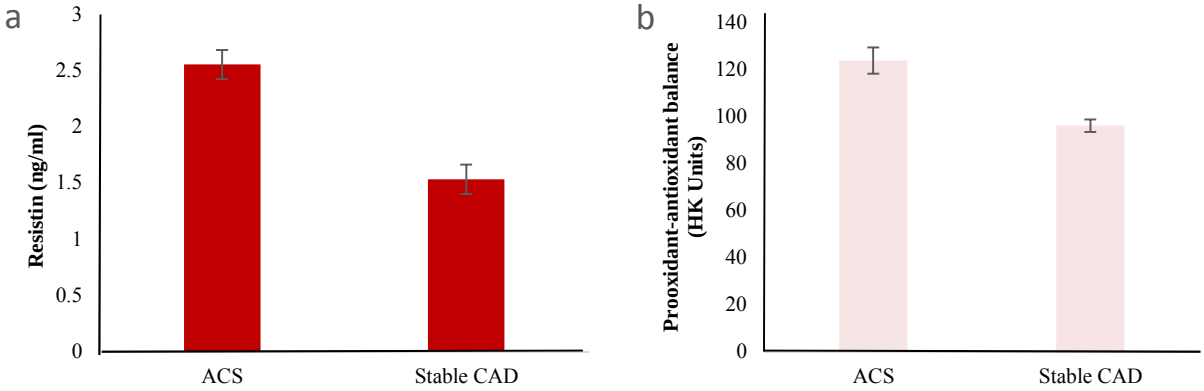

Figure 1. a. Serum resistin levels in patients with acute coronary syndrome and patients with stable coronary heart disease; b. The prooxidant-antioxidant balance value of patients with acute coronary syndrome and patients with stable coronary heart disease

There were significant differences between the resistin or prooxidant-antioxidant balance value of the patients with ACS and patients with stable CHD ($P < 0.001$ for both).

ACS: Acute coronary syndrome; CAD: coronary artery disease; CHD: Coronary heart disease

Illustrating the ability of resistin level and serum prooxidant-antioxidant balance level in predicting the occurrence of acute coronary syndrome

The ROC curve was used to help in discriminating ACS from stable CHD based on resistin and PAB serum levels. The area under the curve (AUC) demonstrates how the resistin and PAB serum levels can act as a prognostic factor of ACS.

Each point on the ROC curve also shows the sensitivity and specificity of these parameters in predicting ACS. ROC analysis provides 2 main outcomes, the diagnostic role of the test and the optimal cut-off point value for the test. Cut-off points dichotomize the test values, and this provides the diagnosis (diseased or not). The identification of the cut-off point value requires a simultaneous assessment of sensitivity and specificity.[28]

The ROC curve for serum resistin was analyzed to predict the occurrence of ACS (Figure 2).

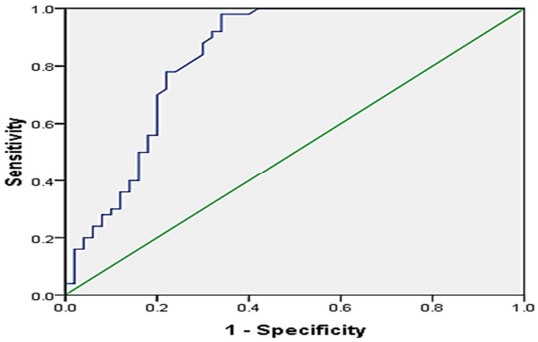

Figure 2. The receiver operating characteristic curve for serum resistin to differentiate acute coronary syndrome from stable coronary heart disease in the study population

The area under the ROC curve for resistin was 0.834 (95% CI: 0.750–0.918; $P < 0.001$). The cut-off point (maximal sensitivity and specificity) for resistin was 1.66 ng/ml (sensitivity: 78.00%; specificity: 76.00%).

Likewise, the ROC curve for serum PAB was analyzed to distinguish ACS from stable CHD (Figure 3).

The area under the ROC curve for PAB was 0.686 (95%CI: 0.577–0.794; $P < 0.001$). The cut-off point (maximal sensitivity and specificity) for PAB was 94.5 HK unite (sensitivity: 62.00%; specificity: 58.00%).

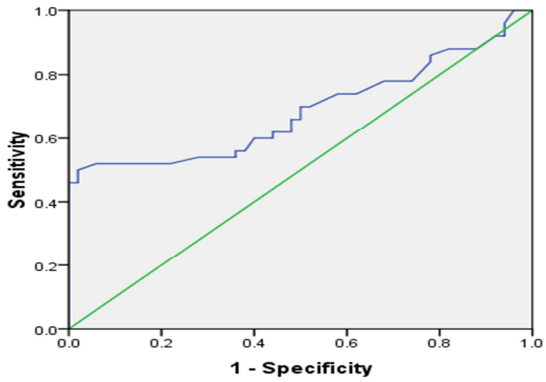

Figure 3. The receiver operating characteristic curve for serum prooxidant-antioxidant balance to distinguish acute coronary syndrome from stable coronary heart disease in the study population

Furthermore, the relationships between serum resistin level and other variables (including demographic variables, lipid profile, and other CVD risk factors) was assessed using the univariate analysis.

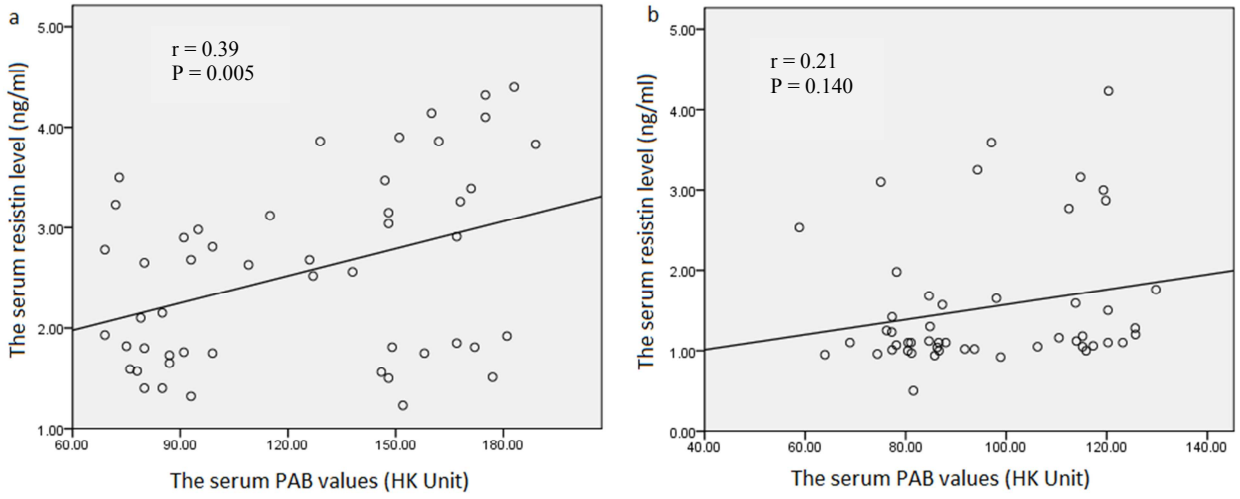

Figure 4. Correlation between serum resistin and prooxidant-antioxidant balance (PAP) in a. patients with acute coronary syndrome (r = 0.39; P = 0.005), and b. patients with stable coronary heart disease (r = 0.21; P = 0.140)

The serum resistin level showed no correlation with demographic variables such as age, BMI, and systolic and diastolic blood pressure. Moreover, serum resistin level showed a negative significant correlation with HDL-C (r = -0.259; P = 0.009), but showed no significant correlation with LDL-C, TC, and TG.

Correlation analysis showed that there was a significant correlation between serum resistin and PAB in patients with ACS (r = 0.39; P = 0.005), but this correlation was not found in patients with stable CHD (r = 0.21; P = 0.140) (Figure 4).

The data analysis also showed a highly significant positive correlation between serum resistin and hs-CRP levels (a serum inflammatory marker) in the ACS group (r = 0.52; P < 0.001), but this correlation was not found in the stable CHD group (r = 0.24; P = 0.090). Moreover, it showed a highly significant positive correlation between serum PAB values and hs-CRP level in the ACS group (r = 0.55; P < 0.001), but this correlation was not found in the stable CHD group (r = -0.02; P = 0.910).

In addition, we found a significant negative correlation between serum PAB values and HDL-C level (r = -0.278; P < 0.010) in the ACS group. Nevertheless, serum PAB value showed no significant correlation with LDL-C, TC, and TG levels.

Discussion

CVDs, including ACS, are among the major causes of morbidity and mortality worldwide. Acute coronary syndrome (ACS) is a multi-factorial disease, and hypercholesterolemia has been recognized as one of its major risk factors.[29] ACS severely threatens human health with increasing morbidity; therefore, early treatment of ACS might improve the adverse events of this disease.[30] The mechanism underlying ACS involves instability and rupture of atherosclerotic plaques, platelet aggregation, and thrombosis.[31] Instability of coronary plaque leads to progression of stable CAD to ACS.[31,32] Multiple biomarkers in the serum or plasma can provide appropriate diagnostic tools for this disease.

A particularly important contributing factor of the arterial plaque vulnerability and instability is inflammation.[33,34] Several factors are involved in inflammation and plaque instability, including adipocytokines and other various inflammatory and proinflammatory molecules.[35] MicroRNAs and adipocytokines is one of the key factors in plaque instability and the manifestation of ACS.

Adipocytokines and oxidative stress are considered as major risk factors for CHD.[6,36] Therefore, this study was designed to investigate the association between resistin serum level and PAB value. This association might help in discriminating ACS from stable CHD.

In the current study, we observed a higher serum resistin level in the ACS group compared to the stable CHD group. Figure 2 shows the cut-off values of resistin, which is associated with ACS.

The study by Qiao et al. showed that serum resistin level increased with inflammatory factors and myocardial impairment.[13] They suggested that human resistin might play an important role in the pathogenesis of atherosclerosis and acute myocardial infarction (AMI) as an inflammatory factor. This finding was in line with that of the

present study, which showed that serum resistin might play an important role in the pathogenesis of ACS. The cut-off point for resistin, as a predictor for ACS, was determined in the present study. We showed that serum resistin at the cut-off of 1.66 ng/ml yielded a sensitivity and specificity of 78% and 76%, respectively, in predicting the occurrence of ACS. The accuracy (AUC) for resistin was 0.834 (95% CI: 0.750–0.917; P < 0.001). These data show that resistin is an appropriate biomarker for predicting ACS. Verma et al. found that resistin may contribute to the atherosclerotic process by activation of endothelial cells thus leading to endothelial dysfunction and thereby the stimulation of multiple pro-atherosclerotic pathways.[37] However, the present study results indicated that serum resistin level can help in discriminating ACS from stable CHD, which is a demanding clinical finding.

We found higher serum PAB values in patients with ACS compared to those with stable CHD. The cut-off point of PAB for predicting ACS was determined using ROC (Figure 3).

Several studies have shown that oxidative stress plays a crucial role in the pathophysiology of atherosclerosis and CHD.[6,7] Environmental stress causes excessive production of reactive oxygen species (ROS), which leads to progressive oxidative damage. ROS acts as the initiator of oxidative cascade, which results in LDL oxidation, endothelial dysfunction, and vascular smooth muscle proliferation and migration.

In the present study, a significant correlation was found between PAB level and the risk of CVDs; thus, prooxidant-antioxidant imbalance is associated with atherosclerosis and CVD.[8,38] Ashok and Ali. also considered increased PAB value as a risk factor for ACD.[39]

In addition to the significant correlation of serum resistin level and PAB with hs-CRP, we found significantly higher values of both serum resistin and PAB in patients with ACS. We believe this correlation predicts the role of both variables among the markers of plaque formation through the inflammatory process.

In clinical practice, increase in inflammatory biomarkers and obesity are considered as prognosticators of cardiovascular events. Adipocytokines and other various inflammatory and proinflammatory molecules are involved in inflammation and plaque instability.[40] Hs-CRP represent the degree of the inflammatory response in the atheromatous plaque and is closely related to the instability of coronary artery plaque, which leads to the occurrence of ACS.

It has been demonstrated that inflammation and atherosclerosis play a key role in the pathogenesis of CVDs including the ACS.[41,42] According to the results of the current study, both resistin and PAB showed a negative significant correlation with HDL-C level, but showed no correlation with total lipid profile. Previous studies have reported similar results. Recent studies are in agreement with these findings. Chen et al.,[43] showed that resistin is negatively associated with HDL-C level in patients with metabolic syndrome. Similarly, Bednarska-Makaruk et al.[44] reported the association of adipokines with inflammatory markers and obesity in dementia. They found a negative correlation between resistin level mn and HDL. Various studies have shown that oxidative stress is negatively related to HDL-C level.[45,46] Not all studies support the present study findings. A few studies including the study performed by Rao and Kiran found no relationship between oxidative stress and HDL-C.[47]

In fact, the correlations of resistin and PAB values with the risk of ACS are evidence that ACS arises from an acute inflammatory condition. However, more studies must be performed to prove this finding and investigate the underlying metabolic pathways.

This reflected a complicated interaction between hs-CRP and resistin that may be through inflammatory mechanisms, given that ACS is an acute inflammatory condition. This finding may be indicative of a possible causal relationship between hs-CRP and resistin in patients with ACS. However, more studies are required to demonstrate this relationship and its metabolic pathways.

Limitations: This present study had a relatively small sample size, so we probably failed to detect a meaningful or obvious effect (lack of statistical power due to small sample size). Moreover, under small sample size conditions, a seemingly meaningful effect can occur by chance, but is not trustworthy. Because of these considerations, we recommend researchers to conduct similar studies with larger sample sizes to achieve more accurate results.

Conclusion

Resistin and PAB levels were found to have a significant correlation with the risk of ACS. Based on our findings, elevated resistin and PAB can both be predictors of the occurrence of ACS.

Furthermore, serum resistin level is highly correlated with PAB and both factors are highly correlated with hs-CRP, which is an inflammatory

marker. Thus, it can be concluded that resistin and PAB values play a crucial role in the pathogenesis of ACS through the inflammatory process.

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Conflict of Interests

Authors have no conflict of interests.

References

1. Alfieri O, Mayosi BM, Park SJ, Sarrafzadegan N, Virmani R. Exploring unknowns in cardiology. Nat Rev Cardiol 2014; 11(11): 664-70.
2. Ozturk HS, Cimen MY, Cimen OB, Kacmaz M, Durak I. Oxidant/antioxidant status of plasma samples from patients with rheumatoid arthritis. Rheumatol Int 1999; 19(1-2): 35-7.
3. Anwaruddin S, Askari AT, Topol EJ. Redefining risk in acute coronary syndromes using molecular medicine. J Am Coll Cardiol 2007; 49(3): 279-89.
4. Ghayour-Mobarhan M, Alamdari DH, Moohebati M, Sahebkar A, Nematy M, Safarian M, et al. Determination of prooxidant--antioxidant balance after acute coronary syndrome using a rapid assay: A pilot study. Angiology 2009; 60(6): 657-62.
5. Harrison D, Griendling KK, Landmesser U, Hornig B, Drexler H. Role of oxidative stress in atherosclerosis. Am J Cardiol 2003; 91(3A): 7A-11A.
6. Criqui MH, Denenberg JO, Ix JH, McClelland RL, Wassel CL, Rifkin DE, et al. Calcium density of coronary artery plaque and risk of incident cardiovascular events. JAMA 2014; 311(3): 271-8.
7. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. J Am Coll Cardiol 2006; 47(8 Suppl): C13-C18.
8. Raffetto JD, Khalil RA. Matrix metalloproteinases and their inhibitors in vascular remodeling and vascular disease. Biochem Pharmacol 2008; 75(2): 346-59.
9. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW. Multiple complex coronary plaques in patients with acute myocardial infarction. N Engl J Med 2000; 343(13): 915-22.
10. Meydani M. Vitamin E modulation of cardiovascular disease. Ann N Y Acad Sci 2004; 1031: 271-9.
11. Rajala MW, Obici S, Scherer PE, Rossetti L. Adipose-derived resistin and gut-derived resistin-like molecule-beta selectively impair insulin action on glucose production. J Clin Invest 2003; 111(2): 225-30.
12. Talman AH, Psaltis PJ, Cameron JD, Meredith IT, Seneviratne SK, Wong DT. Epicardial adipose tissue: Far more than a fat depot. Cardiovasc Diagn Ther 2014; 4(6): 416-29.
13. Qiao XZ, Yang YM, Xu ZR, Yang LA. Relationship between resistin level in serum and acute coronary syndrome or stable angina pectoris. J Zhejiang Univ Sci B 2007; 8(12): 875-80.
14. Charo IF, Ransohoff RM. The many roles of chemokines and chemokine receptors in inflammation. N Engl J Med 2006; 354(6): 610-21.
15. George SJ, Johnson J. Atherosclerosis: Molecular and Cellular Mechanisms. Hoboken, NJ: John Wiley & Sons; 2010.
16. Bokarewa M, Nagaev I, Dahlberg L, Smith U, Tarkowski A. Resistin, an adipokine with potent proinflammatory properties. J Immunol 2005; 174(9): 5789-95.
17. Jung HS, Park KH, Cho YM, Chung SS, Cho HJ, Cho SY, et al. Resistin is secreted from macrophages in atheromas and promotes atherosclerosis. Cardiovasc Res 2006; 69(1): 76-85.
18. Kaser S, Kaser A, Sandhofer A, Ebenbichler CF, Tilg H, Patsch JR. Resistin messenger-RNA expression is increased by proinflammatory cytokines in vitro. Biochem Biophys Res Commun 2003; 309(2): 286-90.
19. Burnett MS, Lee CW, Kinnaird TD, Stabile E, Durrani S, Dullum MK, et al. The potential role of resistin in atherogenesis. Atherosclerosis 2005; 182(2): 241-8.
20. Kawanami D, Maemura K, Takeda N, Harada T, Nojiri T, Imai Y, et al. Direct reciprocal effects of resistin and adiponectin on vascular endothelial cells: A new insight into adipocytokine-endothelial cell interactions. Biochem Biophys Res Commun 2004; 314(2): 415-9.
21. Patel L, Buckels AC, Kinghorn IJ, Murdock PR, Holbrook JD, Plumpton C, et al. Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators. Biochem Biophys Res Commun 2003; 300(2): 472-6.
22. Yang RZ, Huang Q, Xu A, McLenithan JC, Eisen JA, Shuldiner AR, et al. Comparative studies of resistin expression and phylogenomics in human and mouse. Biochem Biophys Res Commun 2003; 310(3): 927-35.
23. Fruhbeck G, Salvador J. Role of adipocytokines in metabolism and disease. Nutr Res 2004; 24(10): 803-26.

24. Li R, Chen LZ, Zhao SP, Huang XS. Inflammation Activation Contributes to Adipokine Imbalance in Patients with Acute Coronary Syndrome. PLoS One 2016; 11(3): e0151916.

25. Darabi F, Aghaei M, Movahedian A, Elahifar A, Pourmoghadas A, Sarrafzadegan N. Association of serum microRNA-21 levels with Visfatin, inflammation, and acute coronary syndromes. Heart Vessels 2017; 32(5): 549-57.

26. Weaver WD, Simes RJ, Betriu A, Grines CL, Zijlstra F, Garcia E, et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: A quantitative review. JAMA 1997; 278(23): 2093-8.

27. Pasterkamp G, Schoneveld AH, Hijnen DJ, de Kleijn DP, Teepen H, van der Wal AC, et al. Atherosclerotic arterial remodeling and the localization of macrophages and matrix metalloproteases 1, 2 and 9 in the human coronary artery. Atherosclerosis 2000; 150(2): 245-53.

28. Unal I. Defining an Optimal Cut-Point Value in ROC Analysis: An Alternative Approach. Comput Math Methods Med 2017; 2017: 3762651.

29. Kotani T, Takeuchi T, Takai S, Yoshida S, Hata K, Nagai K, et al. Serum levels of matrix metalloproteinase (MMP) 9, a risk factor for acute coronary syndrome, are reduced independently of serum MMP-3 by anti-TNF-alpha antibody (infliximab) therapy in patients with rheumatoid arthritis. J Pharmacol Sci 2012; 120(1): 50-3.

30. Anzai A, Maekawa Y, Kodaira M, Mogi S, Arai T, Kawakami T, et al. Prognostic implications of optimal medical therapy in patients undergoing percutaneous coronary intervention for acute coronary syndrome in octogenarians. Heart Vessels 2015; 30(2): 186-92.

31. Libby P. Inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol 2012; 32(9): 2045-51.

32. Madrigal-Matute J, Rotllan N, Aranda JF, Fernandez-Hernando C. MicroRNAs and atherosclerosis. Curr Atheroscler Rep 2013; 15(5): 322.

33. Lendon CL, Davies MJ, Born GV, Richardson PD. Atherosclerotic plaque caps are locally weakened when macrophages density is increased. Atherosclerosis 1991; 87(1): 87-90.

34. Moreno PR, Falk E, Palacios IF, Newell JB, Fuster V, Fallon JT. Macrophage infiltration in acute coronary syndromes. Implications for plaque rupture. Circulation 1994; 90(2): 775-8.

35. DeClercq V, Taylor C, Zahradka P. Adipose tissue: The link between obesity and cardiovascular disease. Cardiovasc Hematol Disord Drug Targets 2008; 8(3): 228-37.

36. Modi KA, Nylk TM, Sheridan FM. Medical management of acute ST elevation myocardial infarction. J La State Med Soc 2001; 153(6): 284-90.

37. Verma S, Li SH, Wang CH, Fedak PW, Li RK, Weisel RD, et al. Resistin promotes endothelial cell activation: Further evidence of adipokine-endothelial interaction. Circulation 2003; 108(6): 736-40.

38. Komorowski J, Pasieka Z, Jankiewicz-Wika J, Stepien H. Matrix metalloproteinases, tissue inhibitors of matrix metalloproteinases and angiogenic cytokines in peripheral blood of patients with thyroid cancer. Thyroid 2002; 12(8): 655-62.

39. Ashok BT, Ali R. The aging paradox: free radical theory of aging. Exp Gerontol 1999; 34(3): 293-303.

40. Bartel DP. MicroRNAs: Genomics, biogenesis, mechanism, and function. Cell 2004; 116(2): 281-97.

41. Bauvois B. New facets of matrix metalloproteinases MMP-2 and MMP-9 as cell surface transducers: Outside-in signaling and relationship to tumor progression. Biochim Biophys Acta 2012; 1825(1): 29-36.

42. Lu P, Takai K, Weaver VM, Werb Z. Extracellular matrix degradation and remodeling in development and disease. Cold Spring Harb Perspect Biol 2011; 3(12).

43. Chen CC, Li TC, Li CI, Liu CS, Wang HJ, Lin CC. serum resistin level among healthy subjects: Relationship to anthropometric and metabolic parameters. Metabolism 2005; 54(4): 471-5.

44. Bednarska-Makaruk M, Graban A, Wisniewska A, Lojkowska W, Bochynska A, Gugala-Iwaniuk M, et al. Association of adiponectin, leptin and resistin with inflammatory markers and obesity in Dementia. Biogerontology 2017; 18(4): 561-80.

45. He L, Hannon GJ. MicroRNAs: Small RNAs with a big role in gene regulation. Nat Rev Genet 2004; 5(7): 522-31.

46. Wightman B, Ha I, Ruvkun G. Posttranscriptional regulation of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in C. elegans. Cell 1993; 75(5): 855-62.

47. Rao V, Kiran R. Evaluation of correlation between oxidative stress and abnormal lipid profile in coronary artery disease. J Cardiovasc Dis Res. 2011;2(1):57-60

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The psychometric properties of the Hypertensive Treatment Adherence Scale

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Original Article

Abstract

BACKGROUND: Hypertension (HTN) is a public concern and treatment adherence has a key role in its management. This study was conducted to develop and test the reliability and validity of the Hypertensive Treatment Adherence scale (HTA-scale).

METHODS: This was a cross-sectional and methodological study. After item generation using a qualitative study and literature review, the scale was developed. The psychometric properties of the scale were evaluated using face, content, construct, and criterion validity and reliability.

RESULTS: Data analysis showed that the HTA-scale had acceptable face and content validity. The scale had excellent stability [Intraclass correlation coefficient (ICC) = 0.74] and good acceptability and internal consistency (Cronbach's α = 0.76). Exploratory factor analysis (EFA) showed that the HTA-scale consisted of 6 meaningful subscales including medication adherence and monitoring, adherence to safe diets, avoiding unsafe diets, self-medication, activity, and smoking. Participants in the controlled blood pressure group had significantly higher HTA-scale scores than the uncontrolled blood pressure group. At the cut-off point of 86, the scale had significant sensitivity and specificity.

CONCLUSION: All of the psychometric properties of the HTA-scale achieved the standard level and were sufficient to recommend this scale for patients with HTN.

Keywords: Hypertension; Treatment Adherence; Psychometrics; Scales

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Introduction

Hypertension (HTN) is one of the most common risk factors for cardiovascular diseases (CVDs) resulting in myocardial infarction (MI), cerebral events, renal and heart failures, and early death. In a meta-analysis conducted by Haghdoost et al., it was shown that 22% of 30-55 year old people and 50% of people older than 55 years were affected by HTN in Iran.[1]

Failure to sufficiently control HTN further complicates this situation. Based on the report of the World Health Organization (WHO), more than half of patients with HTN discontinue their treatments in the first year of diagnosis and 80% of patients who continue their treatments, take prescribed medications.[2] Therefore, 75% of patients do not sufficiently control HTN due to poor adherence to treatment regimen.[2] Non-adherence to treatment regimen is considered as one of the most important clinical problems in the treatment and management of chronic diseases resulting in increased caring costs, rate of hospitalization, and early death.[3]

One of important obstacles to the improvement of adherence to treatment regimen is that it is difficult to measure adherence.

Several medication adherence instruments have been mentioned in published papers including the Hill-Bone Compliance to High Blood Pressure Therapy Scale, Morisky Medication Adherence Scale (MMAS), and Brief Medication Adherence Questionnaire (BMAQ), but such instruments have not been used and compared simultaneously in similar populations and the psychometric properties of these instruments have not been validated. However, there is no key standard questionnaire and each of these instruments is suitable for a special setting and scenario.

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The abovementioned instruments are not general questionnaires and most of them measure only medication adherence. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends anti-hypertensive treatment and lifestyle modification for the prevention and treatment of HTN and focuses on non-medicinal interventions to control HTN. Moreover, weight loss, diet improvement, increased exercise, and stress and anger control are systematically effective on HTN. Therefore, adherence should be evaluated as a whole in relation to different aspects of treatment such as diet, exercise, and medication.[4] The Treatment Adherence Questionnaire for Patients with Hypertension (TAQPH) was designed by Ma et al.[4] in 2011 in China. The TAQPH contains the highest number of items among related questionnaires; thus, it might potentially provide more information for the research investigation. However, in clinical practice, it is necessary that a questionnaire contains the fewest possible items that could be acceptable to both health care professionals and patients. In addition, in the validation process of the TAQPH, its sensitivity, specificity, positive predictive value, and negative predictive value were not assessed. These items are important for using a scale in clinical practice.[5] Nevertheless, this instrument has not been tested in other countries and it has not been validated.

It seems that there is no gold standard instrument for the evaluation of treatment adherence in patients with HTN.[5,6] Therefore, considering the deficiencies and limitations of tools available throughout the world, it is necessary to perform some researches in this regard. The aim of this research was to develop and validate the Hypertensive Treatment Adherence Scale (HTA-scale).

Materials and Methods

This study with methodological design was conducted in educational hospitals of Kerman University of Medical Sciences, Kerman, Iran, and physician's offices. Kerman is the largest city in southeastern Iran with a population of 722,000. To develop a comprehensive scale, a qualitative content analysis and literature review were conducted to generate the item pool. The results of the qualitative content analysis are reported elsewhere in detail.[7] According to the results, an 84-item pool was developed from participants' quotations. In several meetings among the research team, some items that were similar, redundant, or overlapped were omitted or integrated with other items. At this phase, the scale consisted of 36 items. To enrich the scale items and to ensure that all aspects of adherence to HTN treatment were considered, a literature review was performed. The PubMed, ScienceDirect, Ovid, and Google Scholar databases were searched using the terms "treatment adherence", "treatment compliance", "treatment concordance", "medication adherence", "medication compliance", "medication concordance", "hypertension or high blood pressure", "questionnaire", "scale", "instrument", and "psychometric property", "test-retest reliability", "internal consistency", "Cronbach's alpha", "construct validity", "content validity", "face validity", "guidelines", "content analysis", and "qualitative study". The search was limited to English articles published online and no publication date restrictions were applied. In total, 147 articles were retrieved. From among these, the most relevant articles that could help us enrich the item pool were selected. At the end of the literature review, phase 9 items were added to the item pool. At the end of the item generation phase, the scale consisted of 45 items. A 5-point Likert scale ranging from 1 (not important) to 5 (completely important) was used for the scoring of items. Higher scores indicate a higher level of adherence to HTN treatment.

Face validity assessment: The opinions of 25 patients with HTN were asked about the relevancy of the scale items. The participants were older than 18 years and took at least 1 antihypertensive agent. Convenience sampling method was used. Patients with HTN, who were interested in participating in the study, were interviewed in regard with the scale items and their suggestions about the items and scale were recorded. Then, they were asked to complete the scale. Data were collected in one interaction with each patient separately between October, 2, 2014 and October, 16, 2014. Following the interviews, the research team analyzed all comments recorded during the scale administration using content analysis. Based on the results of content analysis, consensus was reached on all changes necessary in the scale. Then, the item impact method was used to determine the importance of each item. If the item impact score was above 1.5, the item was important and maintained in the scale for further evaluation.

Content validity assessment: In the first step, 21 experts were asked to write their comments on the fitness, simplicity, and comprehensiveness of each item individually. In the second step, the experts were asked to rate the necessity of each item [content validity ratio (CVR)] on a 3-point Likert scale (1: not necessary, 2: helpful but not necessary, 3: necessary). To determine the relevancy, simplicity, and clarity of

each item and the scale [content validity index (CVI)], the respondents were asked to grade each item on a 4-point Likert scale (1: not relevant, 2: need minor revision, 3: need major revision, 4: relevant). The experts consisted of physicians, nursing faculty members, and epidemiologists (21 experts) who were experts in their research field. This sampling was conducted from October, 27, 2014 to November, 30, 2014. The research team analyzed all experts' written comments using content analysis. According to the results of content analysis, consensus was reached on all changes made in the scale. To quantify agreement on the scale content, CVR and CVI were used.

According to the Lawshe table, when the total number of experts is 21, the cut-off point value is 0.42.[8] The accepted standard in the literature for item-level CVI (I-CVI) and scale-level CVI (S-CVI) are 0.9 and 0.80, respectively.

Pilot study for the assessment of internal consistency: The third sample (pilot study) was collected to calculate internal consistency evidence and response rate in order to determine homogeneity of the HTA-scale and the appropriateness of the 5-point Likert scale selected for the scale. The participants consisted of 30 patients with HTN in cardiovascular units of 2 educational hospitals, and 3 cardiologists' and 2 nephrologists' offices in Kerman, Iran. Convenience sampling method was used. Patients with HTN were interviewed and were asked to complete the scale using the 5-point Likert scale. Data collection was conducted from December, 10, 2014 to December, 25, 2014. A coefficient value of higher than 0.7 was considered acceptable.[9]

Construct validity assessment: The fourth sample was collected to calculate construct and criterion validity, sensitivity and specificity, internal consistency, and practicability and acceptability of the HTA-scale. Using multistage random cluster sampling, 300 patients with HTN were selected. The selected patients were divided into 2 categories of in-patients and out-patients. Then, 150 subjects were selected from in-patient centers (13 hospital wards; cardiovascular, internal, and emergency wards considered as clusters) and 150 subjects were selected from out-patient centers (12 cardiologists' and nephrologists' offices, and 1 sub-specialty educational clinic considered as clusters). Sociodemographic data, such as age, gender, marital status, educational and occupational status, duration of HTN, duration of taking anti-hypertensive drugs, and having other diseases, were collected. In addition, blood pressure was measured using an aneroid sphygmomanometer (ALPK2, Japan) and the average of 2 measurements taken 5 minutes apart was presented. Systolic and diastolic blood pressures were obtained from the right arm of the subjects using standard procedure. For illiterate individuals, interviews were used instead of the self-administration method. Data collection was performed from January, 01, 2015 to February, 30, 2015. Exploratory factor analysis (EFA) was conducted to verify the factorial design of the HTA-scale using principal axis factoring (PAF) with varimax rotation. The following criteria were used to determine the number of factors in the scales: eigenvalues > 1, scree plots, and items with loadings of 0.4 or greater on any one factor.

Criterion validity assessment: To verify concurrent criterion validity, the difference in the HTA-scale score between patients with controlled and uncontrolled HTN was analyzed using t-test (data were distributed normally). Patients younger than 60 years of age who had blood pressure ≥ 140/90 and 60-year-old or older patients who had blood pressure ≥ 150/90 were considered as the uncontrolled HTN group. Moreover, patients who had a blood pressure lower than these ranges were considered as the controlled HTN group.[10,11]

Sensitivity and specificity assessment: The sensitivity and specificity of the HTA-scale were calculated using receiver operating characteristic (ROC) curve analysis. An accuracy of 50-70% was considered as acceptable.[9] Acceptability or practicability of the HTA-scale was assessed by calculating missing values and the average time needed to complete the scale. Furthermore, floor/ceiling effect was assessed. The amount of missing values and floor/ceiling effect should be less than 10% and 80%, respectively, in order that the scale obtains acceptability.

Stability assessment: The fifth sample was collected to determine the test-retest reliability of the HTA-scale. The scale was completed by 35 patients with HTN twice (with a 2-week interval). Patients with HTN were interviewed. The second data collection was conducted through telephone calls. Data collection was conducted from March, 05, 2015 to March, 25, 2015. The intraclass correlation coefficient (ICC) (two-way mixed) was used to assess the repeatability of the HTA-scale. To interpret the obtained coefficients, values above 0.7 were considered as excellent reliability.[9] In this study, all analyses were performed using SPSS software (version 19.0, SPSS Inc., Chicago, IL, USA).

Ethical consideration: Kerman University of Medical Sciences approved this project (ethic code: K/93/580). After coordinating with the university,

the clinical centers, sub-specialty educational clinic, and physicians we provided with information for the subjects. The information addressed the objectives of the study, the confidentiality of the data, the anonymity of the participants, and their freedom to withdraw from the study at any time. Then, informed consent was obtained verbally.

Results

Content validity: According to the experts' comments, 1 item was divided into 2 separate items, 1 item was added to the scale, and 4 items were omitted due to "conceptual overlap", and "lack of comprehensiveness or relevancy". In total, 39 items displayed acceptable (> 0.42) CVR scores, while the CVR scores of 4 items were below the accepted standard (-0.14 to 0.33). The I-CVI scores of all items (between 0.84 and 1) exceeded the accepted standard of > 0.80. In addition, the S-CVI was 0.95. At the end of the content validity phase, the HTA-scale contained 40 items. It should be noted that the research team decided to maintain the item "Do you eat votive foods if available?", which did not have an acceptable CVR score, because it was a context-based item (Table 1).

Table 1. Content validity ratio and content validity index scores of the Hypertensive Treatment Adherence scale (n = 21)

No	Items	CVR	CVI
1	Do you eat boiled foods?	0.81	1.00
2	Do you consume high fat food and animal fat?	0.71	0.92
3	Do you eat high fat dairy?	0.6	0.92
4	Do you eat votive food if available?	-0.14	0.84
5	Do you comply with a low salt diet?	0.81	0.92
6	Do you sprinkle salt on your meals?	0.43	0.95
7	Do you eat fast foods such as sandwiches and pizza?	0.71	0.92
8	Do you eat sugar, sugar cubes, or sweets?	0.81	0.93
9	Do you eat junk foods such as chips and cheese puff?	0.71	0.95
10	Do you eat canned foods?	0.62	0.93
11	Do you eat red meat less than before?	0.81	0.95
12	Do you eat eggs less than before?	0.81	0.95
13	Do you eat high fiber foods and vegetables daily?	0.9	0.97
14	Do you eat fruits daily?	0.71	0.97
15	Do you eat whole grain products such as barley bread daily?	0.81	0.94
16	Do you eat beans and cereals?	0.52	0.87
17	Do you sometimes fast?	0.33	0.92
18	Do you overeat?	0.81	0.95
19	Do you take your antihypertensive medication based on its prescription?	0.90	0.98
20	Do you take your antihypertensive medication irregularly?	0.33	0.89
21	Do you ever purchase and continue your previous antihypertensive medication without referring to your physician?	0.62	0.97
22	Do you use medications prescribed for other people with the same symptoms?	0.62	0.98
23	Do you sometimes stop taking your medication due to any reason?	0.90	0.95
24	Do you stop taking your medication without consulting with your physician?	0.71	0.95
25	Have you ever reduced or increased your medication?	0.33	0.95
26	Do you take your antihypertensive medications with or without having symptoms?	0.81	0.87
27	Do you take blood tests as regularly as prescribed by your physician?	0.90	1.00
28	Do you control your blood pressure weekly?	0.81	0.97
29	Do you go to your doctor to monitor your blood pressure status every 3-6 months?	0.90	1.00
30	Do you go to your doctor on pre-determined appointments?	0.81	0.98
31	Do you measure your weight every week?	0.81	0.98
32	Do you measure your waist circumference?	0.62	0.95
33	Do you do exercises such as walking, swimming, or cycling 4-7 days per week?	0.71	0.89
34	Do you exercise or walk for about 30-60 minutes on each exercise session?	0.81	0.95
35	Do you smoke cigarettes?	0.71	0.95
36	Do you consume traditional or industrial drugs such as opium, crack, or crystal?	0.71	0.98
37	Do you smoke hookah (shisha)?	0.71	0.97
38	Are you constantly exposed to cigarette and opium smoke?	0.81	0.95
39	Are you able to control your stress?	0.62	0.90
40	Are you able to control your anger?	0.71	1.00
41	Do you take psychiatric medications?	0.71	0.93
42	Do you drink coffee?	0.52	0.89
43	Do you drink alcohol?	0.71	1.00

CVR: Content validity ratio; CVI: Content validity index

Table 2. Internal consistency of the Hypertensive Treatment Adherence scale [pilot study (n = 30)]

No	Items	Cronbach's alpha if item is deleted	Corrected item-total correlation
1	Do you eat boiled foods?	0.76	0.22
2	Do you consume high fat food and animal fat?	0.76	0.17
3	Do you eat high fat dairy?	0.74	0.51
4	Do you eat votive food if available?	0.74	0.46
5	Do you comply with a low salt diet?	0.77	-0.09
6	Do you sprinkle salt on your meals?	0.76	0.21
7	Do you eat fast foods such as sandwiches and pizza?	0.75	0.28
8	Do you eat sugar, sugar cubes, or sweets?	0.74	0.43
9	Do you eat junk foods such as chips and cheese puff?	0.76	0.13
10	Do you eat canned foods?	0.76	0.02
11	Do you eat red meat less than before?	0.76	0.08
12	Do you eat eggs less than before?	0.77	-0.13
13	Do you eat high fiber foods and vegetables daily?	0.74	0.52
14	Do you eat fruits daily?	0.74	0.57
15	Do you eat whole grain products such as barley bread daily?	0.74	0.51
16	Do you eat beans and cereals?	0.76	0.15
17	Do you overeat?	0.75	0.41
18	Do you take your antihypertensive medication based on its prescription?	0.75	0.38
19	Do you ever purchase and continue your previous antihypertensive medication without referring to your physician?	0.75	0.26
20	Do you use medications prescribed for other people with the same symptoms?	0.77	-0.07
21	Do you sometimes stop taking your medication due to any reason?	0.75	0.31
22	Do you increase or decrease the dosage of your medication without consulting your physician?	0.76	0.10
23	Do you take your antihypertensive medications with or without having symptoms?	0.77	-0.07
24	Do you take blood tests as regularly as prescribed by your physician?	0.73	0.63
25	Do you control your blood pressure weekly?	0.75	0.31
26	Do you refer to your doctor to monitor your blood pressure status every 3-6 months?	0.74	0.53
27	Do you refer to your doctor on pre-determined appointments?	0.74	0.45
28	Do you measure your weight every week?	0.76	0.19
29	Do you measure your waist circumference?	0.76	-0.13
30	Do you do exercises such as walking, swimming, or cycling 4-7 days per week?	0.76	0.20
31	Do you exercise or walk for about 30-60 minutes on each exercise session?	0.75	0.34
32	Do you smoke cigarettes?	0.76	0.16
33	Do you consume traditional or industrial drugs such as opium, crack, or crystal?	0.75	0.46
34	Do you smoke hookah (shisha)?	0.76	0.06
35	Are you constantly exposed to cigarette and opium smoke?	0.75	0.33
36	Are you able to control your stress?	0.77	-0.24
37	Are you able to control your anger?	0.76	0.07
38	Do you take psychiatric medications?	0.76	0.19
39	Do you drink coffee?	0.76	0.20
40	Do you drink alcohol?	0.76	0.19

Face validity: In total, 7 items of the 45-item scale were revised according to respondents' comments. Of these items, 2 had an item impact scores below 1.5. The item impact scores of the other items ranged from 1.68 to 4.72. At the end of this phase, the research team decided to maintain all items for the next phase (content validity), so no item was omitted at the end of the face validity phase.

Pilot study (Internal consistency and response rate) (Table 2): The value of Cronbach's α for the HTA-scale was 0.76. The HTA-scale item-total correlations ranged from -0.24 to 0.63.

Table 3. Demographic characteristics of the study participants (n = 300)

Quantitative variables		**Mean ± SD**
Age (year)		59.96 ± 12.12
Duration of hypertension (month)		57.40 ± 39.60
Duration of treatment for hypertension (month)		56.59 ± 37.55
Systolic blood pressure (mmHg)		130.20 ± 7.24
Diastolic blood pressure (mmHg)		87.92 ± 7.54
Qualitative variables		
Quantitative variables		**n (%)**
Gender	Female	150 (50.2)
	Male	149 (49.8)
Marital status	Single	4 (1.4)
	Married	194 (64.7)
	Divorced	11 (3.7)
	Widowed	86 (29.2)
Educational status	Illiterate	64 (21.8)
	Pre-diploma	114 (38.7)
	Diploma	74 (25.2)
	Bachelor's degree or higher	42 (14.3)
Occupation	Unemployed	30 (10.3)
	Employed	97 (33.3)
	Pensioner	74 (25.2)
	Housewife	91 (31.2)
Antihypertensive drugs	One drug	183 (63.3)
	Two drugs	94 (32.5)
	Three drugs	12 (4.2)
Having diabetes mellitus	Yes	47 (15.7)
	No	252 (84.3)
Having diseases other than diabetes	Yes	133 (44.5)
	No	166 (55.5)

SD: Standard deviation

The item-total correlations were 0.20 or greater for 22 items of the 40-item HTA-scale. To improve the Cronbach's α coefficient of the scale, 5 items that had negative item-total correlation were omitted and the internal consistency was recalculated. As a result, the Cronbach's α coefficient of the scale increased to 0.81. It should be noted that the research team decided to maintain the item "Do you comply with a low salt diet?", which had a negative item-total correlation, in the scale because of its importance.

Construct validity (Socio-demographic characteristics): In total, 300 patients with HTN were assessed. The response rate was more than 98%; 5 patients refused to participate in the study. The mean age of the patients was 59.96 ± 12.12 years. Nearly half of the participants were men (49.8%), 64.7% of the participants were married, less than 22% were illiterate, and 10.3% were unemployed. The mean duration of HTN was 57.4 ± 39.6 months. The mean duration of taking antihypertensive drugs was 56.59 ± 37.55 months. Moreover, 15.7% of the participants had diabetes, and 44.5% of the participants had other diseases (Table 3).

More than 80% of the participants had perfect adherence to 3 items (28, 29, and 35). In addition, the lowest amount of adherence was related to the items on exercise (26 and 27) (Table 4).

Exploratory factor analysis: To verify the construct validity of the HTA-scale, PAF with varimax rotation was used. In the first step, Bartlett's and Kaiser-Meyer-Olkin (KMO) tests were used to verify the normal distribution of data and adequacy of sample size for EFA. The results of Bartlett's test were significant [$\chi^2 = 3705.36$; degree of freedom (df) = 595; $P < 0.001$] and the KMO coefficient was 0.775 that exceeded the accepted standard of > 0.7. In the second step, PAF with varimax rotation was conducted and 10 factors with eigenvalues of > 1 were retrieved. The total variance explained by these 10 factors was 63.7%. According to the factor loading of > 0.4, 3 items (2, 29, and 35) were not loaded in any factors. EFA was conducted again after omitting items 2, 29, and 35. In this stage, KMO coefficient was 0.788 and Bartlett's test was significant ($\chi^2 = 3422.07$; df = 496; $P < 0.001$). Nine factors with eigenvalues of > 1 were retrieved that explained 63.75% of total variance. According to the factor loading of > 0.4, 5 items (3, 10, 11, 15, and 25) were not loaded in any factors.

Table 4. Distribution of the responses to the Hypertensive Treatment Adherence scale (n = 300)

No	Items	Missing (n)	Response [n (%*)]				
			No	Yes but rarely	Yes, occasionally	Yes, frequently	Yes, always
1	Do you eat boiled foods?	**0**	28 (9.3)	71 (23.7)	76 (25.3)	81 (27.0)	44 (14.7)
2	Do you consume high fat food and animal fat?	1	52 (17.4)	121 (40.5)	95 (31.8)	30 (10.0)	1 (0.1)
3	Do you eat high fat dairy?	4	38 (12.8)	114 (38.5)	89 (30.1)	45 (15.2)	10 (3.4)
4	Do you eat votive food if available?	1	22 (7.4)	86 (28.8)	64 (21.4)	90 (30.1)	5 (12.4)
5	Do you comply with a low salt diet?	0	12 (4.0)	49 (16.3)	85 (28.3)	96 (32.0)	58 (19.4)
6	Do you sprinkle salt on your meals?	0	96 (32.0)	118 (39.3)	61 (20.3)	17 (5.7)	8 (2.7)
7	Do you eat fast foods such as sandwiches and pizza?	1	119 (39.8)	95 (31.8)	63 (21.1)	21 (7.0)	1 (0.3)
8	Do you eat sugar, sugar cubes, or sweets?	1	53 (17.7)	69 (23.1)	56 (18.7)	74 (24.7)	47 (15.7)
9	Do you eat junk foods such as chips and cheese puff?	0	115 (38.3)	87 (29.0)	74 (24.7)	20 (6.7)	4 (1.3)
10	Do you eat canned foods?	1	85 (28.4)	104 (34.8)	82 (27.4)	24 (8.0)	4 (1.3)
11	Do you eat red meat less than before?	4	5 (1.7)	76 (25.7)	96 (32.4)	99 (33.4)	20 (6.8)
12	Do you eat high fiber foods and vegetables daily?	1	5 (1.7)	33 (11.0)	81 (27.1)	115 (38.5)	65 (21.7)
13	Do you eat fruits daily?	6	1 (0.3)	23 (7.8)	37 (12.6)	96 (32.7)	137 (46.6)
14	Do you eat whole grain products such as barley bread daily?	2	9 (3.0)	59 (19.8)	70 (23.5)	96 (32.2)	64 (21.5)
15	Do you eat beans and cereals?	1	4 (1.3)	52 (17.4)	72 (24.1)	106 (35.5)	65 (21.7)
16	Do you overeat?	7	107 (36.5)	103 (35.2)	59 (20.1)	14 (4.8)	10 (3.4)
17	Do you take your antihypertensive medication based on its prescription?	2	5 (1.7)	15 (5.0)	29 (9.7)	86 (28.9)	163 (54.7)
18	Do you ever purchase and continue your previous antihypertensive medication without referring to your physician?	4	61 (20.6)	75 (25.3)	74 (25.0)	48 (16.2)	38 (12.8)
19	Do you sometimes stop taking your medication due to any reason?	2	69 (23.2)	133 (44.6)	68 (22.8)	23 (7.7)	5 (1.7)
20	Do you increase or decrease the dosage of your medication without consulting with your physician?	4	182 (61.5)	59 (19.9)	30 (10.1)	22 (7.4)	3 (1.0)
21	Do you take blood tests as regularly as prescribed by your physician?	0	14 (4.7)	19 (6.3)	59 (19.7)	99 (33.0)	109 (36.3)
22	Do you control your blood pressure weekly?	1	18 (6.0)	74 (24.7)	70 (23.4)	55 (18.4)	82 (27.4)
23	Do you refer to your doctor to monitor your blood pressure status every 3-6 months?	3	9 (3.0)	47 (15.8)	78 (26.3)	77 (25.9)	86 (29.0)
24	Do you refer to your doctor on pre-determined appointments?	1	10 (3.3)	23 (7.7)	44 (14.7)	89 (29.8)	133 (44.5)

Table 4. Distribution of the responses to the Hypertensive Treatment Adherence scale (n = 300) (continue)

No	Items	Missing (n)	Response [n (%*)]				
			Response [n (%*)]	No	Items	Missing (n)	Response [n (%*)]
25	Do you measure your weight every week?	4	55 (18.6)	110 (37.2)	73 (24.7)	31 (10.5)	26 (8.8)
26	Do you do exercises such as walking, swimming, or cycling 4-7 days per week?	1	74 (24.7)	108 (36.1)	63 (21.1)	38 (12.7)	16 (5.4)
27	Do you exercise or walk for about 30-60 minutes each time?	3	59 (19.9)	130 (43.8)	74 (24.9)	28 (9.4)	6 (2.0)
28	Do you smoke cigarettes?	2	241 (80.9)	21 (7.0)	18 (6.0)	6 (2.0)	12 (4.0)
29	Do you consume traditional or industrial drugs such as opium, crack, or crystal?	0	263 (87.7)	15 (5.0)	12 (4.0)	5 (1.7)	5 (1.7)
30	Do you smoke hookah (shisha)?	3	235 (79.1)	41 (13.8)	19 (6.4)	1 (0.3)	1 (0.3)
31	Are you constantly exposed to cigarette and opium smoke?	3	102 (34.3)	94 (31.6)	61 (20.5)	20 (6.7)	20 (6.7)
32	Are you able to control your anger?	8	21 (7.2)	56 (19.2)	67 (22.9)	70 (24.0)	78 (26.7)
33	Do you take psychiatric medications?	2	177 (59.4)	37 (12.4)	25 (8.4)	25 (8.4)	34 (11.4)
34	Do you drink coffee?	1	124 (41.5)	53 (17.7)	60 (20.1)	40 (13.4)	22 (7.4)
35	Do you drink alcohol?	1	286 (95.7)	11 (3.7)	1 (0.3)	1 (0.3)	-

* Valid percent

We decided to omit these items and perform EFA again. In this stage, the KMO coefficient was 0.792 and Bartlett's test was significant ($\chi^2 = 3017.49$; df = 351; P < 0.001). Eight factors with eigenvalues of > 1 were retrieved that explained 66.66% of total variance. According to the factor loading of > 0.4, all items were loaded in the 8 factors. Among 27 items, 3 items (16, 32, and 33) did not have a meaningful pattern in the factors they were loaded on; we could keep these items based on the presumption that these items are hidden conceptual aspects of the variable (factor) or omit them if their interpretation was difficult.[12] Therefore, we decided to omit these non-meaningful items and reanalyze the rest of the items. In this stage, The KMO coefficient was 0.791 and Bartlett's test was significant ($\chi^2 = 2685.26$; df = 276; P < 0.001). Eight factors with eigenvalues of > 1 were retrieved that explained 70.58% of total variance. According to the factor loading of > 0.4, all items were loaded in the 8 factors.

The scree plot begins to level off after the second and third, and slightly after the sixth and eighth factors. Therefore, to determine the best number of factors, EFA was conducted again by limiting PAF to a fixed number of extractions (2-factor, 3-factor, and then, 6-factor extraction) and their results were assessed. The 6-factor extraction was the most meaningful among them. The 6-factor extraction explained 61.69% of total variance. Excluding item 5, all other items were loaded in the factors with a meaningful pattern. At the end of EFA, 12 items were omitted and the HTA-scale contained 23 items (Table 5).

Table 5. Rotated factor matrix of the Hypertensive Treatment Adherence scale

No	Items	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
		Medication adherence and monitoring	Adherence to safe diets	Avoiding unsafe diets	Self-medication	Activity	Smoking
17	Do you take your antihypertensive medication based on its prescription?	0.56					
21	Do you take blood tests as regularly as prescribed by your physician?	0.70					
22	Do you control your blood pressure weekly?	0.62					

Table 5. Rotated factor matrix of the Hypertensive Treatment Adherence scale (continue)

No	Items	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
		Medication adherence and monitoring	Adherence to safe diets	Avoiding unsafe diets	Self-medication	Activity	Smoking
23	Do you refer to your doctor to monitor your blood pressure status every 3-6 months?	0.76					
24	Do you refer to your doctor on pre-determined appointments?	0.64					
1	Do you eat boiled foods?		0.64				
4	Do you eat votive foods if available?		0.45				
5	Do you comply with a low salt diet?		0.56				
12	Do you eat high fiber foods and vegetables daily?		0.50				
13	Do you eat fruits daily?		0.56				
14	Do you eat whole grain products such as barley bread daily?		0.61				
7	Do you eat fast foods such as sandwiches and pizza?			0.71			
8	Do you eat sugar, sugar cubes, or sweets?			0.73			
9	Do you eat junk foods such as chips and cheese puff?			0.70			
34	Do you drink coffee?			0.45			
18	Do you ever purchase and continue your previous antihypertensive medication without referring to your physician?				0.57		
19	Do you sometimes stop taking your medication due to any reason?				0.70		
20	Do you increase or decrease the dosage of your medication without consulting your physician?				0.69		
26	Do you do exercises such as walking, swimming, or cycling 4-7 days per week?					0.86	
27	Do you exercise or walk for about 30-60 minutes each time?					0.84	
28	Do you smoke cigarettes?						0.72
29	Do you smoke hookah (shisha)?						0.40
30	Are you constantly exposed to cigarette and opium smoke?						0.79
Eigenvalue		4.80	3.72	1.85	1.71	1.45	1.28
Percentage of explained variance		20.01	15.50	7.71	7.11	6.05	5.31

Factor loads > 0.40 are mentioned.

Table 6. Correlations between the Hypertensive Treatment Adherence scale score and its subscales

Factors	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6	Total
Factor 1	1						
Factor 2	0.30*	1					
Factor 3	0.10	0.30*	1				
Factor 4	0.29*	-0.04	-0.23*	1			
Factor 5	0.27*	0.28*	-0.10	0.09	1		
Factor 6	0.09	0.22*	0.21*	0.04	0.12*	1	
Total	0.66*	0.77*	0.38*	0.26*	0.45*	0.46*	1

* P < 0.050

In addition, the correlations between HTA-scale score and each dimension ranged from 0.26 to 0.77 and the correlations of each dimension with other dimensions ranged from 0.04 to 0.33 (Table 6). Note that, in order to calculate factor analysis, missing values were replaced with means.

The final HTA-scale included 23 items and respondents were easily able to complete it. The mean time for completing the scale was 9 ± 3.48 minutes (range: 2 to 22 minutes). The time for completing the scale was more than 15 minutes in only 15 patients. The missing values varied between 0% and 2% (mean = 0.61%). Of the 23 items of the scale, only 1 item ("do you smoke?") had floor/ceiling effect.

Criterion validity: The results of independent t-test showed a significant difference in the HTA-scale score between the controlled hypertension group and uncontrolled hypertension group (Table 7).

Sensitivity and specificity: To calculate the ROC curve, the missing values were replaced with their median. Controlled/uncontrolled hypertension was considered as golden standard. The area under the ROC curve was 0.57 [confidence interval (CI): 0.50-0.63] that was significant (P = 0.048). On the point of 85.5, the sensitivity and specificity of the scale were 57.2% and 52.5%, respectively. In addition, on the point of 86.6, the sensitivity and specificity of the scale were 60% and 50%, respectively. Therefore, we decided to choose the midpoint of these two numbers, i.e., the point of 86, which had sensitivity and specificity values of 59% and 51%, respectively. According to this cut-point, values ≤ 86 and values > 86 were, respectively, considered as signifying low adherence and high adherence to HTN treatment regimen.

Reliability (Internal consistency and test-retest): The Cronbach's α for total sample size (n = 300) and ICC for a sample size of 35 patients were assessed. The value of Cronbach's α for the whole scale was 0.76. The Cronbach's α values of the subscales were within the range of 0.66 to 0.87. The results of test-retest with a 2-week interval showed that the repeatability and stability of the scale was excellent (ICC: 0.74; CI: 0.55-0.86) (Table 8).

Discussion

As a result of the psychometric results of the HTA-scale, a 23-item scale was achieved. This scale includes the 6 dimensions of medication adherence and monitoring, self-medication (8 items), adherence to safe diets, avoiding unsafe diets (10 items), exercise (2 items), and smoking (3 items). The scores resulted from the scale ranged between 23 and 115. Reverse scoring was used in 10 items (2, 3, 4, 15, 16, 17, 18, 21, 22, and 23). In the present study, the CVR, CVI-I, and CVI-S of the HTA-scale were good and acceptable. In this study, 6 factors were extracted using PFA with varimax rotation which explained 61.69% of total variance; the higher the percentage of the variances is, the higher the validity of the model is.[13] Pituch and Stevens suggested a total variance of higher than 75%,[14] but Henson and Roberts questioned whether a total variance of higher than 75% was rational for psychological researches or not.[15]

They stated that the total amount of variance is reduced when the number of items is high.[15] Moreover, the correlation of different dimensions with the total score should be high and their correlation with each other should be low. High dependency of the different dimensions of the instrument on each other results in co-linearity, and using two or more dependent factors is not correct.[4,9]

Table 7. Comparison of the Hypertensive Treatment Adherence (HTA) scale score between controlled and uncontrolled hypertension

Variable	Hypertensive Treatment Adherence scale score		Independent t-test/df	P
Group	Frequency	Mean ± SD		
Controlled hypertension	120	85.69 ± 9.82	t = 2.12	0.035
Uncontrolled hypertension	180	83.21 ± 10.19	df = 298	

SD: Standard deviation; df: Degree of freedom

Table 8. Internal consistency of the Hypertensive Treatment Adherence scale and intraclass correlation

No	Items	Cronbach's alpha if item is deleted (n = 300)	Corrected Item-Total Correlation	ICC (CI) (n = 35)	P
17	Do you take your antihypertensive medication based on its prescription?	0.76	0.32	0.72 (0.51-0.85)	< 0.001
21	Do you take blood tests as regularly as prescribed by your physician?	0.75	0.45	0.91 (0.83-0.95)	< 0.001
22	Do you control your blood pressure weekly?	0.76	0.21	0.85 (0.72-0.92)	< 0.001
23	Do you refer to your doctor to monitor your blood pressure status every 3-6 months?	0.74	0.51	0.85 (0.72-0.92)	< 0.001
24	Do you refer to your doctor on pre-determined appointments?	0.74	0.56	0.43 (0.71-0.92)	0.005
Medication adherence and monitoring subscale			0.81	0.84 (0.71-0.92)	< 0.001
1	Do you eat boiled foods?	0.74	0.52	0.90 (0.82-0.95)	< 0.001
4	Do you eat votive foods if available?	0.75	0.33	0.76 (0.57-0.87)	< 0.001
5	Do you comply with a low salt diet?	0.74	0.49	0.54 (0.26-0.74)	0.004
12	Do you eat high fiber foods and vegetables daily?	0.75	0.39	0.91 (0.83-0.95)	< 0.001
13	Do you eat fruits daily?	0.75	0.46	0.72 (0.52-0.85)	< 0.001
14	Do you eat whole grain products such as barley bread daily?	0.75	0.41	0.86 (0.74-0.93)	< 0.001
Avoiding unsafe diets subscale			0.76	0.78 (0.60-0.88)	< 0.001
7	Do you eat fast foods such as sandwiches and pizza?	0.75	0.48	0.20 (-0.14-0.49)	0.120
8	Do you eat sugar, sugar cubes, or sweets?	0.77	0.09	0.48 (0.17-0.7)	0.002
9	Do you eat junk foods such as chips and cheese puff?	0.76	0.29	0.28 (-0.05-0.56)	0.047
34	Do you drink coffee?	0.78	-0.02	0.92 (0.84-0.96)	< 0.001
Avoiding unsafe diets subscale			18.00	18.00	18.00
18	Do you ever purchase and continue your previous antihypertensive medication without referring to your physician?	0.78	-0.10	0.87 (0.77-0.93)	< 0.001
19	Do you sometimes stop taking your medication due to any reason?	0.76	0.24	0.94 (0.89-0.97)	< 0.001
20	Do you increase or decrease the dosage of your medication without consulting your physician?	0.77	0.13	0.74 (0.54-0.86)	< 0.001
Self-medication subscale			0.69	0.96 (0.92-0.98)	< 0.001
26	Do you do exercises such as walking, swimming, or cycling 4-7 days per week?	0.76	0.32	0.92 (0.84-0.96)	< 0.001
27	Do you exercise or walk for about 30-60 minutes each time?	0.75	0.35	0.73 (0.53-0.86)	< 0.001
Activity subscale			0.87	0.88 (0.77-0.94)	< 0.001
28	Do you smoke cigarettes?	0.76	0.32	0.90 (0.82-0.95)	< 0.001
30	Do you smoke hookah (shisha)?	0.76	0.31	0.87 (0.76-0.93)	< 0.001
31	Are you constantly exposed to cigarette and opium smoke?	0.76	0.23	0.82 (0.67-0.91)	< 0.001
Smoking subscale			0.66	0.90 (0.81-0.95)	< 0.001

ICC: Intraclass correlation coefficient; CI: Confidence interval

The correlation of the subscales of the HTA-scale with its total score was high, while the correlation of each dimension with other dimensions was low. This shows that the HTA-scale has good construct validity.

Criterion validity determines the accuracy and sufficiency of the score of an instrument as a key standard.[16] In the present study, patients' blood pressure was selected as the key standard (controlled and uncontrolled blood pressure). Although the scale score significantly differed between patients with controlled and uncontrolled hypertension, the difference was not high. This might be due to the key standard selected for criterion validity in this study. Generally, there is no key standard for measuring treatment adherence in patients with HTN, but 2 criteria have been used to determine criterion validity in previous studies. Some studies have considered patients' HTN as the key standard,[17-20] and others have used different instruments and questionnaires such as the MMAS.[4] The most common scales related to medication and treatment adherence in patients with HTN are the MMAS and Hill-Bone Compliance to High Blood Pressure Therapy Scale.

The psychometric properties of both scales have been measured in Iran by Dehghan et al.[10] and Dehghan et al.[21]; neither of them had enough validity in the population under consideration. In addition, the TAQPH was assessed in Iran and it was found to have good reliability and validity, but based on the Iranian context the original 28-item scale was reduced to a 25-item scale.[22] This scale has not been assessed in other countries and has not been generally used. The criterion validity of the MMAS has been confirmed in different studies,[20,21,23-27] while the criterion validity of the Hill-Bone Compliance to High Blood Pressure Therapy Scale has only been confirmed in some studies.[28] Its criterion validity was not confirmed in the studies by Dehghan et al.,[10] Koschack et al.,[18] and Lambert et al.[28]

Lambert Considering its cut-off point of 86, the sensitivity and specificity of the HTA-scale was moderate. The mean amount of sensitivity and specificity can be affected by some factors such as the key standard, sampling, and completion precision of the scale. In the present study, the scale in the validity evaluation phase contained 35 items.

In addition, the mean age of the participants was 60 years; therefore, the length of the scale and old age of the subjects might have had negative effects on scale completion precision, and resulted in low sensitivity and specificity. In previous studies, the sensitivity and specificity of the MMAS has been reported as 11-93% and 31-73%, respectively.[20,21,23-27] Furthermore, the sensitivity and specificity of the Brief Medication Questionnaire (BMQ) in different studies have been reported within the ranges of 70-100% and 27-100%, respectively.[29-31]

Cronbach's α coefficient of the HTA-scale was acceptable. However, a high alpha value does not always indicate high internal homogeneity because Cronbach's α is strongly affected by the number of items.[32,33] In the present study, the α value of some subscales of the HTA-scale was less than 0.7. The low alpha values of the "self-medication" and "smoking" subscales can be explained by the effect of the number of items on alpha value. The reliability of some similar scales such as MMAS has been reported to be within the range of 0.4 to 0.83 in different studies.[20,21,23-27] Moreover, the reliability of the Hill-Bone Compliance to High Blood Pressure Therapy Scale has been reported to be within the range of 0.44 to 0.84 in different studies.[10,17,28]

Apparently, the reliability of each scale may be different in different populations and countries. Therefore, it is better to use a context-based scale, such as the HTA-scale, to assess treatment adherence in an Iranian community.

The content of the HTA-scale is to some extent different from the other scales available for studying adherence in patients with HTN. Except for the TAQPH[4] and Hill-Bone Compliance to High Blood Pressure Therapy Scale[17] that have similarities with the HTA-scale, other instruments presented in this field only focus on medication adherence. Although the psychometric properties of most of these instruments have been measured in patients with HTN, they do not assess other aspects of treatment of patients with HTN completely. Therefore, other aspects of treatment of patients with HTN have not been considered in such instruments.[3,4,17,19,29,34,35] The HTA-scale measures medication adherence based on regular consumption of medication according to the physician's prescription, taking medication higher or lower than the prescribed dosage without referring to the physician, and long-term medication consumption. One of the most important differences of the subscales of the HTA-scale with that of other scales regarding medication adherence is that medication adherence and self-medication are two completely different dimensions in the HTA-scale. Regarding adherence to lifestyle

modifications, the HTA-scale measures issues related to disease monitoring, safe diet, and avoiding unsafe foods and activity, and smoking. Regular blood pressure measurement, regular physician referrals, and periodic examinations based on the doctor's prescription are issues related to disease monitoring. Except for the Hill-Bone Compliance to High Blood Pressure Therapy Scale that includes 2 items related to physician referrals, the other instruments do not focus on disease monitoring.[4,17]

According to the guidelines for controlling and measuring blood pressure, physician referrals and health status management are components of the anti-hypertensive treatment regimen and patient should adhere to them.[4,35-38]

In the present study, subscales related to adherence to diet concentrate on issues such as reduction of salt, fat, fast food, sugar, coffee, and nuts and increasing of fruits, vegetables, and whole grains. The HAT-scale is compatible with the latest available guidelines.[39,40] All recommendations regarding a safe diet are present in the HAT-scale, except consumption of low fat dairy products. According to available guidelines, the weight and waist circumference of the patient should be measured to determine weight gain because maintaining body weight within the normal range [Body mass index (BMI): 18.5-24.9; waist circumference of less than 102 cm in men and less than 88 cm in women] is recommended for the reduction of blood pressure. In order to control weight, dietary regimen and increased exercise are recommended.[39,40] Weight gain has a direct relationship with high consumption of sugar products, junk food, high fat products, and high-energy foods.[41-45] Since high consumption of sugar and junk food increases weight that leads to HTN, items related to sugar, junk food, and fast food were included in the HAT-scale. Presence of such items in the scale can implicitly reflect on patient's adherence to weight management.[46-50] Although the reduction of salt, fat, and cholesterol has been emphasized in the Hill-Bone Compliance to High Blood Pressure Therapy Scale,[17] other recommendations related to dietary regimen have not been considered in this scale.[4,51] The HTA-scale and TAQPH were similar in their detailed assessment of dietary adherence,[4] but the subscale of dietary adherence differed between the HTA-scale and TAQPH in that the items related to safe dietary adherence and avoiding unsafe foods are placed in two separated dimensions in the HTA-scale. Therefore, the amount of adherence to each dimension can be measured separately because each dimension can be considered as a scale.[4,52]

Exercise was another dimension of the HTA-scale. This subscale measures the frequency of doing exercises such as walking, swimming, or cycling per week. Evidences indicate that mean intensity aerobic exercises reduce blood pressure in healthy people and those with HTN. Moreover, studies have shown that resistance exercises with higher intensity are not more effective on blood pressure than moderate intensity exercises.[39,40,53,54] Guidelines available on the management and treatment of HTN recommend moderate intensity exercises, such as walking, cycling, and swimming, 4-7 days per week for 30-60 minutes.[40,41] Except for the questionnaire designed by Ma et al., other treatment adherence instruments have not considered the measurement of exercise in patients with HTN.[4]

The last subscale of the HTA-scale is smoking. The items of this subscale measure behaviors such as cigarette smoking, hookah (shisha), or exposure to cigarette and opium smoke. Although the role of smoking or being exposed to smoke have been confirmed in CVDs,[55] the direct role of smoking in HTN has not yet been confirmed. Some studies suggest that the prevalence of HTN is higher among people who smoke or are exposed to smoke compared to other people.[56-59] Studies also indicated that hookah increases blood pressure.[60-62] Therefore, due to the increasing application of hookah,[63-65] 1 item related to this topic was included in the HTA-scale. Among the instruments available for treatment adherence in patients with HTN, the Hill-Bone Compliance to High Blood Pressure Therapy Scale did not pay attention to smoking and only 1 item was dedicated to this topic, but no items to exposure to smoke or being a passive smoker, in the TAQPH.[4,17] However, in the present study, issues related to smoking have been addressed in detail.

Based on guidelines on the treatment and management of HTN, reduction of alcohol consumption is one of the most important behaviors that patients should adhere to. Moreover, these guidelines recommend that stress be reduced and psychosomatic diseases be addressed in patients with HTN (whose blood pressures may have been increased by stress).[39,40,63] In the present study, the omission of the item related to alcoholic drinks was predictable because most Iranian people are Muslims and in Islam alcoholic drinks are forbidden.

According to a systematic review, acute stress is probably not a risk factor for HTN, while chronic stress and non-adaptive response to stress are more likely the causes of sustained elevation of blood pressure.[66] However, the benefit of specific stress-reduction techniques in patients with HTN remains unproven.[67] Concerning the lack of emphasis on stress control as a general strategy in guidelines for patients with HTN,[68] it seems that the omission of items related to stress has no major impact on the comprehensiveness of the HTA-scale.

Conclusion

Recently, treatment adherence in patients with HTN has received much attention. The clinical consequences of adherence are different because there is no suitable instrument to evaluate all treatment aspects such as taking medication and lifestyle in patients with HTN. Therefore, it is important for health providers to correctly measure treatment adherence in these patients. Based on the obtained results, a new scale was designed to measure adherence in patients with HTN.

The psychometric properties of the HTA-scale showed that this scale has suitable internal consistency and stability. Furthermore, the HTA-scale has an acceptable face validity, and content validity ratio and index. In addition, the content validity index of the total scale was very good. The results of factor analysis indicated that this scale included the 6 dimensions of medication adherence and monitoring, self-medication, adherence to safe diets, avoiding unsafe diets, exercise, and smoking. The mean score of the scale significantly differed between the controlled and uncontrolled HTN groups, which illustrates the acceptable criterion validity of the scale.

The HTA-scale had 59% sensitivity and 51% specificity at the cut-off point of 86. Moreover, the scale had a very good acceptability. The results showed that the HTA-scale is valid for use in research investigations and clinical centers.

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Conflict of Interests

Authors have no conflict of interests.

References

1. Haghdoost AA, Sadeghirad B, Rezazadehkermani M. Epidemiology and heterogeneity of hypertension in Iran: A systematic review. Arch Iran Med 2008; 11(4): 444-52.
2. Sabate E. Adherence to Long-term Therapies: Evidence for Action. Geneva, Switzerland: World Health Organization; 2003.
3. Voils CI, Maciejewski ML, Hoyle RH, Reeve BB, Gallagher P, Bryson CL, et al. Initial validation of a self-report measure of the extent of and reasons for medication nonadherence. Med Care 2012; 50(12): 1013-9.
4. Ma C, Chen S, You L, Luo Z, Xing C. Development and psychometric evaluation of the Treatment Adherence Questionnaire for Patients with Hypertension. J Adv Nurs 2012; 68(6): 1402-13.
5. Perez-Escamilla B, Franco-Trigo L, Moullin JC, Martinez-Martinez F, Garcia-Corp JP. Identification of validated questionnaires to measure adherence to pharmacological antihypertensive treatments. Patient Prefer Adherence 2015; 9: 569-78.
6. Garfield S, Clifford S, Eliasson L, Barber N, Willson A. Suitability of measures of self-reported medication adherence for routine clinical use: A systematic review. BMC Med Res Methodol 2011; 11: 149.
7. Nayeri ND, Dehghan M, Iranmanesh S. Being as an iceberg: Hypertensive treatment adherence experiences in southeast of Iran. Glob Health Action 2015; 8: 28814.
8. Lawshe CH. A quantitative approach to content validity. Pers Psychol 1975; 28(4): 563-75.
9. Chehrei A, Haghdoost AA, Fereshtehnejad SM, Bayat A. Statistical methods in medical science researches using SPSS software. Tehran, Iran: Elm Arya Publications; 2016. [In Persian].
10. Dehghan M, Dehghan Nayeri N, Iranmanesh S. Validating the persian version of the hill-bone's scale of "compliance to high blood pressure therapy". Br J Med Med Res 2020.
11. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014; 311(5): 507-20.
12. Yong AG, Pearce S. A Beginner's Guide to Factor Analysis: Focusing on Exploratory Factor Analysis. Tutor Quant Methods Psychol 2013; 9(2): 79-94.
13. Lorenzo-Seva U. How to report the percentage of explained common variance in exploratory factor analysis [Online]. [cited 2013]; Available from: URL: http://psico.fcep.urv.cat/utilitats/factor/Width1
14. Pituch KA, Stevens JP. Applied multivariate

statistics for the social sciencES: Analyses with SAS and IBM's SPSS. London, UK: Routledge; 2009.
15. Henson RK, Roberts JK. Use of Exploratory Factor Analysis in Published Research: Common Errors and Some Comment on Improved Practice. Educ Psychol Meas 2006; 66(3): 393-416.
16. Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, et al. COSMIN checklist manual. Amsterdam, Netherlands: VU University Medical Center; 2012.
17. Kim MT, Hill MN, Bone LR, Levine DM. Development and testing of the Hill-Bone Compliance to High Blood Pressure Therapy Scale. Prog Cardiovasc Nurs 2000; 15(3): 90-6.
18. Koschack J, Marx G, Schnakenberg J, Kochen MM, Himmel W. Comparison of two self-rating instruments for medication adherence assessment in hypertension revealed insufficient psychometric properties. J Clin Epidemiol 2010; 63(3): 299-306.
19. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens (Greenwich) 2008; 10(5): 348-54.
20. Saleem F, Azmi Hassali M, Akmal S, Morisky DE, Atif M, Al-Qazaz HK, et al. Translation and validation study of Morisky Medication Adherence Scale (MMAS): The Urdu version for facilitating person-centered healthcare in Pakistan. Int J Pers Cent Med 2012; 2(3): 384-90.
21. Dehghan M, Dehghan Nayeri N, Karimzadeh P, Iranmanesh S. Psychometric properties of the Persian version of the morisky medication adherence scale-8. Br J Med Med Res 2015; 9(9): 1-10.
22. Dehghan M, Dehghan-Nayeri N, Iranmanesh S. Translation and validation of the Persian version of the treatment adherence questionnaire for patients with hypertension. ARYA Atheroscler 2016; 12(2): 76-86.
23. Al-Qazaz HK, Hassali MA, Shafie AA, Sulaiman SA, Sundram S, Morisky DE. The eight-item Morisky Medication Adherence Scale MMAS: Translation and validation of the Malaysian version. Diabetes Res Clin Pract 2010; 90(2): 216-21.
24. de Oliveira-Filho AD, Morisky DE, Neves SJ, Costa FA, de Lyra DPJ. The 8-item Morisky Medication Adherence Scale: Validation of a Brazilian-Portuguese version in hypertensive adults. Res Social Adm Pharm 2014; 10(3): 554-61.
25. Lee WY, Ahn J, Kim JH, Hong YP, Hong SK, Kim YT, et al. Reliability and validity of a self-reported measure of medication adherence in patients with type 2 diabetes mellitus in Korea. J Int Med Res 2013; 41(4): 1098-110.
26. Sakthong P, Chabunthom R, Charoenvisuthiwongs R. Psychometric properties of the Thai version of the 8-item Morisky Medication Adherence Scale in patients with type 2 diabetes. Ann Pharmacother 2009; 43(5): 950-7.
27. Kim JH, Lee WY, Hong YP, Ryu WS, Lee KJ, Lee WS, et al. Psychometric properties of a short self-reported measure of medication adherence among patients with hypertension treated in a busy clinical setting in Korea. J Epidemiol 2014; 24(2): 132-40.
28. Lambert EV, Steyn K, Stender S, Everage N, Fourie JM, Hill M. Cross-cultural validation of the hill-bone compliance to high blood pressure therapy scale in a South African, primary healthcare setting. Ethn Dis 2006; 16(1): 286-91.
29. Svarstad BL, Chewning BA, Sleath BL, Claesson C. The Brief Medication Questionnaire: a tool for screening patient adherence and barriers to adherence. Patient Educ Couns 1999; 37(2): 113-24.
30. Sriwarakorn S, Krittiyanunt S, Sakulbumrungsil R. Sensitivity and specificity of thai-version brief medication questionnaire. J Health Res 2018; 24(3): 129-34.
31. Ben AJ, Neumann CR, Mengue SS. The Brief Medication Questionnaire and Morisky-Green test to evaluate medication adherence. Rev Saude Publica 2012; 46(2): 279-89.
32. Gliem JA, Gliem RR. Calculating, interpreting, and reporting Cronbach's alpha reliability coefficient for likert-type scales [Online]. [cited 2003]; Available from: URL: https://scholarworks.iupui.edu/handle/1805/281
33. Tavakol M, Dennick R. Making sense of Cronbach's alpha. Int J Med Educ 2011; 2: 53-5.
34. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care 1986; 24(1): 67-74.
35. Risser J, Jacobson TA, Kripalani S. Development and psychometric evaluation of the Self-efficacy for Appropriate Medication Use Scale (SEAMS) in low-literacy patients with chronic disease. J Nurs Meas 2007; 15(3): 203-19.
36. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003; 42(6): 1206-52.
37. Jolles EP, Padwal RS, Clark AM, Braam B. A Qualitative Study of Patient Perspectives about Hypertension. Hypertension 2013; 2013: 671691.
38. Noohi F, Sarrafzadegan N, Khosravi A, Andalib E. The first Iranian recommendations on prevention, evaluation and management of high blood pressure. ARYA Atheroscler 2012; 8(3): 97-118.
39. Dasgupta K, Quinn RR, Zarnke KB, Rabi DM, Ravani P, Daskalopoulou SS, et al. The 2014 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and

treatment of hypertension. Can J Cardiol 2014; 30(5): 485-501.
40. Hackam DG, Quinn RR, Ravani P, Rabi DM, Dasgupta K, Daskalopoulou SS, et al. The 2013 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol 2013; 29(5): 528-42.
41. Drewnowski A, Bellisle F. Liquid calories, sugar, and body weight. Am J Clin Nutr 2007; 85(3): 651-61.
42. Ebbeling CB, Feldman HA, Chomitz VR, Antonelli TA, Gortmaker SL, Osganian SK, et al. A randomized trial of sugar-sweetened beverages and adolescent body weight. N Engl J Med 2012; 367(15): 1407-16.
43. Ebbeling CB, Feldman HA, Osganian SK, Chomitz VR, Ellenbogen SJ, Ludwig DS. Effects of decreasing sugar-sweetened beverage consumption on body weight in adolescents: A randomized, controlled pilot study. Pediatrics 2006; 117(3): 673-80.
44. Epstein LH, Gordy CC, Raynor HA, Beddome M, Kilanowski CK, Paluch R. Increasing fruit and vegetable intake and decreasing fat and sugar intake in families at risk for childhood obesity. Obes Res 2001; 9(3): 171-8.
45. Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain: A systematic review. Am J Clin Nutr 2006; 84(2): 274-88.
46. Hamer M. Coffee and health: Explaining conflicting results in hypertension. J Hum Hypertens 2006; 20(12): 909-12.
47. Jee SH, He J, Whelton PK, Suh I, Klag MJ. The effect of chronic coffee drinking on blood pressure: A meta-analysis of controlled clinical trials. Hypertension 1999; 33(2): 647-52.
48. Klag MJ, Wang NY, Meoni LA, Brancati FL, Cooper LA, Liang KY, et al. Coffee intake and risk of hypertension: The Johns Hopkins precursors study. Arch Intern Med 2002; 162(6): 657-62.
49. Zhang Z, Hu G, Caballero B, Appel L, Chen L. Habitual coffee consumption and risk of hypertension: A systematic review and meta-analysis of prospective observational studies. Am J Clin Nutr 2011; 93(6): 1212-9.
50. Uiterwaal CS, Verschuren WM, Bueno-de-Mesquita HB, Ocke M, Geleijnse JM, Boshuizen HC, et al. Coffee intake and incidence of hypertension. Am J Clin Nutr 2007; 85(3): 718-23.
51. Bharucha NE, Kuruvilla T. Hypertension in the Parsi community of Bombay: A study on prevalence, awareness and compliance to treatment. BMC Public Health 2003; 3: 1.
52. DeVellis RF. Scale development: Theory and applications. Thousand Oaks, CA: SAGE; 2003.
53. Choudhury A, Lip GY. Exercise and hypertension. J Hum Hypertens 2005; 19(8): 585-7.
54. Wallace JP. Exercise in hypertension. A clinical review. Sports Med 2003; 33(8): 585-98.
55. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012; 33(13): 1635-701.
56. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: An update. J Am Coll Cardiol 2004; 43(10): 1731-7.
57. Niskanen L, Laaksonen DE, Nyyssonen K, Punnonen K, Valkonen VP, Fuentes R, et al. Inflammation, abdominal obesity, and smoking as predictors of hypertension. Hypertension 2004; 44(6): 859-65.
58. Narkiewicz K, Kjeldsen SE, Hedner T. Is smoking a causative factor of hypertension? Blood Press 2005; 14(2): 69-71.
59. Talukder MA, Johnson WM, Varadharaj S, Lian J, Kearns PN, El-Mahdy MA, et al. Chronic cigarette smoking causes hypertension, increased oxidative stress, impaired NO bioavailability, endothelial dysfunction, and cardiac remodeling in mice. Am J Physiol Heart Circ Physiol 2011; 300(1): H388-H396.
60. Al-Safi SA, Ayoub NM, Mosab AA, Al-Doghim I, Aboul-Enein FH. Does shisha smoking affect blood pressure and heart rate? J Public Health 2009; 17(2): 121-6.
61. Islami F, Pourshams A, Vedanthan R, Poustchi H, Kamangar F, Golozar A, et al. Smoking water-pipe, chewing nass and prevalence of heart disease: A cross-sectional analysis of baseline data from the Golestan Cohort Study, Iran. Heart 2013; 99(4): 272-8.
62. Shaikh RB, Vijayaraghavan N, Sulaiman AS, Kazi S, Shafi MS. The acute effects of Waterpipe smoking on the cardiovascular and respiratory systems. J Prev Med Hyg 2008; 49(3): 101-7.
63. Rawaf D, Elgindi A, Ismail S. Asking the shisha question. Br J Gen Pract 2013; 63(608): 127.
64. Taremian F, Bolhari J, Peyravi H, Asgari A. Drug use prevalence among students of universities of medical sciences in Tehran. Journal of Research on Addiction 2014; 7(28): 9-21.
65. Yousefi F, Darabi H, Nabipour I, Assadi M, Vahdat K, Kardeh E, et al. Prevalence of Tobacco Smoking in Bushehr Province: Comparison of Two Phases of the Persian Gulf Healthy Heart Study. Iran South Med J 2014; 17(3): 487-95. [In Persian].
66. Sparrenberger F, Cichelero FT, Ascoli AM, Fonseca FP, Weiss G, Berwanger O, et al. Does psychosocial stress cause hypertension? A systematic review of observational studies. J Hum

Hypertens 2009; 23(1): 12-9.
67. Nagele E, Jeitler K, Horvath K, Semlitsch T, Posch N, Herrmann KH, et al. Clinical effectiveness of stress-reduction techniques in patients with hypertension: Systematic review and meta-analysis. J Hypertens 2014; 32(10): 1936-44.
68. Mancia G, De BG, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2007; 28(12): 1462-536.

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Knowledge production in Iranian cardiovascular research centers: A way to reduce the burden of disease

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Original Article

Abstract

BACKGROUND: According to the World Health Organization (WHO), non-communicable diseases (NCDs) including cardiovascular diseases (CVDs) will be responsible for almost 70% of all deaths in 2020. Therefore, knowledge production to find suitable ways to prevent, diagnosis, and effectively cover this disease in research centers is mandatory. Therefore, the present study is carried out with the aim to examine the results of studies performed in three years in Iranian cardiovascular centers.

METHODS: Iranian cardiovascular research centers with more than three years of activity from 2015 to 2017 were evaluated. Research output, international collaboration, high quality publication, total citation, and average h-index (H) were evaluated and scored.

RESULTS: 23 cardiovascular diseases research centers (CVDRCs) related to 15 universities of Medical Sciences (UMSs) were evaluated. The mean and standard deviation (SD) of age of the research activities in CVDRCs was 11.47 ± 8.60 years. Based on the research ranking, the first three centers were Isfahan Cardiovascular Research Center, Iran, Tehran Heart Center, and Shaheed Rajaei Cardiovascular Medical and Research Center, Iran, respectively, all of which have independent budget line. However, there is not any CVD research center in some provinces such as Zanjan, Kurdistan, Lorestan, and Arak, Iran.

CONCLUSION: Mission oriented research activities in Iranian cardiovascular research centers may be effective in reducing the burden of CVDs. Moreover, establishment of CVD research centers in high risk areas may be useful.

Keywords: Cardiovascular Diseases; Evaluation Program; Global Burden of Disease

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Introduction

According to the World Health Organization (WHO), non-communicable diseases (NCDs) including cardiovascular diseases (CVDs) will be responsible for almost 70% of all deaths in 2020.[1,2] Based on the third Sustainable Development Goal, among NCDs, CVDs are responsible for one-third of mortalities.[3] Additionally, it has been estimated that 30.5% of deaths in the world will be caused by CVDs by 2030.[4]

In Iran, based on a cohort study in Isfahan in 2013, CVD mortality rate was estimated to be 331 and 203 per 100000 person-years in men and women,

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respectively.[5] Moreover, in 2016, years of potential life lost (YPLL) [95% confidence interval (CI)] for CVDs was 22.7 (19.8-25.6).[6]

Despite the numerous efforts made to control CVDs worldwide, these diseases continue to rise.[7] This is partly due to changing the pattern of the disease from communicable to non-communicable and injuries, especially in developing countries, besides, it may be due to the fact that secondary and tertiary prevention in CVDs are very expensive.[8] So, it is needed to find low-cost and effective methods based on research to control this problem and establish research centers that are important to conduct related projects.

Now, in Iran, there are more than 800 research centers in different fields, only 27 of which are active in the field of CVDs.[9] The first Iranian CVD research center was established in 1974 in Tehran.

Distribution of CVDs in Iranian provinces shows that in many provinces, CVDs increase by 13%, and heart diseases due to hypertension increase by 38%, which have been considered as the two major causes of early deaths.[10]

In 2007, hypertension was the third most common cause of deaths and disabilities in Iran, which has risen to 24% over the past 10 years and in 2017, it was ranked first.[11]

The key question is "what is the role of cardiovascular research centers in CVD prevention or hypertension control in Iran"? Based on a Global Burden of Disease (GBD) study in 2011, the prevalence of hypertension was more than 28% in 15 provinces in Iran.[12]

Meanwhile, numerous research projects have been designed and implemented to prevent CVDs, especially hypertension. Accordingly, the present study is conducted to evaluate knowledge production based on these studies in Iranian CVD research centers.

Materials and Methods

The current study was implemented in Iran where there are 56 universities of medical sciences (UMSs) and more than 800 Medical Research Centers (MRCs) in clinical and biomedical fields. In clinical field, there are two main subgroups concluding communicable diseases (CDs) and NCDs. Based on another categorization, all of the approved MRCs are divided into two groups according to the budget line assigned (independent, dependent). All of MRCs are evaluated after at least one year of establishment by the Iranian Ministry of Health and Medical Education (MOHME).

This was a cross-sectional study in which the total number of cardiovascular disease research centers in Iran established from 2015 to 2017 was evaluated. The study inclusion criteria were:

a- Having a principled agreement from legal and competent authorities
b- Having more than three years of research activity

The research indicators were designed based on peers' opinions in the expert panel. Representatives from research centers and UMSs, as well as three scientometric experts and research team were the members of this panel. It is worth noting that the indicators are revised and developed annually based on health policies considering the opinions of the stakeholders. Research indicators were classified to five main groups and their subgroups as follow:

a- Research output:
- The number of published articles indexed in International Scientific Indexing (ISI) during 2015-2017
- The number of published articles indexed in PubMed database during 2015-2017
- The number of published articles indexed in Scopus database during 2015-2017
- The number of published books indexed in Scopus database during 2015-2017
- The number of conference papers/meeting abstracts and proceedings indexed in ISI and Scopus databases during 2015-2017

b- International cooperation(IC):
- The number of articles published with international cooperation during 2015-2017

c- High quality publication (Q1):
- The number of articles published in the best quartile journals in each subject during 2015-2017

d- Citation (C)
- The total citations during 2015-2017 and articles published in the five past years in Scopus database

e- Average H-index (H) in 2015-2017

The steps of evaluation process were: i) extracting the scientific documents of each research center based on its affiliation in ISI, PubMed, and Scopus databases; ii) designing the end note data base for each MRC; iii) eliminating data overlapping via Access software; and iv) scoring all research indicators.

The scoring system for data weighing was designed by peer review opinions through the expert panel. The scores for each published article indexed in ISI, PubMed, and Scopus were 2, 1.5, and 1, respectively. Each book had 2 points and the score of each conference paper was 0.5.

The weight of the main groups was determined based on their importance and that of the research output, collaboration, qualification, citation, and h-index were 250, 150, 200, 400, and 100, respectively, thus the maximum score was 1050 (Table 1).

Table 1. Scoring system in Cardiovascular Diseases Research Centers (CVDRCs) evaluation

Main Indicators	SGI	Score per SGI	Weight	Calculation method
RO	a- published article indexed in ISI	2.0	250	$\sum\{a\times2),(b\times1.5),(c\times1),(d\times2),\times(e\times0.5)\}$ =T(RO)
	b- published article indexed in PubMed	1.5		*Max T(RO) in n*RC =Max weight =250*
	c- published article indexed in Scopus	1.0		*& For (n-1): Adjusted T(RO)*
	d- published books indexed in Scopus	2.0		
	e- conference paper/meeting abstract	0.5		
IC	f- published article with international cooperation	1.0	150	$\sum f=T(IC)$ *Max T(IC) in n*RC= Max weight=150 & For (n-1): Adjusted T(IC)*
Q1	g- published articles in the best quartile journals		200	$\sum g=T(Q1)$ *Max T(Q1) in n*RC= Max weight=200 & For (n-1): Adjusted T(Q1)*
C	h- total citation to five past years published articles		400	$h=T(C)$ *Max T(C) in n*RC= Max weight=400 & For (n-1): Adjusted T(C)*
H	i- Average H-index		100	$i=T(H)$ *Max T(H) in n*RC= Max weight=100 & For (n-1): Adjusted T(H)*
Total Score		$\sum\{(TRO),T(IC),T(Q1),T(C),T(H)\}$		

SGI: Subgroup indicators; RO: Research output; IC: International cooperation; Q1: High quality publication; C: Citation; H: H-index; TRO: Total research output

* Number of cardiovascular research centers

The data obtained were analyzed using SPSS software (version 19.0, SPSS Inc., Chicago, IL, USA) and the P values < 0.050 were considered statistically significant. Descriptive analysis and some tests such as independent t-test were used for data reporting.

In this study, all of ethical considerations were met.

Results

In this study, out of the total 27 cardiovascular diseases research centers (CVDRCs) in Iran, 23 ones with more than three years of activity related to 15 UMSs were included. Table 2 demonstrates the name, number, and budget line of the research centers related to UMSs.

Table 2. Frequency and distribution of Cardiovascular Diseases Research Centers (CVDRCs) in Iran

Name of UMS	Name of CVDRC	Budget line
Ahvaz Jundishapur	Atherosclerosis	Lack of independent budget line
Baqiyatallah	Atherosclerosis	Lack of independent budget line
Shahid Beheshti	Cardiovascular Diseases	Lack of independent budget line
Birjand	Cardiovascular Diseases	Lack of independent budget line
Golestan	Ischemic Disorders	Lack of independent budget line
Iran	Cardiac Electrophysiology, Cardiovascular Intervention, Echocardiography, Heart Valve Disease, Prevention of Cardiovascular Disease, Cardiovascular Diseases	Lack of independent budget line except Shaheed Rajaei Cardiovascular Medical and Research Center
Isfahan	Cardiac Rehabilitation, Interventional Cardiology, Cardiovascular, Hypertension, Heart Failure	Lack of independent budget line except Cardiovascular Diseases Research Center
Kerman	Cardiovascular Diseases	Lack of independent budget line
Hormozgan	Cardiovascular Diseases	Lack of independent budget line
Mazandaran	Cardiovascular Diseases	Lack of independent budget line
Shiraz	Cardiovascular Diseases	Lack of independent budget line
Tabriz	Cardiovascular Diseases	Lack of independent budget line
Shahid Sadoughi Yazd	Cardiovascular Diseases	Lack of independent budget line
Tehran	Tehran Heart Center	With independent budget line

UMS: University of Medical Sciences; CVDRC: Cardiovascular disease research center

Based on the statistical analysis, there was a significant correlation between the independent budget line and the score obtained ($P < 0.050$).

The mean and standard deviation (SD) of age of the research activities in CVDRCs was 11.47 ± 8.60 years, with minimum and maximum ages of 5 and 45 years, respectively.

Based on the results, there was a significant difference between the year of activity and total research score ($P < 0.050$).

The number of published articles indexed in ISI, PubMed, and Scopus by CVDRCs during 2014 to 2017 was estimated to be 1851, about 50% of which being published in research centers affiliated to UMSs with domestic cooperation. Almost 12% of the articles published in the best quartile journals in each subject and in more than 16% of cases, the articles had at least one foreign counterpart. The highest international cooperation was related to cardiovascular research centers in Tabriz and Isfahan. Tehran Heart Center with 46 high quality publications was the first center among CVDRCs. Moreover, cardiovascular research center in Isfahan had the highest number of citations and h-index. After scoring and weighing, the first three centers were Isfahan Cardiovascular Research Center, Tehran Heart Center, and Shaheed Rajaei Cardiovascular Medical and Research Center, respectively (Table 3).

Discussion

Based on the review results, there were 23 CVD research centers with more than three years of activity affiliated to 15 UMSs in 10 provinces consisting of Tehran, Golestan, Kerman, Isfahan, Mazandaran, Shiraz, Tabriz, Ahvaz, Birjand, and Hormozgan.

The total number of published articles indexed in ISI, PubMed, and Scopus was estimated 1851. Almost 12% of articles were published in the best quartile journals. 50% and 16% of cases were performed with domestic and foreign cooperation, respectively.

Comparing the results of evaluation of research activities in CVDRCs shows that there are more knowledge production and research scores in research centers with independent budget line, which may be due to attracting more scholars, other resources, equipment, and so on.[13] The maximum research score in this evaluation was related to Isfahan Cardiovascular Research Center. This center not only has more qualified published papers and citations, but also many valuable projects such as Isfahan Healthy Heart Programme (IHHP) were designed and implemented by its researchers.[14]

The geographical distribution of cardiovascular research centers indicates that the establishment of these centers has not completely been based on the burden of CVDs. For example, based on Iranian surveys on NCD risk factors in 2004 and 2011, the prevalence of hypertension in 17 provinces was more than 28%, while there was a CVDRC in only five of them, including Golestan, Mazandaran, Tabriz, Ahvaz, and Hormozgan (Figure 1).[9,15]

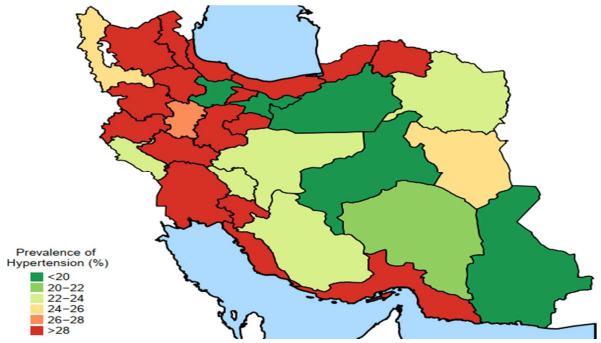

Figure 1. Illustrates the prevalence of hypertension in different provinces in Iran.[15]

Additionally, in some provinces such as Zanjan, Kurdistan, Lorestan, Arak, and Hormozgan, Iran, despite many efforts, treatment coverage has not been effective. It seems that in the research field, it is necessary for cardiovascular researchers to identify barriers to effective control and therapies through scientific methods.[15]

Based on a study by Adedapo, in areas with high prevalence of CVDs, the number of related studies and publications is less compared to other cases.[16]

Considering that CVDRC in Hormozgan Province had the fewest score in research evaluation, it is necessary to make much more effort in community heart health promotion. Moreover, establishing mission oriented cardiovascular research centers in Zanjan, Kurdistan, Lorestan, and Arak, Iran, with implementing applied research in heart health promotion can be useful.[17]

In Tehran, the capital of Iran, there are nine CVDRCs with more than three years of activity. These RCs are affiliated to Tehran, Iran, Baqiyatallah, and Shahid Beheshti UMSs. Tehran is one of the largest metropolises in Iran with a high air pollution level, so it is an alarm of the increased CVD incidence rate, and consequently the high mortality rate.[18]

Based on the lipid and glucose study in Tehran, the prevalence of coronary heart diseases (CHDs) and its associated risk factors in adult residents of Tehran is high and the age-adjusted prevalence of CHD is 21.8% (22.3% and 18.8% in women and men, respectively).[19]

Table 3. Results of Heart Research Center (HRC) ranking in Iran

Name of UMS	Name of CVDRC	Number of three years*				Average H*	Total score	Rank
		Output	Q1	IC	C			
Golestan	Ischemic Disorders	27 (21.57)	8 (34.78)	7 (18.42)	120 (16.74)	6.7 (15.87)	107.39	11
Iran	Cardiovascular Intervention	74 (54.36)	4 (17.39)	3 (7.89)	38 (5.30)	3.7 (8.73)	93.67	13
	Echocardiography	42 (32.36)	3 (13.04)	3 (7.89)	47 (6.56)	5.7 (13.49)	73.35	16
	Cardiac Electrophysiology	19 (13.75)	2 (8.70)	5 (13.16)	54 (7.53)	4.7 (11.11)	54.24	17
	Heart Valve Disease	39 (29.82)	9 (39.13)	7 (18.42)	37 (5.16)	3.3 (7.94)	100.47	12
	Prevention of Cardiovascular Disease	15 (11.21)	2 (8.70)	5 (13.16)	7 (0.98)	1.3 (3.17)	37.21	21
	Cardiovascular Diseases-Shahid Rajaee	339 (250.00)	25 (108.70)	29 (76.32)	370 (51.60)	9.3 (22.22)	508.84	3
Kerman	Cardiovascular Diseases	52 (39.55)	7 (30.43)	2 (5.26)	53 (7.39)	4.3 (10.32)	92.96	14
Tehran	Tehran Heart Center	249 (186.34)	46 (200.00)	29 (76.32)	1841 (256.76)	24 (57.14)	776.56	2
Isfahan	Cardiovascular	240 (180.20)	41 (178.26)	55 (144.74)	2868 (400.00)	42 (100.00)	1003.20	1
	Cardiac Rehabilitation	124 (93.06)	12 (52.17)	24 (63.16)	762 (106.28)	14 (33.33)	348.00	5
	Interventional Cardiology	27 (19.67)	2 (8.70)	5 (13.16)	23 (3.21)	2.3 (5.56)	50.29	19
	Hypertension	67 (50.76)	12 (52.17)	14 (36.84)	368 (51.32)	10 (23.81)	214.91	7
	Heart Failure	27 (19.25)	2 (8.70)	2 (5.26)	45 (6.28)	4.7 (11.11)	50.59	18
Mazandaran	Cardiovascular Diseases	14 (8.88)	0 (0.00)	0 (0.00)	24 (3.35)	2.3 (5.56)	17.79	22
Shiraz	Cardiovascular Diseases	77 (60.70)	9 (39.13)	3 (7.89)	183 (25.52)	7.7 (18.25)	151.50	8
Tabriz	Cardiovascular Diseases	183 (139.59)	17 (73.91)	57 (150.00)	624 (87.03)	13.7 (32.54)	483.08	4
Yazd	Cardiovascular Diseases	104 (73.82)	9 (39.13)	24 (63.16)	297 (41.42)	9 (21.43)	238.96	6
Ahvaz	Atherosclerosis	34 (23.27)	1 (4.35)	3 (7.89)	35 (4.88)	3.7 (8.73)	49.12	20
Baqiyatallah	Atherosclerosis	30 (23.90)	4 (17.39)	6 (15.79)	51 (7.11)	4 (9.52)	73.72	15
Shahid Beheshti	Cardiovascular Diseases	61 (45.90)	3 (13.04)	10 (26.32)	154 (21.48)	7 (16.67)	123.40	9
Birjand	Cardiovascular Diseases	82 (60.07)	6 (26.09)	4 (10.53)	53 (7.39)	4 (9.52)	113.60	10
Hormozgan	Cardiovascular Diseases	3 (2.33)	0 (0.00)	0 (0.00)	32 (4.46)	3.7 (8.73)	15.52	23

UMS: University of Medical Sciences; CVDRC: Cardiovascular Disease Research Center; Q1: High quality publication; IC: International cooperation; C: Citation; H: H-index
* Adjusted T

Due to the higher prevalence of hypertension in the north, west, and south of Iran, it is mandatory to provide the license necessary for the establishment of cardiovascular research centers in these areas. It is obvious that designing the strategic planning and determining main missions for the prevention, diagnosis, effective treatment, and rehabilitation of patients with CVDs through research projects by the CVDRCs can decrease the burden of the disease.

This study has two strengths. First, it evaluates knowledge production in the field of CVDs in order to make appropriate policies to reduce one of the most important disease burden in Iran. Second, based on geographic distribution of CVDRCs, it specified the provinces needing the establishment of such centers in them.

Failure to address the outcomes and impacts in this evaluation process is one of the limitations of the present study. A peer-based evaluation of research activities in these centers seems to lead us to more equitable judgments.

Conclusion

Mission oriented research activities in Iranian cardiovascular research centers may be effective to reduce the burden of CVDs. Furthermore, it is necessary to carry out a quantitative and qualitative evaluation for an accurate and comprehensive assessment.

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Conflict of Interests

Authors have no conflict of interests.

References

1. Benziger CP, Roth GA, Moran AE. The global burden of disease study and the preventable burden of NCD. Glob Heart 2016; 11(4): 393-7.
2. World Health Organization. Global status report on noncommunicable diseases 2014. Geneva, Switzerland: WHO; 2014.
3. Nilsson M, Griggs D, Visbeck M. Policy: Map the interactions between Sustainable Development Goals. Nature 2016; 534(7607): 320-2.
4. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380(9859): 2095-128.
5. Talaei M, Sarrafzadegan N, Sadeghi M, Oveisgharan S, Marshall T, Thomas GN, et al. Incidence of cardiovascular diseases in an Iranian population: The Isfahan Cohort Study. Arch Iran Med 2013; 16(3): 138-44.
6. Saadat S, Yousefifard M, Asady H, Moghadas JA, Fayaz M, Hosseini M. The most important causes of death in Iranian population; A retrospective cohort study. Emerg (Tehran) 2015; 3(1): 16-21.
7. Sarrafzadegan N, Kelishadi R, Esmaillzadeh A, Mohammadifard N, Rabiei K, Roohafza H, et al. Do lifestyle interventions work in developing countries? Findings from the Isfahan Healthy Heart Program in the Islamic Republic of Iran. Bull World Health Organ 2009; 87(1): 39-50.
8. Forouzanfar MH, Sepanlou SG, Shahraz S, Dicker D, Naghavi P, Pourmalek F, et al. Evaluating causes of death and morbidity in Iran, global burden of diseases, injuries, and risk factors study 2010. Arch Iran Med 2014; 17(5): 304-20.
9. Deputy of Research and Technology. Results of ranking the research activities in medical sciences research centers 2018 [Online]. [cited 2018]; Available from: URL: http://hbi.ir/Forms/Special.aspx?hbsId=1348&category=1&templateid=1&hdlId=4
10. Rabani S, Sardarinia M, Akbarpour S, Azizi F, Khalili D, Hadaegh F. 12-year trends in cardiovascular risk factors (2002-2005 through 2011-2014) in patients with cardiovascular diseases: Tehran lipid and glucose study. PLoS One 2018; 13(5): e0195543.
11. Abbasi M, Neishaboury M, Koohpayehzadeh J, Etemad K, Meysamie A, Asgari F, et al. National prevalence of self-reported coronary heart disease and chronic stable angina pectoris: Factor analysis of the underlying cardiometabolic risk factors in the SuRFNCD-2011. Glob Heart 2018; 13(2): 73-82.
12. Farzadfar F, Murray CJ, Gakidou E, Bossert T, Namdaritabar H, Alikhani S, et al. Effectiveness of diabetes and hypertension management by rural primary health-care workers (Behvarz workers) in Iran: A nationally representative observational study. Lancet 2012; 379(9810): 47-54.
13. Peters DH, Peters MA, Wickramasinghe K, Osewe PL, Davidson PM. Asking the right question: implementation research to accelerate national non-communicable disease responses. BMJ 2019; 365: l1868.
14. Nouri F, Feizi A, Mohammadifard N, Sarrafzadegan N. Methods of sampling and sample size determination of a comprehensive integrated community-based interventional trial: Isfahan Healthy Heart Program. ARYA Atheroscler 2018; 14(2): 58-70.

15. Ahmadi S. Estimation of effective coverage of diabetes and hypertension treatment at the national and subnational levels and evaluating its social determinants among Iranian adult population during 2005-2011 [PhD Thesis]. Tehran, Iran: University of Social Welfare and Rehabilitation Sciences; 2018. [In Persian].
16. Adedapo AD. Rising trend of cardiovascular diseases among South-Western Nigerian female patients. Nigerian Journal of Cardiology 2017; 14(2): 71-4.
17. Sarraf-Zadegan N, Sadri G, Malek Afzali H, Baghaei M, Mohammadi Fard N, Shahrokhi S, et al. Isfahan Healthy Heart Programme: A comprehensive integrated community-based programme for cardiovascular disease prevention and control. Design, methods and initial experience. Acta Cardiol 2003; 58(4): 309-20.
18. Kermani M, Dowlati M, Jonidi Jafari A, Rezaei Kalantari R. Number of total mortality, cardiovascular mortality and Chronic Obstructive Pulmonary Disease due to exposure with Nitrogen dioxide in Tehran during 2005-2014. Stud Med Sci 2017; 28(4): 22-32. [In Persian].
19. Hadaegh F, Harati H, Ghanbarian A, Azizi F. Prevalence of coronary heart disease among Tehran adults: Tehran Lipid and Glucose Study. East Mediterr Health J 2009; 15(1): 157-66.

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Accuracy of the amount of trans-fatty acids in traffic light labelling of traditional sweets distributed in Isfahan, Iran

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Original Article

Abstract

BACKGROUND: High consumption of trans-fatty acids (TFAs) is introduced as dietary risk factor of cardiovascular diseases (CVDs). The accuracy of the information shown on the traffic light (TL) labelling has a significant influence on consumers to reduce TFA content in foods. This study is conducted aiming to determine the TFA content in traditional sweets distributed in Isfahan, Iran. Furthermore, the accuracy of the amount of TFAs on TL was considered by comparing it with the experimentally analyzed values.

METHODS: In this cross-sectional study, a total of 99 Iranian traditional sweets with a TL label were randomly collected from confectionary shops located in Isfahan. TFAs were analyzed by gas chromatography (GC).

RESULTS: TFAs were detected in all samples with the total average of 1.6 ± 0.3% in total fat (range of 0.040 ± 0.001 to 7.900 ± 1.100%). More than half of the samples had less than 2% of TFAs in the total fat. Overall, 81.8% of the studied products with TL labelling showed a discrepancy in the TFAs in the values analyzed in laboratory.

CONCLUSION: In the present study, the discrepancy of TFAs in the experimentally measured values with TL food labelling was observed in more than 80% of Iranian traditional sweets. Most of the samples contained less than 2% of TFAs that is defined as a limit in Iran Food and Drug Administration (IFDA). These findings could be alarming for the consumers of this kind of products.

Keywords: Trans Fatty Acids; Food; Data Accuracy; Iran

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Introduction

The epidemics of non-communicable diseases (NCDs) as a main cause of mortality has globally spread at an incredible speed nowadays.[1] Of the major NCDs, cardiovascular diseases (CVDs) are responsible for nearly half (45%) of all fatalities caused by NCDs.[2] Unhealthy diet is introduced as a modifiable risk factor to prevent CVDs. High level intake of trans fatty acids (TFAs) through consumption of food is of particular importance because this risk factor is correlated to the increased CVDs.[3,4] Confectionery and sweet products with ingredients of saturated fats and also partially hydrogenated oil as a source of TFAs are among the food products leading to CVDs.[5,6] Using high temperature in the preparation processes of sweets could lead to the formation of TFAs from the hydrogenated vegetable oils used.[7]

Awareness of consumers about the content of TFAs is important at the point of purchase of sweets. The information of food labelling is potentially helpful for consumers to monitor the amounts of TFAs and to change the purchasing decisions to

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select healthier food.[8] For this purpose, the status of dietary risk factors related to NCDs such as energy, sugar, fat, salt, and TFAs is displayed in the traffic light (TL) labelling. The inclusion of TL with colors red (stop), yellow (wait and watch), and green (go) was applied as a simplified guide and source to understand in food labelling in different countries. In Iran, the TL application in food labelling has been implemented with the collaboration of Iran Food and Drug Administration (IFDA) and food manufacturers. Amendments to IFDA in 2015 included mandatory declaration of TL on most packaged food to enhance knowledge among the consumers to provide their nutritional requirements (Figure 1).[9] The information and color mentioned in TL can be a reference guide for consumers at the time of purchase. Therefore, the accuracy of the nutritional requirements is vital to increase the consumer's confidence.[10] In some studies, the discrepancy and lack of accuracy were observed in the information reported on food labelling and the results obtained.[5,8,10,11]

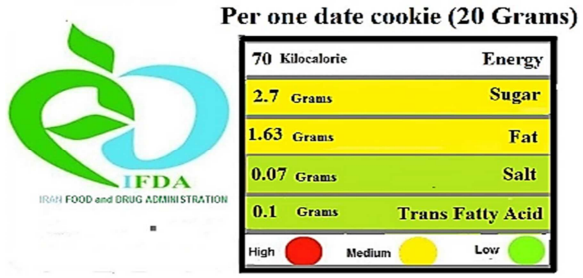

Figure 1. Image of traffic light (TL) label inserted on a date cookies

There was no study assessing the accuracy of TL-stated TFA contents of food products in Iran. Besides, among the high levels of TFAs reported in junk foods and bakery products, the cakes possessed the highest level of TFAs.[12] The presentation of incorrect information on food labelling can have adverse consequences on the consumers' health and reliability. In this regard, the present study is carried out with the primary objective to determine the TFA level in traditional sweets distributed in Isfahan. In the next step, the accuracy of the measured values for TFAs in the laboratory was evaluated with the amounts reported in TL food labelling.

Materials and Methods

In this descriptive-analytical study, a total of 99 well-known and highly demanded Iranian traditional sweets from 11 kinds (9 samples from each type) with the TL inserted on the label were randomly purchased from some renowned confectionary shops located in Isfahan. The sweets chosen for this project were from Baghlava, Bereshtuk sweet, Date cookie, Korki sweet, Loz, Chickpea sweet, Qottab, Yazd Brass sweet, Kermanshah Brass bread, Cookie, and Raisin cake brands. The traditional sweets were manufactured using wheat, rice, or chickpea flours with the mixture of oil, sugar, egg, and some aromatic seasonings and fruit.[13] To measure TFAs, the samples were transferred to a laboratory nationally accredited by IFDA. The TL logo image inserted in date cookies is shown in figure 1. As can be seen, the portion size with units of measurement in grams are shown at the top part of TL, with the color guideline for amounts of low, medium, and high shown at the bottom. In the main part of TL, the indices for energy, sugar, fat, salt, and TFAs are included with amount and related colors with IFDA logo on the left.[3,9]

An amount of 200 g of samples were homogenized and around 7 ml hexane was added to them. The mixture was then placed in a dark place for 5 days, filtered, and then heated at 50 °C to evaporate the solvent by using a rotary evaporator (IKA, RV010, Germany). The oil extracted was kept at 105 °C for 30 minutes to remove the moisture in an oven (ED 56, United Kingdom) and then filtered again.[14] The conversion of the extracted fat into methyl esters was performed by adding 7 ml of N-hexane and 2 M potassium hydroxide to 3 drops of oil. The tubes were incubated at Benmari (WNE 7, Germany) at 50 °C for 5 minutes and shaken 3 times. Around 1 µl of clear transient phase was transferred into gas chromatography (GC) equipped and adjusted with a capillary column (length of 60 mm, outer diameter of 0.25 mm, and inner diameter of 0.2 µm), flame ionization detector at temperature of 280 °C, and a Hamilton injector of 10 µl (split ratio 1:100). Hydrogen was used as the carrier at the pressure of 60 psi. All TFA standards were purchased from Merk Company, Germany. The initial temperature of GC was 110 °C and increased at 5 °C/minute rate to final temperature of 210 °C. The flow rate was 2 ml/minute. The chromatogram peaks provided by the software (YL-Clarity) were assigned based on comparison with the fatty acid standards. All the results of fatty acids were expressed as the percent of fatty acids in the sample fat content. The fatty acids measured were from 14 to 18 carbons of 5 trans isomers of fatty acids (C14:1t, C16:1t, C18:1t, C18:2t, C18:3t).

The amount of TFAs was reported as mean ± SD (standard deviation). T-test was used to compare the mean difference of TFAs between the label and laboratory values at the 99% confidence level

(P < 0.001). Data analysis was performed in Statistical Package for the Social Sciences (SPSS) (version 16, SPSS Inc., Chicago, IL, USA).

Results

In this study, TFAs were detected in all samples with the total average 1.6 ± 0.3% in total fat (range of 0.040 ± 0.001 to 7.900 ± 1.100%); with the lowest and highest average values belonging to Loz and cookie, respectively. Among all samples analyzed, cookie and raisin cakes contained more than 7% of TFAs (18.2% of total samples), while 54.5% of the total samples had less than 2% of TFAs in the total fat that is defined as a limit in IFDA. Three kinds of sweets (Bereshtuk, Chickpea, and Korki sweets) had some TFA content between 2% and 3% in the total fat (27.3% of all samples).

As shown in table 1, in six groups of sweets including Baghlava, Kermanshah Brass sweet, raisin cake, Bereshtuk, Korki and Chickpea sweets, the TFAs laboratory value exceeded the label value. In three groups of sweets including Loz, Yazd Brass bread, and cookie, the TFAs laboratory value was less than the label value (P < 0.001). In the Date cookie and Qottab, the TFAs laboratory value had no statistically significant difference with the label value (P > 0.001). Overall, 81.8% of the studied products showed a discrepancy of the experimentally analyzed values of TFAs with the TL food labelling ones.

Discussion

The information inserted on the labels of the food products is important to purchasers. The introduction of risk factors of NCDs on TL with colors of green, yellow, and red since 2015 has been a suitable policy in helping to inform the Iranian society to choose healthier food products. In a limited study in Iran, it was observed that more than 15% of participants always choose their food products based on the color and amount of TFAs in TL food labelling.[9] Therefore, the accuracy of information on food labelling is vital. This study examined the accuracy of TFA amount mentioned in TL food labelling and observed the discrepancy of the information on labelling and laboratory-measured values.

Increased intake of TFAs is linked with increased risk of CVDs.[15] In this study, TFAs were detected in all samples with the total average of 1.6 ± 0.3% in total fat. Other studies reporting the TFA levels have found that the highest average of TFAs belonged to the group of biscuits, wafers, and cookie with an average of 3.42% (0.21%-30.20%) in total fat. For the pastry group, TFAs content ranged from 0.07 to 8.47% with an average of 1.96%.[16] The results obtained in Spain in 2015 showed less than 2% of TFAs in the total fat in the confectionery sweets and pastries (0.034%), representing a significant decline since 2010 (0.657%).[17] In Sweden, a recent study has revealed TFA levels in bakery products, with 5.9% in 2001, and 0.7% in 2007, in total fatty acids.[18] Additionally, the highest mean value of TFAs in the total fat was seen in the bakery products in Swiss (6.07% of TFAs).[19] TFAs varied from 2.70% to 0.78% in the total fatty acids in 2005 and 2010 in the Swedish pastries, respectively.[20] It has been pointed out that Turkish bakery products have the highest TFAs content, as compared with other products analyzed, ranging from 0.99 to 17.77% of the total fat.[21]

The results of the current study showed a much lower TFA average for the pastry and confectionary products, as compared with some of the previous studies.[16,19,21] Cakes with 36.1% of TFAs had the highest level among other bakery products and junk foods in a study performed in Iran.[12] In confirmation of the results obtained from a previous study in Iran[12], in the present study, too much TFAs were measured in raisin cake (7.8 ± 1.6 percent of TFAs). Reduction of the TFAs content in cakes investigated in the present study might be related to the improvement of baking methods and the strict supervision of IFDA since the previous study conducted in Iran.

In this study, 81.8% of the products examined showed a discrepancy of the analyzed value with the label value. Based on the limits stated by the IFDA,[22] in some samples (Kermanshah Brass bread, Bereshtuk, Korki, and Chickpea Sweet), even the color shown on labels was not consistent with the analyzed value, in a way that the color of green was displayed instead of using the yellow color. This is the first study in Iran to evaluate the accuracy of TFA content on the TL. However, there are limited reports on this issue in other countries.[5,8,10,11] For example, in China, Kong et al. showed that the accuracy of the carbohydrate, protein, and fat values on the label of food packaging was 100, 94.4, and 96.0%, respectively.[8]

In the United States, Jumpertz et al. indicated that the caloric content in a sample of the most commonly consumed energy-dense snack foods was overall slightly higher than those stated on the nutrition label, moreover, in a small convenience sample of the tested snack foods, carbohydrate content exceeded the label statements by 7.7%. However, fat and protein content were not significantly different from the label statements.[11]

Table 1. Comparison of label values with those determined by laboratory analysis for trans fatty acid (g per serving size)

Product name (n = 9)	t					% Total TFAs in fat	Laboratory lue (Mean ± SD)[€]	Label value	% of non-compliance	P
	14:1	16:1	18:1	18:2	18:3					
Baghlava[*]	ND	0.15 ± 0.03	0.11 ± 0.02	0.03 ± 0.02	0.17 ± 0.03	0.46 ± 0.17	0.051 ± 0.006	0.000	5.1	< 0.001
Bereshtuk sweet[**]	ND	0.02 ± 0.01	0.88 ± 0.05	1.10 ± 0.07	0.45 ± 0.02	2.50 ± 0.07	0.670 ± 0.010	0.160	51.0	< 0.001
Date cookie[***]	ND	0.02 ± 0.01	0.04 ± 0.01	0.34 ± 0.09	0.54 ± 0.10	0.94 ± 0.10	0.090 ± 0.006	0.100	1.0	0.014
Korki sweet[**]	ND	0.08 ± 0.01	0.89 ± 0.09	0.90 ± 0.10	0.45 ± 0.08	2.30 ± 0.90	0.640 ± 0.010	0.160	48.0	< 0.001
Loz[£]	ND	ND	0.01 ± 0.01	ND	0.03 ± 0.01	0.04 ± 0.01	0.008 ± 0.000	0.023	1.5	< 0.001
Chickpea sweet[**]	ND	0.17 ± 0.04	0.81 ± 0.09	0.89 ± 0.07	0.47 ± 0.04	2.30 ± 0.10	0.640 ± 0.030	0.000	64.0	< 0.001
Qottab[§]	ND	0.05 ± 0.04	0.89 ± 0.05	0.20 ± 0.03	0.25 ± 0.02	1.40 ± 0.50	0.210 ± 0.008	0.2.00	1.0	0.015
Yazd Brass sweet[λ]	ND	0.06 ± 0.02	0.01 ± 0.01	0.48 ± 0.05	0.30 ± 0.00	0.85 ± 0.07	0.090 ± 0.002	0.130	4.0	< 0.001
Kermanshah Brass bread[λ]	ND	0.06 ± 0.01	0.60 ± 0.04	0.30 ± 0.06	0.29 ± 0.00	1.30 ± 0.20	0.250 ± 0.010	0.000	25.0	< 0.001
Cookie[‡]	ND	0.02 ± 0.20	ND	7.50 ± 0.06	0.34 ± 0.02	7.90 ± 0.07	2.370 ± 0.011	2.700	33.0	< 0.001
Raisin cake[¥]	ND	0.07 ± 0.03	0.19 ± 0.04	7.30 ± 0.08	0.24 ± 0.05	7.80 ± 1.60	3.800 ± 0.027	0.200	360.0	< 0.001

TFAs: Trans-fatty acids; SD: Standard deviation; ND: Not Detected

[*] Origin from Yazd province; Outer layer made of flour, oil, yolk, and milk; with the inner layer made of sugar, powdered nuts, and cardamom.

[**] Three kinds of sweets with the same ingredients, is made in different shapes and belongs to different provinces, origins from Isfahan, Qazvin, and Yazd provinces, Iran; made of chickpea or wheat flour, sugar, hydrogenated oil, spices including cinnamon, cardamom, saffron, almonds, and pistachios.

[***] Origin from Khuzestan Province; made of wheat flour, invert syrup, vegetable oil, and date.

[£] Origin from Yazd Province; made of flour, sugar, oil, egg, milk, and rose water.

[§] Origin from Yazd Province; Outer layer made of flour, oil, yolk, and water, with the inner layer made of sugar, powdered edible nuts, and aromatic spices such as cardamom and cinnamon.

[λ] Origin from Yazd or Kermanshah Provinces; made of rice and wheat flour, syrup or sugar, oil, egg, milk, rose water, purslane, and cardamom.

[‡] Origin from Mazandaran Province; made of wheat flour, sugar, oil, egg, and water.

[¥] Made of sugar, animal oil, egg, raisin, baking powder, milk powder, vanilla, and water.

[€] Laboratory value: To compare the total TFAs in fat with label value, It was calculated in portion size-stated content listed on the label.

In a study in Ireland, it was stated that the accuracy of the values on food labels was variable based on the nutrient kind. On average, 51% of nutritional labels were over and above 45% of nutritional labels were lower than those measured for the nutrients.[23] In Canada, Fitzpatrick et al. found that 16.7% (n = 169) of analyzed products were "unsatisfactory" with laboratory values exceeding the nutrition facts values shown on the label. Sodium and TFAs accounted for the highest and lowest number of unsatisfactory products (n = 49, 18.4%) and (n = 16, 4.3%), respectively. The proportion of unsatisfactory products for saturated fatty acids (SFAs), calories, and sugar was 15.8%, 14.2%, and 12.9%, respectively. All of the unsatisfactory products had excess nutrient content relative to the nutrition facts. The proportion of unsatisfactory bakery products was 19.6%, which was considerably higher than the number of unsatisfactory products in snacks (11.8%) and sugar/sweets (9.5%).[10]

A study by Pantazopoulos et al. indicated no significant difference between the laboratory and food label values for cookies, crackers, granola bars, breakfast bars, and frozen foods for TFAs and SFAs. It was concluded that food labels are accurate and credible for consumers regarding TFAs and SFAs content.[5]

This study included a relatively large number of samples but the results may not be generalizable to all sweet products in Iran that could be regarded as a limitation of this study. These results can be variable over time and even at different locations.

Conclusion

The findings of the current study showed differences between the Tl and laboratory values in more than 80% of traditional sweet products examined in this study. Furthermore, most of the samples contained less than 2% of TFAs in the total fat. The consumption of high amounts of traditional sweets could be alarming.

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Conflict of Interests

Authors have no conflict of interests.

References

1. Peykari N, Hashemi H, Dinarvand R, Haji-Aghajani M, Malekzadeh R, Sadrolsadat A, et al. National action plan for non-communicable diseases prevention and control in Iran; a response to emerging epidemic. J Diabetes Metab Disord 2017; 16: 3.
2. Kiani K, Roohafza H, Gharipour M, Dianatkhah M, Talaei M, Oveisgharan S, et al. The association between the serum 25-hydroxyvitamin D level and cardiovascular events in individuals with and without metabolic syndrome. ARYA Atheroscler 2018; 14(6): 254-9.
3. Esfandiari Z, Mirlohi M, Jila M Tanha JM, Hadian M, Mossavi SI, Ansariyan A, et al. Effect of Face-to-Face Education on Knowledge, Attitudes, and Practices Toward "Traffic Light" Food Labeling in Isfahan Society, Iran. Int Q Community Health Educ 2020; 272684X20916612.
4. World Health Organization. Guidelines: Saturated fatty acid and trans-fatty acid intake for adults and children [Online]. [cited 2018]; Available from: URL: https://extranet.who.int/dataform/upload/surveys/666752/files/Draft%20WHO%20SFA-TFA%20guidelines_04052018%20Public%20Consultation(1).pdf
5. Pantazopoulos P, Kwong K, Lillycrop W, Wong L, Gao Y, Chalouh S, et al. Trans and saturated fat on food labels in Canada: Fact or fiction? Can J Public Health 2011; 102(4): 313-6.
6. Ghazavi N, Rahimi E, Esfandiari Z, Shakarian A. Analytical study of saturated fatty acids as an important indicator of cardiovascular disease in Iranian traditional sweets. J Shaheed Sadoughi Univ Med Sci 2018; 26(9): 770-83. [In Persian].
7. Asgary S, Nazari B. Facts about trans fatty acids. ARYA Atheroscler 2008; 4(1): 42-7.
8. Kong K, Liu F, Tao Y. The presence and accuracy of nutritional labelling of pre-packaged foods in Shanghai. Asia Pac J Clin Nutr 2017; 26(3): 478-83.
9. Esfandiari Z, Marasi MR, Estaki F, Sanati V, Panahi E, Akbari N, et al. Influence of education on knowledge, attitude and practices of students of Isfahan University of Medical Sciences to traffic light inserted on food labeling. Tehran Univ Med J 2019; 77(1): 54-62. [In Persian].
10. Fitzpatrick L, Arcand J, L'Abbe M, Deng M, Duhaney T, Campbell N. Accuracy of Canadian food labels for sodium content of food. Nutrients 2014; 6(8): 3326-35.
11. Jumpertz R, Venti CA, Le DS, Michaels J, Parrington S, Krakoff J, et al. Food label accuracy of common snack foods. Obesity (Silver Spring) 2013; 21(1): 164-9.

12. Nazari B, Asgary S, Azadbakht L. Fatty acid analysis of Iranian junk food, dairy, and bakery products: Special attention to trans-fats. J Res Med Sci 2012; 17(10): 952-7.
13. Institute of Standards and Industrial Research of Iran. Microbiological of pastry and confectionary product-Specifications and test method. No: 2395. [Online]. [cited 2018]; Available from: URL: http://standard.isiri.gov.ir/StandardView.aspx?Id=46634
14. Horwitz W. Official methods of analysis of the AOAC International. Rockville, MA: Association of Official Analytical Chemists; 2012.
15. Wang Q, Afshin A, Yakoob MY, Singh GM, Rehm CD, Khatibzadeh S, et al. Impact of nonoptimal intakes of saturated, polyunsaturated, and trans fat on global burdens of coronary heart disease. J Am Heart Assoc 2016; 5(1).
16. Costa N, Cruz R, Graca P, Breda J, Casal S. Trans fatty acids in the Portuguese food market. Food Control 2016; 64: 128-34.
17. Perez-Farinos N, Dal Re Saavedra MA, Villar VC, Robledo de DT. Trans-fatty acid content of food products in Spain in 2015. Gac Sanit 2016; 30(5): 379-82.
18. Trattner S, Becker W, Wretling S, Ohrvik V, Mattisson I. Fatty acid composition of Swedish bakery products, with emphasis on trans-fatty acids. Food Chem 2015; 175: 423-30.
19. Scheeder MR, Shawish KA, Colombani RC. Trans fatty acid content of selected Swiss foods: The TransSwissPilot study. Journal of Food Composition and Analysis 2009; 22: 479-84.
20. Becker W, Eriksson A, Haglund M, Wretling S. Contents of total fat, fatty acids, starch, sugars and dietary fibre in Swedish market basket diets. Br J Nutr 2015; 113(9): 1453-65.
21. Karabulut I. Fatty acid composition of frequently consumed foods in Turkey with special emphasis on trans fatty acids. Int J Food Sci Nutr 2007; 58(8): 619-28.
22. Iranian Food and Drug Administration. Instructions and guidelines for traffic light indicator [Online]. [cited 2017]; Available from: URL: http://fdo.tums.ac.ir/html
23. Food Safety authority of Ireland. Accuracy of nutrition labelling of pre-packaged food in Ireland [Online]. [cited 2010]; Available from: URL: https://www.fsai.ie

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Comparison of survival rate and complications of percutaneous coronary intervention, coronary artery bypass graft, and medical treatment in patients with left main and/or three vessel diseases

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Original Article

Abstract

BACKGROUND: The probable complications of 3 different cardiovascular diseases treatment options including percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), and medical therapy (MT), especially in individuals suffering from left main (LM) and/or three vessel diseases (3VDs), have received less attention. Thus, the aim of this study was to compare the complications of the aforementioned therapeutic strategies in patients admitted with LM coronary artery disease (CAD) and/or having 3VDs.

METHODS: From March 2018 to March 2019, a total number of 251 eligible individuals (87, 86, and 78 subjects treated with PCI, CABG, and MT, respectively) were recruited in this cohort study. After the initiation of treatment, all individuals were followed for 6 months. Occurrence of any complications including chest pain (CP), re-hospitalization due to cardiac problems, heart failure (HF), death, myocardial infarction (MI), and stroke as well as major adverse cardiac events (MACE) were assessed.

RESULTS: Significantly lower percentages of CP, readmission, and HF were observed in the CABG group compared to the PCI and MT groups (24.4% vs. 47.1% and 53.9%, P < 0.001; 3.5% vs. 13.8% and 5.1%, P = 0.020; 1.2% vs. 2.3% and 9%; P = 0.040, respectively). Further analysis revealed an increased likelihood of hospitalization in the PCI group (OR: 3.82, 95% CI: 1.01-14.41, P = 0.040), and a lower risk of CP and HF occurrence in the CABG group subjects compared to the MT group (OR: 0.28, 95% CI: 0.13-0.62, P = 0.002 and OR: 0.05, 95% CI: 0.004-0.71, P = 0.030, respectively). This pattern was also observed in the PCI group in terms of HF (OR: 0.12, 95% CI: 0.02-0.83, P = 0.030).

CONCLUSION: Patients suffering from LM and/or 3VDs would most likely benefit from CABG followed by PCI, rather than MT. Further large-scale studies are required to confirm these results.

Keywords: Coronary Artery Bypass Grafting; Percutaneous Coronary Intervention; Coronary Vessels; Coronary Artery Disease

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Introduction

One of the leading causes of death among all nations is cardiovascular diseases (CVDs); 50 and 25% of deaths are attributable to CVDs in developed and developing countries, respectively.[1,2] Due to the importance of the diagnosis and treatment of these disorders, several diagnostic and therapeutic procedures have been introduced in this regard; the

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oldest diagnostic method is coronary angiography that was performed for the first time in 1929.[3] Coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI) are 2 other methods first introduced in 1968 and 1977, respectively.[4,5] CABG was first considered for complex coronary lesions and was announced as a standard therapy for left main (LM) coronary artery disease (CAD); however, technology and device improvement in PCI method have been so great that this procedure has been categorized as an alternative way of managing complex coronary artery lesions.[6-8] However, each modality has its own advantages and disadvantages especially in terms of the procedure itself and post procedural complications. In comparison to CABG, in some studies PCI has been associated with increased incidence of repeat revascularization, re-infarction, or angina recurrence.[1,9-11] On the other hand, in spite of the heightened quality of life (QOL) after CABG surgery reported in some researches, this procedure has been associated with increased prevalence of complications including stroke, cardiac death, or heart failure (HF) worsening compared to PCI.[12,13] Moreover, insignificant associations have been reported between aforementioned variables in addition to the comparison of the 2 methods with medical therapy in some other articles.[1,14]

Due to the controversial findings of previous studies and considering that no previous study was found to compare the occurrence of complications after PCI, CABG, or medical treatment between patients suffering from LM CAD, the aim of the current study was to evaluate the incidence of complications including chest pain (CP), re-hospitalization due to cardiac problems, HF, death, myocardial infarction (MI), stroke, and major cardiac events (death, fatal/nonfatal MI, and stroke) in Iranian adults suffering from LM CAD and/or 3 vessel diseases (3VDs) who had experienced 3 distinct therapeutic strategies including PCI, CABG, or medical treatment (MT) within 6 months after the initiation date of treatment.

Materials and Methods

This prospective, cohort study was performed from March 2018 to March 2019 in 2 governmental hospitals (Chamran and Asgariye) in Isfahan, Iran. Any individual aged at least 18 years who had LM coronary artery lesion and/or 3VDs and was willing to participate would be recruited for this study. Based on therapeutic strategies, the participants were divided into 3 distinct groups including PCI, CABG, and MT. The decision to perform each aforementioned modality was based on the cooperative interaction of patient and physician. Patients preference, anatomical conditions of coronary arteries, as well as utilization of appropriate guidelines[15] for the correct selection of patients were some contributing factors that ultimately resulted in the classification of participants in our pre-defined treatment options. Presence of any conditions including incompleteness of profiles in data registry or during follow-up evaluation, previously defined malignancy or New York Heart Association (NYHA) class of IV HF were the exclusion criteria. After the implementation of the inclusion and exclusion criteria, data on 251 individuals (PCI = 87, CABG = 86, and MT = 78) were available for analysis. All participants were totally free to leave the study at any time without any probable future consequences. This study was approved by the ethics committee of Isfahan University of Medical Sciences, Isfahan, Iran (IR.MUI.MED.REC.1397.332).

Demographic characteristics and past medical histories including age, smoking status, hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or consuming anti-hypertensive agents), hyperlipidemia (using medications for lipid disorders, triglyceride ≥ 150 mg/dl, total cholesterol ≥ 220 mg/dl, or low density lipoprotein cholesterol ≥ 160 mg/dl), diabetes mellitus (DM) (fasting blood sugar ≥ 126 mg/dl, or using anti-diabetic drugs), history of previous MI, stroke, transient ischemic attack (TIA), peripheral vascular diseases, chronic obstructive pulmonary disease (COPD), and chronic kidney diseases (CKD) were measured and assessed through a dichotomous scale (yes/no questions), wherever it was appropriate. The number of coronary artery occlusions as well as specific involved vessels was assessed through each participant's relevant documentations including medical forms or coronary angiography videos. Information about the cause of hospitalization was gathered through a questionnaire scored on a 4-point scale [stable angina, unstable angina, ST-segment elevation MI (STEMI), non-STEMI (NSTEMI)].

A follow-up assessment was conducted for each patient within 6 months after the initiation of each treatment strategy. In the follow-up assessment, the participants were contacted by phone and asked about the occurrence of any complications

including CP, re-hospitalization due to cardiac problems, HF, death, MI, and stroke. The term "major adverse cardiac events" (MACE) was defined in order to aggregate and assess the 3 most life-threatening and debilitating cardiovascular complications including death, and fatal/nonfatal MI or stroke. In the case of incidence of any adverse events, the patient or family members were asked to bring relevant documentations of the declared complication. A group consisting of 2 cardiologists and 1 neurologist made the ultimate decision about the mentioned adverse outcomes.

Categorical and continuous variables were reported as frequency (percentage) and mean ± standard deviation (SD), respectively. The chi-square test (Fisher's exact test when assumptions of chi-square test were violated) and one way ANOVA were, respectively, used to compare categorical and continuous variables between the 3 treatment groups. Cardiovascular events including CP, HF, and re-hospitalization due to cardiac problems were compared using logistic regression and crude and adjusted Cox proportional hazards regression model (adjusted for age, gender, smoking status, DM, CKD, LM with 3VDs and gender, and DM and CKD). These comparisons were performed between the 3 groups (considering the MT group as reference) and as pairwise comparisons. The Kaplan-Meier curves with assessment of group differences using log-rank test were constructed for individuals who had undergone PCI, CABG, and MT to re-hospitalization. All analyses were performed using Stata statistical software (version 11.0; StataCorp., College Station, Tex, USA). P-values of less than 0.050 were considered statistically significant.

Results

Among the 251 participants of this cohort study, 192 (76.4%) were men. The mean age of the total population was 64.53 ± 10.2 years. Baseline characteristics of the study participants in total and according to treatment groups are presented in table 1.

Table 1. Demographic characteristics of the study population according to different categories of treatment modalities

Variables		Total (n = 251)	PCI (n = 87)	CABG (n = 86)	Medical Treatment (n = 78)	P
Age (year)		64.53 ± 10.2	63.85 ± 11.4	63.84 ± 9.2	66.0 ± 9.9	0.310*
Male (%)		192 (76.4)	69 (79.3)	65 (75.6)	58 (74.4)	0.730**
Smoking (%)		27 (10.9)	12 (14.1)	10 (11.8)	5 (6.4)	0.270**
Hypertension (%)		95 (40.1)	32 (38.6)	32 (40.0)	31 (41.9)	0.910**
Hyperlipidemia (%)		44 (18.4)	15 (18.1)	10 (12.4)	19 (25.3)	0.110**
Diabetes mellitus (%)		91 (36.3)	28 (32.2)	27 (31.4)	36 (46.2)	0.090**
MI history (%)		4 (1.6)	1 (1.2)	2 (2.3)	1 (1.3)	1.000***
Stroke history (%)		0 (0.0)				
TIA history (%)		0 (0.0)				
Peripheral vascular disease (%)		1 (0.4)	1 (1.2)	0 (0.0)	0 (0.0)	0.650***
COPD (%)		2 (0.8)	1 (1.2)	0 (0.0)	1 (1.3)	0.080***
CKD (%)		22 (8.8)	12 (13.8)	4 (4.7)	6 (7.7)	0.090**
Lesion extent (%)	LM and Single vessel	11 (4.4)	2 (2.3)	8 (9.3)	1 (1.3)	0.030***
	LM and Two vessels	32 (12.8)	7 (8.1)	19 (22.1)	6 (7.7)	0.006**
	Three vessels	204 (81.3)	78 (89.7)	55 (64.0)	71 (91.0)	< 0.001**
	Left main	105 (41.8)	24 (27.6)	69 (80.2)	12 (15.4)	< 0.001**
	TVD and LM	58 (23.1)	15 (17.2)	38 (44.2)	5 (6.4)	< 0.001**
Lesion segment (%)	LAD	242 (96.4)	86 (98.9)	78 (90.7)	78 (100.0)	0.002**
	LCX	222 (88.5)	81 (93.1)	69 (80.2)	72 (92.3)	0.010**
	RCA	222 (88.5)	81 (93.1)	65 (75.6)	78 (97.4)	< 0.001**
Clinical status on admission (%)	Stable angina	148 (59.0)	43 (49.4)	55 (64.0)	50 (64.1)	0.080**
	Unstable angina	60 (23.9)	20 (23.0)	20 (23.3)	20 (25.6)	0.910**
	STEMI					
	Non-STEMI					

* One-way ANOVA, ** Chi-square test, *** Fisher's exact test

PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; MI: Myocardial infarction; TIA: Transient ischemic attack; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; TVD & LM: Three vessel disease with left main disease; LAD: Left anterior descending; LCX: Left circumflex coronary artery; RCA: Right coronary artery; STEMI: ST-segment elevation myocardial infarction

Table 2. Cardiovascular outcomes incidence of the study population across different categories of treatment modalities

Variables	Total (n = 251)	PCI (n = 87)	CABG (n = 86)	MT (n = 78)	P
Chest pain (%)	104 (41.4)	41 (47.1)	21 (24.4)	42 (53.9)	< 0.001*
Hospitalization due to cardiac problems (%)	19 (7.6)	12 (13.8)	3 (3.5)	4 (5.1)	0.020*
Heart failure (%)	10 (3.4)	2 (2.3)	1 (1.2)	7 (9.0)	0.040**
Death (%)	6 (2.4)	2 (2.3)	2 (2.3)	2 (2.6)	1.000**
Myocardial infarction (%)	2 (0.8)	1 (1.2)	1 (1.2)	0 (0.0)	0.990**
Stroke (%)	3 (1.2)	2 (2.3)	1 (1.2)	0 (0.0)	0.770**
MACE (%)	10 (4.0)	4 (4.6)	4 (4.7)	2 (2.6)	0.740*

* Chi-square test, ** Fisher exact test

PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; MT: Medical treatment; MACE: Major adverse cardiac events

There were no significant differences between the groups in terms of age, gender, smoking, hypertension, hyperlipidemia, DM, history of previous MI, peripheral vascular disease, COPD, CKD, stable and unstable angina, STEMI and NSTEMI. However, we observed significant differences between these groups in terms of lesion extent and lesion segment; patients with LM and single vessel, LM and two vessels, LM and three vessels, and isolated LM were significantly dominated in CABG group. Furthermore, participants in the MT group had higher percentages of isolated three vessels involvement. Although the MT group had higher percentages of left anterior descending (LAD) and right coronary artery[1] obstruction, left circumflex (LCX) artery occlusion was more prevalent among patients who had undergone PCI.

The incidence of cardiovascular events at the end of the follow-up period is presented in table 2. Among all outcomes investigated during the 6-month follow-up period, there were only significant differences between the groups in terms of CP, HF, and re-hospitalization due to cardiac problems. CP was the most prevalent outcome during a 6-month period after the beginning of the treatment. Other outcomes occurred less frequently in the total population. The comparison of these outcomes between the groups illustrated significant differences in terms of CP, re-hospitalization due to cardiac problems, and HF. While the MT group had the highest incidence rate of HF and CP compared with its counterparts, patients who had undergone PCI had the highest incidence rate of re-hospitalization due to cardiac problems.

Due to lack of data on the exact time of occurrence of CP and HF, we were not able to estimate the hazard ratio of these outcomes based on various treatment groups using the Cox proportional hazards model. Therefore, we had to use odds ratio (OR) using logistic regression (Table 3). After adjustment of all potential confounders, participants who had undergone CABG had lower odds of CP and HF compared to the MT group (OR: 0.28, 95% CI: 0.13–0.62, P = 0.002 and OR: 0.05, 95% confidence interval (CI): 0.00–0.71, P = 0.030, respectively). Similarly, the PCI group showed reduced odds of HF in comparison to the reference group (OR: 0.12, 95% CI: 0.02–0.83, P = 0.030).

Table 3. Odds ratio of chest pain and heart failure across different categories of treatment modalities

Outcomes	Models	Treatment options	OR (95% CI)	P
Chest pain	Unadjusted	Medical treatment	1.00 (reference)	-
		PCI	0.76 (0.41-1.04)	0.380
		CABG	0.28 (0.14-0.54)	< 0.001
	Adjusted*	Medical treatment	1.00 (reference)	-
		PCI	0.75 (0.38-1.48)	0.410
		CABG	0.28 (0.13-0.62)	0.002
Heart failure	Unadjusted	Medical treatment	1.00 (reference)	-
		PCI	0.24 (0.05-1.12)	0.080
		CABG	0.12 (0.01-0.99)	0.040
	Adjusted*	Medical treatment	1.00 (reference)	-
		PCI	0.12 (0.02-0.83)	0.030
		CABG	0.05 (0.00-0.71)	0.030

* Adjusted for age, gender, smoking status, diabetes mellitus, chronic kidney disease, and left main with three vessel diseases

OR: Odds ratio; CI: Confidence interval; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft

The estimated hazard ratio of re-hospitalization due to cardiac problems in PCI and CABG groups compared with the MT group using the Cox proportional hazards model is presented in table 4. In individuals who had previously undergone PCI as the pre-defined therapeutic modality, the likelihood of re-hospitalization due to cardiac problems had increased during the follow-up period in comparison to the MT group (OR: 3.82, 95% CI: 1.01-14.41, P = 0.040).

Table 4. Hazard ratio of re-hospitalization due to cardiac problems across different categories of treatment modalities

Models	Variables	HR (95% CI)	P
Unadjusted	Medical treatment	1.00 (reference)	-
	PCI	4.23 (1.13-15.83)	0.030
	CABG	0.81 (0.16-4.01)	0.790
Adjusted*	Medical treatment	1.00 (reference)	-
	PCI	3.82 (1.01-14.41)	0.040
	CABG	0.88 (0.18-4.43)	0.870

* Adjusted for gender, diabetes mellitus, and chronic kidney disease HR: Hazard ratio; CI: Confidence interval; PCI: Percutaneous coronary intervention; CABG: Coronary Artery Bypass Graft

The results of pairwise comparisons of CP, HF, and re-hospitalization according to different treatment options are presented in table 5. Compared to the PCI and MT groups, individuals who had undergone CABG had lower odds of CP after adjustment of potential confounding variables (OR: 0.30, 95% CI: 0.14-0.63, P = 0.002 and OR: 0.30, 95% CI: 0.13-0.68, P = 0.004, respectively). In terms of HF, both CABG and PCI groups had lower odds in comparison to the MT group (OR: 0.06, 95% CI: 0.01-0.72, P = 0.020 and OR: 0.15, 95% CI: 0.02-0.93, P = 0.040, respectively), but the difference between the PCI and CABG groups was not statistically significant (P = 0.670). The odds of re-hospitalization was lower in participants who had undergone CABG compared to the PCI group (OR: 0.23, 95% CI: 0.06-0.88, P = 0.030), but patients with a history of PCI showed an increased odds of readmission rather compared to the MT group (OR: 4.09, 95% CI: 1.05-15.89, P = 0.040).

The Kaplan-Meier curves for re-hospitalization due to cardiac problems according to treatment groups are displayed in Figure 1. Figure 1 shows that individuals with prior PCI had a significantly lower readmission free interval compared to the other treatment categories (P = 0.007).

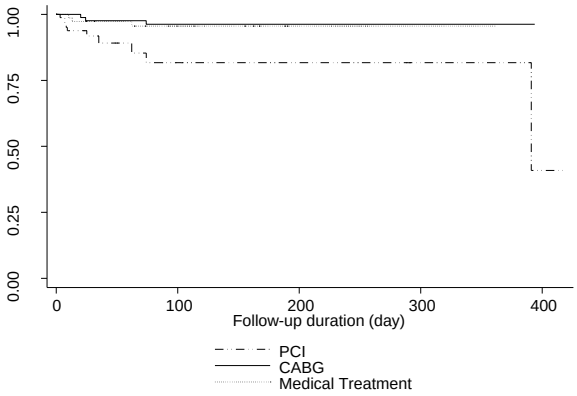

Figure 1. Kaplan-Meier curves for hospitalization due to cardiac problems according to different categories of treatment modalities

PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft

Discussion

The aim of the current study was to evaluate the probability of the occurrence of cardiovascular complications in patients who had LM and/or 3VDs and had undergone 3 different treatment methods including PCI, CABG, and MT. Our findings revealed significantly lower prevalence of CP, HF, and re-hospitalization rate among individuals who had undergone CABG compared to other therapy modalities. Further analysis during a 6-month follow-up period revealed 72% and 95% decrease in likelihood of CP and HF incidence, respectively, in the CABG group in comparison to the MT group. Similarly, the PCI group had an 88% reduction in the risk of HF compared to individuals who had not received any invasive procedures. Moreover, a 3.82 times higher risk of re-hospitalization due to cardiac problems within a 6-month follow-up duration was observed in the PCI group compared to individuals who preferred only medication usage. Furthermore, in pairwise comparisons, the CABG group had lower risk of CP compared with either the PCI or MT group. Although both CABG and PCI methods have been associated with a lower risk of HF in comparison to MT as reference group, the comparison of this variable between the CABG and PCI groups did not reveal any significant differences. With respect to re-hospitalization, participants who had undergone CABG and PCI had reduced and increased odds of this outcome compared with the PCI and MT groups, respectively.

Table 5. Odds ratio of chest pain and heart failure, and hazard ratio of re-hospitalization due to cardiac problems across different categories of treatment modalities

Outcomes	Models	Treatment options	OR (95% CI)	P
Chest pain	Unadjusted	PCI	1.00 (reference)	0.002
		CABG	0.36 (0.19-0.69)	
	Adjusted*	PCI	1.00 (reference)	0.002
		CABG	0.30 (0.14-0.63)	
	Unadjusted	Medical treatment	1.00 (reference)	< 0.001
		CABG	0.28 (0.14-0.54)	
	Adjusted*	Medical treatment	1.00 (reference)	0.004
		CABG	0.30 (0.13-0.68)	
	Unadjusted	Medical treatment	1.00 (reference)	0.390
		PCI	0.76 (0.41-1.41)	
	Adjusted*	Medical treatment	1.00 (reference)	0.460
		PCI	0.78 (0.39-1.51)	
Heart failure	Unadjusted	PCI	1.00 (reference)	0.570
		CABG	0.50 (0.04-5.61)	
	Adjusted*	PCI	1.00 (reference)	0.670
		CABG	2.38 (0.04-124.08)	
	Unadjusted	Medical treatment	1.00 (reference)	0.040
		CABG	0.12 (0.01-0.99)	
	Adjusted*	Medical treatment	1.00 (reference)	0.020
		CABG	0.06 (0.01-0.72)	
	Unadjusted	Medical treatment	1.00 (reference)	0.080
		PCI	0.24 (0.05-1.18)	
	Adjusted*	Medical treatment	1.00 (reference)	0.040
		PCI	0.15 (0.02-0.93)	
Outcomes	**Models**	**Treatment options**	**Hazard Ratio (95% CI)**	**P**
Re-hospitalization due to cardiac problems	Unadjusted	PCI	1.00 (reference)	0.010
		CABG	0.18 (0.05-0.70)	
	Adjusted**	PCI	1.00 (reference)	0.030
		CABG	0.23 (0.06-0.88)	
	Unadjusted	Medical treatment	1.00 (reference)	0.830
		CABG	0.84 (0.17-4.14)	
	Adjusted**	Medical treatment	1.00 (reference)	0.880
		CABG	0.88 (0.17-4.56)	
	Unadjusted	Medical treatment	1.00 (reference)	0.030
		PCI	4.17 (1.10-15.78)	
	Adjusted**	Medical treatment	1.00 (reference)	0.040
		PCI	4.09 (1.05-15.89)	

OR: Odds ratio; CI: Confidence interval; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft
* adjusted for age, gender, smoking status, diabetes mellitus, chronic kidney disease, and left main with three vessel diseases
** adjusted for gender, diabetes mellitus, and chronic kidney disease

Since CVDs remain the main cause of mortality and morbidity all over the world, the selection of appropriate treatment modalities in order to decline the rates of possible complications is reasonable, especially in patients with LM and/or 3VDs. The findings of several published studies were in agreement with our findings in this regard. For instance, in a randomized clinical trial, 1800 patients suffering from LM CAD or 3VDs were randomly assigned to CABG (n = 897) and PCI (n = 903) categories. After 5 years of follow-up, their outcomes suggested that CABG was associated with lower prevalence of repeated coronary revascularization in comparison to PCI (13.7% vs. 25.9%, P < 0.0001). Similarly, no significant differences were found in terms of death or stroke occurrence between the two distinct interventions.[10] Deo et al. performed a systematic review and meta-analysis study in order to investigate possible cardiovascular complications in CABG or PCI method.[11] Their analysis on 12 relevant studies including 7 randomized clinical trials and 5 observational articles on more than 2000 individuals within 2-5 years after treatment implementation revealed that, in spite of the insignificant difference in terms of mortality between PCI and CABG method, angina and necessity for coronary artery revascularization were less frequently observed in

individuals who had undergone CABG compared to PCI, especially with the usage of drug-eluting stent [relative risk (RR): 3.4, 95% CI: 1.9-6.2, P < 0.001 and RR: 4.16, 95% CI: 2.7-6.6, P < 0.001, respectively).[11] In the study by Mercado et al., a total number of 2051 individuals were divided into CABG (n = 1533) and PCI (n = 1518) categories and were assessed after 1 year of follow-up using a database of 4 distinct trials and probable adverse events related to the aforementioned treatment options.[1] They reported neither death nor MI as well as a difference in stroke prevalence between the groups. However, participants who had undergone PCI had, respectively, lower and increased likelihood of chest pain free intervals and repeated coronary artery revascularization compared to those who had undergone surgery (77% vs. 82%, P = 0.002 and 18% vs. 4.4%, HR: 4.4, 95% CI: 3.3-5.9, respectively).[1] Furthermore, Wang et al. performed a systematic review on 16900 individuals using data from 19 related articles in order to compare complications in subjects with a history of PCI or CABG on LM coronary artery lesions.[8] Their pooled analysis failed to prove any significant differences in terms of all-cause mortality in either groups, but patients who had undergone PCI had a higher chance of repeat revascularization compared to those who had undergone CABG (OR: 2.47, 95% CI: 1.80-3.37).[8] Another meta-analysis performed on 1611 subjects with a pre-defined follow-up duration of 1 year revealed that there were no significant differences in terms of all major adverse cardiac and cerebrovascular events including death, stroke, MI, and target vessel re-intervention between individuals with LM coronary artery lesion who had undergone PCI and CABG.[16] Moreover, angina relief has been reported to be more common in individuals after CABG than PCI, especially 6 months post-intervention.[12] Even in the case of drug non-compliance after either CABG or PCI, a lower prevalence of adverse events including nonfatal MI, repeated intervention, or all-cause death were observed in CABG.[17] A data analysis of 7182 individuals suffering from stable CADs suggested that despite the lack of a significant difference between PCI and MT in terms of nonfatal MI, repeated revascularization, or mortality in all follow-up durations (1 year, 1-5 years, and more than 5 years), the PCI group subjects were mostly free from angina in comparison with the MT group subjects (RR: 1.20, 95% CI: 1.06-1.37).[18]

In spite of the insignificant difference between CABG and PCI in terms of stroke incidence, data analysis of 10944 patients in the CABG and PCI groups showed that CABG was associated with higher occurrence of stroke either after a 1-month or 1-year follow-up compared to PCI (OR: 2.94, 95% CI: 1.69-5.09, P < 0.001 and OR: 1.67, 95% CI: 1.09-2.56, P = 0.020, respectively). However, the results of some studies were not in agreement with that of the present study, such as the study by Palmerini et al.[13] Their lack of consideration of stroke risk factors or variant definitions of the aforementioned diseases in different trials used for this systematic review study might have influenced the generalization of their findings.[13] Another study on 126 individuals with LM CAD duration of more than 60 years who had undergone PCI or CABG reported that the latter modality was associated with a higher prevalence of stroke and death plus HF exacerbation, but the former procedure was associated with a higher incidence rate of chest pain (P = 0.040). The non-random assignment of the therapeutic modalities might be one of the main factors influencing their findings.[9] According to a study patients who had undergone PCI experienced significantly higher health-related QOL within 6 months after revascularization compared with individuals who had undergone CABG.[19] The results of the study by Khosravi et al. indicated that patients who had undergone emergent PCI encountered more complications than patients who had undergone elective PCI.[20] Considering the higher percentage of STEMI or non-STEMI on admission in the PCI group compared with the two other therapeutic methods, some of our reported differences between the CABG and PCI groups might be attributable to the severity of complaints.

To best of our knowledge, this study was the first to compare the complications of cardiovascular events between 3 distinct treatment options in patients suffering from LM and/or 3VDs in a Middle Eastern country (Iran). The extensive pre-defined adverse events spectrum used was one of the strengths of this study. This retrospective cohort study had several limitations that should be considered. The small sample size as well as short follow-up duration might have affected our reported findings. In addition, we were not able to use the Cox models used routinely in the analysis of cohort data due to unknown occurrence date of CP and HF.

Conclusion

In conclusion, our findings revealed that it would be reasonable to recommend the CABG procedure to patients with LM and/or 3VDs due to its lower

prevalence of complications including CP or HF followed by PCI rather than medical treatment alone. Several randomized controlled trials must be performed in order to confirm these associations.

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Conflict of Interests

Authors have no conflict of interests.

References

1. Mercado N, Wijns W, Serruys PW, Sigwart U, Flather MD, Stables RH, et al. One-year outcomes of coronary artery bypass graft surgery versus percutaneous coronary intervention with multiple stenting for multisystem disease: A meta-analysis of individual patient data from randomized clinical trials. J Thorac Cardiovasc Surg 2005; 130(2): 512-9.
2. Alaei Faradonbeh N, Nikaeen F, Akbari M, Almasi N, Vakhshoori M. Cardiovascular disease risk prediction among Iranian patients with diabetes mellitus in Isfahan Province, Iran, in 2014, by using Framingham risk score, atherosclerotic cardiovascular disease risk score, and high-sensitive C-reactive protein. ARYA Atheroscler 2018; 14(4): 163-8.
3. Mueller RL, Sanborn TA. The history of interventional cardiology: Cardiac catheterization, angioplasty, and related interventions. Am Heart J 1995; 129(1): 146-72.
4. Favaloro RG. Saphenous vein autograft replacement of severe segmental coronary artery occlusion: Operative technique. Ann Thorac Surg 1968; 5(4): 334-9.
5. Gruntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: Percutaneous transluminal coronary angioplasty. N Engl J Med 1979; 301(2): 61-8.
6. Chaitman BR, Fisher LD, Bourassa MG, Davis K, Rogers WJ, Maynard C, et al. Effect of coronary bypass surgery on survival patterns in subsets of patients with left main coronary artery disease. Report of the Collaborative Study in Coronary Artery Surgery (CASS). Am J Cardiol 1981; 48(4): 765-77.
7. Caracciolo EA, Davis KB, Sopko G, Kaiser GC, Corley SD, Schaff H, et al. Comparison of surgical and medical group survival in patients with left main equivalent coronary artery disease. Long-term CASS experience. Circulation 1995; 91(9): 2335-44.
8. Wang Z, Zhan B, Bao H, Huang X, Wu Y, Liang Q, et al. Percutaneous coronary intervention versus coronary artery bypass grafting in unprotected left main coronary artery stenosis. Am J Med Sci 2019; 357(3): 230-41.
9. Wei Z, Xie J, Wang K, Kang L, Dai Q, Bai J, et al. Comparison of percutaneous coronary intervention versus coronary artery bypass graft in aged patients with unprotected left main artery lesions. Int Heart J 2016; 57(6): 682-8.
10. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013; 381(9867): 629-38.
11. Deo SV, Sharma V, Shah IK, Erwin PJ, Joyce LD, Park SJ. Minimally invasive direct coronary artery bypass graft surgery or percutaneous coronary intervention for proximal left anterior descending artery stenosis: A meta-analysis. Ann Thorac Surg 2014; 97(6): 2056-65.
12. Kulik A. Quality of life after coronary artery bypass graft surgery versus percutaneous coronary intervention: What do the trials tell us? Curr Opin Cardiol 2017; 32(6): 707-14.
13. Palmerini T, Biondi-Zoccai G, Reggiani LB, Sangiorgi D, Alessi L, De Servi S, et al. Risk of stroke with coronary artery bypass graft surgery compared with percutaneous coronary intervention. J Am Coll Cardiol 2012; 60(9): 798-805.
14. Kimura T, Morimoto T, Furukawa Y, Nakagawa Y, Shizuta S, Ehara N, et al. Long-term outcomes of coronary-artery bypass graft surgery versus percutaneous coronary intervention for multivessel coronary artery disease in the bare-metal stent era. Circulation 2008; 118(14 Suppl): S199-S209.
15. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019; 40(2): 87-165.
16. Capodanno D, Stone GW, Morice MC, Bass TA, Tamburino C. Percutaneous coronary intervention versus coronary artery bypass graft surgery in left main coronary artery disease: A meta-analysis of randomized clinical data. J Am Coll Cardiol 2011; 58(14): 1426-32.
17. Kurlansky P, Herbert M, Prince S, Mack M. Coronary artery bypass graft versus percutaneous coronary intervention: Meds matter: Impact of

adherence to medical therapy on comparative outcomes. Circulation 2016; 134(17): 1238-46.
18. Pursnani S, Korley F, Gopaul R, Kanade P, Chandra N, Shaw RE, et al. Percutaneous coronary intervention versus optimal medical therapy in stable coronary artery disease: A systematic review and meta-analysis of randomized clinical trials. Circ Cardiovasc Interv 2012; 5(4): 476-90.
19. Yazdani-Bakhsh R, Javanbakht M, Sadeghi M, Mashayekhi A, Ghaderi H, Rabiei K. Comparison of health-related quality of life after percutaneous coronary intervention and coronary artery bypass surgery. ARYA Atheroscler 2016; 12(3): 124-31.
20. Khosravi A, Pourmoghaddas M, Asadi K, Abdi A, Gholamrezaei A. Immediate results and six-month outcomes after percutaneous coronary intervention in a referral heart center in Isfahan, Iran. ARYA Atheroscler 2011; 7(1): 24-30.

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Enzymatic antioxidant system and endothelial function in patients with metabolic syndrome

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Original Article

Abstract

BACKGROUND: This study examined the relationship between serum glutathione peroxidase 1 (GPx-1) activity and endothelial dysfunction in the subjects with and without metabolic syndrome (MetS).

METHODS: This case-control study was conducted on 76 subjects, 38 were patients with MetS and 38 were without MetS. The demographic, clinical, and laboratory features of the subjects were measured and then compared. The MetS was diagnosed according to the definitions of the National Cholesterol Education Program (NCEP) and International Diabetes Federation (IDF). Serum GPx-1 activity was measured by standard methods. Endothelial dysfunction was assessed with flow-mediated dilation (FMD) technique.

RESULTS: In case-control study of 76 subjects, all of MetS risk factors including abdominal obesity, triglyceride (TG), low serum level of high-density lipoprotein cholesterol (HDL-C), hypertension (HTN), and fasting plasma glucose (FPG) were significantly higher than healthy individuals ($P < 0.050$). FMD was significantly lower than normal subjects ($P < 0.050$). Serum GP-1 activity was significantly lower in patients with MetS compared to normal subjects (21.7 ± 13.5 vs. 79.0 ± 38.6, respectively) ($P = 0.001$). The value of GPx-1 was significantly correlated with diastolic blood pressure (DBP) ($r = -0.249$, $P = 0.040$), C-reactive protein (CRP) ($r = -0.409$, $P = 0.014$), and FMD ($r = 0.293$, $P = 0.050$) in patients with MetS. The results of logistic regression showed that a unite increase in CRP (mg/dl), FMD (%), and endothelin-1 (ET-1) (pg/ml) and a unit decrease in GPx significantly increased the odds ratio (OR) of MetS; after adjusting for age and sex the results remained significant except for FMD ($P < 0.050$)

CONCLUSION: Endothelial dysfunction is related to serum GPx-1 activity in patients with MetS. GPX-1 activity is associated with risk of cardiovascular diseases (CVDs) and peripheral vascular diseases (PVDs) in patients with MetS.

Keywords: Glutathione Peroxidase-1; Endothelium; Enzyme Activity; Metabolic Syndrome

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Introduction

The metabolic syndrome (MetS) is currently characterized by a bunch of risk factors mainly for atherosclerosis and type-2 diabetes mellitus (T2DM).[1,2] Typical features of MetS are low level of high-density lipoprotein cholesterol (HDL-C), high level of hyperglycemia, hypertriglyceridemia, hypertension (HTN), and abdominal obesity.[3] The incidence of MetS is epidemiologically due to complex interactions between genetic and environmental factors, as well as predominant

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sedentary lifestyles and unhealthy dietary habits.[4] Recent experiments have proposed that MetS may be the result of different but interrelated pathophysiological mechanisms, such as endothelial dysfunction, inflammatory process, visceral obesity, oxidative stress (OxS), and genetic factors.[5] Different studies have revealed that subjects with MetS have altered antioxidant protection as well as elevated oxidative damage.[6] Although insulin resistance is regarded as a core of the MetS, one of the main mechanisms underlying this pathology is OxS.[7]

OxS occurred as a result of dysregulation in the production and degradation of reactive oxygen species (ROS).[8] Anti-oxidative enzymes including glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase inactivate ROS. In mammalian cells, glutathione (GSH) and the GPx form the principal antioxidant defense system.[9]

The GPx is a selenocysteine-containing protein that acts against OxS via utilizing reduced GSH to reduce hydrogen peroxide (H_2O_2) and lipid peroxides to their corresponding alcohols.[10]

Different reports have shown that upon the increase of adipose tissue, the activity of antioxidant enzymes such as GPx is significantly attenuated. This leads to various abnormalities, among which endothelial dysfunction was found.[11] It was reported that individuals with T2DM showed significantly diminished plasma GSH in comparison with the control group, which is associated with ROS markers.[12,13] In addition, subjects with MetS have decreased antioxidant enzymes activity levels such as catalase, SOD, and GPx.[14,15] Controversially, other studies found no differences in the levels of GPx activity in subjects with MetS.[16]

The term endothelial dysfunction refers to the loss of a range of normal homeostatic functions of the endothelium such as vasodilation, inhibition of platelet aggregation, and leukocyte adhesion.[17] Vascular cells are exclusively sensitive to plasma glucose levels fluctuations because glucose uptake by these cells is mainly insulin-independent. Thus, higher plasma glucose concentrations tend to enter into endothelial cells and cause glucose-mediated injury. Indeed, endothelial dysfunction as a result of glucose-mediated injury is suggested to accelerate atherosclerosis. So, there is a progressive interest to find a first line of defense against vascular complications.[18]

Endothelin-1 (ET-1) is a powerful endogenous vasoconstricting peptide that is produced and released by the vascular endothelium,[19] and it has been linked to the pathogenesis of HTN, heart failure (HF), and atherosclerotic vascular disease.[20,21]

Endothelial function is achieved in vivo by measuring flow-mediated dilation (FMD) in the brachial artery. FMD has been proven to be a strong predictor of cardiovascular events.[22]

Following these assumptions, the purpose of the current study was to examine the relationship between serum GPx-1 activity and different factors related to endothelial dysfunction such as FMD, ET-1, and C-reactive protein (CRP) in subjects with MetS compared to healthy subjects.

Materials and Methods

Subjects and design: By using a modified version of the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATPIII), subject's eligibility was determined according to published criteria.[23] From 80 participants chosen in the study, 4 withdrew due to personal reasons. Participants were divided into two groups, either with or without MetS and were required to meet at least three of the following five criteria: (a) abdominal obesity, defined as waist circumference (WC) > 102 cm for men or > 88 cm for women, (b) elevated serum triglyceride (TG) (≥ 150 mg/dl), (c) low serum HDL-C (< 40 mg/dl for men and < 50 mg/dl for women), (d) HTN [blood pressure (BP) ≥ 130/85 mmHg] or current treatment for HTN, and (e) impaired fasting plasma glucose (FPG) ≥ 110 mg/dl); age > 18 years; free of diseases affecting serum lipids (e.g., thyroid disorders and pancreatitis); free of liver or kidney disease; not being substance abuser (including alcohol) or smoker; and (6) not being pregnant or lactating (for women).

Thus, 38 patients with MetS and 38 control patients without MetS (and nonsmoker) formed the basis for all subsequent analyses.

The Medical Ethics Committee of the Isfahan Cardiovascular Research Institute, Isfahan, Iran, under the approval no. 91115 approved the study protocol. The collected anthropometric data for all subjects were evaluated in Isfahan Cardiovascular Research Institute. Blood samples (5 ml) were collected in vacutainer tubes (after 12 hours of fasting) without anticoagulant; samples were stored on dry ice and centrifuged within first 2-3 hours (10000 g, 10 minutes) to obtain serum. Fresh serum samples were used for the measurement of FPG, total cholesterol (TC), TG, low-density lipoprotein cholesterol (LDL-C), and HDL-C. Remaining serum samples were kept at -70 °C until laboratory analyses. Enzymatic methods with commercial kits were used for the measurement of lipid profile

parameters in all subjects [enzyme-linked immunosorbent assay (ELISA) kits read by Stat Fax 2100 Auto Microplate Reader].

Since patients were referred to the laboratory for initial control and were not aware of their MetS, they did not take medication. After the diagnosis, patients were referred to the physician.

Determination of GPx activity: GPx activity was evaluated based on Wendel study[24] by ELISA kits (ZellBio GmbH, Commercial ELISA kit, Ulm, Germany). Biocore Diagnostika GPx Assay Kit provides a simple, reproducible, and standardized tool for assessment of GPx activity in biological sample e.g., plasma, serum, tissue homogenates, and cell lysates. The GPx activity was determined colorimetrically at 412 nm. The reaction was carried out at 25 °C in 600 μl of solution containing 100 mM (pH: 7.7) potassium phosphate buffer, 1 mM ethylenediaminetetraacetic acid (EDTA), 0.4 mM sodium azide, 2 mM GSH, 0.1 mM reduced nicotinamide adenine dinucleotide phosphate (NADPH), and 0.62 U of GSH reductase (GSSG-R). The activity of GPx was measured taking tert-butyl hydroperoxide (tBuOOH) as a substrate at 340 nm. The contribution of spontaneous NADPH oxidation was always subtracted from the overall reaction rate. GPx activity was expressed as nmol NADPH oxidized per minute per mg protein.

Quantitation of plasma ET-1: For plasma ET-1, 10 ml of venous blood was collected into an EDTA tube and centrifuged immediately at 2500 g for 20 minutes at 4 °C. ET-1 was quantitated using commercially available ELISA kits (Morinaga and R&D System).[25] Standards, reagents, and test samples were prepared and assayed according to the instructions of the manufacturer.

FMD measure: FMD was measured by ultrasonography with an automated edge tracking system (UNEX 18G, UNEX Co., Nagoya, Japan) as previously described.[26]

Results

Data are presented as mean ± standard deviation (SD) for quantitative variables and frequency and percentage for qualitative variables in table 1. Two independent samples t-test was used to compare mean of study variables between study groups and Mann-Whitney test was used if normality assumption not hold. Frequency of sex was compared between study groups using chi-square test.

Crude and adjusted relationships between the levels of CRP, FMD, ET-1, GPx-1, and the components of MetS were evaluated using Pearson's correlation and multiple linear regression analyses, respectively; age and sex were used as adjustment in regression model.

Table 1. Anthropometric, cardiac, and biochemical parameters of each group

Parameters	Normal group	MetS group	P
Sex (men)	20 (52.6)	20 (52.6)	0.999**
Age (year)	34.24 ± 10.50	44.02 ± 11.01	< 0.001*
BMI (kg/m^2)	22.26 ± 4.33	28.89 ± 4.78	< 0.001*
WC (cm)	85.76 ± 10.20	101.42 ± 9.48	< 0.001*
Hip circumference (cm)	100.45 ± 6.09	111.16 ± 8.67	< 0.001*
WHR (cm)	0.88 ± 0.07	0.92 ± 0.05	< 0.001
SBP (mmHg)	106.89 ± 9.62	123.92 ± 13.43	< 0.001*
DBP (mmHg)	68.66 ± 6.94	77.76 ± 9.56	< 0.001*
FMD (%)	4.17 ± 0.69	3.84 ± 0.55	0.024*
FBG (mmol/l)	82.39 ± 6.04	96.26 ± 18.53	< 0.001*
TG (mmol/l)	113.71 ± 32.29	208.47 ± 69.29	< 0.001*
TC (mmol/l)	176.03 ± 40.32	208.58 ± 41.47	< 0.001*
HDL-C (mmol/l)	44.89 ± 7.51	38.45 ± 6.36	< 0.001*
LDL-C (mmol/l)	89.24 ± 23.92	97.82 ± 22.51	< 0.001*
CRP (mg/dl)	2.85 ± 1.05	4.11 ± 1.58	< 0.001*
GPx-1	79.00 ± 38.60	21.75 ± 13.55	< 0.001*
ET-1 (pg/ml)	51.25 ± 8.95	97.30 ± 90.03	< 0.001*

Data are shown as mean ± standard deviation (SD) or frequancy and percentage
* Two independent samples t-test or Mann-whitney test was used, ** Chi-square test was used
MetS: Metabolic syndrome; BMI: Body mass index; WC: Waist circumference; WHR: Waist-to-hip ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FMD: Flow-mediated dilation; FBG: Fasting blood glucose; TG: Triglyceride; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; CRP: C-reactive protein; GPx-1: Glutathione peroxidase-1; ET-1: Endothelin-1

Table 2. The relationship between glutathione peroxidase-1 (GPx-1) and study variables in each study group

GPx-1		Normal group		MetS group	
		Crude**	Adjusted*	Crude**	Adjusted*
BMI (kg/m^2)	r	0.139	0.095	-0.008	-0.010
	P	0.450	0.531	0.975	0.051
SBP (mmHg)	r	0.039	0.032	-0.249	-0.234
	P	0.821	0.853	0.040	0.171
DBP (mmHg)	r	0.109	0.110	-0.193	-0.165
	P	0.524	0.526	0.282	0.312
FBG (mg/dl)	r	0.157	0.149	0.085	-0.006
	P	0.370	0.373	0.623	0.971
TG (mg/dl)	r	0.206	-0.419	-0.170	0.268
	P	0.132	0.008	0.380	0.103
TC (mg/dl)	r	-0.282	-0.305	-0.113	0.139
	P	0.105	0.068	0.490	0.429
HDL-C (mg/dl)	r	0.308	0.241	0.142	0.095
	P	0.109	0.110	0.502	0.501
LDL-C (mg/dl)	r	-0.129	-0.131	-0.111	0.011
	P	0.450	0.450	0.940	0.948
CRP (mg/dl)	r	0.245	-0.247	-0.409	-0.402
	P	0.142	0.148	0.014	0.014
FMD (%)	r	0.207	0.296	0.293	-0.155
	P	0.293	0.014	0.050	0.296
ET-1 (pg/ml)	r	0.215	0.203	0.130	0.099
	P	0.197	0.237	0.130	0.573

Data are shown as crude correlation coefficient or adjusted standardized beta regression
* Coefficients are adjusted for age and sex using multiple linear regression; ** Crude correlation coefficient computed using Pearson's correlation analysis
GPx-1: Glutathione peroxidase-1; MetS: Metabolic syndrome; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBG: Fasting blood glucose; TG: Triglyceride; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; CRP: C-reactive protein; FMD: Flow-mediated dilation; ET-1: Endothelin-1

Crude and adjusted coefficients were presented in table 2. Logistic regression models also were used for examining effects of a unite increase in CRP, FMD, ET-1, and GPx-1 on odds of MetS. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for MetS were presented in table 3. Age and sex were used as adjustments. Statistical analysis was performed using SPSS software (version 15, SPSS Inc., Chicago, IL, USA). The $P < 0.050$ was considered as statistically significant.

Anthropometric and cardiac variables as well as biochemical parameters of the study participants are summarized in table 1. Except sex, there were significant differences between anthropometric, cardiac, and biochemical parameters of the study groups. Data from the study revealed that in patients with MetS, serum GPx-1 activity was significantly lower than healthy individuals (21.7 ± 13.5 vs. 79.0 ± 38.6, respectively) ($P = 0.001$) (Figure 1).

The correlations between the levels of GPx-1 with variables studied in the MetS group and normal group are shown in table 2.

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs) of metabolic syndrome (MetS) by serum glutathione peroxidase-1 (GPx-1) activity using a logistic regression model

MetS	Factors	OR	(95% CI)	P
Crude model	CRP (mg/dl)	2.17	(1.37-3.44)	0.001
	FMD (%)	2.42	(1.09-5.35)	0.030
	ET-1 (pg/ml)	1.01	(1.00-1.02)	0.019
	GPx	0.83	(0.75-0.92)	< 0.001
Adjusted model*	CRP (mg/dl)	2.25	(1.33-3.80)	0.002
	FMD (%)	1.85	(0.62-5.52)	0.264
	ET-1 (pg/ml)	1.01	(1.00-1.01)	0.019
	GPx	0.79	(0.67-0.93)	0.004

Data are shown as crude or adjusted odds ratio (OR) and 95% confidence interval (CI), * Adjusted for age and sex
CRP: C-reactive protein; FMD: Flow-mediated dilation; ET-1: Endothelin-1; GPx: Glutathione peroxidase; OR: Odds ratio; CI: Confidence interval; MetS: Metabolic syndrome
A unit increase in CRP (mg/dl), FMD (%), ET-1 (pg/ml) increases OR of MetS and a unit increase in GPx decreases the OR of MetS.

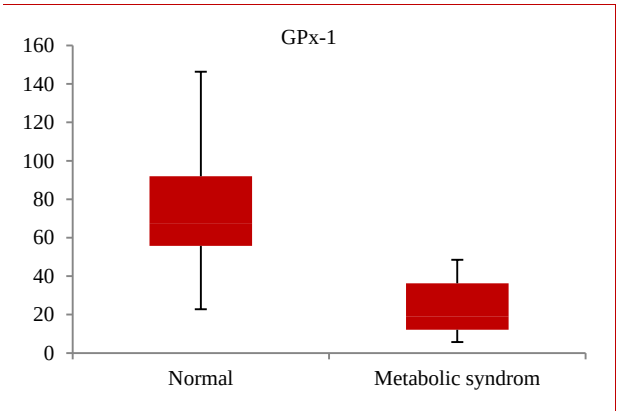

Figure 1. Comparing glutathione peroxidase-1 (GPx-1) level in metabolic syndrome (MetS) and normal groups [patients with MetS were determined using a modified version of the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATPIII) criteria for MetS, according to published criteria][23]

The values of GPx-1 were significantly correlated with diastolic blood pressure (DBP) ($r = -0.249$, $P = 0.040$), CRP ($r = -0.409$, $P = 0.014$), and FMD ($r = 0.293$, $P = 0.050$).

OR and 95% CI of Mets based on a unit change in CRP (mg/dl), FMD (%), ET-1 (pg/ml), and GPx are 2.17 (1.37-3.44), 2.42 (1.09-5.35), 1.01 (1.00-1.02), and 0.81 (0.75-0.92), respectively and were significant ($P < 0.050$). After adjusting for age and sex, the results remained significant except for FMD ($P < 0.050$).

Discussion

This study revealed some significant associations of serum GPx-1 concentration activity with some cardiometabolic risk factors, notably components of MetS, among patients with MetS.[27]

OxS plays important roles in the pathogenesis of different diseases.[28] In the condition of patients with DM, OxS impairs glucose uptake in muscle and fat tissues,[29] and it has a negative effect on insulin secretion from pancreatic β cells.[30] Increased OxS also underlies the pathophysiology of HTN[31] and atherosclerosis,[32] by directly affecting vascular wall cells.

We have analyzed the GPx-1 activity in the patients with MetS and without MetS and found a level of OxS in MetS group (Figure 1). In another study, results showed that in > 45-year-old subjects in the MetS group, the peroxidases activity was significantly decreased.[33] Previous studies indicated that development of MetS was associated with OxS.[34]

GPx removes H_2O_2 by coupling the oxidation of GSH, an abundant thiol-containing tripeptide. GPx-1 activity, a major intracellular and extracellular enzymatic defense system against superoxides, was significantly lower in subjects with MetS, and there was a negative correlation between GPx-1 levels with systolic blood pressure (SBP) and CRP.

In coronary artery disease (CAD), OxS plays an important role. GPx is the most important part of the antioxidant defense system,[35] and in the eukaryotic cells, GPx-1 is among the most abundant isoforms. Modulatory role of GPx-1 in the vascular function was reported in the in vivo studies in knockout and transgenic mice.[36] In this study a positive correlation was found between GPx-1 levels and FMD. In addition, in this study the ORs of MetS were calculated based on the levels of CRP, ET-1, and GPx-1. Subjects with higher levels of CRP and ET-1 had a significantly greater risk of MetS after adjusting for age and gender.

OxS is associated with many components of MetS. Significant decrease in GPx-1 activity in MetS group compared to nonMetS group indicates a higher decrease, leading to the concept of amelioration of risk factors comprising MetS, including insulin resistance, elevated BP, elevated lipid levels, inflammation, and endothelial dysfunction may ameliorate OxS and thus, curtail the progression of metabolic disease complications.[37]

While the association between OxS and the development of both endothelial dysfunction and coronary arteriosclerosis was investigated before,[38,39] the role of oxidative damage markers received comparatively little attention as a prognostic factor, and the results have not been clear so far. Indeed, in the particular case of GPx-1, few study reports have examined its association with the onset of cardiovascular events, and the results (an inverse association between higher GPx-1 and the rate of adverse events during follow-up) were in disagreement with those of our study.[40,41] Admittedly, those study populations comprised mostly persons with stable ischemic heart disease (IHD), whereas in this study all patients were admitted with acute coronary syndrome (ACS). Another factor to consider is that the method by which GPx-1 was determined in our study was different from that used in previous studies, which might also yield different results.

We calculated the ORs of MetS according to the levels of GPx-1 (Table 2). Reducing GPx and increasing the amount of CRP and ET-1 increase

the chance of MetS. Our results could be interpreted such that GPx-1 can protect patients against OxS in MetS.

Our results are similar to those of Sutipornpalangkul et al. who reported that increased lipid peroxidation occurred along with elevated GPx-1 activity and lower concentrations of total GSH, an indication of increased production of ROS in patients with osteoarthritis (OA).[42] As suggested by the authors, the increased activity of the antioxidant enzyme GPx-1 "may be a compensatory regulation in response to increased OxS".[42]

Previous studies found a lower activity of GPx-1 in a group of subjects with hypertriglyceridemia, a part of MetS presence, and the drop of its activity was almost to 75% of that of the control group.[43,44] Bougoulia et al. showed a decreased activity of GPx-1 in obese subjects as well as an increase after weight reduction.[45]

Because of its high reactivity with GPx-1 and thiols,[9] it is extremely difficult to detect, in vivo, a physiological modification of H_2O_2 concentration. However, the activity of GPx-1 and GSSG-R as well as the level of total GSH are accessible especially in erythrocytes, cells without nuclear capacity to restore homeostasis. Therefore, a modification in the blood GSH level can be an early biomarker of chronic OxS; then, can be an early step in the development of cardiometabolic complications.

Conclusion

Data show that endothelial dysfunction is related to serum GPx-1 activity in patients with MetS. GPx-1 activity is associated with risk of cardiovascular diseases (CVDs) and peripheral vascular diseases (PVDs) in patients with MetS and it can be an early biomarker of chronic cardiometabolic disease.

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Conflict of Interests

Authors have no conflict of interests.

References

1. Vavrova L, Kodydkova J, Zeman M, Dusejovska M, Macasek J, Stankova B, et al. Altered activities of antioxidant enzymes in patients with metabolic syndrome. Obes Facts 2013; 6(1): 39-47.
2. Karaman A, Aydin H, Geckinli B, Cetinkaya A, Karaman S. DNA damage is increased in lymphocytes of patients with metabolic syndrome. Mutat Res Genet Toxicol Environ Mutagen 2015; 782: 30-5.
3. Yubero-Serrano EM, Delgado-Lista J, Pena-Orihuela P, Perez-Martinez P, Fuentes F, Marin C, et al. Oxidative stress is associated with the number of components of metabolic syndrome: LIPGENE study. Exp Mol Med 2013; 45: e28.
4. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA 2003; 289(1): 76-9.
5. Baez-Duarte BG, Zamora-Ginez I, De Jesus KL, Torres-Rasgado E, Gonzalez-Mejia ME, Porchia L, et al. Association of the metabolic syndrome with antioxidant defense and outstanding superoxide dismutase activity in Mexican subjects. Metab Syndr Relat Disord 2016; 14(3): 154-60.
6. Baez-Duarte BG, Mendoza-Carrera F, Garcia-Zapien A, Flores-Martinez SE, Sanchez-Corona J, Zamora-Ginez I, et al. Glutathione peroxidase 3 serum levels and GPX3 gene polymorphisms in subjects with metabolic syndrome. Arch Med Res 2014; 45(5): 375-82.
7. Pena-Orihuela P, Camargo A, Rangel-Zuniga OA, Perez-Martinez P, Cruz-Teno C, Delgado-Lista J, et al. Antioxidant system response is modified by dietary fat in adipose tissue of metabolic syndrome patients. J Nutr Biochem 2013; 24(10): 1717-23.
8. Anagnostis P, Efstathiadou ZA, Gougoura S, Polyzos SA, Karathanasi E, Dritsa P, et al. Oxidative stress and reduced antioxidative status, along with endothelial dysfunction in acromegaly. Horm Metab Res 2013; 45(4): 314-8.
9. Beckett GJ, Arthur JR. Selenium and endocrine systems. J Endocrinol 2005; 184(3): 455-65.
10. Forgione MA, Weiss N, Heydrick S, Cap A, Klings ES, Bierl C, et al. Cellular glutathione peroxidase deficiency and endothelial dysfunction. Am J Physiol Heart Circ Physiol 2002; 282(4): H1255-H1261.
11. Fernandez-Sanchez A, Madrigal-Santillan E, Bautista M, Esquivel-Soto J, Morales-Gonzalez A, Esquivel-Chirino C, et al. Inflammation, oxidative stress, and obesity. Int J Mol Sci 2011; 12(5): 3117-32.

12. Calabrese V, Cornelius C, Leso V, Trovato-Salinaro A, Ventimiglia B, Cavallaro M, et al. Oxidative stress, glutathione status, sirtuin and cellular stress response in type 2 diabetes. Biochim Biophys Acta 2012; 1822(5): 729-36.
13. Jain SK, Micinski D, Huning L, Kahlon G, Bass PF, Levine SN. Vitamin D and L-cysteine levels correlate positively with GSH and negatively with insulin resistance levels in the blood of type 2 diabetic patients. Eur J Clin Nutr 2014; 68(10): 1148-53.
14. Chen SJ, Yen CH, Huang YC, Lee BJ, Hsia S, Lin PT. Relationships between inflammation, adiponectin, and oxidative stress in metabolic syndrome. PLoS One 2012; 7(9): e45693.
15. Yokota T, Kinugawa S, Yamato M, Hirabayashi K, Suga T, Takada S, et al. Systemic oxidative stress is associated with lower aerobic capacity and impaired skeletal muscle energy metabolism in patients with metabolic syndrome. Diabetes Care 2013; 36(5): 1341-6.
16. Collazo-Roman M, Munoz-Forti K, Gonzalez A, Jimenez G, Mangual R, Perez Y, et al. Levels of antioxidant activity and oxidative stress in metabolic syndrome Puerto Rican participants (1138.9). The FASEB Journal 2014; 28(1_supplement): 1138-9.
17. Thomas SR, Witting PK, Drummond GR. Redox control of endothelial function and dysfunction: Molecular mechanisms and therapeutic opportunities. Antioxid Redox Signal 2008; 10(10): 1713-65.
18. de Haan JB, Cooper ME. Targeted antioxidant therapies in hyperglycemia-mediated endothelial dysfunction. Front Biosci (Schol Ed) 2011; 3: 709-29.
19. Yang ZH, Richard V, von SL, Bauer E, Stulz P, Turina M, et al. Threshold concentrations of endothelin-1 potentiate contractions to norepinephrine and serotonin in human arteries. A new mechanism of vasospasm? Circulation 1990; 82(1): 188-95.
20. Miyauchi T, Masaki T. Pathophysiology of endothelin in the cardiovascular system. Annu Rev Physiol 1999; 61: 391-415.
21. Touyz RM, Schiffrin EL. Role of endothelin in human hypertension. Can J Physiol Pharmacol 2003; 81(6): 533-41.
22. Rossi R, Nuzzo A, Origliani G, Modena MG. Prognostic role of flow-mediated dilation and cardiac risk factors in post-menopausal women. J Am Coll Cardiol 2008; 51(10): 997-1002.
23. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 2001; 285(19): 2486-97.
24. Wendel A. Glutathione peroxidase. Methods Enzymol 1981; 77: 325-33.
25. Bondonno CP, Yang X, Croft KD, Considine MJ, Ward NC, Rich L, et al. Flavonoid-rich apples and nitrate-rich spinach augment nitric oxide status and improve endothelial function in healthy men and women: A randomized controlled trial. Free Radic Biol Med 2012; 52(1): 95-102.
26. Maruhashi T, Soga J, Fujimura N, Idei N, Mikami S, Iwamoto Y, et al. Nitroglycerine-induced vasodilation for assessment of vascular function: A comparison with flow-mediated vasodilation. Arterioscler Thromb Vasc Biol 2013; 33(6): 1401-8.
27. Samsamshariat SZA, Sakhaei F, Salehizadeh L, Keshvari M, Asgary S. Relationship between resistin, endothelin-1, and flow-mediated dilation in patient with and without metabolic syndrome. Adv Biomed Res 2019; 8: 16.
28. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature 2001; 414(6865): 813-20.
29. Maddux BA, See W, Lawrence JC Jr, Goldfine AL, Goldfine ID, Evans JL. Protection against oxidative stress-induced insulin resistance in rat L6 muscle cells by mircomolar concentrations of alpha-lipoic acid. Diabetes 2001; 50(2): 404-10.
30. Kaneto H, Katakami N, Matsuhisa M, Matsuoka TA. Role of reactive oxygen species in the progression of type 2 diabetes and atherosclerosis. Mediators Inflamm 2010; 2010: 453892.
31. Nakazono K, Watanabe N, Matsuno K, Sasaki J, Sato T, Inoue M. Does superoxide underlie the pathogenesis of hypertension? Proc Natl Acad Sci U S A 1991; 88(22): 10045-8.
32. Ohara Y, Peterson TE, Harrison DG. Hypercholesterolemia increases endothelial superoxide anion production. J Clin Invest 1993; 91(6): 2546-51.
33. Samsam-Shariat SZ, Bolhasani M, Sarrafzadegan N, Najafi S, Asgary S. Relationship between blood peroxidases activity and visfatin levels in metabolic syndrome patients. ARYA Atheroscler 2014; 10(4): 218-26.
34. Rains JL, Jain SK. Oxidative stress, insulin signaling, and diabetes. Free Radic Biol Med 2011; 50(5): 567-75.
35. Sies H. Glutathione and its role in cellular functions. Free Radic Biol Med 1999; 27(9-10): 916-21.
36. Weiss N, Zhang YY, Heydrick S, Bierl C, Loscalzo J. Overexpression of cellular glutathione peroxidase rescues homocyst(e)ine-induced endothelial dysfunction. Proc Natl Acad Sci U S A 2001; 98(22): 12503-8.

37. Wiwanitkit V. Oxidative stress and metabolic syndrome. Korean J Fam Med 2014; 35(1): 44.
38. Stephens JW, Gable DR, Hurel SJ, Miller GJ, Cooper JA, Humphries SE. Increased plasma markers of oxidative stress are associated with coronary heart disease in males with diabetes mellitus and with 10-year risk in a prospective sample of males. Clin Chem 2006; 52(3): 446-52.
39. Vassalle C, Boni C, Di Cecco P, Landi P. Elevated hydroperoxide levels as a prognostic predictor of mortality in a cohort of patients with cardiovascular disease. Int J Cardiol 2006; 110(3): 415-6.
40. Forsberg L, de Faire U, Morgenstern R. Oxidative stress, human genetic variation, and disease. Arch Biochem Biophys 2001; 389(1): 84-93.
41. Blankenberg S, Rupprecht HJ, Bickel C, Torzewski M, Hafner G, Tiret L, et al. Glutathione peroxidase 1 activity and cardiovascular events in patients with coronary artery disease. N Engl J Med 2003; 349(17): 1605-13.
42. Sutipornpalangkul W, Morales NP, Charoencholvanich K, Harnroongroj T. Lipid peroxidation, glutathione, vitamin E, and antioxidant enzymes in synovial fluid from patients with osteoarthritis. Int J Rheum Dis 2009; 12(4): 324-8.
43. Cardona F, Tunez I, Tasset I, Montilla P, Collantes E, Tinahones FJ. Fat overload aggravates oxidative stress in patients with the metabolic syndrome. Eur J Clin Invest 2008; 38(7): 510-5.
44. Cardona F, Tunez I, Tasset I, Murri M, Tinahones FJ. Similar increase in oxidative stress after fat overload in persons with baseline hypertriglyceridemia with or without the metabolic syndrome. Clin Biochem 2008; 41(9): 701-5.
45. Bougoulia M, Triantos A, Koliakos G. Plasma interleukin-6 levels, glutathione peroxidase and isoprostane in obese women before and after weight loss. Association with cardiovascular risk factors. Hormones (Athens) 2006; 5(3): 192-9.

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Large pericardial mesothelial cyst coexisting with hypertrophic obstructive cardiomyopathy

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Case Report

Abstract

BACKGROUND: Pericardial mesothelioma cyst occurs rarely, and is often found incidentally. The coexistence between large pericardial mesothelial cyst and hypertrophic obstructive cardiomyopathy (HOCM) can make difficulties in medical management.

CASE REPORT: Our case was a 33-year-old man presented with dizziness and pallor while standing since four years before, and recent syncope. On admission, transthoracic echocardiography reveled presence of hypertrophic cardiomyopathy in association with relatively small right ventricular and atrium due to compression effect by a large echo-free space at the right side of heart suggestive of pericardial cyst. Cardiac computed tomography confirmed presence of HOCM and large pericardial cyst. Patient underwent surgical septal myectomy and large mesothelial pericardial cyst excision because of persistent symptoms and compression effect of cyst on the right chambers despite beta-blocker therapy.

CONCLUSION: To best of our knowledge, the coexistence of the large pericardial mesothelial cyst and HOCM has not been reported before.

Keywords: Mesothelioma; Pericardial Cyst; Cardiomyopathy Hypertrophic Obstructive

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Introduction

Pericardial mesothelioma cyst, or so-called benign cystic mesothelioma, occur with an incidence of approximately one per 100,000.[1] These cysts are commonly with few symptoms, and are often found incidentally.[2] The coexistence between large pericardial mesothelial cyst and hypertrophic obstructive cardiomyopathy (HOCM) has not been reported before. Hereby, we report coexistent large pericardial mesothelial cyst and HOCM, which can make difficulties in medical management; as when the cyst is large size with compressive effect on the right chambers, giving high dose of beta-blockers would be risky.

Case Report

Our case was a 33-year-old man presented with dizziness and pallor while standing since last four years, which the last time was associated with syncope and face trauma; so, patient was admitted. He had positive family of sudden cardiac death in his

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father at the age of 43 years old.

Chest X-ray showed large cystic lesion in right lung space. Transthoracic echocardiography showed normal left ventricular size and mild systolic dysfunction, severe left ventricular hypertrophy with significant asymmetric septal hypertrophy, severe systolic anterior motion resulting in significant left ventricular outflow tract (LVOT) obstruction consistent with HOCM (maximal late peaking gradient at rest = 64 mmHg), and relatively small right ventricular size due to compression effect of a large echo-free space at the right side of heart suggestive of pericardial cyst, which had compressive effect on right atrium, too (Figure 1).

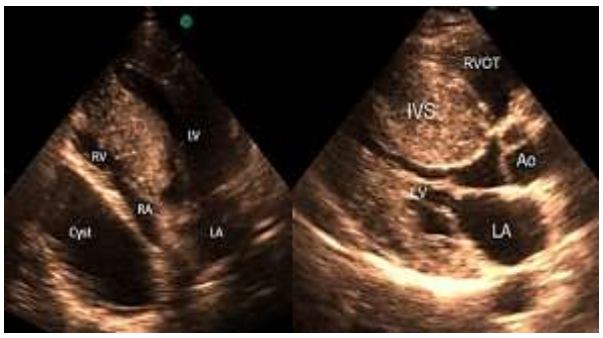

Figure 1. Transthoracic echocardiography view demonstrates the presence of hypertrophic obstructive cardiomyopathy

Cardiac computed tomography (CT) scan confirmed the presence of HOCM, and introduced the echo-free space as a large pericardial cyst (Figure 2). After electrophysiology consultation and rule out of ventricular arrhythmia, myectomy and excision of pericardial cyst was recommended.

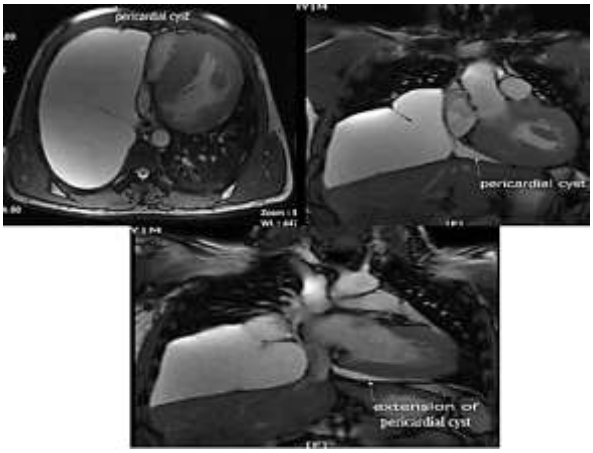

Figure 2. Cardiac computed tomography (CT) demonstrates an echo-free space as a large pericardial cyst in association with hypertrophic obstructive cardiomyopathy (HOCM)

He underwent transaortic surgical septal myectomy via a standard median sternotomy, and by surgical exploration, a large cyst was found attached to the pericardium, anterior of right phrenic nerve, with 5 cm distance from diaphragm, and was extended totally into right pleural space. The cyst was excised and macroscopic examination showed the cystic pieces (12 × 12 × 3 cm) with smooth interior wall and wall thickness of about 1 mm, consistent with mesothelial cyst. Microscopic evaluation [hematoxylin and eosin (H&E) ×100] identified thin-walled cyst lined by single cell lining of non-pleomorphic cells with abundant eosinophilic cytoplasm, vesicular nuclei, and small nucleoli (Figure 3).

Figure 3. Fibroconnective tissue lined by a layer of mesothelial cells in microscopic evaluation

Discussion

HOCM is a genetic disease with various presentations as heart failure, arrhythmia, sudden cardiac death, and so on. Indications for septal myectomy, as gold standard therapy, include symptomatic patients with left ventricular outflow tract gradient of more than 50 mmHg, and symptoms refractory to medical therapy.[3]

Pericardial cysts are often intrathoracic and most common are considered as congenital cysts.[4] Congenital cysts are fluid-filled enclosed space, lined by mesothelial cells.[5] These cysts are often found incidentally, and are benign lesions. Treatment is just advocated for symptomatic cases due to compression effect of cyst. The differentiation between pericardial and plural cyst are most often straight forwards; but in some circumstances, it would be difficult. Pericardial cysts have no communication with pericardial space, but attached to pericardium directly or by a pedicle.[6] Mesothelial cysts occur due to aberration in

formation of somatic cavities.[7] To best of our knowledge, the coexistence of large mesothelial cyst and HOCM has not been reported previously.

Coexisted large pericardial mesothelial cyst and HOCM is a rare abnormality, which make difficulties in medical management; since giving beta-blocker in HOCM is treatment of choice. But in the presence of a large cyst with compressive effect on the right chambers, giving high dose of beta-blocker would be risky. Despite the fact that coexisting of HOCM and mesothelial cysts can be an incidental finding, the possible common genetic origin can be assessed.

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Conflict of Interests

Authors have no conflict of interests.

References

1. Sharma R, Harden S, Peebles C, Dawkins KD. Percutaneous aspiration of a pericardial cyst: An acceptable treatment for a rare disorder. Heart 2007; 93(1): 22.
2. Elamin WF, Hannan K. Pericardial cyst: An unusual cause of pneumonia. Cases J 2008; 1(1): 26.
3. van der Wall EE. New ESC guidelines on hypertrophic cardiomyopathy: New insights in invasive treatment? Neth Heart J 2015; 23(1): 1-3.
4. Comoglio C, Sansone F, Delsedime L, Campanella A, Ceresa F, Rinaldi M. Mesothelial cyst of the pericardium, absent on earlier computed tomography. Tex Heart Inst J 2010; 37(3): 354-7.
5. Klein AL, Abbara S, Agler DA, Appleton CP, Asher CR, Hoit B, et al. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease: Endorsed by the Society for Cardiovascular Magnetic Resonance and Society of Cardiovascular Computed Tomography. J Am Soc Echocardiogr 2013; 26(9): 965-1012.
6. Michelotto E, Tarantino N, Ostuni V, Pedote P, Colonna P, Guglielmi R. An Uncommon Pericardial Cyst in the Central Mediastinum: Incremental Diagnosis with Contrast-Enhanced Three-Dimensional Transesophageal Echocardiography. J Cardiovasc Echogr 2013; 23(4): 106-10.
7. Patel S, Hajmedi P, Fischbein J. Common symptoms with rare entity: A giant pericardial cyst. Am J Med 2015; 128(10): e27-e28.