Isfahan Cardiovascular Research Institute

ARYA Atherosclerosis

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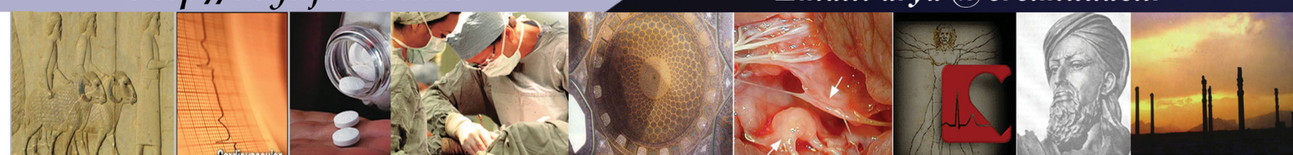

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2. Bonow RO, Mann DL, Zipes DP, Libby P. Braunwald's Heart Disease E-Book: A Textbook of Cardiovascular Medicine. 7th ed. Philadelphia, PA: Elsevier Health Sciences; 2007. p. 1976, 1981, 1982.

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* All the words of the article containing the references; each table is considered as 300 words.

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Predictive factors of short-term survival from acute myocardial infarction in early and late patients in Isfahan and Najafabad, Iran

Mohammad Abdolazimi[(1)], Alireza Khosravi[(2)], Masoumeh Sadeghi[(3)], Abdollah Mohammadian-Hafshejani[(4)], Nizal Sarrafzadegan[(5)], Hamid Salehiniya[(6)], Jafar Golshahi[(3)]

Original Article

Abstract

BACKGROUND: Cardiovascular disease (CVD) is the primary cause of mortality in the world and Iran. The aim of this study was to determine the prognostic factors of short-term survival from acute myocardial infarction (AMI) in early and late patients in the Najafabad and Isfahan County, Iran.

METHODS: This hospital-based cohort study was conducted using the hospital registry of 1999-2009 in Iran. All patients (n = 14426) with an AMI referred to hospitals of Isfahan and Najafabad were investigated. To determine prognostic factors of short-term (28-days) survival in early and late patients, unadjusted and adjusted hazard ratio (HR) was calculated using univariate and multivariate Cox regression.

RESULTS: The short-term (28-day) survival rate of early and late patients was 96.64% and 89.42% (P < 0.001), respectively. In 80% of early and 79.3% of late patients, mortality occurred during the first 7 days of disease occurrence. HR of death was higher in women in the two groups; it was 1.97 in early patients was (CI95%: 1.32-2.92) and 1.35 in late patients (CI95%: 1.19-1.53) compared to men. HR of death had a rising trend with the increasing of age in the two groups.

CONCLUSION: Short-term survival rate was higher in early patients than in late patients. In addition, case fatality rate (CFR) of AMI in women was higher than in men. In both groups, sex, age, an atomic location of myocardial infarction based on the International Classification of Disease, Revision 10 (ICD10), cardiac enzymes, and clinical symptoms were significant predictors of survival in early and late patients following AMI.

Keywords: Myocardial Infarction; Survival Rate; Early; Late; Regression Analysis; Iran

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Introduction

Cardiovascular disease (CVD) is the most important reason of death in residents of Iran.[1] Every month around 11500 decease owing to coronary heart disease happens in Iran, about 50% of this deaths occurs as a result of acute myocardial infarction (AMI).[2] This disease is the major cause of disability, morbidity, and mortality in Iran residents.[3-5] Age is one of the important factors that have a massive influence on decease after heart attack so that older individuals are at bigger hazard of mortality from AMI.

In several studies that conducted around the word and detected that the mean age of patients who deceased in 28 days afterward the incidence of AMI and patients who deceased beforehand getting hospital, respectively, in average were 10 and 7 years older than survived patients.[6,7] Clearly, the possibility of decease from AMI was higher in elderly. Moreover, albeit only about 10% of the entire patients with AMI are < 45 years old.[6,7] AMI

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is a common cause of disability and mortality in a lot of countries and causes additional disadvantages, especially when it occurs in early patients. In studies that have been conducted in different parts of the world, factors such as age, sex, type of AMI, electrokardiogram (EKG), symptom, cardiac enzymes (lactate dehydrogenase, creatine kinase, and troponin), hypertension, previous MI, diabetes mellitus (DM), hyperlipidemia, season of disease event, and smoking introduced as the predictor of death from AMI.[8-10]

Therefore, identifying prognostic factors of mortality in patients could have an important effect in decreasing deaths from the disease,[11-13] especially in countries such Iran that dispersed information has about the factors affecting the survival from AMI, particularly in early patients that this information is little or does not be existent. Therefore, the aims of this study are determent prognostic factors of 28-day survival rate after AMI in teen year's period in early (younger) and late (older) patients in Isfahan and Najafabad County, Iran.

Materials and Methods

This study is a hospital-based cohort study that implemented to determent predictive factors of 28-day survival rate from AMI in 10 year's period in Isfahan and Najafabad. The population entered in the study involved of all patients (census) that diagnosis with first AMI for the period of 1999-2009 in all infirmary and hospitals in Isfahan and Najafabad. All patients examined afterward admittance to hospitals, then patients by AMI related to unalike event locations allocated a specific code pursuant to International Classification of Diseases-version 10 (ICD-10) based on the final diagnosis of hospital cardiologist.

Trained nurses, who used special questioner for gathering evidence about the patients with an interview with patients or check the hospital records, gathered basic information related to demographic and clinical and laboratory characteristics of patients and then all documents collected in the Isfahan Cardiovascular Research Center.

By definition of MONICA and the World Health Organization (WHO) protocol, AMI as a 28-day repeated attack, and separate attacks not considered according to this definition, but in fact related the first AMI; however, following the primary night of the 27th day after the first attack, it is considered as a new attack. It should be mentioned patients who died along the first 28 days are considered as death due to first AMI.[14] Patients are divided into two categories: (1) Early patients group (male with age 50 years and below and female with 55 years and below) and (2) late patients group (male with 51 years and older and female with 56 years and older).

After gathering basic information of the patients, their survival or deaths during days after the AMI examined. For discharged patients, follow-up was first executed by telephone, but when he did not answer the phone 3 times, we went to the patient's homes. When previous trying to getting information about survival rate failed, using the National Organization for Civil Registration and Isfahan Cemetery, we tried to find out the cause of death if the patient had died; and precise date and place of the burial.

This study encompassed merely patients who were resident in Isfahan and Najafabad with primary AMI. Overall, 16259 patients (12046 male and 4213 female) with primary AMI, that inhabitants in Isfahan and Najafabad entered in the study, 997 patients (632 male and 365 female) omitted because their AMI kind undetermined according to the ICD-10. In addition, 152 patient (107 male and 45 female) exclude from the study because they were died along the 28 days after the first attack without mention any CVD due to accident, suicide, homicide, chronic obstructive pulmonary disease (COPD), types of cancer, cirrhosis, rheumatic heart disease, atherosclerosis, or vascular disease; and 438 patients (305 men and 133 female) omitted because outcome of disease was unknown. Furthermore, 145 patients (96 men and 49 female) excluded from the study because the unknown exact date of the occurrence or death from the disease and the 28-day duration after the attack could not calculate in these cases.[14] Moreover, 101 patients (56 men and 45 female) excluded because symptom or cardiac enzymes were not recorded. Therefore, 14426 patients, 10850 (75.2%) men and 3576 (24.8%) female, stayed in the study and 11.27% of patient censored. Detailed description of the material and methods utilized in this scheme provided in previous reports.[10,12,13,15-17]

Variables that considered in the study include age that divide in six subgroup (39 years and lower, 40-49, 50-59, 60-69, 70-79, and 80 and older); streptokinase use (receiving or not receiving); kind of AMI-based ICD-10 that include six categories: (I21.0) Acute transmural MI of anterior wall, (I21.1) acute transmural MI of inferior wall, (I21.2) acute transmural MI of other sites, (I21.3) acute transmural MI of unspecified site, (I21.4) acute subendocardial MI, (I21.9) AMI; unspecified, the

first center that patient referred for get medical care (non-specialized hospitals, specialized hospital, unknown, health network, or clinic); symptoms (typical, atypical, others, not clear); cardiac enzymes (atypical, typical, others, not clear); and hospital status (privative hospitals and academic hospitals).

In this study, continuous variables presented as mean ± standard deviation (SD). To compare average age in two genders, we use of the independent t-test. Time-dependent event (survival) rates were estimated by Kaplan–Meier method, and P values were determined by use of log-rank statistics. The assumption of proportional hazards assessed by the log-minus-log diagram. Furthermore, to calculate the hazard ratio (HR) of death in 28 days of onset AMI, multivariate cox regression was used for calculation adjusted HR and category that have the lowest mortality, considered as the reference group. In calculate of adjusted HR every variable adjusted for other variables. Statistical significance assumed in conditions that $P < 0.050$. All testified P values are two-sided. Statistical analyzes performed with using SPSS software (version 15, SPSS Inc., Chicago, IL, USA).

Results

In overall, 14426 patients with AMI throughout the study period admitted in Isfahan and Najafabad hospitals. From this patients, 10850 (75.2%) was male, and 3576 (24.8%) was female. Sex ratio (male/female) was 3.03. In this study, the mean age of the patients in the disease occurrence time was (14426 patients) 60.83 ± 12.22, in male (10850 patients) 58.96 ± 11.92, and in female (3576 patients) 66.50 ± 11.34 and that different between average age in two genders was statically significant ($P < 0.001$).

Short-term (28-day) survival rate in study period was 91.5% (93.0% in male and 86.8% in female) ($P < 0.001$). Short-term (28-day) survival rate in early patients was 96.6% and in late patients was 89.4% ($P < 0.001$), in early patients was 94.2 and 97.4% ($P = 0.556$) and in late patients 85.4 and 91.8% ($P < 0.001$), respectively, for female and male. Short-term (28-day) survival rates of the two groups (early and late patients) for each of the variables are presented in tables 1-3.

In patients with AMI, the highest probability of mortality was during the first 7 days after the disease occurrence. Therefore, that 80.0% of deaths in early patients occurs during the 1st week after the even (39.3% in the day of incidence disease and 40.7% in 1-7 days after the disease occurrence) and in late patients 79.3% (44.3% in the day of incidence disease and 35.0% in 1-7 days after the disease occurrence) (Table 1).

HR of decease in two genders, in female was higher than male. So, in early patients was HR = 1.97; confidence interval (CI) 95%: 1.32-2.92 and in late patients was HR = 1.35; CI 95%: 1.19-1.53. In two groups, HR of death increases with increasing age; so that, in the early patients in age group 40-44 years was HR = 1.46; CI 95%: 0.56-3.79, 45-49 years was HR = 2.71; CI 95%: 1.14-6.44 and in age group 50-55 was HR = 3.44; CI 95%: 1.49-7.92 compared by 39 years and lower age group that HR with 95% CI only for age group 40-44 years was not statistically significant.

Table 1. Patient's demographic and 28 days case fatality rate

Variables	Early patients			Late patients		
	Female < 55	Male < 50	Total	Female > 55	Male > 50	Total
Total [n (%)]	586 (14.1)	3571 (85.9)	4157 (100)	2990 (29.1)	7279 (70.9)	10269 (100)
Sex ratio (male/female)	6.09		-	2.43		-
Age (year) (mean ± SD)	48.5 ± 5.4	47.2 ± 6.2	47.38 ± 6.11	70.02 ± 8.5	64.73 ± 9.58	66.27 ± 9.59
Survival status						
Dead	34	106	140	437	650	1087
Alive	552	3465	4017	2553	6629	9182
CFR (%)	5.8	2.96	3.4	14.6	8.9	10.6
Survival rate (%)	94.2	97.4	96.6	85.4	91.1	89.4
Means for survival time (day)	26.06	27.31	27.21	24.47	25.93	25.5
CI 95%	26.12-27.6	27.18-27.45	27.08-27.34	24.15-24.78	25.77-25.65	25.36-25.65
Day of death after hospitalization and survival rate [n (%)]						
Day 0	11 (32.4)	44 (41.9)	55 (39.6)	214 (49.0)	268 (41.2)	482 (44.3)
Days 1-7	20 (58.8)	37 (35.2)	57 (41.0)	146 (33.4)	234 (36.0)	380 (35.0)
Days 8-14	1 (2.9)	13 (12.4)	14 (10.1)	48 (11.0)	78 (12.0)	126 (11.6)
Days 15-21	2 (5.9)	9 (8.6)	11 (7.5)	23 (5.3)	49 (7.5)	72 (6.6)
Days 22-28	0 (0)	3 (1.9)	3 (1.8)	6 (1.4)	21 (3.2)	27 (2.5)

SD: Standard deviation; CI: Confidence interval; CFR: Case fatality rate

In late patients, in age group 60-69 years was HR = 2.03; CI 95%: 1.64-2.5, 70-79 years was HR = 2.88; CI 95%: 2.35-3.53, and in 80 years and older was HR = 3.85; CI 95%: 3.06-4.84 compared by 50-59 years age group.

In both groups, HR of death in patients with acute sub-endocardial MI was lowest and acute transmural MI of unspecified site was highest; so, in early patients was HR = 22.42; CI 95%: 4.24-118.37 and in late patients was HR = 10.52; CI 95%: 6.41-17.28 (Tables 2 and 3).

Receiving streptokinase therapy in predicting survival in early and late patients is not a determining factor so that the HR of occurrence of death in patients who have not received the drug, respectively, in early and late patients were HR = 1.01; CI 95%: 0.71-1.46 and HR = 1.09; CI 95%: 0.95-1.24 that is not statistically significant. HR for other variables presented in tables 2 and 3.

Discussion

In this study, 28-day survival rate was 91.5%, in early patients 96.6% and in late patients 89.4%, and the highest probability of mortality (80.0%) was during the first 7 days after the disease occurrence. HR of demise in female was higher than male and increases with increasing age; acute sub-endocardial MI has lowest and acute transmural MI of the unspecified site have highest HR for mortality in first 28 days of disease start.

From 14426 patients with AMI that entered in the study, 10850 (75.2%) were male and sex ratio (male/female) was 3.03, parallel results in this context found in other studies.[18,19] The average age of patients in disease occurrence time in female was 7/5 years upper than male and these results also been observed in other studies.[9,20,21] Short-term (28-day) survival rate in the entire patients in the study was 91.5% - for males 93.0% and females 86.8%; and in early patients were 96.6% and in late patients were 89.4%. In fact, the risk ratio of death in 28 days after the onset of disease in late patients is 3.2 times higher than early patients. In a study that conducted in Yazd, Iran, by Soltani et al.[22] on 815 patients with AMI, patients divided into two age groups: ≤ 45 years (young) and > 45 years (old). In two genders, young patients had less in-hospital mortality than old patients, so in male was 1.2 vs. 9.1% (P = 0.005) and in female was 10.0 vs. 19.9% (P = 0.300). Similar results observed in other studies.[7,12] Therefore, age has an important role in determining survival rate in the patients with AMI. So, in both group (early and late patients) with increasing age-adjusted HR of mortality increased compared to baseline group, in a study that conducted by Stevenson et al.,[23] age of patients was important determent factor in 6-month survival rate in patients with AMI. However, this result that the risk of death increased with rising age has been observed in other studies.[24,25]

HR of death in 28 days after the onset of disease in female are 2.23 and 1.78 time higher than male, respectively, for early and late disease type. Perhaps, higher death in the first 28 days after the happening of AMI in female, resulting from the higher age, higher prevalence of diabetes, higher ratio of female with poor prognosis who survived to hospital, and also, because aging is reduced pain perception and response to pain.[13,20,26-32] Nevertheless, in this study due to lack of availability of data on the above variables, we cannot analysis effect of this variable on survival based on gender.

According to ICD-10, MI divided into six groups. In this study, for determent the HR of mortality from AMI considered a group of patients who had the higher survival rate as a base group (acute subendocardial MI), HR of other groups determined. In two groups (early and late patients), acute transmural MI of the unspecified site has highest HR compare basic group and after, AMI, unspecified (Tables 1 and 2). Furthermore, in both groups (early and late patients), acute transmural MI of the anterior wall has higher HR compare acute transmural MI of inferior wall. Thus, in this study, the anatomic location of MI was a significant predictor of survival in early and late patients. In a number of studies, the prognosis of MI-based location was different so that the anterior surface infarction has a worse prognosis compared to inferior level.[9,24,33]

However, according to the method of data analysis in this study, we adjusted difference in various types of MI, and after calculated adjusted HR. Therefore, difference between adjusted HR for mortality from AMI according to ICD-10 cannot cause by a variety of factors such as: gender, age, kind of hospital, receive or did not receive streptokinase, and also difference in symptoms (typical, atypical, others, and miss), cardiac enzymes (atypical, typical, other and not clear), and EKG (definite, probable, ischemic, other, impossible coding, miss).

In England, overall 82.0% of hospitals used streptokinase for treatment of patients that for the first time suffering from AMI and have medical conditions of receiving this drug.[34]

Table 2. Predictive factors in 28-day survival rate in early patients with acute myocardial infarction in Isfahan

Variables	The number of patients alive at 28-day after the first MI (%)	The number of deaths occurred in the first 28-day after MI	Survival rates at 28-day after the occurrence of the disease (%)	HR for death in the first 28-day after a first MI with 95% CI (unadjusted)	HR for death in the first 28-day after a first MI with 95% CI (adjusted)*
Sex					
Male	3571	106	97.0	-	-
Female	586	34	94.2	1.98 (1.34-2.91)	1.97 (1.32-2.92)
Age group (year)					
39 year and lower	440	6	98.6	-	-
40-44	739	15	98.0	1.49 (0.57-3.84)	1.46 (0.56-3.79)
45-49	1124	38	96.6	2.49 (1.05-3.84)	2.71 (1.14-6.44)
50-55	1854	81	95.6	3.24 (1.41-7.42)	3.43 (1.49-7.92)
Streptokinase					
Receiving	2509	77	96.9	-	-
Not receiving	1648	63	96.2	1.24 (0.89-1.74)	1.01 (0.71-1.46)
ICD-10					
Acute subendocardial MI	331	2	99.4	-	-
Acute transmural MI of other sites	103	5	95.1	8.18 (1.58-42.20)	8.70 (1.66-45.63)
Acute transmural MI of inferior wall	1334	25	98.1	3.12 (0.73-13.17)	3.38 (0.77-14.75)
Acute transmural MI of anterior wall	1420	39	97.3	4.59 (1.10-19.00)	4.92 (1.15-21.06)
AMI, unspecified	932	64	93.1	11.70 (2.86-47.80)	11.62 (2.79-48.33)
Acute transmural MI of unspecified site	37	5	86.5	24.18 (4.69-124.66)	22.42 (4.24-118.37)
Symptoms					
Typical	3542	112	96.8	-	-
Atypical	477	17	96.4	1.12 (0.67-1.88)	0.99 (0.59-1.67)
Others	128	10	92.2	2.52 (1.32-4.81)	2.11 (1.08-4.10)
Miss	10	1	90.0	3.35 (0.46-24.03)	0.54 (0.06-4.28)
Cardiac enzymes					
Others	384	9	97.7	-	-
Typical	3189	93	97.1	1.24 (0.62-2.47)	1.40 (0.69-2.80)
Atypical	478	20	95.8	1.80 (0.82-3.96)	1.93 (0.87-4.26)
Not clear	106	18	83.0	7.96 (3.57-17.73)	7.27 (3.22-16.4)
EKG					
Ischemic	675	16	97.6	-	-
Probable	80	7	91.2	3.79 (1.55-9.21)	3.37 (1.36-8.36)
Other	39	1	97.4	1.07 (0.14-8.07)	1.03 (0.13-7.90)
Definite	3268	102	96.9	1.32 (0.78-2.23)	1.60 (0.91-2.81)
Impossible coding	50	10	80.0	9.59 (4.35-21.13)	6.73 (2.96-15.30)
Miss	45	4	91.1	3.90 (1.30-11.67)	5.57 (1.81-17.10)

*Every variable adjusted for other variables; ICD: International Classification of Disease; AMI: Acute myocardial infarction; EKG: Electrokardiogram; HR: Hazard ratio; CI: Confidence interval

Table 3. Predictive factors in 28-day survival rate in late patients with acute myocardial infarction in Isfahan

Variables	The number of patients alive at 28-day after the first MI (%)	The number of deaths occurred in the first 28-day after MI	Survival rates at 28-day after the occurrence of the disease (%)	HR for death in the first 28-day after a first MI with 95% CI (unadjusted)	HR for death in the first 28-day after a first MI with 95% CI (adjusted)*
Sex					
Male	7279	650	91.1	-	-
Female	2990	437	85.4	1.68 (1.49-1.90)	1.35 (1.19-1.53)
Age group (year)					
50-59	2893	126	95.6	-	-
60-69	3381	311	90.8	2.16 (1.76-2.66)	2.03 (1.64-2.50)
70-79	3038	447	85.3	3.54 (2.91-4.32)	2.88 (2.35-3.53)
80 and higher	957	203	78.8	5.26 (4.21-6.58)	3.85 (3.06-4.84)
Streptokinase					
Receiving	5118	497	90.3	-	-
Not receiving	5151	590	88.5	1.18 (1.05-1.33)	1.09 (0.95-1.24)
ICD-10					
Acute subendocardial MI	979	26	97.3	-	-
Acute transmural MI of other sites	263	14	94.7	2.04 (1.06-3.92)	1.67 (0.87-3.20)
Acute transmural MI of inferior wall	2839	175	93.8	2.36 (1.56-3.56)	1.73 (1.13-2.64)
Acute transmural MI of anterior wall	3391	317	90.7	3.63 (2.43-5.41)	2.81 (1.86-4.23)
AMI, unspecified	2674	513	80.8	7.86 (5.30-11.65)	5.40 (3.62-5.07)
Acute transmural MI of unspecified site	123	42	65.9	15.24 (9.34-24.86)	10.52 (6.41-17.28)
Symptoms					
Typical	8461	829	90.2	-	-
Atypical	1202	124	89.7	1.05 (0.87-1.27)	0.96 (0.79-1.16)
Others	555	123	77.8	2.41 (1.99-2.91)	1.52 (1.24-1.85)
Miss	51	11	78.4	2.36 (1.30-4.28)	1.61 (0.88-2.93)
Cardiac enzymes					
Atypical	1344	104	92.3	-	-
Typical	7602	726	90.4	1.23 (1.08-1.52)	1.29 (1.05-1.59)
Other	896	77	91.4	1.12 (0.83-1.50)	1.19 (0.88-1.60)
Not clear	427	180	57.8	7.03 (5.52-8.95)	5.17 (4.04-6.63)
EKG					
Other	49	2	95.9	-	-
Probable	187	26	86.1	3.57 (0.84-15.05)	2.27 (0.53-9.60)
Ischemic	1721	110	93.6	1.56 (0.38-6.33)	1.06 (0.26-4.32)
Definite	7954	859	89.2	2.69 (0.67-10.79)	2.07 (0.51-8.36)
Impossible coding	208	50	76.0	6.46 (1.57-26.58)	2.64 (0.64-10.89)
Miss	150	40	73.3	7.58 (1.83-31.30)	3.08 (0.74-12.83)

*Every variable adjusted for other variables; ICD: International Classification of Disease; AMI: Acute myocardial infarction; EKG: Electrokardiogram; HR: Hazard ratio; CI: Confidence interval

In this study, although short-term (28-day) survival rate in early and late patients that receive streptokinase are higher from not receiving group but adjusted HR for death in not receiving group and are not significant. So that, patients who not received treatment, compared to the group receiving the drug, respectively, in early and late patients have adjusted HR = 1.01; CI 95%: 0.71-1.46 and HR = 1.09; CI 95%: 0.95-1.24. Thus, it can be seen that in both groups, receive and not receiving streptokinase are not significant determinate of short-term (28-day) survival in AMI patients. This article extracted from a research project with code 84130 in 2011 in Isfahan Cardiovascular Research Institute.

Limitation

A trouble of this study is a shortage of complete, community-based case ascertainment, which contains through protocols for discovery community fatal and non-fatal MI patients who not admitted to the hospitals. Most important is the shortage of information about out of hospital fatal cases such as MI cases that receive care managed at the house or in health centers. This figure is unimportant because in Iran care system MI events consider as emergency condition and all hospitals must admit such patients irrespective of their insurance position. In the study in Danish MONICA population, this patient contains < 1% of total MI cases. Therefore, the missing these patients would not lead to severe changes in case fatality rate (CFR).

Conclusion

The short-term survival rate in early patients is higher than late. In addition, CFR from AMI in female is higher than male. The highest probability of mortality (80.0% in early and 79.3% in late patients) was during the first 7 days after the disease occurrence. In both groups (early and late patients): sex, age, anatomic location of MI-based ICD-10, cardiac enzymes, and clinical symptoms are significant prognostic factors of survival in patients following AMI.

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Conflict of Interests

Authors have no conflict of interests.

References

1. Lopez A, Mathers CD, Ezzati M, Jamison D, Murray C. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. The Lancet 2006; 367(9524): 1747-57.
2. Naghavi M, Jafari N. Death statistics in Iran. Tehran, Iran: Arvij Publications; 2007. [In Persian].
3. Hatmi ZN, Tahvildari S, Gafarzadeh Motlag A, Sabouri Kashani A. Prevalence of coronary artery disease risk factors in Iran: a population based survey. BMC Cardiovasc Disord 2007; 7: 32.
4. Kazemi T, Rezvani MR, Sharifzadeh GR, Sadri A, Mashraghi Moghaddam HR, Hosseinzadeh Maleki M. The prevalence of traditional cardiovascular risk factors in low socioeconomic use individuals in Birjand 2008 (East IRAN). Journal of Cardio-Thoracic Medicine 2015; 3(1): 263-9.
5. Ahmadi A, Mobasheri M, Soori H. Prevalence of major coronary heart disease risk factors in Iran. International Journal of Epidemiologic Research 2014; 1(1): 3-8.
6. Morillas PJ, Cabadés A, Bertomeu V, Echanove I, Colomina F, Cebrian J, et al. Acute myocardial infarction in patients under 45 years. Rev Esp Cardiol 2002; 55(11): 1124-31.
7. Doughty M, Mehta R, Bruckman D, Das S, Karavite D, Tsai T, et al. Acute myocardial infarction in the young--The University of Michigan experience. Am Heart J 2002; 143(1): 56-62.
8. Davies CA, Leyland AH. Trends and inequalities in short-term acute myocardial infarction case fatality in Scotland, 1988-2004. Popul Health Metr 2010; 8: 33.
9. Kubota I, Ito H, Yokoyama K, Yasumura S, Tomoike H. Early mortality after acute myocardial infarction: observational study in Yamagata, 1993-1995. Jpn Circ J 1998; 62(6): 414-8.
10. Mohammadian-Hafshejani A, Sarrafzadegan N, Hosseini S, Baradaran HR, Roohafza H, Sadeghi M, et al. Seasonal pattern in admissions and mortality from acute myocardial infarction in elderly patients in Isfahan, Iran. ARYA Atheroscler 2014; 10(1): 46-54.
11. White HD, Chew DP. Acute myocardial infarction. Lancet 2008; 372(9638): 570-84.
12. Mohammadian Hafshejani A, Baradaran H, Sarrafzadegan N, Asadi Lari M, Ramezani A, Hosseini S. Predicting factors of short-term survival in patients with acute myocardial infarction in Isfahan using a cox regression model. Iran J Epidemiol 2012; 8(2): 39-47. [In Persian].
13. Mohammadian Hafshejani A, Baradaran Attar Moghaddam HR, Sarrafzadegan N, Allah Bakhsi Hafshejani F, Hosseini S, AsadiLari M, et al.

Evaluation of short-term survival of patients with acute myocardial infarction and the differences between the sexes in Isfahan and Najaf Abad between (1378–1387). Razi j Med Sci 2012; 19(95): 25-34. [In Persian].
14. Mähönen M, Tolonen H, Kuulasmaa K. MONICA coronary event registration data book 1980-1995 [Online]. [cited 2000 Oct]; Available from: URL: http://www.thl.fi/publications/monica/coredb/coredb.htm
15. Mohammadian Hafshejani A, Oveisgharan S, Sarrafzadegan N. The most frequent and fatal types of acute myocardial infarction in Isfahan, Iran. J Isfahan Med Sch 2013; 30(216): 2140-3. [In Persian].
16. Mohammadian Hafshejani A, Sarrafzadegan N, Baradaran Attar Moghaddam HR, Hosseini S, Hosseini S. Gender difference in determinants of short-term survival of patients with acute myocardial infarction in Isfahan, Iran. J Isfahan Med Sch 2012; 30(209): 1611-21. [In Persian].
17. Mohammadian M, Hosseini S, Sadeghi M, Sarrafzadegan N, Salehiniya H, Roohafza H, et al. Trends of 28 days case fatality rate after first acute myocardial infarction in Isfahan, Iran, from 2000 to 2009. ARYA Atheroscler 2015; 11(4): 233-43.
18. Pop C, Pop L, Dicu D. Epidemiology of acute myocardial infarction in Romanian county hospitals: a population-based study in the Baia Mare district. Rom J Intern Med 2004; 42(3): 607-23.
19. Vrbova L, Crighton EJ, Mamdani M, Moineddin R, Upshur RE. Temporal analysis of acute myocardial infarction in Ontario, Canada. Can J Cardiol 2005; 21(10): 841-5.
20. MacIntyre K, Stewart S, Capewell S, Chalmers JW, Pell JP, Boyd J, et al. Gender and survival: a population-based study of 201,114 men and women following a first acute myocardial infarction. J Am Coll Cardiol 2001; 38(3): 729-35.
21. Weaver WD, White HD, Wilcox RG, Aylward PE, Morris D, Guerci A, et al. Comparisons of characteristics and outcomes among women and men with acute myocardial infarction treated with thrombolytic therapy. GUSTO-I investigators. JAMA 1996; 275(10): 777-82.
22. Soltani MH, Sadr M, Rafee M, Imami M, Motafakker M. Acute myocardial Infarction in the Young. Iran Heart J 2005; 6(1-2): 52-4.
23. Stevenson R, Ranjadayalan K, Wilkinson P, Roberts R, Timmis AD. Short and long term prognosis of acute myocardial infarction since introduction of thrombolysis. BMJ 1993; 307(6900): 349-53.
24. Lee KL, Woodlief LH, Topol EJ, Weaver D, Betriu A, Col J, et al. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. GUSTO-I Investigators. Circulation 1995; 91(6): 1659-68.
25. Goldberg RJ, McCormick D, Gurwitz JH, Yarzebski J, Lessard D, Gore JM. Age-related trends in short- and long-term survival after acute myocardial infarction: a 20-year population-based perspective (1975-1995). Am J Cardiol 1998; 82(11): 1311-7.
26. Gottlieb S, Harpaz D, Shotan A, Boyko V, Leor J, Cohen M, et al. Sex differences in management and outcome after acute myocardial infarction in the 1990s: A prospective observational community-based study. Israeli thrombolytic survey group. Circulation 2000; 102(20): 2484-90.
27. Herman B, Greiser E, Pohlabeln H. A sex difference in short-term survival after initial acute myocardial infarction. The MONICA-Bremen acute myocardial infarction registers, 1985-1990. Eur Heart J 1997; 18(6): 963-70.
28. Kudenchuk PJ, Maynard C, Martin JS, Wirkus M, Weaver WD. Comparison of presentation, treatment, and outcome of acute myocardial infarction in men versus women (the Myocardial Infarction Triage and Intervention Registry). Am J Cardiol 1996; 78(1): 9-14.
29. Chandra NC, Ziegelstein RC, Rogers WJ, Tiefenbrunn AJ, Gore JM, French WJ, et al. Observations of the treatment of women in the United States with myocardial infarction: a report from the National Registry of Myocardial Infarction-I. Arch Intern Med 1998; 158(9): 981-8.
30. Woodfield SL, Lundergan CF, Reiner JS, Thompson MA, Rohrbeck SC, Deychak Y, et al. Gender and acute myocardial infarction: Is there a different response to thrombolysis? J Am Coll Cardiol 1997; 29(1): 35-42.
31. Tunstall-Pedoe H, Morrison C, Woodward M, Fitzpatrick B, Watt G. Sex differences in myocardial infarction and coronary deaths in the Scottish MONICA population of Glasgow 1985 to 1991. Presentation, diagnosis, treatment, and 28-day case fatality of 3991 events in men and 1551 events in women. Circulation 1996; 93(11): 1981-92.
32. Marrugat J, Sala J, Masia R, Pavesi M, Sanz G, Valle V, et al. Mortality differences between men and women following first myocardial infarction. RESCATE Investigators. Recursos Empleados en el Sindrome Coronario Agudo y Tiempo de Espera. JAMA 1998; 280(16): 1405-9.
33. Haim M, Hod H, Reisin L, Kornowski R, Reicher-Reiss H, Goldbourt U, et al. Comparison of short- and long-term prognosis in patients with anterior wall versus inferior or lateral wall non-Q-wave acute myocardial infarction.

Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT) Study Group. Am J Cardiol 1997; 79(6): 717-21.

34. Boland A, Dundar Y, Bagust A, Haycox A, Hill R, Mota RM, et al. Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation. Health Technology Assessment 2003; 7(15): 1-136.

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Association of I405V polymorphism of colesteryl ester transfer protein gene with coronary artery disease in men with type 2 diabetes

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Original Article

Abstract

BACKGROUND: Colesteryl ester transfer protein (CETP) plays a key role in the metabolism of lipoproteins; therefore, polymorphisms of its gene can affect susceptibility to coronary artery disease (CAD) in diabetes mellitus. The aim of the present study was to investigate association between I405V polymorphism of CETP gene and risk of CAD in patients with type 2 diabetes mellitus.

METHODS: The current case-control study was conducted on 143 patients with type 2 diabetes and angiographically diagnosed CAD and 150 patients with type 2 diabetes and without CAD. Genotyping was performed through polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The presence of CAD was defined as higher than 50% reduction in coronary artery diameter.

RESULTS: The genotype frequencies of I405V polymorphism were II (27.3% vs. 23.2%), IV (61.5% vs. 67.5%), and VV (11.2% vs. 9.3%) in diabetic with CAD compared to diabetic without CAD ($\chi^2 = 1.164$) ($P = 0.55$). The I and V alleles were found at frequencies of 63.6% and 61.6% in the diabetic with CAD group and 36.4% and 38.4% in the diabetic without CAD group ($\chi^2 = 0.263$) ($P = 0.60$). No significant difference was observed between two groups in terms of genotype and allele frequency. Moreover, no significant association was observed between II, IV, and VV genotypes and lipid profiles in both groups. However, a significant difference was observed between genotype distributions of I405V polymorphism in men according to the severity of CAD.

CONCLUSION: It is speculated that I405V polymorphism may be associated with the severity of coronary artery stenosis only in men with type 2 diabetes mellitus.

Keywords: Cholesterol Ester Transfer Protein; Polymorphism; Type 2 Diabetes Mellitus; Coronary Artery Disease

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Introduction

Cardiovascular disease (CVD) and atherosclerosis are two common causes of mortality and morbidity and their related complications in patients with type 2 diabetes mellitus. Hyperlipoproteinemia is the main cause of atherosclerosis and its related conditions such as peripheral vascular disease and coronary heart disease (CHD).[1-3] Several studies have been determined an inverse relationship between plasma high-density lipoprotein cholesterol (HDL-C) and CVDs risk factors[4-6] and recommended that high plasma HDL has an anti-atherosclerotic role. Cholesteryl ester transfer protein (CETP), also known plasma lipid transfer protein, is a 74-KD plasma glycoprotein[7,8] consisting of 476 amino acids and its circulating form mainly bound to the HDL. It is a key enzyme in the metabolism of HDL and has a pivotal role in the redistribution of cholesterol ester and triglyceride (TG) between high dense lipoproteins

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such as HDL and low or very low-density lipoproteins including (LDL and VLDL). The role of CETP in the inverse cholesterol transport pathway is important for the elimination of accumulated cholesterol from vessel into the liver for its final catabolism.[9-11] It is still remains controversial whether circulating CETP acts in a pro- or anti-atherogenic manner in human.[12,13]

The CETP gene, consisting of a 25 Kb genomic DNA, located on chromosome 16 that is comprised of 16 exons and 15 introns (Gene ID 1071).[12] The gene has been reported extremely polymorphic and consisting of several single nucleotide polymorphisms (SNPs) in both its coding and non-coding regions which are responsible for changes in its transcription and sequence.[14] The CETP I405V polymorphism is a very common SNP (rs5882) located in exon 14 and is caused by A to G substitution at this locus. This mutation resulting in changes in the primary structure of CETP which identified by an isoleucine to valine substitution at codon 405 (I405V).[15] V allele is the less common allele (405V) and exists at a frequency of > 25% in the most populations.[16] A report indicated that VV genotype of this polymorphism has been associated with higher HDL-C levels and lower plasma CETP concentration.[17] In addition, V allele frequency is a very different in various ethnic groups.[10] In this study, we assessed the association between I405V variation in the CETP gene and risk of coronary artery disease (CAD) in Iranian subjects with type 2 diabetes mellitus.

Materials and Methods

The current case-control study consisting of 293 patients with type 2 diabetes mellitus (133 males, 161 females, mean age 51.92 ± 6.67), in which coronary angiographally were performed due to chest pain at the Department of Cardiology, Ahwaz Imam Khomeini Hospital, Iran. Information of data collection, including inclusion and exclusion criteria, the severity of CAD, processing, and relevant corresponding clinical characteristics, is published elsewhere.[18] Patients with infectious disease, renal disease, pregnancy, diagnosed myocardial infarction (MI) in recent 3 months, and current smoking were excluded from the study population. Diabetes was defined based on American Diabetes Association (ADA) criteria.[19] Furthermore, the CAD was determined as a reduction in luminal diameter of a major coronary artery branch by > 50%. According to the angiography results, diabetic patients were categorized into two groups as follow: 143 diabetic with CAD and 150 diabetic without CAD. Diabetic patients with CAD were classified based on the number of significantly stenosis in the coronary artery vessels into angiographically one-vessel (n = 39), two-vessel (n = 42), and three-vessel (n = 62) sub-groups. From all subjects was obtained written informed consent for participation in this study.

Venous blood was drawn from subjects who were, at least, 10-12 hours of fasting. A value of 2 ml of the sample was transferred into tubes containing ethylenediamine tetraacetic acid as an anticoagulant for DNA extraction and the remaining sample was collected in glass tubes. Full-fasted lipid profile containing of TGs, total cholesterol (TC), HDL-C, LDL-C, and plasma glucose concentration was measured using enzymatic method by Vital Scientific Spankeren autoanalyzer. Demographic parameters including systolic and diastolic blood pressure, height, weight and body mass index (BMI) were measured by standard methods and preliminary results previously presented elsewhere.[18]

Polymerase chain reaction (PCR) amplification and genotyping for SNP I405V

Genomic DNA was isolated from nucleated blood cells by salting out method and was frozen at -20 °C, as previously described elsewhere.[18] Genotyping of I405V polymorphism was characterized using PCR and restriction fragment length polymorphism (PCR-RFLP) method. Important advantages of the PCR-RFLP technique are that no expensive, no prior sequence information, and no requirement of advanced instruments, is required. Moreover, the primer design for PCR-RFLP analyses generally is easy and can be accomplished using public available programs. A 308 bp fragment in exon 14 was amplified using of the following oligonucleotide primer set: forward, 5′-GCA GAA CAG TAG TGG CCA AGC AGC G-3′, and reverse, 5′-GCG GTG ATC ATT GAC TGC AGG AAG CTC TGT A -3′. Amplification was done in a total volume of 25 µl comprising 12.5 µl available premix (AccuPower PCR Premix; Bioneer, Daejeon, South Korea) consisting of deoxynucleotide (dNTP), Taq DNA polymerase, $MgCl_2$, × 10 buffer, 2.0 µl (10 pmol/µl) of each primer, 2.0 µl (50 ng/µl) templates DNA, and 6.5 µl sterile nuclease-free water. The PCR state was as follows: primary denaturation at 95 °C for 5 minutes, and followed by 30 cycles of denaturation at 95 °C for 30 seconds, annealing at 66 °C for 30 seconds,

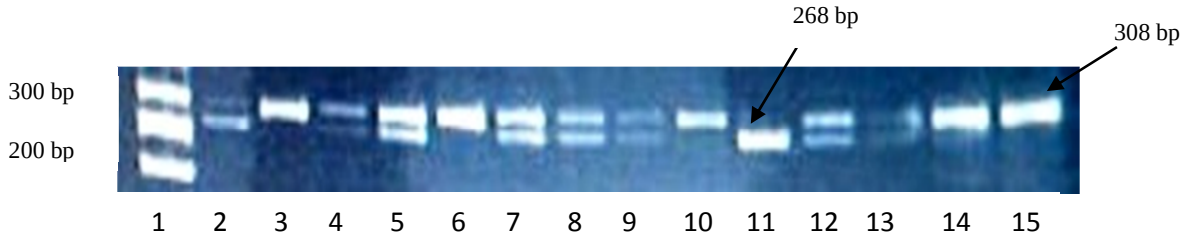

Figure 1. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) products of I405V polymorphism separated on 10% polyacrylamide gel
Lane 1 shows DNA size marker 50 bp; Lanes 2, 4,5,7,8,9,12 and 13 show IV genotype; Lanes 3, 6, 10, 14, and 15 show II genotype; Lane 11 shows VV genotype

extension at 72 °C for 30 seconds, and a final extension at 72 °C for 5 minutes. The PCR products were treated with RsaI restriction enzyme at 37 °C overnight and then fragments were electrophoresed on 10% native polyacrylamide gel that giving 40 and 268 bp length fragments in the existence of less common V allele (Figure 1).

All statistical analysis was performed using the statistical software package SPSS (version 20, SPSS Inc., Chicago, IL, USA). Normal distribution of the data was tested by the Kolmogorov-Smirnov test, a P value more than 0.050 considered as the calculated variable distribution is not statistically significant difference from the expected normal distribution. The quantitative data are reported as mean ± standard deviation (SD) and qualitative data are introduced as number and percentage. Genotypes and alleles frequency were compared between groups using the Chi-square (χ^2) analysis. Hardy-Weinberg equilibrium was calculated for the expected genotype distribution. Comparison of mean serum lipid profiles among different genotypes was performed by one-way ANOVA test. The association of various genotypes with the risk of CAD were estimated by logistic regression using odds ratio (OR) and 95% confidence intervals (95% CI). The comparison of V allele frequency between Iranian population and other four major populations was tested using weighted χ^2 test. In all statistical analyses, value of $P < 0.050$ was considered to be significant.

Results

Demographic and biochemical characteristics of the studied subjects

Demographic indices consisting of BMI, systolic blood pressure (SBP) and diastolic blood pressure (DBP), as well as a full-fasted lipid profile containing TG, TC, HDL-C, LDL-C were measured and results presented elsewhere.[18] briefly, diabetic patients with CAD were significantly older than those without CAD ($P < 0.001$). Furthermore, the mean value of BMI and blood glucose in patients with CAD was significantly higher than those in patients without CAD ($P = 0.010$). According to the lipid profile, the mean TC and TG in patients with CAD were significantly higher than those in patients without CAD ($P = 0.030$). While the mean HDL-C in patients without CAD was higher than that in patients with CAD ($P < 0.001$).

Association of SNP I405V of CETP gene with the risk of CAD

The CETP I405V genotype and allele frequencies in diabetic with CAD and without CAD groups are shown in table 1. The genotype frequencies were not consistent with Hardy-Weinberg equilibrium for I405V polymorphism. Between group with and without CAD, the frequency of genotype and allele of SNP I405V were not significantly different ($P = 0.550$ and $P = 0.600$, respectively) (Table 1). Moreover, no significant difference was observed in the distribution of genotypes between two groups based on gender (results not shown here). The frequency V allele of CETP gene in the current studied population was compared with the other four major populations (Table 2). Our result indicated that there was a significant difference according to the V allele frequency between Iranian studied population and Tamilians ($P = 0.023$), Asians ($P < 0.001$), and African Americans ($P = 0.001$). However, similar difference was not found between Iranians and Caucasians (Table 2).

Finally, we analyzed the association of this polymorphism with the risk of CAD, which was not found a significant association between various genotypes and increased risk of CAD in the studied population. The OR related to the IV and VV genotypes for the risk of CAD were (OR = 1.292; 95% CI = 0.754-2.21, P = 0.350 and OR = 0.975; 95% CI = 0.417-2.28, P = 0.950), respectively.

Table 1. Distribution of I405V genotype and allele frequency and association of genotype with the risk of coronary artery disease (CAD) in studied population

Variables	Diabetic with CAD [n (%)]	Diabetic without CAD [n (%)]	χ^2	P	OR (95% CI)	P
Genotypes						
II	39 (27.3)	35 (23.2)	1.077	0.580	1.00	
IV	88 (61.5)	101 (67.4)			1.292 (0.75-2.21)	0.350
VV	16 (11.2)	14 (9.3)			0.975 (0.41-2.28)	0.950
Alleles						
I	181 (63.6)	186 (61.6)			1.00	
V	104 (36.4)	116 (38.4)	0.263	0.600	1.022 (0.78-1.52)	0.830

The χ^2 test was used to determine the significant differences were observed between two groups. Logistic regression analysis was used to estimate the OR for CAD in studied population.
CAD: Coronary artery disease; OR: Odds ratio; CI: Confidence interval

Regarding to the frequency of SNP I405V genotype based on the number of coronary artery stenosis, a significant difference was observed in diabetic with CAD (P < 0.010) (Table 3). Similarly, concerning to the frequency of SNP I405V genotype based on the number of coronary artery stenosis, a significant difference was observed only in men subjects with CAD (P = 0.020) (Table 3).

Association of I405V genotypes with measured characteristics

Association of I405V genotype with baseline characteristics in diabetic with CAD and without CAD is summarized in table 4.

No significant relationship was observed between II, IV and VV genotypes of I405V polymorphism and anthropometric indices, clinical status, and biochemical parameters in the patients with and without CAD.

Discussion

In the several population-based study, results demonstrated that CETP has both pro- and anti-atherogenic effects.[20,21] Variations in the CETP gene seem to cause changes in the HDL-C level. Results from the Rotterdam study indicated that VV genotype of I405V polymorphism was correlated with low CETP level, increased HDL levels and decreased risk of CAD.[22] In the current study, the relationship between I405V polymorphism of CETP gene and demographic indices, lipid profiles, and CAD in subjects with type 2 diabetes was investigated. We failed to show a statistically significant relationship between I405V polymorphism of CETP, lipid profiles and CAD. The frequency of 405V allele of CETP gene in our population was 0.37 which is higher than that reported from Caucasians (0.318) and lower than that reported from Asians, Tamilians, and African Americans.[10,23] Several studies reported that subjects whom carrying of 405V allele had increased plasma levels of HDL-C,[24,25] but our study, there were no variations in the plasma levels of HDL-C according to the different I405V genotypes.

The current study shows there is no significant difference in genotype distribution and allele frequency of I405V polymorphism between two studied groups. Moreover, according to the gender-based analysis, similar results were obtained. BMI, SBP and DBP in diabetic with CAD were significantly higher than those in diabetic without CAD. CETP plays a key role in reverse cholesterol transport and modulating of HDL-C concentrations and may therefore alter the susceptibility to CAD.

Kolovou et al.[26] reported TaqIB polymorphism is important in screening individuals who are at higher risk for CAD, also there was no any association between I405V polymorphism and CAD. In a study conducted by Dogru-Abbasoglu

Table 2. The comparison of V allele frequency of I405V polymorphism in Iranian population with other major populations

Allele	Current study (n = 293)	Tamilians[26] (n = 171)	Caucasians[25] (n = 2188)	Asians[27] (n = 148)	African Americans[27] (n = 30)
V	0.374	0.530	0.318	0.617	0.611
P*	-	0.023	0.457	< 0.001	0.001

*P < 0.050 is significant when Iranian population compared to the other population.
V: V allele of I405V polymorphism

Table 3. Genotypes distribution of I405V polymorphism in diabetic with CAD according to the severity of vessel stenosis

Genotypes	Number of vessels involved				P
	1 VD [n (%)]	2 VD [n (%)]	3 VD [n (%)]	Total [n (%)]	
Male					
II	5 (26.3)	6 (27.3)	7 (21.2)	18 (24.3)	0.020
IV	14 (73.7)	16 (72.7)	18 (54.6)	48 (64.9)	
VV	0 (0.0)	0 (0.0)	8 (24.2)	8 (10.8)	
Total	19	22	33	74	
Female					
II	7 (35.0)	7 (35.0)	7 (24.1)	21 (30.4)	0.250
IV	13 (65.0)	11 (55.0)	16 (55.2)	40 (58.0)	
VV	0 (0)	2 (10.0)	6 (20.7)	8 (11.6)	
Total	20	20	29	69	
Total					
II	12 (30.8)	13 (30.9)	14 (22.6)	39 (27.3)	0.010
IV	27 (69.2)	27 (64.3)	34 (54.8)	88 (61.5)	
VV	0 (0)	2 (4.8)	14 (22.6)	16 (11.2)	

The χ^2 test was used to determine the significant difference were observed in each gender.
VD: Vessel stenosis more than 50% reported by angiography; 1VD: One vessel stenosis more than 50%; 2VD: Two vessel stenosis more than 50%; 3VD: Three vessel stenosis more than 50%, CAD: Coronary artery disease

et al.[27] in a Turkish population, the allele frequencies of TaqIB and I405V polymorphisms were 0.38 and 0.46, respectively, which is similar to some European populations. The mean HDL-C levels were higher in VV genotype compared to the II genotype. TG levels and gender have an influence on the relationship between HDL-C and I405V polymorphism; therefore, this polymorphism may affect HDL-C levels in this population. Moreover, there was no significant association between TaqIB polymorphism and HDL-C concentrations. In some populations such as Iranian[28] Chinese[29] and Framingham populations,[21] a significant association of the B2 allele with increased HDL-C was also determined, and suggested the protective effects of B2 allele in these studies were due to decreased CETP activity and increased HDL-C levels.

Furthermore, our results indicated there was no significant difference in allele frequency of this polymorphism based on gender in two studied groups. Since I405V mutation of CETP was not sex-related, the absence of any relationship between it and gender was predictable.

Padmaja et al.[10] studied the common variants in the gene of CETP and their relationship with lipid profile in a population healthy subject from south India. They reported no statistically significant difference for studied variables between men and women participated in the study. Furthermore, they found no a statistically significant difference between genotypes of the TaqIB and I405V polymorphisms in men, women and total population of Tamilian. Moreover, the I405V genotypes were not associated with HDL-C level. Moreover, there was an increase in HDL-C and decrease in TG in carriers of B2B2 genotype in men; this result was in contrast to the results was observed in women.[8]

In a study conducted by Okumura et al.[17] in Japanese subjects, the effect of TaqIB and I405V polymorphisms of CETP gene on LDL particle size was investigated. Plasma CETP concentration was lower in patients with VV genotype and LDL particle size was also significantly smaller in this patients. Similar effects were observed for B2B2 genotype with the exception that the B2B2 genotype had no effect on the LDL particle size. The results of their study showed that loss of CETP activity resulting fromI405V polymorphism but not by TaqIB polymorphism is associated with increased CAD, despite the fact that both are increasing HDL-C concentration.

Although, results from a study performed on 504 patients with verified CHD and 338 controls in Indian population[30] revealed that the B1B1 genotype of the CETP TaqIB mutation was related to increased CHD risk. However, no statistically significant relationship between the I405V mutation and CHD was reported. In a population-based study, it was reported that the B2 and V alleles of the TaqIB and I405V polymorphisms despite an increased HDL-C, were not associated with a reduced risk of CAD. In addition, they reported that the less common allele 405V of I405V mutation was feebly related to CHD risk after matching of HDL-C.[13]

Table 4. Clinical findings in diabetic with and without CAD according to I405V genotypes

Variables	Diabetic with CAD			P	Diabetic without CAD			P
	Genotypes				Genotypes			
	II	IV	VV		II	IV	VV	
Age (year) (mean ± SD)	53.89 ± 5.62	54.13 ± 6.08	56.69 ± 6.52	0.250	51.06 ± 6.95	49.34 ± 6.18	47.13 ± 6.65	0.230
BMI (kg/m^2) (mean ± SD)	26.70 ± 3.45	27.58 ± 5.30	27.35 ± 3.61	0.630	25.95 ± 2.57	26.02 ± 5.66	25.24 ± 3.72	0.850
FPG (mg/dl) (mean ± SD)	149.58 ± 42.21	154.38 ± 48.44	169.91 ± 42.54	0.430	143.71 ± 40.21	138.48 ± 37.96	136.41 ± 45.09	0.800
SBP (mm Hg) (mean ± SD)	135.57 ± 19.31	129.14 ± 29.76	128.33 ± 25.16	0.470	123.67 ± 18.45	126.16 ± 16.22	130.91 ± 17.29	0.460
DBP (mm Hg) (mean ± SD)	82.00 ± 10.99	85.10 ± 17.71	82.08 ± 16.44	0.600	75.91 ± 10.26	78.13 ± 10.08	84.55 ± 14.74	0.060
TC (mg/dl) (mean ± SD)	185.93 ± 56.98	179.92 ± 44.46	209.33 ± 45.17	0.250	168.96 ± 20.22	174.43 ± 24.85	173.82 ± 23.9	0.620
HDL-C (mg/dl) (mean ± SD)	41.83 ± 12.24	38.27 ± 9.99	39.63 ± 8.28	0.360	44.09 ± 9.33	46.38 ± 10.36	46.69 ± 14.32	0.520
LDL-C (mg/dl) (mean ± SD)	112.77 ± 52.59	111.81 ± 38.09	131.50 ± 36.62	0.490	101.06 ± 32.26	109.22 ± 35.03	100.23 ± 27.10	0.380
TG (mg/dl) (mean ± SD)	181.84 ± 85.15	158.30 ± 64.76	183.64 ± 55.12	0.260	145.42 ± 50.81	151.34 ± 56.65	163.43 ± 36.54	0.750

Comparisons were made using one-way ANOVA followed by Tukey's post-hoc test. $P < 0.050$ was considered to be significant.
BMI: Body mass index; FPG: Fasting plasma glucose; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TC: Total cholesterol; HDL-C: High density lipoprotein-cholesterol; LDL: Low density lipoprotein-cholesterol; TG: Triglyceride; CETP: Colesteryl ester transfer protein; CAD: Coronary artery disease

Isaacs et al. reported a positive association between the 405V allele and reduced risk of myocardial infraction.[22] The significant deference was observed between genotype of I405V polymorphism in men according to the severity of CAD, in part possibly consequence of sex hormones difference that might regulate lipoprotein metabolism or CETP activity between men and women in different fashion. Our result is inconsistent with the finding reported by Ghatreh Samani et al.[31] from a study performed in other Iranian CAD patents, including, they found no statistically significant difference in genotype distribution of I405V polymorphism based on severity of CAD.

Conclusion

Although, results of the current study indicated there was no significant association between CETP I405V polymorphism and CAD risk in Iranians subjects with type 2 diabetes. However, a statistically significant difference was observed between genotypes of I405V polymorphism according to the severity of CAD only in men. It is speculated that I405V polymorphism may be involved in the severity of CAD only in men subjects with type 2 diabetes.

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Conflict of Interests

Authors have no conflict of interests.

References

1. Hsieh MC, Tien KJ, Chang SJ, Lo CS, Hsin SC, Hsiao JY, et al. Cholesteryl ester transfer protein B1B1 genotype as a predictor of coronary artery disease in Taiwanese with type 2 diabetes mellitus. Metabolism 2007; 56(6): 745-50.
2. Rosamond WD, Chambless LE, Folsom AR, Cooper LS, Conwill DE, Clegg L, et al. Trends in the incidence of myocardial infarction and in mortality due to coronary heart disease, 1987 to 1994. N Engl J Med 1998; 339(13): 861-7.
3. Mazaheri S, Sadeghi M, Sarrafzadegan N, Sanei H, Hekmatnia A, Tavakoli B. Correlation between body fat distribution, plasma lipids and apolipoproteins with the severity of coronary involvement in patients with stable angina. ARYA Atheroscler 2011; 6(4): 140-3.
4. Khosravi A, Akhavan TA, Golshadi I, Dana SZ, Bahonar A, Zarfeshani S, et al. The relationship between weight and CVD risk factors in a sample population from central Iran (Based on IHHP). ARYA Atheroscler 2012; 8(2): 82-9.
5. Brousseau ME, O'Connor JJ, Ordovas JM, Collins D, Otvos JD, Massov T, et al. Cholesteryl ester transfer protein TaqI B2B2 genotype is associated with higher HDL cholesterol levels and lower risk of coronary heart disease end points in men with HDL deficiency: Veterans Affairs HDL Cholesterol Intervention Trial. Arterioscler Thromb Vasc Biol 2002; 22(7): 1148-54.
6. Plengpanich W, Siriwong S, Khovidhunkit W. Two novel mutations and functional analyses of the CETP and LIPC genes underlying severe hyperalphalipoproteinemia. Metabolism 2009; 58(8): 1178-84.
7. Barter PJ, Nicholls S, Rye KA, Anantharamaiah GM, Navab M, Fogelman AM. Antiinflammatory properties of HDL. Circ Res 2004; 95(8): 764-72.
8. Pan SL, Wang F, Lu ZP, Liu CW, Hu CY, Luo H, et al. Cholesteryl ester transfer protein TaqIB polymorphism and its association with serum lipid levels and longevity in Chinese Bama Zhuang population. Lipids Health Dis 2012; 11: 26.
9. Takata M, Inazu A, Katsuda S, Miwa K, Kawashiri MA, Nohara A, et al. CETP (cholesteryl ester transfer protein) promoter -1337 C>T polymorphism protects against coronary atherosclerosis in Japanese patients with heterozygous familial hypercholesterolaemia. Clin Sci (Lond) 2006; 111(5): 325-31.
10. Padmaja N, Ravindra KM, Soya SS, Adithan C. Common variants of Cholesteryl ester transfer protein gene and their association with lipid parameters in healthy volunteers of Tamilian population. Clin Chim Acta 2007; 375(1-2): 140-6.
11. Bruce C, Chouinard RA Jr, Tall AR. Plasma lipid transfer proteins, high-density lipoproteins, and reverse cholesterol transport. Annu Rev Nutr 1998; 18: 297-330.
12. Akbarzadeh M, Hassanzadeh T, Saidijam M, Esmaeili R, Borzouei S, Hajilooi M, et al. Cholesteryl Ester Transfer Protein (CETP) -629C/A polymorphism and it's effects on the serum lipid levels in metabolic syndrome patients. Mol Biol

Rep 2012; 39(10): 9529-34.
13. Borggreve SE, Hillege HL, Wolffenbuttel BH, de Jong PE, Zuurman MW, van der Steege G, et al. An increased coronary risk is paradoxically associated with common cholesteryl ester transfer protein gene variations that relate to higher high-density lipoprotein cholesterol: a population-based study. J Clin Endocrinol Metab 2006; 91(9): 3382-8.
14. Lloyd DB, Lira ME, Wood LS, Durham LK, Freeman TB, Preston GM, et al. Cholesteryl ester transfer protein variants have differential stability but uniform inhibition by torcetrapib. J Biol Chem 2005; 280(15): 14918-22.
15. Agellon LB, Quinet EM, Gillette TG, Drayna DT, Brown ML, Tall AR. Organization of the human cholesteryl ester transfer protein gene. Biochemistry 1990; 29(6): 1372-6.
16. Boekholdt SM, Thompson JF. Natural genetic variation as a tool in understanding the role of CETP in lipid levels and disease. J Lipid Res 2003; 44(6): 1080-93.
17. Okumura K, Matsui H, Kamiya H, Saburi Y, Hayashi K, Hayakawa T. Differential effect of two common polymorphisms in the cholesteryl ester transfer protein gene on low-density lipoprotein particle size. Atherosclerosis 2002; 161(2): 425-31.
18. Ghaffari MA, Askari Sede M, Rashtchizadeh N, Mohammadzadeh G, Majidi S. Association of CRP gene polymophism with CRP levels and coronary artery disease in type 2 diabetes in Ahvaz, southwest of Iran. Bioimpacts 2014; 4(3): 133-9.
19. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010; 33(Suppl 1): S62-S69.
20. Spielmann N, Leon AS, Rao DC, Rice T, Skinner JS, Bouchard C, et al. CETP genotypes and HDL-cholesterol phenotypes in the HERITAGE Family Study. Physiol Genomics 2007; 31(1): 25-31.
21. Ordovas JM, Cupples LA, Corella D, Otvos JD, Osgood D, Martinez A, et al. Association of cholesteryl ester transfer protein-TaqIB polymorphism with variations in lipoprotein subclasses and coronary heart disease risk: the Framingham study. Arterioscler Thromb Vasc Biol 2000; 20(5): 1323-9.
22. Isaacs A, Sayed-Tabatabaei FA, Hofman A, Oostra BA, Klungel OH, Maitland-Vander Zee AH, et al. The cholesteryl ester transfer protein I405V polymorphism is associated with increased high-density lipoprotein levels and decreased risk of myocardial infarction: the Rotterdam study. Eur J Cardiovasc Prev Rehabil 2007; 14(3): 419-21.
23. Thompson JF, Durham LK, Lira ME, Shear C, Milos PM. CETP polymorphisms associated with HDL cholesterol may differ from those associated with cardiovascular disease. Atherosclerosis 2005; 181(1): 45-53.
24. Kakko S, Tamminen M, Paivansalo M, Kauma H, Rantala AO, Lilja M, et al. Variation at the cholesteryl ester transfer protein gene in relation to plasma high density lipoproteins cholesterol levels and carotid intima-media thickness. Eur J Clin Invest 2001; 31(7): 593-602.
25. Lewis GF, Rader DJ. New insights into the regulation of HDL metabolism and reverse cholesterol transport. Circ Res 2005; 96(12): 1221-32.
26. Kolovou G, Vasiliadis I, Kolovou V, Karakosta A, Mavrogeni S, Papadopoulou E, et al. The role of common variants of the cholesteryl ester transfer protein gene in left main coronary artery disease. Lipids Health Dis 2011; 10: 156.
27. Dogru-Abbasoglu S, Parildar-Karpuzoglu H, Depboylu B, Cine N, Uysal M, Aykac-Toker G. I405V and TaqIB polymorphisms of the cholesteryl ester transfer protein and their relation to serum lipid and lipoprotein levels in a Turkish population. Cell Biochem Funct 2009; 27(2): 76-80.
28. Kashani Farid MA, Azizi F, Hedayati M, Daneshpour M, Shamshiri AR, Siassi F. Association between CETP Taq1B and LIPC -514C/T polymorphisms with the serum lipid levels in a group of Tehran's population: a cross sectional study. Lipids Health Dis 2010; 9: 96.
29. Wu Y, Bai H, Liu R, Liu Y, Liu BW. Analysis of cholesterol ester transfer protein gene Taq IB and -629 C/A polymorphisms in patients with endogenous hypertriglyceridemia in Chinese population. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2006; 23(6): 640-6.
30. Kolovou G, Mihas C, Anagnostopoulou K, Kolovou V, Giannakopoulou V, Kostakou P, et al. Cholesteryl ester transfer protein gene and effectiveness of lipid lowering of atorvastatin. Open Cardiovasc Med J 2010; 4: 297-301.
31. Ghatreh Samani K, Noori M, Rohbani Nobar M, Hashemzadeh Chaleshtori M, Farrokhi E, Darabi Amin M. I405V and -629C/A polymorphisms of the cholesteryl ester transfer protein gene in patients with coronary artery disease. The Iranian Biomedical Journal 2009; 13(2): 103-8.

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Translation and validation of the Persian version of the treatment adherence questionnaire for patients with hypertension

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Original Article

Abstract

BACKGROUND: Hypertension is a global public health crisis. Poorly controlled high blood pressure is one of the major factors contributed to this crisis. As lack of treatment adherence is often considered the main reason for this failure, the Treatment Adherence Questionnaire for Patient with Hypertension (TAQPH) was developed. Since this questionnaire should be reliable and strongly valid to be used in clinics and research, this study was performed to test the reliability and validity of the TAQPH.

METHODS: A cross-sectional study was conducted to validate the Persian version of TAQPH after using a modified forward/backward translation procedure. A total of 330 hypertensive patients were participated in this study. Construct and criterion validity, Cronbach's alpha, and test-retest reliability were used to validate the Persian scale.

RESULTS: Data analysis showed that the scale had excellent stability (intraclass correlation = 0.95) and good acceptability of internal consistency (α = 0.80). The exploratory factor analysis (EFA) was meaningful but was not confirmed with confirmatory factor analysis (CFA). The scale score was correlated with Morisky Medication Adherence Scale (MMAS) score (P = 0.27).

CONCLUSION: In total, most of the psychometric properties of the 25-item P-TAQHP achieved the standard level and were sufficient to recommend for general use.

Keywords: Hypertension; Treatment Adherence; Validation; Questionnaires

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Introduction

Hypertension is the most prevalent health concern among adult patients affecting approximately one billion persons worldwide.[1] It is one of the major risk factors for cardiovascular, cerebrovascular, renal diseases, or other end-organ damage leading to premature death.[2,3] In developing countries, the mean awareness, treatment, and control of hypertension among men were 40.6, 29.2, and 9.8 percent, and among women were 52.7, 40.5, and 16.2 percent, respectively.[4] The prevalence of hypertension in Iran is estimated by 23% in 30-55 aged population and by 50% in the population older than 55-year-old.[5]

According to the World Health Organization, a low adherence level of hypertensive patients is one of the major reasons for uncontrolled blood pressure.[6] Javadi showed that only 5% of Iranian hypertensive patients comply with their prescribed regimen and have control blood pressure.[7] Non-adherence to treatment regimen may lead to the worsening of disease, increasing morbidity and mortality, frequent hospitalization, and significant healthcare costs.[8,9]

To understand and facilitate adherence for hypertensive patients, the first step is to measure patient adherence to recommended treatment regimen. Therefore, a valid and reliable tool is required. Different adherence scales have been designed in various settings to assess patient-reported compliance levels.[10-12] The Morisky Medication Adherence Scale (MMAS), the Self-efficacy for Appropriate Medication Use Scale, the Brief Medication Questionnaire, the Medication Adherence Rating Scale, and The Hill-Bone compliance with High Blood Pressure Therapy Scale were developed by Morisky et al.,[13,14] Risser et al.,[15] Svarstad et al.,[16] Thompson et al.,[17] and Kim et

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al.,[18] respectively. Some of these scales are hypertensive specific[18] while the others are general[13,15,16] or specific for other diseases.[17] However, most of these scales are mainly focused on medication adherence. The Seventh Report of the Joint National Committee (JNC-7) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommended both use of antihypertensive medication and health-promoting lifestyle to cure and manage high blood pressure.[19] Beside medication therapy, a healthy diet, weight control, and regular exercise all have been shown to have potential benefits to improve blood pressure control and even reduce medication needs.[20] Regarding these recommendations, Ma et al.[1] developed the Treatment Adherence Questionnaire for Patients with Hypertension (TAQPH) in a Chinese population. They evaluated psychometric properties of the TAQPH and showed that it was a reliable and valid scale. According to this scale different aspects of hypertensive treatment adherence were addressed including medication compliance, diet, weight control, exercise, stimulation, and stress relive.[1] This scale is a more comprehensive than other scales which only addressed medication compliance, appointment keeping, and low salt diet.[18] However, literature review showed no previous study assessed TAQPH validity in other countries.

In Iran, treatment adherence was mostly measured using researcher-designed questionnaires, however, the validating process of developing these questionnaires was not sufficient.[21,22] Dehghan et al.[23] have evaluated the psychometric properties of Hill-Bone Scale and found that this scale was not validated in Iranian population. Therefore, a valid, reliable, and concise scale are required to measure treatment adherence in Iranian hypertensive patients. A valid and reliable scale would be helpful in both selecting patients that are likely to be poor adherents and finding out why patients do not comply with their prescribed treatment. The aim of this research was to validate the Persian version of "TAQPH" (P-TAQPH).

Materials and Methods

This was a methodological study conducted in educational hospitals in Kerman (the largest city in southeastern Iran with a population of 722000) where hypertensive patients are being actively treated.

TAQPH

To evaluate treatment adherence, Ma et al.[1] developed the TAQPH in 2011. TAQPH is a 4-point Likert-type scale that consisted of 28 items grouped into six factors labeled as follows: medication (9 items), diet (9 items), exercise (2 items), stimulation (3 items), weight control (2 items), and relieving stress (3 items). The range of potential scores varied between 28 and 112. The higher scores indicated a higher level of adherence. The authors evaluated the psychometric properties of the Chinese version of TAQPH (the original version). According to their report, content validity index was 0.93. Construct validity had been confirmed by the exploratory factor analysis (EFA) and confirmatory factor analysis (CFA). Cronbach's alpha of the overall questionnaire was 0.86 and the test-retest reliability was 0.82.[1]

The Persian MMAS-8 (P-MMAS-8)

P-MMAS-8 is a generic assessment of medication-taking behavior. This self-reported measure of medication taking was developed from a previously validated four-item scale[14] and supplemented with additional items addressing the circumstances surrounding adherence behavior. The MMAS comprises seven questions with a yes/no response format and one question with 5-point Likert response. The authors reported acceptable reliability and validity of the original version.[13] Dehghan et al.[24] and Moharamzad et al.,[25] have validated the P-MMAS-8. They indicated that the Persian version was valid and reliable to use in Iranian context (good face validity, significant known-groups validity, and significant test-retest reliability).

Translation

As the Persian translation did not exist for TAQPH, we generated Persian language version of this scale using a modified forward/backward translation procedure.[26,27] In this procedure, the original English-language version of the scale was first translated into Persian (the Iranian language) by two experienced Iranian health experts, independently. If there was any difference between two translations, the problem was resolved through discussion with the translators to yield a provisional forward translation. To check the adequacy of the first translation, the initial Persian version was translated back into English by two independent translators who had no previous knowledge of the scale. The original and back-translated versions were discussed in a bilingual expert panel to check semantic, idiomatic, experiential and conceptual equivalence and to resolve the discrepancies.

In the next step, 25 hypertensive patients were selected to test the face validity of the pre-final version of the Persian scale. Each subject should completed the scale and was interviewed about the meaning of each item. Regarding the results of this pilot study, the final version of the Persian scale was confirmed after revising the difficult to understand and confusing questions. The face validity was acceptable.

The study population consisted of hypertensive patients, older than 18 years who were taking at least one antihypertensive medication. Patients were asked about socio-demographic data such as gender, age, marital status, education, and occupational status. The patients also were asked for the dates of the hypertension diagnosis and the initiation of drug treatment. Blood pressure was measured with an aneroid sphygmomanometer (ALPK2, Japan) using the average of two measurements by 5-minute interval. To validate the aneroid sphygmomanometer, the readings from this instrument were compared by those of a mercury sphygmomanometer in the same patients. The readings were not significantly different. Systolic blood pressures (SBP) and diastolic blood pressures (DBP) were obtained from the right arm of the subjects in a seated position. The subjects were required to avoid caffeine (coffee, colas) intake and not to smoke 30 minutes before blood pressure measurement. If the blood pressure was ≥ 140/90 mmHg (in patients with diabetes ≥ 130/80 mmHg), indicated insufficiently controlled, and if it was < 140/90 mmHg (in patients with diabetes < 130/80 mmHg), considered as sufficiently controlled hypertension.[12,13]

All patients were approached during their hospitalization and asked to participate in the study. In addition, a convenience sampling technique was utilized to select 330 hypertensive patients who had been referred to the above-mentioned centers from November 2013 to March 2014. Furthermore, we used interviews instead of the self-administered method for illiterate individuals.

Tehran University of Medical Sciences (TUMS), Iran, approved this project. After approval of TUMS and coordination with Kerman University of Medical Sciences and the clinical centers, we provided information for the subjects. The information addressed: (1) The goal and objectives of the study, (2) the confidentiality of the data, and (3) the participants would be anonymous and were free to withdraw from this study at any time. Then, the informed consent was obtained verbally. Finally, we appreciated participants.

All analyses were performed using SPSS software (version 19.0, SPSS Inc., Chicago, IL, USA) and LISREL (version 8.70, Scientific Software International, Chicago, IL, USA). Descriptive statistics [frequency and percentage, mean, and standard deviation (SD)] and analytical statistics (Mann-Whitney U, Spearman rho correlation, and factor analysis) were used to analyze the data. The 0.05% significance level was used in this study. Psychometric properties of the P-TAQPH were evaluated in terms of validity and reliability.

Construct validity

To verify construct validity, the factorial design of the TAQPH was analyzed using both EFA and CFA. EFA was performed to investigate the factor structure of the scales by principal component analysis (PCA) with varimax rotation.[28] At first, we tested the factorability of the intercorrelation matrix of the 28 items according to the Kaiser–Meyer–Olkin (KMO) coefficient (should be > 0.50).[29] In the second step, we conducted a PCA to derive an initial solution. Third, we determined the number of factors to be extracted according to three different criteria: (1) Eigen values > 1, (2) Cattell's scree plot, and (3) items with loadings of 0.4 or greater on each factor.[30] In the final step, we compared the unrotated versus the rotated factor solutions. The rotating factors have been applied to obtain a simple factor structure that is more easily interpreted and compared. We chose the varimax rotation as the most popular method of orthogonal rotation. Each factor will tend to have either large or small loadings of any particular variable. Construct validity was further assessed by CFA. CFA was used to test the goodness-of-fit of the structural equation model in which the observed variables (items) correlated with their underlying latent constructs (subscales). Model adequacy was evaluated by the chi-square test. The main model fit indices were the goodness-of-fit index (GFI), adjusted GFI (AGFI), comparative fit index (CFI), root mean squared error of approximation (RMSEA), non-normed fit index (NNFI), and standard root mean square residual (SRMR). The acceptable model fit is indicated by χ^2/degree of freedom (df) < 3.0, RMSEA < 0.08, and SRMR < 0.8. The values of GFI, AGFI, CFI and NNFI indices are 0.9 or greater.[28,31,32]

Criterion validity: Concurrent validity

To assess the concurrent validity, we calculated association between scale score and the sufficiently controlled versus uncontrolled blood pressure using

Mann-Whitney U-test. Furthermore, we calculated the correlation of the scale with the SBP, DBP and P-MMAS-8 score using Spearman rho coefficient.

Reliability: Internal consistency and repeatability

Internal consistency refers to the extent to which items of the scale measure the same construct (i.e., homogeneity of the scale) and was assessed in our study by Cronbach's alpha (should be > 0.70) for 330 hypertensive patients. We used the test-retest method to evaluate the repeatability of the TAQPH. To do so, 25 hypertensive patients completed this scales twice (at 2-week intervals). To interpret the obtained coefficients values above 0.7 were considered as excellent reliability.[33]

Results

Socio-demographic characteristics

In total, 330 hypertensive patients were assessed. The mean age of participants was 55.7 ± 8.9 years. 64.7% (n = 213) of them were men. 75.8% (n = 248) were married who their partners were alive, 18.3% (n = 60) were widows/ers and the rest were single. 42.0% (n = 136) were illiterate. 52.6% (n = 172) of patients were employed. 27.9% of participants were diabetic. Duration of having hypertension was 42.5 ± 28.4 months and initiation of hypertension drug therapy was 41.0 ± 28.4 months. 52.6% (n = 172) of patients have been prescribed more than one antihypertensive drug. The mean scores of SBP and DBP were 139.8 ± 13.6 mmHg and 98.0 ± 13.5 mmHg, respectively. 85.6% (n = 280) of participants had insufficiently controlled blood pressure. The hypertensive medication adherence was 69.4 ± 9.6 according to the P-TAQPH. The distribution of the responses to each item in the P-TAQPH is presented in table 1. More than half of the respondents reported perfect adherence only for three of the 28 items (items 9, 19 and 20).

Construct validity

For the validity of the construct, the P-TAQPH was examined by undertaking PCA with a varimax rotation. At first, Bartlett's test of sphericity was used to determine if the sample size were appropriate for a factor analysis and to determine whether the data came from a sample of the normal distributed population. This test showed statistical significance (χ^2 = 4944.6, df = 378, P < 0.001). In addition to Bartlett's test, the KMO measure of sampling adequacy was examined. In this study, the KMO coefficient was 0.76, confirming factorability of the correlation matrix of the P-TAQPH. PCA with varimax rotation was conducted, and an eight-factor solution with an Eigen value > 1 was retrieved. The total variance explained by these eight factors was 68.8%. Note that the scree plot begins to level off after six components, with a decrease of the Eigen values from 1.5 to 1.3, which was consistent with the number of subscales. Therefore, we preferred the six-factor solution with an Eigen value (% variance explained) of 7.07 (25.2%), 2.54 (9.1%), 2.16 (7.7%), 1.87 (6.7%), 1.73 (6.2%), and 1.50 (5.4%) which together accounted for 60.3% of total variance. 26 items (out of 28 items) loaded above 0.4. Two items did not load in any factors (item 4 and 20). Four items loaded in two factors (item 5, 10, 14, and 24). Depending on value of item load, positive or negative correlation between item and factors, and the underlying meaning, we decided to dedicate item 5 to the fifth factor, item 10 and 24 to the first, item 14 to the third factor. Thus, seven items of the "medication subscale" loaded on the second and fifth factor. The nine items of diet subscale' loaded in the first and third factor. Two items of "stress relieve subscale" loaded in the sixth factor and the two items related to "exercise subscale" loaded in the fourth factor. One of the three items related to "stimulation subscale" loaded in the fourth factor and another in the sixth factor.

The two items of "weight control subscale" loaded in the first factor. Therefore, the first and third factors were related to "diet and weight control subscales," the second and fifth factors to "medication subscale," the fourth factor to "stimulation and exercise subscales," and the sixth factor to "stress relieve subscale." Approximately, all factor-related items were meaningful except the item 6 which loaded in the first factor and item 28 which loaded in the second factor. EFA showed that the six factors of TAQHP could be merged to four factors of "diet and weight control," "medication," "stimulation and exercise," and "stress relieve" in the observed variables in the Iranian context (Table 2). Since items 7 and 19 were negatively correlated with the second and sixth factors, respectively, these items and the two items (4 and 20) not loaded in any factors were candidates for omission (Table 2). Note that, to calculate the factor analysis, missing responses were replaced with means.

Following the identification of a six-factor solution using EFA, CFA was performed to further test the factor model that emerged from

Table 1. Distribution of the responses to the P-TAQPH

Question: Would you…	Missing (No)	Mean	Response [n (%*)]			
			Never	Some of the time	Most of the time	All of the time
Comply with the total times of prescribed medications?	4	2.90	6 (1.8)	105 (32.2)	130 (39.9)	85 (26.1)
Comply with the total number of pills consumed daily?	1	3.05	3 (0.9)	81 (24.6)	142 (43.2)	103 (31.1)
Comply with the required time to take prescribed medications every day?	1	3.15	5 (1.5)	39 (11.9)	186 (56.5)	99 (30.1)
Never stop taking prescribed medications?	1	3.24	19 (5.8)	28 (8.5)	136 (41.3)	146 (44.4)
Never increase or decrease tablets by yourself?	2	3.32	3 (0.9)	25 (7.6)	163 (49.7)	137 (41.8)
Adhere to take prescribed medications, whether in hypertension symptoms or not?	2	2.47	73 (22.3)	101 (30.8)	82 (25.0)	72 (22.0)
Never forget to take prescribed medications?	2	3.28	1 (0.3)	11 (3.4)	211 (64.3)	105 (32.0)
Never stop taking prescribed medications when you feel better?	1	3.32	-	15 (4.6)	194 (59.0)	120 (36.5)
Never stop taking prescribed medications when you feel badly?	2	3.43	12 (3.7)	21 (6.4)	108 (32.9)	187 (57.0)
Comply with low salt diet?	3	2.53	63 (19.3)	111 (33.9)	71 (21.7)	82 (25.1)
Comply with low fat diet?	1	2.88	21 (6.4)	103 (31.3)	100 (30.4)	105 (31.9)
Comply with low cholesterol diet?	1	2.88	46 (14.0)	61 (18.5)	110 (33.4)	112 (34.0)
Reduce intake of sugar and sweets?	1	2.74	53 (16.1)	78 (23.7)	98 (29.8)	100 (30.4)
Eat more roughage?	1	2.51	57 (17.3)	104 (31.6)	111 (33.7)	57 (17.3)
Increase intake of fresh vegetables?	2	2.64	10 (3.0)	159 (48.5)	98 (29.9)	61 (18.6)
Increase intake of fresh fruits?	3	2.72	10 (3.1)	139 (42.5)	109 (33.3)	69 (21.1)
Eat more bean products?	3	2.67	11 (3.4)	150 (45.9)	102 (31.2)	64 (19.6)
Increase intake of low fat dairy products?	2	2.65	24 (7.3)	138 (42.1)	95 (29.0)	71 (21.6)
Reduce intake of coffee?	2	3.46	27 (8.2)	21 (6.4)	55 (16.8)	225 (68.6)
Give up drinking?	1	3.90	1 (0.3)	3 (0.9)	23 (7.0)	302 (91.8)
Give up smoking?	0	2.77	53 (16.1)	105 (31.8)	38 (11.5)	134 (40.6)
Exercise for 5 times and above per week?	0	1.92	94 (28.5)	183 (55.5)	40 (12.1)	13 (3.9)
Exercise more than 30 minutes per time?	0	2.04	95 (28.8)	145 (43.9)	70 (21.2)	20 (6.1)
Limit the total diet?	0	2.41	55 (16.7)	131 (39.7)	97 (29.4)	47 (14.2)
Control weight?	1	2.14	78 (23.7)	141 (42.9)	95 (28.9)	15 (4.6)
Leave some time to relax every day?	1	1.84	141 (42.9)	113 (34.3)	61 (18.5)	14 (4.3)
Adopt methods to relieve stress?	0	1.98	132 (40.0)	105 (31.8)	60 (18.2)	33 (10.0)
Get a hold of yourself when facing with any incidents?	0	2.78	33 (10.0)	101 (30.6)	102 (30.9)	94 (28.5)

*Valid percent, P-TAQPH: Persian Treatment Adherence Questionnaire for Patients with Hypertension

Table 2. Rotated factor matrix: The P-TAQPH

Question: Would you…	Rotated matrix					
	Decrease unsafe diet and weight control	Medication	Increase safe diet	Stimulation and exercise	Avoiding self-medication	Stress retrieve
	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
1. Comply with the total times of prescribed medications?		0.74				
2. Comply with the total number of pills consumed daily?		0.88				
3. Comply with the required time to take prescribed medications every day?		0.73				
7. Never forget to take prescribed medications?		-0.64				
28. Get a hold of yourself when facing with any incidents?		0.41				
5. Never increase or decrease tablets by yourself?		-0.52			0.43	
8. Never stop taking prescribed medications when you feel better?					0.68	
9. Never stop taking prescribed medications when you feel badly?					0.79	
6. Adhere to take prescribed medications, whether in hypertension symptoms or not?	0.45					
10. Comply with low salt diet?	0.62		0.42			
11. Comply with low fat diet?	0.79					
12. Comply with low cholesterol diet?	0.88					
13. Reduce intake of sugar and sweets?	0.86					
24. Limit the total diet?	0.52	0.40				
25. Control weight?	0.52					
14. Eat more roughage?	0.63		0.43			
15. Increase intake of fresh vegetables?			0.79			
16. Increase intake of fresh fruits?			0.85			
17. Eat more bean products?			0.76			
18. Increase intake of low fat dairy products?			0.48			
21. Give up smoking?				0.43		
22. Exercise for 5 times and above per week?				0.88		
23. Exercise more than 30 minutes per time?				0.87		
19. Reduce intake of coffee?						-0.61
26. Leave some time to relax every day?						0.79
27. Adopt methods to relieve stress?						0.63
Items not loaded						
20. Give up drinking?	-	-	-	-	-	-
4. Never stop taking prescribed medications?	-	-	-	-	-	-
Eigen value	7.07	2.54	2.16	1.87	1.73	1.50
Percentage of explained variance	25.2	9.10	7.70	6.70	6.20	5.40

Factor load > 0.40 are mentioned. P-TAQPH: Persian Treatment Adherence Questionnaire for Patients with Hypertension

EFA. The first- and second-order CFA models were used. In Model 1 (first-order model), we assumed that the P-TAQHP was composed of six separate correlated dimensions, and in Model 2 (second-order model), we assumed that a higher-order factor accounted for the relationships between the individual factors. GFI were examined to determine the degree of fit between the data and the results of the hypothesized models. In M1, the loadings of items were statistically significant at the 0.05 level ($t > 1.96$) except for items19 and 20. In M2, all of the factors loadings were significant ($t > 1.96$) except for the sixth factor. The χ^2-associated P value was below the 0.050 significance level in both models (M1: $\chi^2 = 1690.58$, df = 335, and $P < 0.001$) (M2: $\chi^2 = 1729.07$, df = 344, and $P < 0.001$).

None of the fit indices reached acceptable levels in both models (M1: $\chi^2/df = 5.05$, RMSEA = 0.11, SRMR = 0.1, GFI = 0.73, AGFI = 0.67, CFI = 0.81, IFI = 0.81, and NNFI = 0.79) (M2: $\chi^2/df = 5.03$, RMSEA = 0.11, SRMR = 0.1, GFI = 0.73, AGFI = 0.68, CFI = 0.82, IFI = 0.81, and NNFI = 0.79). Consequently, based on these models, we could not confirm the structure resulting from the EFA. Since items 19 and 20 were not significant in the confirmatory model and item 4 was not loaded on any factors in EFA, these items were removed from the model. The modification of the structures in M2 showed that the fit indices did not improve considerably (modified second-order CFA model: $\chi^2 = 1493.64$, df = 269 and $P < 0.001$; $\chi^2/df = 5.55$, RMSEA = 0.12, SRMR = 0.11, GFI = 0.73, AGFI = 0.68, CFI = 0.82, IFI = 0.82, and NNFI = 0.80). Based on the fit indices, the modified model did not provide a reasonable fit to the data.

Concurrent criterion validity

To measure the concurrent validity, the correlation was assessed between SBP and DBP and the P-TAQHP and the P-TAQHP-25 item. None of them was correlated with SBP or DBP ($P > 0.050$).

Moreover, there were no differences between sufficiently control group versus insufficiently in P-TAQHP score (Mann-Whitney U = 4.14, P = 0.690). The correlation between the P-TAQHP and P-MMAS was assessed (Table 3). The correlation between these two scales was positively significant ($P < 0.001$).

Reliability

The value of Cronbach's alpha for the P-TAQPH was 0.80. The P-TAQPH item-total correlations ranged from -0.39 (Item 5) to 0.70 (Item 12). The item-total correlations were 0.20 or greater for 19 items of the P-TAQPH. The Cronbach's alpha coefficient of the P-TAQPH increased slightly (0.82) when item 5 was not used in the calculation. The test-retest reliability of the P-TAQPH indicated excellent reliability at a two-week interval with an intraclass correlation coefficient (ICC) of 0.95 [confidence interval (CI): 0.88-0.98] (Table 4).

Table 3. Association between The P-TAQPH and the P-MMAS and systolic and diastolic blood pressure

Variables	The P-TAQPH score	
	Spearman rho coefficient	P
Systolic blood pressure	$\rho = 0.08$	0.140
Diastolic blood pressure	$\rho = 0.01$	0.870
The P-MMAS score	$\rho = 0.27$	< 0.001

P-TAQPH: Persian Treatment Adherence Questionnaire for Patients with Hypertension; P-MMAS: Persian Morisky Medication Adherence Scale

Discussion

According to the results, "the P-TAQPH" had sufficient psychometric quality in different aspects of reliability, criterion, and construct validity. The repeatability of the P-TAQPH was excellent. The internal consistency of the P-TAQPH was acceptable. The mean score of the P-TAQPH was significantly correlated with the mean score of the P-MMAS-8. In total, the EFA was meaningful. However, the factors structure was not confirmed by CFA.

Despite an extensive search, we could not access relevant articles, and we could not find any article that validated this scale in other contexts. The different aspects of reliability (repeatability and internal consistency) of the P-TAQPH were excellent. This was comparable with the original version. Ma et al.[1] reported that the TAQPH reliability was more than 0.80 in both aspects of internal consistency and stability. In this study, the P-TAQPH was positively correlated with P-MMAS-8 but it failed to be correlated with SBP and DBP. The original scale was correlated with MMAS-4.[1] This was in agreement with our study. However, they did not calculate the correlation between TAQPH with blood pressure measures. In this study, hospitalized patients participated. It is assumed that if the patient has low adherence to treatment recommendations hospitalization will be increased. This may affect their blood pressure and the correlation coefficient in our study.

Table 4. Corrected item-to-total correlation, Cronbach's alpha and ICC of The P-TAQPH

Question: Would you…	Corrected item-to-total correlation (n = 330)	Cronbach's alpha if item deleted	ICC (CI) (n = 25)
1. Comply with the total times of prescribed medications?	0.37	0.79	0.88 (0.74-0.94)
2. Comply with the total number of pills consumed daily?	0.38	0.79	0.89 (0.78-0.95)
3. Comply with the required time to take prescribed medications every day?	0.32	0.79	0.91 (0.81-0.96)
4. Never stop taking prescribed medications?	-0.09	0.81	0.97 (0.94-0.99)
5. Never increase or decrease tablets by yourself?	-0.39	0.82	0.86 (0.71-0.93)
6. Adhere to take prescribed medications, whether in hypertension symptoms or not?	0.25	0.80	0.84 (0.68-0.93)
7. Never forget to take prescribed medications?	-0.30	0.81	1 (1-1)
8. Never stop taking prescribed medications when you feel better?	-0.18	0.81	1 (1-1)
9. Never stop taking prescribed medications when you feel badly?	-0.04	0.81	0.96 (0.92-0.98)
10. Comply with low salt diet?	0.63	0.78	0.81 (0.62-0.91)
11. Comply with low fat diet?	0.68	0.78	0.94 (0.88-0.97)
12. Comply with low cholesterol diet?	0.70	0.77	0.95 (0.88-0.98)
13. Reduce intake of sugar and sweets?	0.66	0.78	0.95 (0.90-0.98)
14. Eat more roughage?	0.66	0.78	0.94 (0.87-0.97)
15. Increase intake of fresh vegetables?	0.50	0.79	1 (1-1)
16. Increase intake of fresh fruits?	0.54	0.78	0.98 (0.96-0.99)
17. Eat more bean products?	0.63	0.78	0.77 (0.54-0.89)
18. Increase intake of low fat dairy products?	0.47	0.79	0.88 (0.75-0.94)
19. Reduce intake of coffee?	0.04	0.81	0.88 (0.75-0.94)
20. Give up drinking?	-0.01	0.80	0.80 (0.61-0.91)
21. Give up smoking?	0.00	0.81	0.73 (0.48-0.87)
22. Exercise for 5 times and above per week?	0.39	0.79	0.71 (0.45-0.86)
23. Exercise more than 30 minutes per time?	0.43	0.79	0.73 (0.49-0.87)
24. Limit the total diet?	0.55	0.78	0.50 (0.15-0.74)
25. Control weight?	0.36	0.79	0.95 (0.88-0.98)
26. Leave some time to relax every day?	0.05	0.81	0.88 (0.75-0.95)
27. Adopt methods to relieve stress?	0.38	0.79	0.84 (0.67-0.92)
28. Get a hold of yourself when facing with any incidents?	0.34	0.79	0.77 (0.56-0.89)

The P-TAQPH Cronbach's alpha = 0.80 and ICC = 0.95 (CI: 0.88-0.98); ICC: Intraclass correlation; CI: Confidence interval; P-TAQPH: Persian Treatment Adherence Questionnaire for Patients with Hypertension

In our EFA, six-factor solution was retrieved that was the same as the original version. Item 4; "Never stop taking prescribed medications?" and item 20; "Give up drinking?" did not load in any factors. The majority of Iranians are Muslims. According to "Quran" - Muslims holy book - drinking alcohols is forbidden (2:219). As it is obvious in our findings, more than 90% of subjects did not drink alcohols. Therefore, this may affect loading of this item. In this study, the six factors were related to "decrease unsafe diet and weight control" (7 items), "medication" (5 items), "increase safe diet" (5 items), "stimulation and exercise" (3 items), "avoiding self-medication" (3 items), and "stress retrieve" (3 items), while in the original version, the six factors were related to "medication" (9 items), "diet" (9 items), "exercise" (2 items), "stimulation" (3 items), "weight control" (2 items), and "relieving stress" (3 items).[1] The most important factor in our study was decreasing unsafe diet that was in contrast with the original version of TAQPH. In the original version, "medication subscale" was the first and important factor. In our study, items related to "diet" and "weight control" subscales located in the first and third factors. All items that related to decreasing harmful food and controlling weight such as low salt, fat, cholesterol, and sugar, and limiting the total diet located in the first factor.

All items related to increasing useful food such as eating roughage, fresh vegetables, fresh fruits, bean products, and low-fat dairy products located in the third factor. It means that in Iran, patients believe that decreasing unsafe food will control weight. They also believe that decreasing unsafe food and weight control may have more effect on

their blood pressure than increasing useful food. In Iran, some of patients do not consider to hypertension as a disease so they may not pay enough attention to prescribed medication. Therefore, it is predicted that medication adherence is less important in their opinion. In our finding, items related to exercises and giving up smoking loaded in the fourth factor. It seems that in Iranian population these items are related to safe health behaviors that are more emphasized by physicians. The last factor in our finding was related to stress reduction. Item related to "reducing intake of coffee" was negatively correlated to that factor which was in contrast with the original version. Most of the Iranian populations believe that coffee has a relaxation effect and it is used to reduce tensions. They are not well informed about its negative effect on blood pressure.[34] Therefore, as it is evident in our finding they believed reducing intake of coffee is against of stress reduction. This may explain some differences between the Persian versions and the original Chinese version. In addition, the most popular drink in Iran is tea and our populations do not use coffee regularly.[35] Since the effect of tea on hypertension is controversial,[34] we ignored to replace coffee consumption with tea consumption. Therefore, we preferred to omit this item from the Persian version. The items 6 and 28 had meaningless loading. The item 6: "Adhere to take prescribed medications, whether in hypertension symptoms or not?" loaded in diet subscale and the item 28: "Get a hold of yourself when facing with any incidents?" loaded in medication subscales. These were in contrast with the original version. Therefore, according to the original version, we preferred to keep this item in "medication" and "stress retrieve" subscales. In this study, the CFA did not confirm the model obtained from the EFA. This was in contrast with the original version.[1]

Information gathered with such a scale, can be used to manage patient education and behavioral reinforcement, and reveal reasons of non-adherence. Therefore, it can help the healthcare provider to make better treatment decisions.[36] This scale may be useful to highlight potential reasons for medication non-adherence, such as side effects, denial of illness because of lack of symptom, combine medication, and complexity of drug therapy. However, the scale failed to explain the other potential risk-factors and reasons of treatment non-adherence such as the cost of treatment, dependency to medication, lack of patient involvement in the care plan, patient's cultural differences, beliefs and previous experience with health care system.[19] All these factors may have direct or indirect influence on treatment adherence. Another aspect of antihypertensive treatment adherence that was not addressed directly by the current scale is that of self-efficacy, which has been implicated in a wide range of health behaviors.[37] In patients with chronic diseases, positive self-efficacy appraisals can predict adherence to a variety of health-related behaviors including dietary recommendations, exercise regimens, and self-management behaviors.[38]

Some study identified that low self-efficacy may be a potential barrier to treatment adherence.[37] Beside all pros and cons of the current scale, this scale should be used in conjunction with other information that may influence on treatment adherence such as socio-demographic factors, length of illness and treatment, economic status, the severity of hypertension, and other associated medical concerns.[36]

Like other studies, our study had some limitations. Hospitalized patients participated in the study. We paid attention to the patients' comfort status, and their blood pressures were measured by a standard approach, but their responses may have been affected by their hospitalization. In addition, it is assumed that the hospitalized patient have less treatment adherence. Therefore as we only used hospitalized patients, this may limit generalization of our results. In addition, we used the English translation of Chinese version that Ma et al.[1] had mentioned in their study. They did not explain about forward/backward translation procedure. Hence, if the English translation of the scale has not established in a standard approach, this may affect our results.

Conclusion

The results of this study showed that "P-TAQPH" had excellent stability, good internal consistency, meaningful construct validity, and significant criterion validity. It seems that the P-TAQPH can help healthcare providers assess adherence to the hypertension treatment regimen appropriately. The results suggested that further study is needed to assess the treatment adherence in a different population with various degree of adherence. This may help the researcher to establish an appropriated cut off point according to P-TAQPH. Further studies also are needed to test a more comprehensive and multi-dimensional tool to

measure hypertension-adherence behaviors in the Iranian context.

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Conflict of Interests

Authors have no conflict of interests.

References

1. 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.
2. Aghababaei I, Sadeghi M, Talaei M, Rabiei K, Sarrafzadegan N. Is prehypertension a risk factors for cardiovascular diseases among Iranian women? J Res Med Sci 2012; 17(10): 947-51.
3. Rahmanian K, Shojaie M. The prevalence of pre-hypertension and its association to established cardiovascular risk factors in south of Iran. BMC Res Notes 2012; 5: 386.
4. Pereira M, Lunet N, Azevedo A, Barros H. Differences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. J Hypertens 2009; 27(5): 963-75.
5. Haghdoost AA, Sadeghirad B, Rezazadehkermani M. Epidemiology and heterogeneity of hypertension in Iran: a systematic review. Arch Iran Med 2008; 11(4): 444-52.
6. World Health Organization. Adherence to long-term therapies: evidence for action. Geneva, Switzerland: World Health Organization; 2003.
7. Javadi H. Evaluation of awareness, treatment and drug consumption in hypertensives. J Qazvin Univ Med Sci 2000; 3(4): 59-64. [In Persian].
8. Lavsa SM, Holzworth A, Ansani NT. Selection of a validated scale for measuring medication adherence. J Am Pharm Assoc (2003) 2011; 51(1): 90-4.
9. Voils CI, Hoyle RH, Thorpe CT, Maciejewski ML, Yancy WS. Improving the measurement of self-reported medication nonadherence. J Clin Epidemiol 2011; 64(3): 250-4.
10. 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.
11. 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.
12. Song Y, Han H, Song H, Nam S, Nguyen T, Kim M. Psychometric evaluation of hill-bone medication adherence subscale. Asian Nursing Research, 2011; 5(3): 183-8.
13. 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.
14. 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.
15. 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.
16. 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.
17. Thompson K, Kulkarni J, Sergejew AA. Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses. Schizophr Res 2000; 42(3): 241-7.
18. 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.
19. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA 2003; 289(19): 2560-72.
20. 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.
21. Mohammadi MA, Dadkhah B, Sezavar H, Mozafari N. Effect of follow up on blood pressure control in patients with hypertension. J Ardabil Univ Med Sci 2006; 6(2): 156-62. [In Persian].
22. Mousavifar SA, Zolfaghari M, Pedram S, Haghani H. Evaluation of two follow up methods (Mobile and Phone) on treatment adherence in patients with diabetes. Iran J Diabetes Lipid Disord 2011; 10(4): 407-18. [In Persian].
23. Dehghan M, Dehghan Nayeri N, Iranmanesh S. Validating the Persian version of the hill-bone's scale of "compliance to high blood pressure therapy. British Journal of Medicine and Medical Research 2015; 5(2): 235-46.

24. Dehghan M, Dehghan Nayeri N, Karimzadeh P, Iranmanesh S. Psychometric properties of the Persian version of the Morisky medication adherence scale-8. British Journal of Medicine and Medical Research 2015; 9(9): 1-10.

25. Moharamzad Y, Saadat H, Nakhjavan SB, Rai A, Saadat Z, Aerab-Sheibani H, et al. Validation of the Persian version of the 8-item Morisky Medication Adherence Scale (MMAS-8) in Iranian hypertensive patients. Glob J Health Sci 2015; 7(4): 173-83.

26. Bullinger M, Alonso J, Apolone G, Leplege A, Sullivan M, Wood-Dauphinee S, et al. Translating health status questionnaires and evaluating their quality: the IQOLA Project approach. International quality of life assessment. J Clin Epidemiol 1998; 51(11): 913-23.

27. Acquadro C, Conway K, Hareendran A, Aaronson N. Literature review of methods to translate health-related quality of life questionnaires for use in multinational clinical trials. Value Health 2008; 11(3): 509-21.

28. Tinsley HE, Brown SD. Handbook of applied multivariate statistics and mathematical modeling. Cambridge, MA: Academic Press; 2000.

29. Williams B, Onsman A, Brown T. Exploratory factor analysis: A five-step guide for novices. Journal of Emergency Primary Health Care 2010; 8(3): 1-13.

30. Costello AB, Osborne JW. Best practices in exploratory factor analysis: Four recommendations for getting the most from your analysis. Practical Assessment Research & Evaluatio 2005; 10(7): 1-9.

31. Bollen KA, Barb KH. Pearson's r and coarsely categorized measures. American Sociological Review 1981; 46(2): 232-9.

32. Schumacker R, Lomax RG. A beginner's guide to structural equation modeling. 2nd ed. Abingdon, UK: Psychology Press; 2004.

33. Karimlou M, Zayeri F, Salehi M. Psychometric properties of the Persian version of the World Health Organization's Quality of Life Questionnaire (WHOQOL-100). Arch Iran Med 2011; 14(4): 281-7.

34. Damirchi A, Rahmaninia F, Mirzaei B, Hasan-Nia S, Ebrahimi M. Effect of caffeine on blood pressure during exercise and at rest in overweight men. Int J Endocrinol Metab 2009; 10(6): 623-8. [In Persian].

35. Islami F, Pourshams A, Nasrollahzadeh D, Kamangar F, Fahimi S, Shakeri R, et al. Tea drinking habits and oesophageal cancer in a high risk area in northern Iran: population based case-control study. BMJ 2009; 338: b929.

36. 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.

37. Ogedegbe G, Mancuso CA, Allegrante JP, Charlson ME. Development and evaluation of a medication adherence self-efficacy scale in hypertensive African-American patients. J Clin Epidemiol 2003; 56(6): 520-9.

38. Fernandez S, Chaplin W, Schoenthaler AM, Ogedegbe G. Revision and validation of the Medication Adherence Self-Efficacy Scale (MASES) in hypertensive African Americans. J Behav Med 2008; 31(6): 453-62.

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Biochemical effects of oleuropein in gentamicin-induced nephrotoxicity in rats

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Original Article

Abstract

BACKGROUND: Oleuropein is a natural antioxidant and scavenging free radicals. In the present study, we examined effect of oleuropein on the paraoxonase 1 (PON1) activity, lipid peroxidation, lipid profile, atherogenic indexes, and relationship of PON1 activity by high-density lipoprotein-cholesterol (HDL-C) and atherogenic indices in gentamicin (GM)-induced nephrotoxicity in rats.

METHODS: This is a lab trial study in Khorramabad, Lorestan province of Iran (2013). 30 Sprague-Dawley rats were divided into three groups to receive saline; GM, 100 mg/kg/day; and GM plus oleuropein by 15 mg/kg intraperitoneal daily, respectively. After 12 days, animals were anesthetized, blood samples were also collected before killing to measure the levels of triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL), and very LDL (VLDL), HDL-C, atherogenic index, lipid peroxidation, and the activities of PON1 of all groups were analyzed. Data were analyzed, and $P < 0.050$ was considered significant.

RESULTS: Oleuropein significantly decreased lipid peroxidation, TG, TC, LDL, VLDL, atherogenic index, atherogenic coefficient (AC), and cardiac risk ratio (CRR). HDL-C level was significantly increased when treated with oleuropein. The activity of PON1 in treated animals was (62.64 ± 8.68) that it was significantly higher than untreated animals (47.06 ± 4.10) ($P = 0.047$). The activity of PON1 in the untreated nephrotoxic rats was significantly lower than that of control animals (77.84 ± 9.43) ($P = 0.030$). Furthermore, the activity of PON1 correlated positively with HDL-C and negatively with AC, CRR 1, and CRR 2 in the treated group with oleuropein.

CONCLUSION: This study showed that oleuropein improves PON1 activity, lipid profile, and atherogenic index and can probably decrease the risk of cardiovascular death in nephrotoxic patients.

Keywords: Gentamicin; Paraoxonase 1; Lipid Peroxidation; Nephrotoxicity; Lipid; Rat; Atherogenic Index; Oleuropein

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Introduction

Human serum paraoxonase 1 (PON1) is an antioxidant enzyme in high-density lipoprotein-cholesterol (HDL-C) and is considered the major determinant of the antioxidant action of HDLC.[1] Major part of this enzyme in the serum is associated with HDL-C particles, but a low level of PON1 was also observed in very low-density lipoprotein (VLDL) and postprandial chylomicrons. PON1 inhibits LDL oxidation in vitro, and other studies have shown that PON1 prevents the formation of oxidatively LDL, inactivates LDL-derived oxidized phospholipids, and protects phospholipids in HDL from oxidation.[1,2] PON1 has antiatherogenic properties because PON1 has the ability to protect lipoprotein particles from free radical oxidation, and it can hydrolyze oxidized cholesteryl esters, phosphatidylcholine core aldehydes, and degrade

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hydrogen peroxide.[1-3]

Gentamicin (GM) is a common antibiotic that is used against most of the Gram-negative microorganisms.[4] Therapeutic GM can cause nephrotoxicity and acute kidney injury.[5,6] GM generates reactive oxygen species (ROS) in the kidney.[7] ROS cause of injury and death cells in more tissue such as renal, liver, and lung in pathological conditions.[8] After using GM lipid peroxidation increases and antioxidant such as glutathione, Vitamin E decrease.[9] The most of the researchers recommend the using of natural various antioxidants as supplement or drug against nephrotoxicity and chronic diseases.[10] Natural antioxidant such as rosmarinic acid and coenzyme Q10 and flavonoid compounds such as quercetin have protective effects on various tissue injury such as renal injury and nephrotoxicity.[11-13] Synthetic and chemical antioxidant are not safe, but natural antioxidants are safe and do not side effects; therefore, natural antioxidants are good alternative for prevention of nephrotoxicity induced by GM.[14]

Oleuropein is derived from olive oil and olive leaf.[12] Researchers have reported that oleuropein is a good antioxidant.[15] Previous our study showed that oleuropein has a protective effect on oxidative stress in spinal cord injury.[16] Therefore, oleuropein as antioxidative supplements is good for the prevention of nephrotoxic complications such as hyperlipemia.[17]

Since the effects of oleuropein on lipid profile, atherogenic indexes, PON1 activity and its association with atherogenic indexes in nephrotoxicity induced by GM in rats have not previously been reported; the aims of this lab trial study were to evaluate biochemical effects of oleuropein in GM-induced nephrotoxicity in rats in Khorramabad, Lorestan province of Iran.

Materials and Methods

About 30 male Sprague Dawley rats (180-200 g) were prepared from Pasteur Institute of Tehran, Iran. The animals were divided into three groups randomly including 10 rats each as follows: Group 1 intraperitoneal (i.p.) saline injection, 0.25 ml/day for 12 days; Group 2, GM injection for 12 days; and Group 3, oleuropein, 15 mg/kg/day injection. One hour before, GM injection,[18] 100 mg/kg/day, was injected i.p. for 12 days.[19] After the last injection of GM, blood samples were obtained from animals and serum was separated.

Determination of lipid profile and atherogenic indexes

The serum levels of triglyceride (TG), total cholesterol (TC), LDL, VLDL, HDL-C, and atherogenic index of all groups were measured. TC and TG concentrations were measured by biochemical analyzer using commercial kits (Olympus AU-600, Tokyo, Japan). HDL-C was analyzed by a Pars Azmoon kit from Iran. LDL and VLDL were calculated by Friedewald et al.[20] equation.

The atherogenic index-[log (TG/HDL-C)], the atherogenic coefficient (AC)-[(TC-HDL-C)/HDLC], cardiac risk ratio (CRR): (TC/HDL-C), and CRR: (LDL/HDL-C) were calculated by Ikewuchi and Ikewuchi[21] equation.

Measurement of lipid peroxidation

Serum levels of lipid peroxidation were measured in accordance with previous our study.[22]

Measurement of PON1 activity

PON1 activity was determined using paraoxon as a substrate in accordance with previous our study.[23]

Data between groups were first tested Kruskal–Wallis one-way and then between two groups were analyzed by Mann–Whitney U-test. The Spearman's correlation analysis was used for statistical calculations. Statistical analysis were performed using the SPSS software (version 13, SPSS Inc., Chicago, IL, USA).

Results

The level of FBG, TG, and TC in the untreated nephrotoxic rats was significantly higher than that of control animals. The nephrotoxic rats treated with oleuropein could significantly inhibit the increase of FBG, TG, and TC in comparison with the untreated nephrotoxic animals ($P = 0.001$, $P = 0.001$). The level of TG and TC in the untreated nephrotoxic rats was significantly higher than that of control animals ($P = 0.002$, $P = 0.006$, $P = 0.001$) (Table 1).

The level of HDL in the nephrotoxic rats untreated was not significantly against control animals ($P = 0.615$). The treatment of nephrotoxic rats with oleuropein could not significantly (26.32%) inhibit the decrease of HDL-C in comparison with the nephrotoxic animals ($P = 0.233$) (Table 1). The level of LDL and VLDL in the untreated nephrotoxic rats was higher than that of rats significantly ($P = 0.020$, $P = 0.006$). The treatment of a nephrotoxic animal with oleuropein could significantly inhibit the increase of LDL and in comparison with the untreated nephrotoxic animals ($P = 0.010$).

The level of the atherogenic index and AC in the untreated nephrotoxic rats was significantly higher than that of control animals ($P = 0.044$, $P = 0.003$).

Table 1. Effect of oleuropein on total cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein-cholesterol, very-LDL atherogenic index, atherogenic coefficient, cardiac risk ratio 1, CRR 2, level of lipid peroxidation and paraoxonase 1 activity in nephrotoxic rats

Parameter	Control	Nephrotoxic	Nephrotoxic + OLE	P
	Mean ± SD	Mean ± SD	Mean ± SD	
FBG	111.17 ± 18.90*	143.00 ± 21.27	110.00 ± 13.91*	0.009
TG (mg/dl)	62.00 ± 14.38*	79.71 ± 10.70	83.60 ± 8.08**	0.013
TC (mg/dl)	108.50 ± 13.08*	159.00 ± 39.16	116.00 ± 13.08*	0.009
HDL-C (mg/dl)	47.47 ± 18.48	42.97 ± 12.56	54.28 ± 14.05	0.463
LDL (mg/dl)	48.63 ± 19.78*	100.08 ± 44.85	45.00 ± 25.64*	0.017
VLDL (mg/dl)	12.40 ± 2.87*	15.94 ± 2.14	16.72 ± 1.62**	0.036
Atherogenic index [(units) (log (TG/HDL-C))]	0.13 ± 0.05*	0.29 ± 0.01	0.19 ± 0.02*	0.021
AC [(TC-HDL-C)/HDL-C]	1.51 ± 0.75*	3.06 ± 1.66	1.28 ± 0.68*	0.036
CRR 1 (TC/HDL-C)	2.51 ± 0.75	4.05 ± 1.66	2.28 ± 0.69	0.360
CRR 2 (LDL/HDL-C)	1.23 ± 0.68*	2.65 ± 1.55	2.28 ± 0.69*	0.033
Lipid peroxidation (nmol/mg protein)	82.48 ± 20.40*	128.18 ± 7.36	95.52 ± 38.39*	0.029
PON1 activity (nmol/min/ml)	77.84 ± 9.43*	47.06 ± 4.10	62.64 ± 8.68*	0.039

*Significant change in comparison with nephrotoxic without treatment at P < 0.050, **Significant change in comparison with control at P < 0.050; OLE: Oleuropein; FBG: Fasting blood glucose; TG: Triglyceride; TC: Total cholesterol; HDL-C: High-density lipoprotein-cholesterol; LDL: Low-density lipoprotein; VLDL: Very low-density lipoprotein; PON1: Paraoxonase 1; AC: Atherogenic coefficient; CRR: Cardiac risk ratio

Oleuropein decreases significantly atherogenic index and AC in comparison with the untreated nephrotoxic animals (P = 0.032). The level of AC in the untreated rats was significantly (2.02-fold) higher than that of control animals (P = 0.003, P = 0.002) (Table 1). The level of CRR 1 and CRR 2 in the untreated rats was significantly higher than that of control animals (P = 0.003, P = 0.003). Oleuropein decrease significantly (43.71%) inhibit CRR 1 and CRR 2 in comparison with the untreated animals (P = 0.001, P = 0.001) (Table 1).

The level of lipid peroxidation in the untreated nephrotoxic rats was significantly (1.55-fold) higher than that of control rats (P = 0.032). Oleuropein decrease significantly (25.48%) level of lipid peroxidation in with the untreated nephrotoxic animals (P = 0.050). The treatment of a nephrotoxic animal with oleuropein could significantly (33.11%) elevate the decrease of PON1 activity (Table 1) (P = 0.047).

The activity of PON1 correlated positively with HDL-C (r = 0.291, P = 0.006) (Figure 1). The activity of PON1 correlated coefficient (r = -0.404, P = 0.001) (Figure 2), CRR 1 (r = -0.273, P = 0.009) (Figure 3) and CRR 2 (r = -0.228, P = 0.018) (Figure 4).

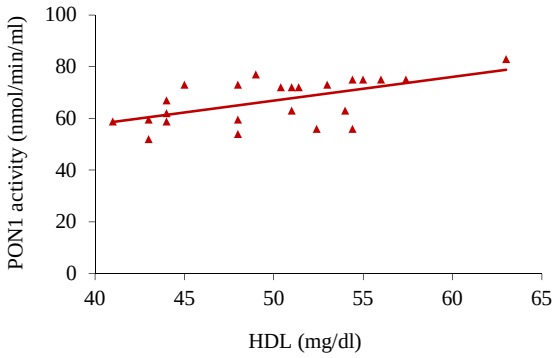

Figure 1. Correlation between maternal serum paraoxonase 1 (PON1) activity and levels of high-density lipoprotein (HDL) cholesterol in nephrotoxic rats treated with oleuropein

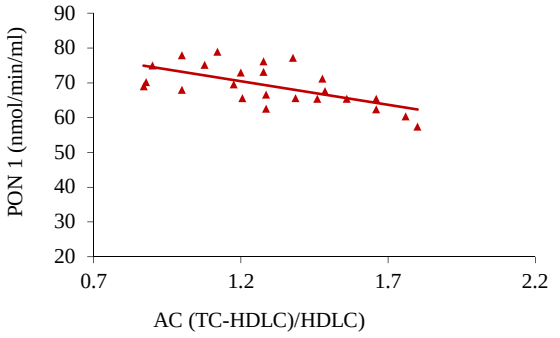

Figure 2. Correlation between maternal serum paraoxonase 1 (PON1) activity and levels of the atherogenic coefficient (AC) [TC (TC-HDL-C)/HDL-C] in nephrotoxic rats treated with oleuropein
TC: Total cholesterol; HDL-C: High-density lipoprotein-cholesterol

Discussion

Effect of oleuropein on serum level of malondialdehyde (MDA) and PON1 activity and it correlation with HDL and atherogenic index nephrotoxicity significantly increased serum lipid peroxidation concentrations and decreased PON1 activity in comparison with the control group.

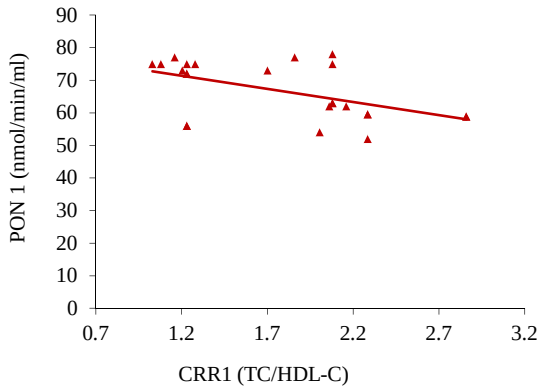

Figure 3. Correlation between maternal serum paraoxonase 1 (PON1) activity and levels of cardiac risk ratio 1 (CRR 1) [CRR (TC/HDL-C)] in nephrotoxic rats treated with oleuropein
TC: Total cholesterol; HDL-C: High-density lipoprotein-cholesterol

Treatment of nephrotoxic animals with oleuropein significantly inhibited the increase of serum lipid peroxidation concentrations. Furthermore, the treatment of nephrotoxic animals with oleuropein significantly inhibited of serum PON1 activity in comparison with the untreated animals. The most relevant finding of this study is that activity of PON1 correlated positively with HDL and negatively with AC CRR 1 and CRR 2 in treated nephrotoxic animals. Researchers showed that PON1 as the antioxidant enzyme inhibit the oxidative modification of LDL and contribute to most of the antioxidative activity that has been attributed to HDL.[24] PON1 activity was positively correlated with HDL-C level.[25]

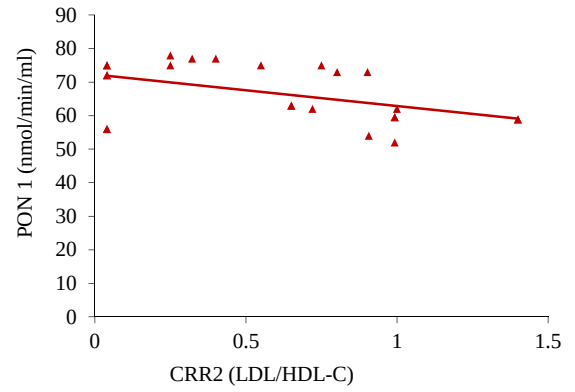

Figure 4. Correlation between maternal serum paraoxonase 1 (PON1) activity and levels of cardiac risk ratio 2 (CRR 2) [CRR (LDL/HDL-C)] in nephrotoxic rats treated with oleuropein
LDL: Low-density lipoprotein; HDL-C: High-density lipoprotein-cholesterol

This study showed that the level of HDL correlated positively with PON1 activity. Furthermore, CRR 1, CRR 2, and AC correlated negatively with PON1 activity in treated animals. Researchers showed that PON1 has good effects on lipid and lipoprotein metabolism.[26] Furthermore; many studies showed that PON1 as the antioxidant enzyme decrease formation of different types modified LDL such as oxidized LDL. Modified LDL such as oxidized LDL and glycosylated LDL are risk factors for atherogenesis. Therefore, PON1 as the antioxidant enzyme inhibit atherogenesis.[25-28] Many studies showed that oxidative stress case creation of nephrotoxic complications such as liver and renal injury and hyperlipemia.[28-30] Therefore, numerous reports and our results indicated that the using of natural antioxidants such as Vitamin E, coenzyme Q10, rosmarinic acid, phenol and flavonoid compounds as supplementary prevent nephrotoxic complications including of liver and renal injury and hyperlipemia.[12,13,31-34]

Effect of oleuropein on serum lipid profile and atherogenic index

Nephrotoxicity significantly increased serum level of FBG, TG, TC, VLDL, and LDL in untreated animals. Treatment of nephrotoxic animals with oleuropein significantly inhibited the increase of serum level of FBG, TG, TC, VLDL and LDL, CRR, AC, and atherogenic index in treated nephrotoxic animals. Moreover, oleuropein significantly inhibited decrease of serum HDL-C concentrations in treated nephrotoxic animals. There are reports that natural antioxidant such as alpha lipoic acid, Vitamin C, Vitamin E, coenzyme Q10, selenium and natural phenolic compounds have hypolipidemic effects.[35,36] In addition, Andreadou et al.[37] showed oleuropein could reduce serum levels of TC and TG in hypercholesterolemic rabbits.

Therefore, numerous reports and our results indicated that the using of oleuropein similarity to natural antioxidants such as Vitamin E, coenzyme Q10, phenol and flavonoid compounds decrease cholesterol, TG, and lipoproteins. As supplementary prevent nephrotoxic complications including of liver and renal injury and hyperlipemia.[35-37]

Therefore, natural antioxidant such as oleuropein has hypolipidemic and antioxidative, and it prevent nephrotoxic complications including of liver and renal injury and hyperlipemia. The mechanisms hypolipidemic effects of oleuropein by which oleuropein is not well known. The

mechanism of hypolipidemic and antiatherogenic action of oleuropein and others natural antioxidant may be due to the inhibition of dietary lipid digestion and absorption and lipid and lipoprotein metabolism pathways.[38-40] Furthermore, oleuropein and anthers antioxidants have antioxidant activities and prevent glycation lipoproteins, enzymes, and proteins that involve lipid and lipoprotein metabolism pathways.[39-42]

Although the detailed molecular protective mechanisms of oleuropein cannot be fully explained by our results, our results are satisfactory oleuropein as a natural antioxidant with multi-beneficial properties can be introduced for inhibition of stress oxidative in patients.

Conclusion

This study showed that oleuropein has beneficial effects in increasing the reduced serum level of HDL and PON1 activity in nephrotoxic rats.

This study showed that level of HDL was correlated positively with PON1 activity HDL, and the atherogenic index was correlated negatively with PON1 activity. Moreover, this study showed oleuropein has hypolipidemic and antiatherogenic effects and protective effects on lipid peroxidation and PON1 activity in nephrotoxic rats. Hence, oleuropein is a good antioxidant, and it introduces as the antiatherogenic compound that can decrease the risk of cardiovascular death in nephrotoxic.

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Conflict of Interests

Authors have no conflict of interests.

References

1. Sumegova K, Nagyova Z, Waczulikova I, Zitnanova I, Durackova Z. Activity of paraoxonase 1 and lipid profile in healthy children. Physiol Res 2007; 56(3): 351-7.
2. Bacanu E, Lixandru D, Stoian I, Ionescu-Targoviste C. Paraoxonase 1 could reverse the oxidative changes induced by triglyceride-rich lipoproteins in diabetes. Proc Rom Acad 2012; 1: 20-6.
3. Sztanek F, Seres I, Harangi M, Locsey L, Padra J, Paragh GJ, et al. Decreased paraoxonase 1 (PON1) lactonase activity in hemodialyzed and renal transplanted patients. A novel cardiovascular biomarker in end-stage renal disease. Nephrol Dial Transplant 2012; 27(7): 2866-72.
4. Nasri H, Nematbakhsh M, Ghobadi S, Ansari R, Shahinfard N, Rafieian-Kopaei M. Preventive and curative effects of ginger extract against histopathologic changes of gentamicin-induced tubular toxicity in rats. Int J Prev Med 2013; 4(3): 316-21.
5. McKeage K, Deeks ED. Doxycycline 40 mg capsules (30 mg immediate-release/10 mg delayed-release beads): anti-inflammatory dose in rosacea. Am J Clin Dermatol 2010; 11(3): 217-22.
6. Manikandan R, Beulaja M, Thiagarajan R, Priyadarsini A, Saravanan R, Arumugam M. Ameliorative effects of curcumin against renal injuries mediated by inducible nitric oxide synthase and nuclear factor kappa B during gentamicin-induced toxicity in Wistar rats. Eur J Pharmacol 2011; 670(2-3): 578-85.
7. Banday AA, Farooq N, Priyamvada S, Yusufi AN, Khan F. Time dependent effects of gentamicin on the enzymes of carbohydrate metabolism, brush border membrane and oxidative stress in rat kidney tissues. Life Sci 2008; 82(9-10): 450-9.
8. Whaley-Connell A, Sowers JR. Oxidative stress in the cardiorenal metabolic syndrome. Curr Hypertens Rep 2012; 14(4): 360-5.
9. Taye A, Ibrahim BM. Activation of renal haeme oxygenase-1 alleviates gentamicin-induced acute nephrotoxicity in rats. J Pharm Pharmacol 2013; 65(7): 995-1004.
10. Randjelovic P, Veljkovic S, Stojiljkovic N, Velickovic L, Sokolovic D, Stoiljkovic M, et al. Protective effect of selenium on gentamicin-induced oxidative stress and nephrotoxicity in rats. Drug Chem Toxicol 2012; 35(2): 141-8.
11. Nematbakhsh M, Ashrafi F, Safari T, Talebi A, Nasri H, Mortazavi M, et al. Administration of vitamin E and losartan as prophylaxes in cisplatin-induced nephrotoxicity model in rats. J Nephrol 2012; 25(3): 410-7.
12. Tavafi M, Ahmadvand H. Effect of rosmarinic acid on inhibition of gentamicin induced nephrotoxicity in rats. Tissue Cell 2011; 43(6):392-397.
13. Ahmadvand H, Ghasemi Dehnoo M, Dehghani A, Bagheri S, Cheraghi RA. Serum paraoxonase 1 status and its association with atherogenic indexes in gentamicin-induced nephrotoxicity in rats treated with coenzyme Q10. Ren Fail 2014; 36(3):413-8.
14. Achat S, Tomao V, Madani K, Chibane M, Elmaataoui M, Dangles O, et al. Direct enrichment of olive oil in oleuropein by ultrasound-assisted maceration at laboratory and pilot plant scale. Ultrason Sonochem 2012; 19(4): 777-86.
15. Rietjens SJ, Bast A, Haenen GR. New insights

into controversies on the antioxidant potential of the olive oil antioxidant hydroxytyrosol. J Agric Food Chem 2007; 55(18): 7609-14.
16. Khalatbary AR, Ahmadvand H. Neuroprotective effect of oleuropein following spinal cord injury in rats. Neurol Res 2012; 34(1): 44-51.
17. Loued S, Berrougui H, Componova P, Ikhlef S, Helal O, Khalil A. Extra-virgin olive oil consumption reduces the age-related decrease in HDL and paraoxonase 1 anti-inflammatory activities. Br J Nutr 2013; 110(7): 1272-84.
18. Alirezaei M, Dezfoulian O, Neamati S, Rashidipour M, Tanideh N, Kheradmand A. Oleuropein prevents ethanol-induced gastric ulcers via elevation of antioxidant enzyme activities in rats. J Physiol Biochem 2012; 68(4): 583-92.
19. Polat A, Parlakpinar H, Tasdemir S, Colak C, Vardi N, Ucar M, et al. Protective role of aminoguanidine on gentamicin-induced acute renal failure in rats. Acta Histochem 2006; 108(5): 365-71.
20. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18(6): 499-502.
21. Ikewuchi CJ, Ikewuchi CC. Alteration of Plasma Lipid Profiles and Atherogenic Indices by Stachytarpheta jamaicensis check for this species in other resources L. (Vahl). Biokemistri, 2009; 21(2): 71-7.
22. Ahmadvand H, Tavafi M, Khosrowbeygi A. Amelioration of altered antioxidant enzymes activity and glomerulosclerosis by coenzyme Q10 in alloxan-induced diabetic rats. J Diabetes Complications 2012; 26(6): 476-82.
23. Charlton-Menys V, Liu Y, Durrington PN. Semiautomated method for determination of serum paraoxonase activity using paraoxon as substrate. Clin Chem 2006; 52(3): 453-7.
24. Aviram M, Kaplan M, Rosenblat M, Fuhrman B. Dietary antioxidants and paraoxonases against LDL oxidation and atherosclerosis development. Handb Exp Pharmacol 2005; (170): 263-300.
25. Mohamadin AM, Habib FA, Elahi TF. Serum paraoxonase 1 activity and oxidant/antioxidant status in Saudi women with polycystic ovary syndrome. Pathophysiology 2010; 17(3): 189-96.
26. Gocmen AY, Sahin E, Kocak H, Tuncer M, Gumuslu S. Levels of asymmetric dimethylarginine, nitric oxide and lipid peroxidation markers in patients with end-stage renal disease having peritoneal dialysis treatment. Clin Biochem 2008; 41(10-11): 836-40.
27. Razavi AE, Ani M, Pourfarzam M, Naderi GA. Associations between high density lipoprotein mean particle size and serum paraoxonase-1 activity. J Res Med Sci 2012; 17(11): 1020-6.
28. Yilmaz N, Simsek N, Aydin O, Yardan E, Aslan S, Eren E, et al. Decreased paraoxonase 1, arylesterase enzyme activity, and enhanced oxidative stress in patients with mitral and aortic valve insufficiency. Clin Lab 2013; 59(5-6): 597-604.
29. Bulbuller N, Eren E, Ellidag HY, Oner OZ, Sezer C, Aydin O, et al. Diagnostic value of thiols, paraoxonase 1, arylesterase and oxidative balance in colorectal cancer in human. Neoplasma 2013; 60(4): 419-24.
30. Ferretti G, Bacchetti T, Masciangelo S, Grugni G, Bicchiega V. Altered inflammation, paraoxonase-1 activity and HDL physicochemical properties in obese humans with and without Prader-Willi syndrome. Dis Model Mech 2012; 5(5): 698-705.
31. Kremastinos DT. Olive and oleuropein. Hellenic J Cardiol 2008; 49(4): 295-6.
32. Matough FA, Budin SB, Hamid ZA, Alwahaibi N, Mohamed J. The role of oxidative stress and antioxidants in diabetic complications. Sultan Qaboos Univ Med J 2012; 12(1): 5-18.
33. Sadeghi F, Nematbakhsh M, Noori-Diziche A, Eshraghi-Jazi F, Talebi A, et al. Protective effect of pomegranate flower extract against gentamicin-induced renal toxicity in male rats. J Renal Inj Prev 2015; 4(2):45-50.
34. Tavafi M. Antioxidants against contrast media induced nephrotoxicity. J Renal Inj Prev 2014; 3(2):55-56.
35. Amom Z, Zakaria Z, Mohamed J, Azlan A, Bahari H, Taufik Hidayat BM, et al. Lipid lowering effect of antioxidant alpha-lipoic Acid in experimental atherosclerosis. J Clin Biochem Nutr 2008; 43(2): 88-94.
36. Shargorodsky M, Debby O, Matas Z, Zimlichman R. Effect of long-term treatment with antioxidants (vitamin C, vitamin E, coenzyme Q10 and selenium) on arterial compliance, humoral factors and inflammatory markers in patients with multiple cardiovascular risk factors. Nutr Metab (Lond) 2010; 7: 55.
37. Andreadou I, Iliodromitis EK, Mikros E, Constantinou M, Agalias A, Magiatis P, et al. The olive constituent oleuropein exhibits anti-ischemic, antioxidative, and hypolipidemic effects in anesthetized rabbits. J Nutr 2006; 136(8): 2213-9.
38. Garjani A, Fathiazad F, Zakheri A, Akbari NA, Azarmie Y, Fakhrjoo A, et al. The effect of total extract of Securigera securidaca L. seeds on serum lipid profiles, antioxidant status, and vascular function in hypercholesterolemic rats.

J Ethnopharmacol 2009; 126(3): 525-32.
39. Heidarian E, Soofiniya Y. Hypolipidemic and hypoglycemic effects of aerial part of Cynara scolymus in streptozotocin-induced diabetic rats. J Med Plant Res 2011; 5(13): 2717-23.
40. Jemai H, Bouaziz M, Fki I, El FA, Sayadi S. Hypolipidimic and antioxidant activities of oleuropein and its hydrolysis derivative-rich extracts from Chemlali olive leaves. Chem Biol Interact 2008; 176(2-3): 88-98.
41. Ahmadvand H, Noori A, Dehnoo MG, Bagheri S, Cheraghi RA. Hypoglycemic, hypolipidemic and antiatherogenic effects of oleuropein in alloxan-induced Type 1 diabetic rats. Asian Pacific Journal of Tropical Disease 2014; 4(Suppl 1): S421-S425.
42. Wainstein J, Ganz T, Boaz M, Bar DY, Dolev E, Kerem Z, et al. Olive leaf extract as a hypoglycemic agent in both human diabetic subjects and in rats. J Med Food 2012; 15(7): 605-10.

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Policy makers' viewpoints on implementation of the World Health Organization Framework Convention on Tobacco Control in Iran: A qualitative investigation of program facilitators

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Original Article

Abstract

BACKGROUND: The epidemic of smoking is a great concern of health systems. Moreover, the number of smokers is increasing worldwide and this has led to an escalating trend of morbidity, mortality, and burden of smoking-related diseases. Therefore, monitoring the implementation of tobacco control laws in different countries is of extreme importance. This study aimed to describe policy makers' experiences and perceptions of the facilitating factors of the implementation of the World Health Organization Framework Convention on Tobacco Control (WHO FCTC) in Iran.

METHODS: This was a qualitative research in which data were collected through individual interviews. The participants included policy makers who were members of the national assembly for tobacco control. In this study, 13 unstructured interviews of about 45 to 60 minutes duration were conducted in an extrapolative manner. The qualitative content analysis method was applied until extrapolation of basic themes was complete.

RESULTS: As a result of the analysis, the themes of performance through training, through research, through intersectoral collaboration, and through setting priorities emerged. The emerged themes connote some critical points that have key roles in promoting the effective implementation of the WHO FCTC. Furthermore, the main role of the health sector becomes predominant.

CONCLUSION: The study findings suggested the managed and coordinated work as one of the main facilitating factors of the implementation of the WHO FCTC at a national level.

Keywords: Tobacco; Policy Makers; Qualitative; WHO; FCTC; Iran

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Introduction

The epidemic of smoking is increasing worldwide and has expanded from high-income countries to low-income regions[1] and it has led to an escalating trend of morbidity, mortality and burden of the smoking-related diseases.[2] Tobacco use is now widely recognized to be the single most important preventable cause of health problems worldwide;[1] it is, therefore, imperative that preventive action is taken against its health hazards.

Similar to many other developing countries, smoking is a public health concern in Iran, with a prevalence of 34.7% among males and 6.7% among females.[3] The mean age of beginning

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smoking is 13 years.[4] Now the smoking has a great economic and disease burden for all age groups in the Iranian Society.[5] Consequently, in response to this challenge, in 2003, the World Health Organization Framework Convention on Tobacco Control (WHO FCTC) was developed in 38 articles, as the first treaty negotiated under the auspices of this organization.[6] The treaty was adopted by the 56th World Health Assembly (WHA). Coming into force on February 27, 2005, the FCTC was signed by 168 countries[7] including Iran[8] and was undertook as an evidence-based public health priority that reaffirms the right of all people to the highest standard of health.

For implementation of FCTC, countries had to ratify their signatures. At the commencement, 40 countries ratified it, and the rest of them ratified it from April 2006. The follow-up and reporting of FCTC implementation is being done by the United Nations Secretariat.

Right away after its approval, according to the first article of this law, the national assembly of tobacco control was structured with the membership of the Ministers of Health and Medical Education, Training and Education and Commerce, as well as the chief of military power, two representative of the parliament health commission, director of national radio and television broadcasting organization and the representative of one non-governmental organization. Codification of this regulation, its implementation and monitoring are assigned by this assembly, and its members are the stakeholders of tobacco and health at country level.

Now the successful implementation of the FCTC regulation needs a great commitment from the health system in collaboration with other related sectors. As considered in FCTC design, "effective laws must not only prescribe evidence-based measures to protect health, but also provide a clear and comprehensive framework that will maximize compliance, ease enforcement, facilitate inspection and monitoring, and minimize the risk of confusion and legal challenge."[6] Therefore, monitoring and evaluation of the implementation of tobacco control laws in different countries is extremely important.

Several studies have tried to discover the influencing factors (consisted of facilitating and restraining factors) of the implementation of the FCTC.[9-12] Nevertheless, there was no similar study in Iran. Therefore, the main study was conducted in 2007-2008 to design a practical model of evaluation of FCTC implementation in Iran with the potential to be adopted in the region.[13] Data were updated and analyzed since 2012. The present study that reports a part of findings of the main study, aimed to introduce some of the main facilitating factors of the implementation of the FCTC in Iran based on the policy makers' experiences and perceptions.

Materials and Methods

A thematic analysis method is followed as an appropriate way to study of the participants' experiences and perceptions in a natural context.

This nationwide study was conducted in Iran. The steering committee was established in Isfahan Cardiovascular Research Center, Iran. The study participants consisted of policy makers who were the members of the national assembly for tobacco control. The eligible policymakers were recruited to the study through purposive sampling method and were interviewed individually. Written informed consent was taken after explaining the objectives of study, moreover, we got their permission to record the interviews, and we assured them that their speeches will be kept confidential. The interview was unstructured; each interview lasted about 45-60 minutes. General question that was asked from the participants were as follows: Please fell your experiences about participating in designing or implementation of FCTC in Iran. All interviews were recorded, then the written transcript was prepared and reviewed several times by the interviewer, and all the sub-concepts of meaning were extracted.

A thematic analysis method[14] was used to analyze the data. The transcripts were read and coded by the two independent researchers. The common codes then were merged to develop related themes and sub-themes using constant comparative analysis. Theme choices were discussed in research team, and the final results were reviewed and agreed by the team members.

An adequate number of participants was recruited to support trustworthiness of the study. Moreover, text coding and data analysis were performed by the two researchers independently to ensure consistency and finally, a level of saturation was reached through the analytical process. Data were collected by the digital audio recorder and recorded interviews were transcribed verbatim to prevent any missing in the data.

Results

A total of 13 policy-makers were interviewed. The following themes have identified as key facilitators to effective implementation of FCTC: (1) doing

through training, (2) doing through research, (3) doing through intersectoral collaboration, and (4) doing through setting priorities.

Theme 1: Doing through training

Based on the findings, training was identified as an appropriate method of ensuring general population and policymakers' readiness to accept and follow the FCTC regulations.

Training of policymakers: As it is evident from the participant's statements, the policymakers' training about the strategies, benefits, and limitations of the FCTC is important to ensure their favorable knowledge and attitudes:

"…policymakers' knowledge about smoking and its harmful effect on community health should increase, and their attitude toward it must change, it can be obtained only through education …" (Participant no. 6).

"…policymakers are decision makers and have key role in carrying out the law, therefore, they should have comprehensive information about FCTC, …" (Participant's no. 3).

The two above sentences refer to this point that periodic education is necessary for policymakers.

Training of general population: General populations are someone who supposed to get benefit from the disease prevention and health promotion strategies such as FCTC. Therefore, it would be important to get sensitized about the health risks and get ready to accept and follow the health promoting directions. Based on the findings, it could be reached through excellent target specific public announcements.

"….designing the caution label on cigarette pockets is one of the ways to inform people about negative outcomes of smoking as a high risk behavior …." (Participant no. 10), participant no. 8 and 13 referred to this subject as well.

"….radio and television broadcasting should have various continuous regular educational programs designed for different age groups about the adverse effects of smoking water pipe on health and introducing it as a high risk behavior to the general population…." (Participant no. 2).

Another participant (no. 13) referred to this point that even negative characters in films should not smoke because this would act as an indirect type of appealing youths to smoking. "….publications and newspapers are an appropriate media for educating the general population about harmful effects of smoking and giving them an opinion to stop smoking…." (Participant no. 1).

Moreover, the findings revealed the importance of training, organizations, and medical universities besides the individual and public levels of training because of their key roles in the community.

"….education and training organization and medical universities have key roles in preventing the configuration of high risk behaviors through arrangement of educational course about smoking, its harmful effects, health hazards and related diseases…." (Participant no. 9).

Strengthening the psychosocial skills was identified as another important training need of population.

"Training the skill of telling no specially to peers, as well as self- regulation are very important in preventing the tendency to high risk behaviors such as smoking…." (Participant no. 7).

Theme 2: Doing through research

The participants believed that the establishment of research and monitoring system would be a key factor to ensure appropriate implementation of the FCTC, although they pointed out that sometimes lack of such system has challenged them in needs assessment and establish tailored regulations and directions. The following statements support our findings:

"….. we do not have a surveillance system for regular collection of valid statistics about trend of smoking in different provinces …" (Participant no. 5).

"…. the reasons of the tendency of adolescents to smoking should be assessed…" (Participant no. 2).

Theme 3: Doing through intersectoral collaboration

The study findings revealed that correct implementation, as well as follow-up of the implementation of interventions at community level would take place within a host of formal and informal intersectoral collaboration. This can be concluded from the following participants' statements who perceived the cooperation and collaboration as one of the main predictors of success in such a national level health related program:

"Based on my experiences … cooperation and coordination between tobacco production company and the Ministry of Agriculture for decision making about cultivating tobacco and related cultivated area is necessary…." (Participant no. 2).

"…. Interaction between governmental and private quarters and follow-up of the common strategies is of high importance…." (Participant no. 3).

Some of the other participants (no. 7, 11, 13, 1, 10, 4, 6 and 9) also believed that various organizations should be united for proper

implementation of FCTC in the country.

Theme 4: Doing through defining rubrics

The study findings revealed that the policymakers could approach the aims of disease prevention and health promotion through setting strategies and priorities of the program. They should also introduce the policies and directions to the stakeholders and the program audiences. Defining rubrics means delineation of a standard of performance for the program audiences. In this study, samples of rubrics was smoking prohibition in roofed places, revising tobacco control policies, smuggling control, increasing the taxes and prices of tobacco products, establishment of tobacco cessation clinics and counseling centers, issuance sale justification for some limited stores with emphasis on prohibit the sale of tobacco to younger people, regular feedback to policymakers about the program progress, practicable decision making about waterpipe use, amount of tobacco cultivation and alternative cultures bear testimony to the executive strategies of implementing FCTC.

The participants emphasized that the strategies and priorities of the program should be outlined and clarified for the program audiences. The following sample statements support our findings:

"…. Smoking in roofed places is forbidden, this rule needs reinforcement. I think that non-smokers individuals can be good supportive group for this program…" (Participant no. 2).

"…. Smoking cessation clinics can give good direction and counseling to people…." (Participant no. 6).

Discussion

The current study aimed to explore and describe the policymakers' experiences and perceptions about facilitating factors of implementation of FCTC in Iran. The findings showed that some factors such as training, search, intersectoral collaboration, identifying strategies, and priorities have key roles in the implementation of FCTC in Iran. Our findings are supported by some researchers who have considered some similar issues as key areas that should be considered in tobacco control.[15] The key role of collaboration to succeed health programs and other initiatives have emphasized in the literature.[16-18]

Doing through training has been perceived as a main strategy through which policy makers attempted to make the stakeholders aware of tobacco control regulations and make them ready to accept and join to tobacco control activities. Therefore, it would be worthwhile to recommend that the health professionals along with people get culture and region specific training. It is demonstrated that lower levels of education and income are associated with higher nicotine dependence and higher heaviness of smoking scores, respectively.[19] Such evidence pose a special responsibility on governments and policymakers to pay more attention to such vulnerable populations and to design some appropriate practical programs for them.

As pursued by Philip Morris, because of core similarities in the lifestyles and needs of young tobacco consumers worldwide, standardized global marketing efforts can be adopted as a central advertising production bank along with creating regionally appropriate individual advertisements.[20] International Tobacco Control project confirmed previous studies that had formed the evidence base for the FCTC policy recommendations, particularly the use of graphic warning labels banning of "light" and "mild" descriptors, smoking bans, increasing tax and price, banning tobacco advertisements and using new cigarette product testing methods.[21]

Another way of promoting tobacco control interventions has been focused on establishing a research and monitoring system through which the policy makers, health professionals as well as people get valid information about the trends of smoking and tobacco control in particular regions. It is demonstrated that integrating evidence-based practice for tobacco control is of particular importance for the people. Therefore, the strategic efforts must be directed at advancing applied health researches that evaluated best educational strategies for promoting tobacco control.[22]

Other researchers have supported our study participants' perception of the importance of intersectoral cooperation and collaboration as one of the main predictors of success in the tobacco control program.[23] The Tobacco Control Program is an excellent situation in which legislators and policy makers of business, education and management sectors could collaborate to reinforce strategies to develop non-smoking and quit-smoking initiatives.[24]

As our study findings showed, another way of ensuring successfully establishing tobacco control initiative is doing through defining rubrics. This idea is also supported and piloted internationally. As an example, in 2003, India has passed its national tobacco control legislation (India Tobacco Control Act) which consisted of provisions to reduce tobacco use and protect citizens from exposure to smoke;

which was found to be effective in reducing prevalence of tobacco use and reduction in the expenditures related to tobacco use in this country.[25] Another study revealed that workplace intervention aiming to help individuals to quit smoking, and consistent evidence was found that workplace tobacco policies and bans can decrease cigarette consumption during the working day by smokers and exposure of non-smoking employees to environmental tobacco smoke at work.[26] Similarly, a study in New-Zealand revealed that the scientific and public health case for introducing comprehensive smoke-free legislation that would cover all indoor places and workplaces should be considered a public health priority for legislators.[2] However, some evidence revealed that existing inconsistencies about the tobacco control directions and legislations may lead to raise disadvantages. For example, Park et al.[27] have emphasized on the Korean policymakers' disagree with the Tobacco Business Act, which aims to improve tobacco business. They believe that this is entirely incompatible with the establishment of active social welfare policies to improve the quality of people's lives.

Hence, it is critical to be sure that the rules and strategies are clearer and consistent with policies to promote health.

Conclusion

The FCTC is considered as an international program to promote public health through reducing the health consequences of tobacco use. In this regard, the points of view of all stakeholders should be taken into account for developing practical and sustainable interventions for this convention. Moreover, scientific evidence shall be used to guide the formulation of evidence-based tobacco control policies. As suggested by the stakeholders in the current study, periodically update and review of the well-defined, comprehensive multisectoral national tobacco control strategies, plan, and programs in agreement with FCTC and policy evaluation studies are necessary to determine policy impact and potential synergies across policies.

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Conflict of Interests

Authors have no conflict of interests.

References

1. World Health Organization. Tobacco or health: a global status report. Geneva, Switzerland: World Health Organization; 1997.
2. Edwards R, Thomson G, Wilson N, Waa A, Bullen C, O'Dea D, et al. After the smoke has cleared: evaluation of the impact of a new national smoke-free law in New Zealand. Tob Control 2008; 17: e2.
3. Farzadfar F, Danaei G, Namdaritabar H, Rajaratnam JK, Marcus JR, Khosravi A, et al. National and subnational mortality effects of metabolic risk factors and smoking in Iran: a comparative risk assessment. Popul Health Metr 2011; 9(1): 55.
4. Kelishadi R, Ardalan G, Gheiratmand R, Majdzadeh R, Delavari A, Heshmat R, et al. Smoking behavior and its influencing factors in a national-representative sample of Iranian adolescents: CASPIAN study. Prev Med 2006; 42(6): 423-6.
5. Asre Khabar. What is the cost of Iranian daily smoking? How many percent of girls smoke? [Online]. [cited 2013 May 21]; Available from: URL: http://www.asrkhabar.com/fa/news/19520 [In Persian].
6. World Health Organization. Who framework convention on tobacco control [Online]. [cited 2003]; Available from: URL: http://www.who.int/tobacco/framework/WHO_FCTC_english.pdf
7. Sarrafzadegan N, Rabiei K, Abedi H, Kelishadi R, Fereydoun Mohaseli K, Alavi M, et al. Indicators developed to evaluate the international framework convention on tobacco control in Iran; A grounded theory study. Iran J Med Sci 2014; 39(2 Suppl): 213-7.
8. Islamic Parliament Research Center. The Government of the Islamic Republic's accession to the World Health Organization Framework Convention on Tobacco Control [Online]. [cited 2005]; Available from: URL: http://rc.majlis.ir/fa/law/show/97946 [In Persian].
9. World Health Organization. Interactive Word-based WHO FCTC reporting instrument and Cover note/instructions [Online]. [cited 2011]; Available from: URL: http://www.who.int/tobacco/framework/cop/reporting_instrument/en/
10. Sarrafzadegan N, Rabiei K, Mohaseli KF, Manzouri L, Roohafza H, Kelishadi R, et al. Do Iranian tobacco growers support the World Health Organization framework convention on tobacco

control? J Educ Health Promot 2014; 3: 32.
11. Fong GT, Cummings KM, Borland R, Hastings G, Hyland A, Giovino GA, et al. The conceptual framework of the International Tobacco Control (ITC) Policy Evaluation Project. Tob Control 2006; 15: iii3-iii11.
12. Erguder T, Cakir B, Aslan D, Warren CW, Jones NR, Asma S. Evaluation of the use of Global Youth Tobacco Survey (GYTS) data for developing evidence-based tobacco control policies in Turkey. BMC Public Health 2008; 8(Suppl 1): S4.
13. Sarrafzadegan N, Kelishad R, Rabiei K, Abedi H, Mohaseli KF, Masooleh HA, et al. A comprehensive model to evaluate implementation of the world health organization framework convention of tobacco control. Iran J Nurs Midwifery Res 2012; 17(3): 244-54.
14. Watson R, McKenna H, Cowman S, Keady J. Nursing research: designs and methods. New York, NY: Elsevier Health Sciences; 2008.
15. Joossens L. From public health to international law: possible protocols for inclusion in the Framework Convention on Tobacco Control. Bull World Health Organ 2000; 78(7): 930-7.
16. Irajpour A, Ghaljaei F, Alavi M. Concept of collaboration from the Islamic perspective: the view points for health providers. J Relig Health 2015; 54(5): 1800-9.
17. Alavi M, Irajpour A, Abdoli S, Saberizafarghandi MB. Clients as mediators of inter professional collaboration in mental health services in Iran. J Interprof Care 2012; 26(1): 36-42.
18. Alavi M, Irajpour A, Giles T, Rabiei K, Sarrafzadegan N. Barriers to education in cardiac rehabilitation within an Iranian society: a qualitative descriptive study. Contemp Nurse 2013; 44(2): 204-14.
19. Siahpush M, McNeill A, Borland R, Fong GT. Socioeconomic variations in nicotine dependence, self-efficacy, and intention to quit across four countries: findings from the International Tobacco Control (ITC) Four Country Survey. Tob Control 2006; 15(Suppl 3): iii71-iii75.
20. Hafez N, Ling P. How Philip Morris built Marlboro into a global brand for young adults: implications for international tobacco control. Tob Control 2005; 14(4): 262-71.
21. Thrasher JF, Chaloupka F, Hammond D, Fong G, Borland R, Hastings G, et al. Evaluating tobacco control policy in Latin American countries during the era of the Framework Convention on Tobacco Control. Salud Publica Mex 2006; 48(Suppl 1): S155-S166.
22. Heath J, Andrews J. Using evidence-based educational strategies to increase knowledge and skills in tobacco cessation. Nurs Res 2006; 55(4 Suppl): S44-S50.
23. Chaudhary K. Tobacco control in India. In: Agarwal SP, Rao YN, Gupta S, Editors. Fifty years of cancer control in India. New Delhi, India: Directorate General of Health Services; 2002. p. 196-211.
24. McMurray A, Clendon J. Community health and wellness: primary health care in practice. Melbourne, Australia: Elsevier Australia; 2010.
25. Sinha DN, Reddy KS, Rahman K, Warren CW, Jones NR, Asma S. Linking Global Youth Tobacco Survey (GYTS) data to the WHO framework convention on tobacco control: the case for India. Indian J Public Health 2006; 50(2): 76-89.
26. Moher M, Hey K, Lancaster T. Workplace interventions for smoking cessation. Cochrane Database Syst Rev 2003; (2): CD003440.
27. Park K, Kim DS, Park DJ, Lee SK. Tobacco control in Korea. Med Law 2004; 23(4): 759-80.

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Saphenous vein graft aneurysm: A case report

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Case Report

Abstract

BACKGROUND: Saphenous vein graft aneurysms (SVGAs) are rare seen issues after coronary artery bypass graft (CABG) operation which may lead to major complications including compression of adjacent structure, myocardial ischemia, rupture, and even death.

CASE REPORT: We report a patient with recurrent SVGA and its treatment by percutaneous intervention with a covered stent, the diagnostic and treatment procedure were based on contrast enhanced computed tomography and myocardial perfusion scintigraphy (MPS).

CONCLUSION: Multimodality imaging is required to demonstrate the true size and complications of the SVGA, the relationship among the adjacent structure, and to assess ischemia and size of myocardial territory supplied by the aneurysmal graft to decide treatment strategy.

Keywords: Coronary Aneurysm; Saphenous Vein; Stents; Computed Tomography; Coronary Artery Bypass Grafting

Date of submission: 20 Oct 2015, ***Date of acceptance:*** 19 Jan 2016

Introduction

Saphenous vein graft aneurysms (SVGAs) occur as a seldom complication of coronary artery bypass graft (CABG) with the likelihood of important consequences such as mortality.[1] Diagnose with coronary artery angiography is usually definitive, but the true dimensions of the aneurysm can be obscured if a mural thrombus exists. We report a patient with recurrent SVGA treated with covered stent percutaneously; diagnose was based on myocardial perfusion scintigraphy (MPS) and contrast-enhanced computed tomography (CT).

Case Report

A 78-year-old man who had CABG operation 6 years ago admitted to our outpatient clinic with stable angina pectoris. In his history, he has had hypertension for 20 years, and abdominal aortic aneurysm (AAA) was diagnosed 4 years ago. A coronary angiography was performed while the intervention to AAA was planning; because a severe stenosis and multiple true aneurysmal dilatations (SVGAs) were detected in the aortosaphenous vein graft to the circumflex artery (Figure 1, A), polytetrafluoroethylene (PTFE)-covered stent was implanted to the graft (Figure 1, B).

After a symptom-free interval of 4 years, he admitted with stable angina pectoris. During examination, chest radiography of the patient revealed an anterior mediastinal mass (Figure 2, A and B). Inferolateral wall hypokinesia with ejection fraction 45% and mild aortic insufficiency were seen by transthoracic echocardiography. CT was performed and demonstrated a detailed anatomy of saphenous true aneurysm which is 5.9 × 4.6 cm in size including mural thrombus, especially the neck of the aneurysm and accompanying significant stenosis beyond the aneurysm (Figure 2, C and D). The newly occurred flow into aneurysmal dilatation at the distal edge of the covered stent was confirmed with coronary angiography (Figure 3, A). The MPS revealed ischemic perfusion defects on inferolateral wall. Because of the high mortality rate and Society of Thoracic Surgery score (20), treatment with the implementation of a PTFE-covered stent by percutaneous intervention again was decided. All the aneurysmal enlargements in the graft including significant stenosis were covered with the PTFE-covered stent (4.8 × 26 mm, GraftMaster, Abbott Vascular, CA, USA) deployment based on the images in the CT (Figure 3, B). CT was repeated for surveillance 6 months after the intervention. There was no more flow into the aneurysm or progressive aneurysmal dilatation, and the PTFE-covered stent was patent (Figure 3, C).

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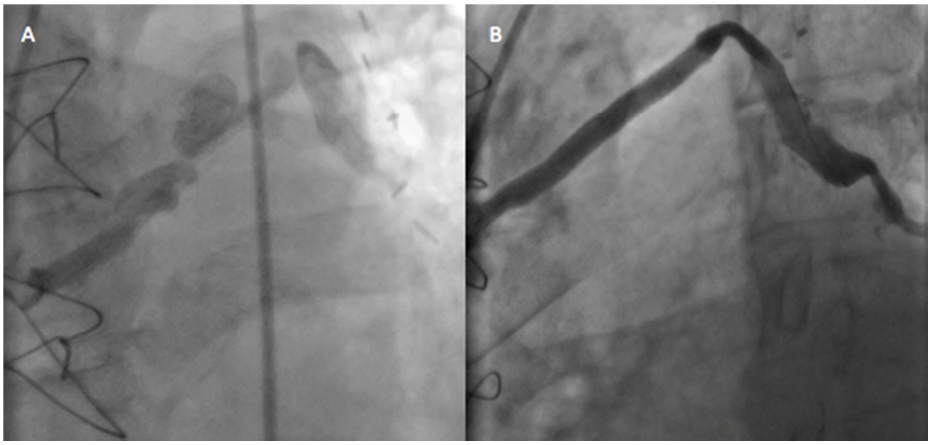

Figure 1. Coronary angiography, (A) Multiple aneurysms and stenosis on the saphenous graft vein to marginal branch of circumflex artery, (B) After polytetrafluoroethylene (PTFE)-covered stent implantation, no flow into aneurysmal graft was seen.

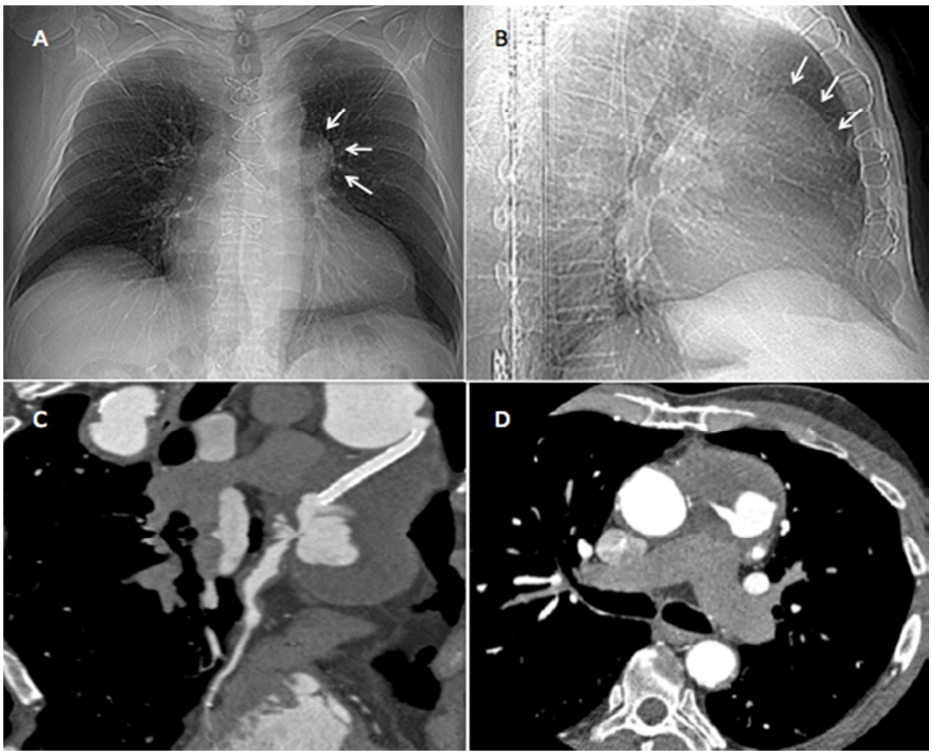

Figure 2. Chest radiography, (A) Mediastinal mass mimicking prominence of aortic arch (posterior-anterior), (B) the anterior mediastina above the heart (left lateral), (C) contrast enhanced computed tomography (CT) confirmed true saphenous vein graft aneurysm (5.9 × 4.6 cm) with mural thrombus and significant stenosis immediately at the end of aneurysm, (D) CT showed that aneurysm is between the pulmonary artery and sternum.

Discussion

Aneurysms are generally defined as a local enlargement of the vessels 1.5 times greater than the proximal reference diameter.[1] SVGA is a rare complication of CABG and can be classified into different groups such as early versus late or true versus pseudoaneurysm. Late aneurysm formation, more than 5 years after CABG may occurs secondary to atherosclerotic degeneration[1] and exposing high arterial pressure of the thin vein vessel wall. Early aneurysms < 12 months after surgery can occur secondary to several reasons caused by

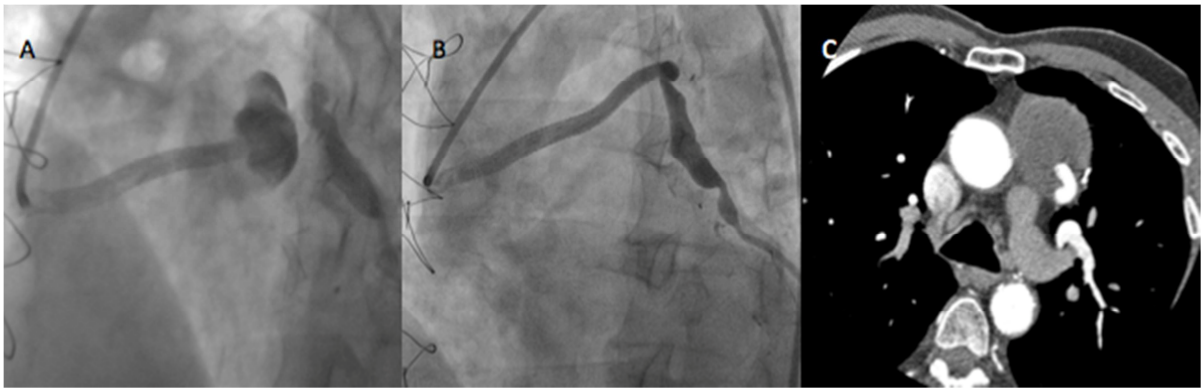

Figure 3. (A) At that time coronary angiography depicted flow into aneurysmal graft on the edge of previous covered stent, (B) after successful polytetrafluoroethylene (PTFE)-covered stent deployment including aneurysm and stenosis, (C) 6 months after latest intervention, contrast enhanced computed tomography showed patency of covered stent and no flow into aneurysmal graft

different pathophysiologies. Infection of the implanted graft,[2] intrinsic weakness of the venous wall (i.e., undetected varicosities)[3] and technical factors relating to conduit harvesting, preparation, and grafting, including conduit injury with or without dissection,[4,5] anastomotic suture disruption,[6] and failure to reverse the SVG at the time of grafting[7] have been implicated in the formation of early SVGAs.

However, true graft aneurysms should be differentiated from pseudoaneurysm. Pseudoaneurysms represent a dilatation of the graft with disruption of one or more layers of its wall rather than with expansion of all layers of the wall.[8] Furthermore, pseudoaneurysm are not endothelia-lined, and they represent focal distension with a hematoma. They usually occur at the proximal and distal ends of the graft.[1] True aneurysms mainly involve the body of the graft and occur less common than pseudoaneurysms.

Most aneurysms are usually asymptomatic, incidentally determined, presenting as mediastinal masses on chest radiography or thoracic CT performed for unrelated causes. Symptomatic aneurysms constitute a diagnostic challenge as they may present in a variety of presumably unrelated symptoms, such as an acute coronary event or congestive heart failure.[1] SVGA may lead to major complications including compression of native coronary vessels, distal embolization, myocardial ischemia and infarction, compression of the right atrium, or fistula formation and rupture into the right atrium.[1] Diagnostic modalities include chest X-ray, echocardiography, thorax CT (contrast enhanced), magnetic resonance imaging angiography, and conventional angiography.[7] Although coronary artery angiography is generally definitive in confirming the graft dilatation, mural thrombus can sometimes obscure the aneurysm's true dimensions. Therefore, in our case, we planned the treatment strategy with the data obtained from both angiography and CT because of highly definitive power of CT.

The goals of treatment are to reduce the risk of complications such as rupture, mass effect, thromboembolism, and myocardial ischemia. Surgical repair may be undertaken in patients those whom are elderly and possess multiple comorbidities, favoring percutaneous approaches include covered stent grafting,[9,10] coil embolization,[11] vascular plug insertion,[12] and alcohol injection to the graft.[13]

A major advantage of covered stent is the protection of distal flow patency.[1] Interventions utilizing coil embolization, vascular plug insertion, or alcohol injection are reported in limited cases where graft occlusion is an acceptable outcome.

SVGAs are rare complications and cause grim consequences. The origin of this condition is unclear, but there are many possible explanations, suggest atherosclerotic process and relevant risk factors. Diagnostic approach to SVGA should include multiple imaging modalities.[11] Multimodality imaging is required to demonstrate the true size and complications of the SVGA, the relationship among the adjacent structure, and to assess ischemia and size of myocardial territory supplied by the aneurysmal graft to decide treatment strategy. MPS also determines strategy about whether saphenous flow patency is important or not for myocardial territory because of showing severity of ischemia and indication of treatment. If myocardial territory

supplied by saphenous graft was dispensable, it could occlude with coil or vascular plug from proximal and distal tip.

In this case, we present and discuss about saphenous graft true aneurysm; underlying mechanisms; its consequences, diagnostic challenges and its treatment options, in these cases like our, percutaneous treatment modalities should be kept in mind. Furthermore, the recurrent pattern of aneurysmal formation should be taken into consideration and should follow these patients.

Acknowledgments

None.

Conflict of Interests

Authors have no conflict of interests.

References

1. Ramirez FD, Hibbert B, Simard T, Pourdjabbar A, Wilson KR, Hibbert R, et al. Natural history and management of aortocoronary saphenous vein graft aneurysms: a systematic review of published cases. Circulation 2012; 126(18): 2248-56.
2. Douglas BP, Bulkley BH, Hutchins GM. Infected saphenous vein coronary artery bypass graft with mycotic aneurysm. Fatal dehiscence of the proximal anastomosis. Chest 1979; 75(1): 76-7.
3. Ennis BM, Zientek DM, Ruggie NT, Billhardt RA, Klein LW. Characterization of a saphenous vein graft aneurysm by intravascular ultrasound and computerized three-dimensional reconstruction. Cathet Cardiovasc Diagn 1993; 28(4): 328-31.
4. Kallis P, Keogh BE, Davies MJ. Pseudoaneurysm of aortocoronary vein graft secondary to late venous rupture: case report and literature review. Br Heart J 1993; 70(2): 189-92.
5. Werthman PE, Sutter FP, Flicker S, Goldman SM. Spontaneous, late rupture of an aortocoronary saphenous vein graft. Ann Thorac Surg 1991; 51(4): 664-6.
6. de Haan HP, Huysmans HA, Weeda HW, Bosker HA, Buis B. Anastomotic pseudoaneurysm after aorto-coronary bypass grafting. Thorac Cardiovasc Surg 1985; 33(1): 55-6.
7. Benchimol A, Harris CL, Desser KB, Fleming H. Aneurysms of an aorto-coronary artery saphenous vein bypass graft--a case report. Vasc Surg 1975; 9(4): 261-4.
8. Stedman TL. Stedman's medical dictionary. 26th ed. Philadelphia, PA: Williams & Wilkins; 1995. p. 1450.
9. Bhindi R, Newton J, Westaby S, Wilson N, Ormerod OJ, Uberoi R. Stent-graft repair of coronary vein graft aneurysm. J Vasc Interv Radiol 2009; 20(5): 649-51.
10. Rahim SA, Pitta SR, Rihal CS. Saphenous vein graft pseudoaneurysm. J Am Coll Cardiol 2009; 53(20): 1918.
11. Maroo A, Rasmussen PA, Masaryk TJ, Ellis SG, Lincoff AM, Kapadia S. Stent-assisted detachable coil embolization of pseudoaneurysms in the coronary circulation. Catheter Cardiovasc Interv 2006; 68(3): 409-15.
12. Mylonas I, Sakata Y, Salinger MH, Feldman T. Successful closure of a giant true saphenous vein graft aneurysm using the Amplatzer vascular plug. Catheter Cardiovasc Interv 2006; 67(4): 611-6.
13. Sonnenberg B, Rutledge J, Welsh RC. Occlusion of a large expanding saphenous vein bypass graft aneurysm with percutaneously injected ethylene-vinyl alcohol copolymer. JACC Cardiovasc Interv 2010; 3(10): 1089-90.

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The vasorelaxant effect of simvastatin in isolated aorta from diabetic rats

Farshad Roghani-Dehkordi[(1)], Mehrdad Roghani[(2)]

Short Communication

Abstract

BACKGROUND: The increasing incidence of diabetes mellitus (DM) is of great clinical significance. In this study, we aimed to investigate whether exposure of endothelium-intact aortic rings to simvastatin could have a vasorelaxant effect in diabetic rats.

METHODS: For induction of diabetes, streptozotocin (STZ) (60 mg/kg, i.p., single dose) was used. After 1 month, the cumulative reaction of isolated endothelium-intact aortic rings was determined to KCl and phenylephrine (PE) in the absence and presence of nitric oxide (NO) synthase inhibitor, i.e., nitro-L-arginine-methyl ester (L-NAME), and prostaglandin synthesis inhibitor, i.e., indomethacin. Meanwhile, the role of extracellular calcium was assessed in this respect.

RESULTS: At the end of the study, the addition of simvastatin (at a concentration ≥ 10^{-5} M) caused a significant concentration-dependent relaxation response of PE-precontracted aortic rings for both control and diabetic groups (at a significant difference of $P < 0.050$), and this difference did not exist for KCl-precontracted aortic rings. Furthermore, both L-NAME (100 µM) and indomethacin (10 µM) significantly diminished the vasorelaxant response following simvastatin addition. Meanwhile, there was no statistically significant difference between control and diabetic groups in the absence of extracellular calcium.

CONCLUSION: The results of this study suggest that simvastatin is able to relax PE-precontracted aortic rings isolated from STZ-diabetic rats via modulation of NO- and prostaglandin-dependent signaling and its effect is not via modulation of calcium mobilization from intracellular stores.

Keywords: Simvastatin; Aorta; Diabetes Mellitus

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Introduction

The increasing epidemic of diabetes mellitus (DM) is of significant concern worldwide.[1,2] Vascular complications in DM, as known as vasculopathy, include macro- and micro-vascular dysfunction and abnormality that is the principal reason of morbidity and mortality in patients with DM.[1,2] Endothelial dysfunction in DM plays a key role in the development and progression of vasculopathy due to DM.[1] Urgent medical interventions are necessary to lower DM vascular complications which require new preventive and treatment strategies.[3] Earlier strategies for controlling and managing the cardiovascular complications of DM mainly target a group of well-defined risk factors such as hyperglycemia, lipid abnormalities, and hypertension.[4] Considering the great developments in human knowledge about DM diversity and knowing that it is one of the major health, social and economic problems worldwide, a need for finding effective treatments with fewer side effects, to treat DM and its complications has been arisen.[5]

Simvastatin is a drug that is generally used in clinics for the treatment of hypercholesterolemia.[6] Simvastatin acts via blocking the key enzyme in the synthesis of cholesterol, 3-hydroxy-3-methylglutaryl-coenzyme A reductase and has found to be useful for lowering plasma low-density lipoprotein cholesterol (LDL-C).[7] Clinical trials have also proven that such enzyme inhibitors are capable to lower cardiovascular disorders and associated morbidity and mortality in patients with coronary artery disease (CAD).[8] In addition, research evidence have indicated that such inhibitors could restore endothelium-dependent responses in the vascular system.[9] Furthermore, it has found out that simvastatin could produce a vasodilation in conductance and small arteries that are an endothelium-dependent response that engages both nitric oxide (NO) and eicosanoid vasodilators.[6]

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Simvastatin is also effective and well-tolerated in the management of lipid disorders in DM.[10] Since no researches have been done on the beneficial effect of simvastatin on the vascular response in diabetic state, therefore, we wanted to explore whether an exposure of endothelium-intact aortic rings to simvastatin could have a vasodilatory effect in streptozotocin (STZ)-diabetic rats and to explore the engagement of NO and prostaglandin and intracellular Ca^{+2} pathways.

Materials and Methods

In this experimental study, male Wistar rats (obtained from Razi Institute, Tehran, Iran), weighing 200-240 g were kept in a housing room on a light/dark cycle (22 ± 2 °C and a humidity of 40-50%) and supplied with standard diet and tap water with no limitation. The used procedures for animals and their care were conducted in accordance to NIH guidelines for the care and use of research animals.

The animals (n = 18) were randomly divided into two groups: control (n = 8) and diabetic (n = 10). For induction of diabetes, STZ (60 mg/kg, i.p., single dose) was used. STZ was freshly dissolved in cold normal saline immediately before its use. For verification of diabetes, serum glucose level > 250 mg/dl was considered using glucose oxidation method (Glucose Oxidase Kit, Zistchimie, Tehran, Iran). The timing of study design has been shown in figure 1.

Aortic rings preparation

At the end of the study, (after 4 weeks), the rats were deeply anesthetized under diethyl ether, euthanized, and after exposing the abdomen and thorax, descending thoracic aorta was excised with extreme care and immediately transferred to cold saline solution [physiological salt solution (PSS)] containing (in mM): NaCl-118, KCl-4.6, $MgSO_4$-1.2, KH_2PO_4-1.2, glucose-11.1, $NaHCO_3$-27.2, and $CaCl_2$-1.8. Thereafter, the aorta was cleaned from extra connective tissue and fat and cut into separate rings of about 4 mm in length. Aortic rings were suspended between two triangular-shaped stainless-steel wires. One wire was attached to a tissue holder in a 50 ml isolated tissue bath containing PSS (pH = 7.4) kept at 37 °C and continuously gassed with a combination of 95% O_2 and 5% CO_2. The other end of each wire attached (via a cotton thread) to an isometric force transducer (Ugo Basile, Comerio, Italy) coupled to a signal amplifier and connected to a computer via an A/D board. Recording and data analysis was conducted using specially designed software.

In all experimental procedures, special care was paid to prevent damage of the luminal surface of aortic rings. The rings were allowed to equilibrate for 90 minutes under a resting tension of 1.5 g before further experiments were started. This resting tension was found to be optimal in our pilot experiments for all groups under study. During equilibration period, the rings were washed every 30 minutes. For assessing the endothelial integrity, phenylephrine (PE, 1 μM)-precontracted rings were exposed acetylcholine (ACh-10 μM).

For exploring the engaged mechanisms for vasodilatory effect of the simvastatin, isolated aortic rings were pretreated with nitro-L-arginine-methyl ester [L-NAME, nitric oxide synthase (NOS) blocker, 100 μM] and indomethacin (10 μM, prostanoid synthesis inhibitor) separately or in combination 30 minutes before the application of the vasoconstrictors and the simvastatin.

For determination of the engagement of intracellular Ca^{+2} mobilization in the vasodilatory effect of the simvastatin, a Ca^{+2}-free PSS was made by replacing $CaCl_2$ with $MgCl_2$ and the addition of ethylene-glycol-tetraacetic acid (EGTA) (0.5 μM) to chelate any free Ca^{+2} in the solution. After a 15-minutes preincubation period with 3-4 washings, PE (1 μM) was applied to stimulate the release of intracellular Ca^{+2} and the contraction recorded for 3 minutes. A similar procedure was applied with Ca^{+2}-free PSS containing the simvastatin (10^{-5} M).

Drugs and chemicals

Simvastatin, PE, ACh-HBr, indomethacin, L-NAME, and STZ were supplied from Sigma-Aldrich (MO, USA). All other chemicals and reagents were supplied from Merck Co. (Germany) and local market. Indomethacin was dissolved in 0.5% w/v sodium bicarbonate. Further dilutions of these drugs were made in PSS. In addition, STZ was freshly dissolved in 0.9% normal saline.

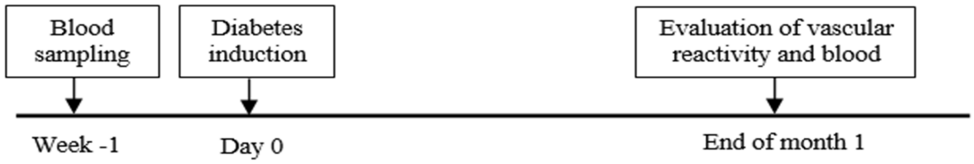

Figure 1. Study timing design

All values were reported as a mean ± standard error (SE). Data were analyzed by statistical tests, i.e., Student's t-test for paired samples, independent sample t-test, and one-way analysis of variance followed by Tukey post-hoc test at a significant level of $P < 0.050$.

Results

During the study, 2 rats were excluded from the diabetic group due to a morbid and fatal condition. After 1 month, the body weight of diabetic animals significantly decreased from an average of 227.5 to 181.6 g ($P = 0.008$). Regarding serum glucose level, it significantly increased to 415.3 ± 21.8 mg/dl from the initial level of 127.2 ± 8.3 mg/dl ($P < 0.001$) (Table 1).

Addition of high K^+ (80 mM)-containing PSS to the tissue bath induced a maximal tension of 258.2 ± 15.3 and 175.6 ± 17.4 mg in control and diabetic groups, respectively. However, the found difference was not statistically significant ($P = 0.080$). The application of simvastatin produced a concentration-dependent relaxation in both control and diabetic groups (Figure 2-A). In this respect, simvastatin-induced vasorelaxation of rings from diabetic group was not significantly lower as compared to control rats ($P = 0.130$).

With respect to contractile response of aortic rings, PE (1 μM) induced a sustained contraction of the rat aorta with a peak tension of 487.3 ± 24.9 and 619.5 ± 26.8 mg in control and diabetic groups, respectively. This difference was statistically significant ($P = 0.007$). Meanwhile, addition of simvastatin produced a concentration-dependent relaxation in both control and diabetic groups (Figure 2-B). In this regard, simvastatin-induced vasodilation of aortic rings isolated from diabetic rats was significantly lower as compared to control rats at concentrations $> 10^{-5}$ M ($P = 0.020$ and $P = 0.040$).

Pretreatment of the tissues with L-NAME and not indomethacin markedly and significantly attenuated the inhibitory effect of simvastatin against PE (1 μM)-induced contraction in both control ($P = 0.020$) (Figure 3-A) and diabetic ($P = 0.030$) groups (Figure 3-B). Meanwhile, in the absence of extracellular Ca^{+2}, PE produced a transient contraction in control and diabetic groups. This difference was not found out to be statistically significant ($P = 0.070$). Furthermore, pretreatment of the aortic rings with simvastatin did not significantly reduce the contractions induced by PE for both control ($P = 0.140$) and diabetic ($P = 0.110$) groups in the absence of extracellular calcium (Figure 4).

Table 1. Body weight and serum glucose level in different groups and weeks

Group	Body weight (g)		Serum glucose (mg/dl)	
	Baseline (mean ± SD)	After 1 month (mean ± SD)	Baseline (mean ± SD)	After 1 month (mean ± SD)
Control	221.8 ± 9.6	241.9 ± 10.3	131.7 ± 10.4	125.7 ± 12.5
Diabetic	227.5 ± 10.2	181.6 ± 11.8*	127.2 ± 8.3	415.3 ± 21.8**

*P = 0.008 (vs. baseline in the same group), **P < 0.001 (vs. baseline in the same group). Student's t-test for paired samples
SD: Standard deviation

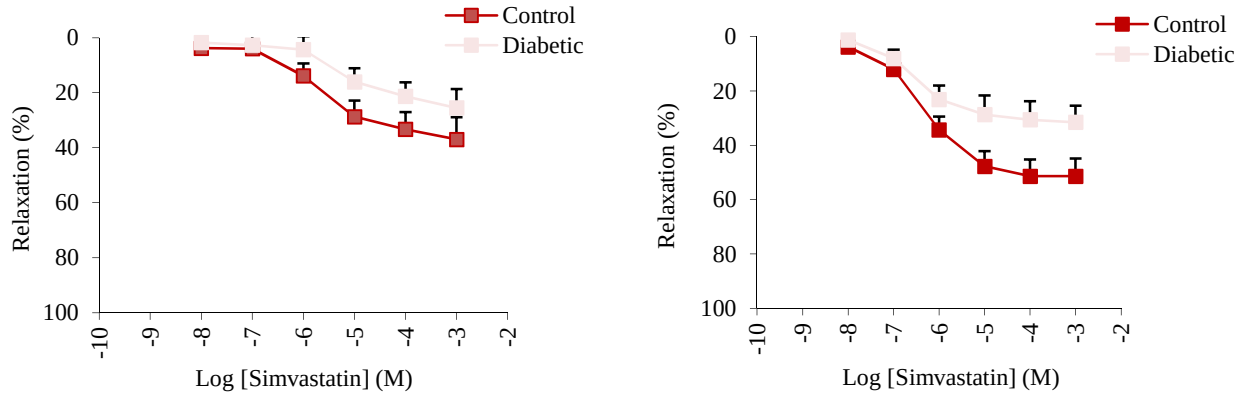

Figure 2. Vasorelaxant effect of simvastatin against KCl (A) and phenylephrine (B)-induced contractions in aortic rings from control (n = 6) and streptozotocin-diabetic (n = 7) rats
Unpaired Student's t-test was used for comparing control and diabetic groups at each concentration of simvastatin ($P = 0.020$, $P = 0.040$) (vs. diabetic).

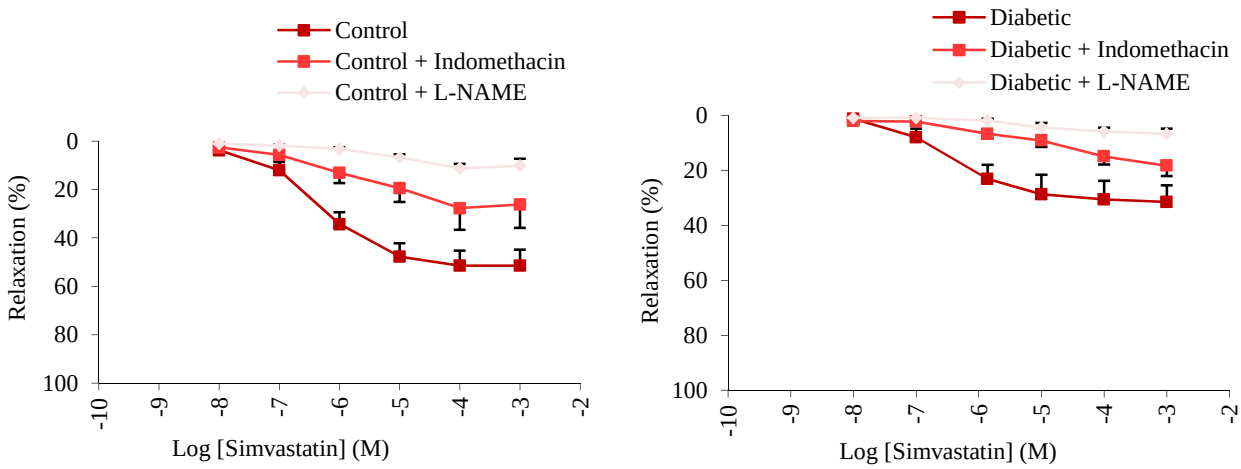

Figure 3. Vasorelaxant effect of simvastatin against phenylephrine-induced contractions in the presence of nitro-L-arginine-methyl ester (L-NAME) or indomethacin in control (n = 6) (A) and diabetic (n = 7) (B) groups
One-way analysis of variance was used for statistical analysis of differences amongst the groups.

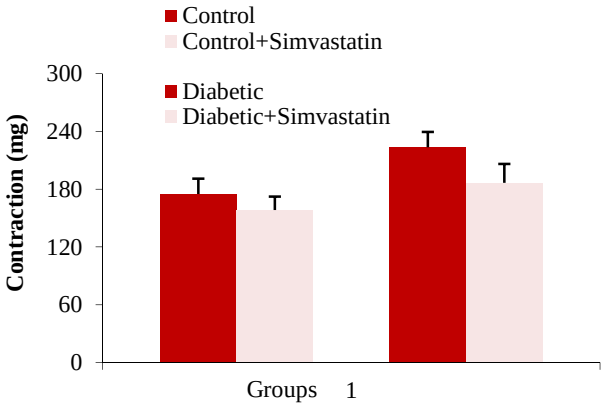

Figure 4. Effect of simvastatin on phenylephrine-induced transient contractions in normal and Ca^{+2}-free physiological salt solution (PSS) in control (n = 5) and diabetic (n = 6) groups
One-way analysis of variance was used for statistical analysis of differences amongst the groups.

Discussion

The present work was performed to investigate the involved mechanisms responsible for simvastatin-induced vasorelaxation in PE-precontracted aortae of STZ-diabetic rats. It was found out that simvastatin-induced and NO- and prostaglandin-dependent vasorelaxation in aortic rings from diabetic rats.

There are two mechanisms for the vasodilation response in the vascular system: the secretion of relaxant factor from vascular endothelium and inhibition of vasoconstriction. The former is mediated by bradykinin, prostacyclin, and NO.[11] The relaxant action of simvastatin was affected by both L-NAME and indomethacin, suggesting that its effect is mediated through endothelium-derived NO and vasodilator eicosanoids. NO which is produced by endothelial NOS is a potent vasodilator by stimulating soluble guanylate cyclase and increasing cyclic guanosine monophosphate levels in smooth muscle cells.[6]

Our results showed that pretreatment of aortic specimens with an NOS inhibitor, L-NAME significantly reduced the vasorelaxant effects of simvastatin. Therefore, our findings may suggest that simvastatin could relax the isolated rat aorta through endothelium-dependent NO pathway. In addition, indomethacin application could have lowered the vasodilatory response of simvastatin in isolated aortic rings from control and diabetic rats, indicating the important role of vasodilator prostaglandins in this regard.

The results of a previous study on relaxation response of simvastatin in normal rats showed that simvastatin is able to induce the synthesis and release of vasodilator products by a mechanism that is sensitive to superoxide scavengers like superoxide dismutase and is partly mediated through tyrosine kinase pathway.[6] Such mechanisms may have occurred in aortic rings from diabetic rats following an in vitro exposure to simvastatin in our study. Furthermore, it has been shown that simvastatin at appropriate concentration, which has occurred in our study, could promote endothelial-dependent relaxation through improving vasomotion at the level of smooth muscle.[12]

Some studies have also claimed that vasorelaxation response to simvastatin is endothelium-independent.[6] There are also some evidence that simvastatin is able to produce

relaxation of both aorta and small arteries in the absence of functional endothelium that might take place via inhibition of agonist-induced increase in cytosolic calcium involved in vascular smooth muscle contraction.[13] These mechanisms may include a decrease in the release of Ca^{2+} from thapsigargin-sensitive pool, inhibition of inositol triphosphate-dependent Ca^{2+} mobilization, and/or blockade of L-type Ca^{2+} channels.[13]

Conclusion

Taken together, our results show that simvastatin could relax the PE-preconstructed rings of aorta in STZ-diabetic rats through NO- and prostaglandin-related pathways and it could not affect the release and mobilization of calcium from the intracellular stores.

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Conflict of Interests

Authors have no conflict of interests.

References

1. Matsumoto T, Lopes RA, Taguchi K, Kobayashi T, Tostes RC. Linking the beneficial effects of current therapeutic approaches in diabetes to the vascular endothelin system. Life Sci 2014; 118(2): 129-35.
2. Sena CM, Matafome P, Louro T, Nunes E, Seica RM. Effects of atorvastatin and insulin in vascular dysfunction associated with type 2 diabetes. Physiol Res 2014; 63(2): 189-97.
3. Patel VB, Parajuli N, Oudit GY. Role of angiotensin-converting enzyme 2 (ACE2) in diabetic cardiovascular complications. Clin Sci (Lond) 2014; 126(7): 471-82.
4. Lin K, Lloyd-Jones DM, Li D, Carr JC. Quantitative imaging biomarkers for the evaluation of cardiovascular complications in type 2 diabetes mellitus. J Diabetes Complications 2014; 28(2): 234-42.
5. Kazemi S, Asgary S, Moshtaghian J, Rafieian M, Adelnia A, Shamsi F. Liver-protective effects of hydroalcoholic extract of allium hirtifolium boiss. In rats with alloxan-induced diabetes mellitus. ARYA Atheroscler 2010; 6(1): 11-5.
6. Alvarez De Sotomayor M, Herrera MD, Marhuenda E, Andriantsitohaina R. Characterization of endothelial factors involved in the vasodilatory effect of simvastatin in aorta and small mesenteric artery of the rat. Br J Pharmacol 2000; 131(6): 1179-87.
7. Qiao Z, Ren J, Chen H. Simvastatin reduces expression and activity of lipoprotein-associated phospholipase A(2) in the aorta of hypercholesterolaemic atherosclerotic rabbits. J Int Med Res 2009; 37(4): 1029-37.
8. Pereg D, Elis A, Neuman Y, Mosseri M, Leader A, Segev D, et al. Lipid control in patients with coronary heart disease treated in primary care or cardiology clinics. J Clin Lipidol 2013; 7(6): 637-41.
9. Seto SW, Au AL, Poon CC, Zhang Q, Li RW, Yeung JH, et al. Acute simvastatin inhibits K ATP channels of porcine coronary artery myocytes. PLoS One 2013; 8(6): e66404.
10. Okeoghene OA, Alfred A. The efficacy and safety of Simvastatin in the treatment of lipid abnormalities in diabetes mellitus. Indian J Endocrinol Metab 2013; 17(1): 105-9.
11. Vaez Mahdavi MR, Roghani M, Baluchnejadmojarad T. Mechanisms responsible for the vascular effect of aqueous Trigonella foenum-graecum leaf extract in diabetic rats. Indian J Pharmacol 2008; 40(2): 59-63.
12. Ng LL, Davies JE, Wojcikiewicz RJ. 3-Hydroxy-3-methyl glutaryl coenzyme A reductase inhibition modulates vasopressin-stimulated Ca2+ responses in rat A10 vascular smooth muscle cells. Circ Res 1994; 74(2): 173-81.
13. Escobales N, Castro M, Altieri PI, Sanabria P. Simvastatin releases Ca2+ from a thapsigargin-sensitive pool and inhibits InsP3-dependent Ca2+ mobilization in vascular smooth muscle cells. J Cardiovasc Pharmacol 1996; 27(3): 383-91.

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One year follow-up effect of renal sympathetic denervation in patients with resistant hypertension

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Short Communication

Abstract

BACKGROUND: Resistant hypertension is a common clinical problem of blood pressure that is not controlled despite the simultaneous application of multiple antihypertensive agents. Ablation of renal afferent nerves has been applied and proved to decrease hypertension and injuries produced by severe sympathetic hyperactivity. The main objective of this study was to investigate the long-term effect of renal artery sympathetic ablation and its complications in patients with treatment-resistant hypertension.

METHODS: In this prospective study which done between March 2012 and November 2013, 30 patients with resistant arterial hypertension despite treatment with ≥3 antihypertensive drugs-were randomly enrolled in this self-control clinical study in Isfahan, Iran. The patients were treated with the renal denervation procedure; the femoral artery was accessed with the standard endovascular technique and the Symplicity catheter was advanced into the renal artery and connected to a radiofrequency generator. Before and 12 months after renal denervation procedure waist, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), metabolic syndrome, fasting blood sugar (FBS), high-density lipoprotein (HDL), and triglyceride were measured in all patients.

RESULTS: Both mean SBP and DBP were significantly decreased, 12 months after renal denervation ($P < 0.001$). The frequency of metabolic syndrome was not significantly different after renal denervation in compare to baseline ($P = 0.174$). Furthermore, a significant decreased in FBS and triglyceride was observed in compare to baseline ($P = 0.001$).

CONCLUSION: This study highlighted the role of renal sympathetic denervation as a modern and secure catheter-based method for sustained reduction hypertension in treatment-resistant cases.

Keywords: Hypertension Resistant; Renal Sympathetic Denervation; Renal Artery Ablation; Angiography; Renal Sympathectomy

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Introduction

Hypertension is one of the severe public health problems worldwide and one of the leading causes of cardiovascular disease and death.[1,2] Annually, about 7.5 million deaths (13% of all deaths) are caused by hypertension.[3,4] Report given by the global burden of hypertension, expressed that, almost one billion adults suffer of hypertension in 2000, and it is expected to enlarge to 1.56 billion until 2025.[5] In spite of wide efforts to handle hypertension, just half of treated individuals are controlled and the rest is cases with resistant hypertension.[6,7] Resistant hypertension is a common clinical problem of blood pressure that is not controlled despite the simultaneous application of multiple antihypertensive agents.[8,9] Physician inertia, medication side effects, non-conformity to lifetime pharmacological remedy by patients, and drug incompetence have been expressed as reasons of failure in the pharmacological strategy.[10,11]

Several studies have indicated that kidney has an important impact on blood pressure regulation; it has

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been proved that augmented activity in the sympathetic nervous system contributes to the hypertension pathogenesis.[12,13] Hence, ablation of renal afferent nerves has been applied and proved to decrease hypertension and injuries produced by severe sympathetic hyperactivity.[14,15] Traditionally, surgical sympathectomy had been successfully applied in decreasing blood pressure in individuals with chronic hypertension.[16] Given that, this method was founded to have abundant large scale perioperative mortality and long-lasting complications, was forsaken until the advent of catheter-based method.[17] Catheter-based renal sympathetic denervation has been expressed as a safe, helpful, and cost-effective intervention in patients with resistant hypertension.[18,19] Reduction in blood pressure and diminishing the possibility of stroke, left ventricular hypertrophy, chronic renal, and heart failure by catheter-based renal sympathetic denervation in combination with pharmacologic remedy have been reported.[20]

However, the long-term effect of renal sympathetic denervation and its complications in patients with treatment-resistant hypertension is not clearly understood. Toward this end, the present survey tries to investigate the long-term effect of renal artery sympathetic ablation and its complications in patients with treatment-resistant hypertension. This study designed to assess the feasibility, safety, and effectiveness of renal sympathetic denervation in patients with resistant arterial hypertension.

Materials and Methods

This single-center, prospective study was approved by the Ethical Review Committees of Isfahan University of Medical Sciences, Isfahan, Iran. After a full explanation of the study, written informed consent was obtained from all the patients.

In total 30 patients with resistant arterial hypertension despite treatment with ≥ 3 antihypertensive drugs (at least one of the antihypertensive medications was required to be a diuretic) were enrolled in this study. Inclusion criteria were age more than 15 years in both sex, with systolic blood pressure (SBP) ≥ 160 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg. Exclusion criteria were pregnancy; have any known secondary cause of hypertension; severe renal artery stenosis, previous renal stenting or angioplasty, or known dual renal arteries type 1 diabetes, hemodynamically major renal artery stenosis, previous renal artery intervention, renal artery anatomy that precluded treatment (< 4 mm diameter, or < 20 mm length), an estimated glomerular filtration rate of < 45 ml/minutes, heart disease, planned pregnancy during the study, and a history of myocardial infarction (MI) and unstable angina in the previous 6 months.

Resistant hypertension is defined as blood pressure that remains above goal despite concurrent use of three antihypertensive agents of different classes, one of which should be a diuretic.[1] Patients whose blood pressure is controlled with four or more medications are considered to have resistant hypertension.

Selected patients were treated with the renal denervation procedure, the femoral artery was accessed with the standard endovascular technique, and the Symplicity catheter was advanced into the renal artery and connected to a radiofrequency generator. Blood pressure was measured twice in sitting position after 5 minutes resting by mercury sphygmomanometer. The mean of the two recordings was reported as patient's blood pressure. Subjects who had three or more of the criteria defined by National Cholesterol Education Program (NCEP) were diagnosed with metabolic syndrome. The criteria of NCEP include: (1) Central obesity as the waist circumference > 102 cm in men and > 88 cm in women; (2) fasting plasma triglycerides ≥ 150 mg/dl; (3) low high-density lipoprotein cholesterol (HDL-C) < 40 mg/dl in men and < 50 mg/dl in women; (4) SBP ≥ 130 mm Hg and/or DBP 85 mm Hg and/or antihypertensive agents (5) hyperglycemia with fasting plasma glucose (FPG) ≥ 100 mg/dl and/or hypoglycemic medications.[10]

Before and 12 months after renal denervation procedure waist, body mass index (BMI), SBP, DBP, metabolic syndrome, fasting blood sugar (FBS), HDL, and triglyceride were measured in all patients. Change in the mean of measurements of SBP and DBP from baseline to 12 months after renal denervation were the main effectiveness endpoint of this study, also, chronic procedural safety such as death, MI, stroke, congestive heart failure (CHF), and renal arterial stenosis were assessed in all patients after 12 months. To measure renal arterial stenosis 12 months after renal denervation, angiography performed in any of patients who were willing and ready.

With a sample of 30 patients, we calculated that the study would have at least 80% power to show benefit of renal denervation, assuming at least a 10 mm Hg difference with a 21 mm Hg standard deviation (SD) of the change in SBP from baseline to 12 months.

The pattern of medication use was defined

Table 1. Clinical characteristics of studied patients at baseline and 12 months follow-up after renal denervation

Variable	Baseline	12 months after renal denervation	P	Δ between two phase
	Mean ± SD	Mean ± SD		Mean ± SD
BMI (kg/m^2)	28.3 ± 2.8	27.9 ± 2.5	0.008	-0.90 ± 1.20
Waist circumference (cm)	92.3 ± 10.4	91.1 ± 10.2	0.003	-0.34 ± 0.02
SBP (mm Hg)	169.8 ± 10.5	147.5 ± 14.9	< 0.001	-22.30 ± 10.04
DBP (mm Hg)	95.7 ± 9.7	83.8 ± 7.5	< 0.001	-11.83 ± 5.63
FBS (mg/dl)	111.7 ± 15.7	107.2 ± 12.9	0.001	-4.50 ± 2.31
HDL (mg/dl)	45.1 ± 5.5	48.3 ± 5.4	0.002	3.27 ± 1.03
Triglyceride (mg/dl)	165.9 ± 53.8	146.5 ± 38.1	0.001	-19.43 ± 10.02

P values calculated by pair t-test.

SD: Standard deviation; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBS: Fasting blood sugar; HDL: High-density lipoprotein

according to the type of drugs used to control and/or treat hypertension. Medicines were classified according to pharmacological category.

The collected data were analyzed statistically with SPSS software (version 20, SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov normality test was used before analysis, and in case of abnormality in data transformation was used. Continuous variables present as mean ± SD and categorical variables as number (%). Studied variables after renal denervation in compare to baseline were assessed using pair t-test. The frequency of metabolic syndrome was tested by McNamara's test. $P < 0.050$ was considered significant.

Results

During the study period (March 2012 to November 2013), a total of 37 patients were consented for enrollment. During the screening process, seven patients were excluded (three patients did not met inclusion criteria and four refused informed consent). In total, 30 patients completed baseline evaluation and underwent the renal denervation procedure. Within the 12 months follow-up period one patient died, and finally, 29 patients completed the study and analyzed. The mean age of studied patients was 56.3 ± 10.8 years old, 14 of patients (47%) were male and 16 patients (53%) were female.

Clinical characteristics of studied patients at baseline in compare to 12 months follow-up after renal denervation are shown in table 1. BMI and waist after renal denervation significantly decreased in compare to baseline ($P < 0.050$). SBP at baseline was 169.8 mm Hg and after renal denervation meaningfully reduced to 147.5 mm Hg ($P < 0.001$). DBP was significantly decreased of 95.7 mm Hg at baseline to 83.8 mm Hg after renal denervation ($P < 0.001$). The distribution of metabolic syndrome was not significantly different after renal denervation in compare to baseline ($P = 0.170$). Moreover, a significant decreased in FBS and triglyceride after renal denervation was observed in compare to baseline ($P = 0.001$). HDL significantly increased in compare to baseline ($P = 0.002$).

Distribution of SBP levels at baseline in compare to 12 months post-renal denervation. At baseline, all studied patients had SBP higher than 140 mm Hg and only 7% had SBP between 140 and 160 mm Hg and 93% had SBP higher than 160 mm Hg. 12 months after renal denervation 3.3% of subjects had SBP lower than 140 mm Hg and 20.0% had SBP between 140 and 160 mm Hg. Decline in SBP in 7% of patients was lower than 10 mm Hg, which were defined as no decrease in SBP. 93% of patients had the SBP reduction of ≥ 10 mm Hg. Moreover, also 12 months after renal denervation 23.3% of patients achieved the SBP of < 140 mm Hg. Table 2 shows there are no significant differences in the pattern of ntihypertensive medication at baseline and 12 months follow-up after renal denervation.

Table 2. Prevalence of antihypertensive medication at baseline and 12 months follow-up after renal denervation

Drug	Value (%)	Value (%)
ACE inhibitor	51.0	49.9
Angiotensin receptor blocker	67.3	67.5
Calcium channel blocker	27.6	28.1
Diuretic	58.8	59.2
Aldosterone antagonist	18.4	17.8
β blocker	81.6	82.2
α androgenic blocker	8.2	8.3
Direct renin inhibitor	16.3	16.7
Thiazides	4.0	4.3

ACE: Angiotensin-converting-enzyme

The mean of decreases in both SBP and DBP was 22.3 and 11.83 mm Hg, respectively. The mean of decreases in BMI, waist, FBS and triglyceride after follow-up was 0.9, 0.34, 4.5 and 19.4, respectively; and the mean of increased in the level of HDL was 3.27. Post-procedure within the follow-up period we detected the following side effects: MI was occurred in two patients. One of patient's died from a MI. One of the patients had stroke and one patient had CHF. Angiography was done in eight patients who were willing and renal arterial stenosis (50%) was observed in two of them.

Discussion

In present single-center, prospective study showed renal sympathetic denervation as a modern and secure catheter-based method for sustained reduction hypertension in treatment-resistant cases is useful method so renal denervation provides harmless and continued drop of blood pressure to 2 years. Similar to our results Esler et al. demonstrated control hypertensive subjects who crossed over to renal denervation with the Symplicity system demonstrated a meaningful decline in blood pressure alike to that observed in subjects obtaining urgent denervation.[21]

As with the former available reports concerning this method, our findings, reaffirm the effectiveness of catheter-based therapy for hypertension resistant subjects and clarified that renal sympathetic denervation creates a secure and sustained blood pressure reduction during 12 months after treatment follow-up. A highly significant reduction of SBP and DBP were observed. SBP at baseline was 169.8 mm Hg and after renal denervation significantly decreased to 147.5 mm Hg ($P < 0.001$). Furthermore, DBP was significantly decreased from 95.7 mm Hg at baseline to 83.8 mm Hg after renal denervation ($P < 0.001$). Our findings are keeping with Katholi and Rocha-Singh,[19] they have expressed that catheter-based renal denervation offers sustained and considerable reduction of blood pressure in resistant hypertension patients. They also reported that catheter-based renal denervation causes no severe unpleasant complication, and mentioned the necessities of prospective randomized clinical trials for proving their findings.[19]

Hypertension reduction using catheter-based renal sympathetic denervation along with pharmaceutical remedy have been shown to be effective in decreasing the stroke risk, heart failure, left ventricular hypertrophy, and severe renal failure.[21]

Moreover, it has been suggested that after 6 months, analogs significant reduction in blood pressure like as individuals receiving immediate renal sympathetic denervation were observed and the secure and sustained reduction of blood pressure exist in 1 year follow-up. Our results confirm this safety and sustainability of renal sympathetic denervation method in 21 months follow-up period.[21]

It's worth noting that we measured the amount of triglyceride, HDL and FBS after renal sympathetic denervation according to the results triglyceride, HDL, and FBS meaningfully decreased from baseline to 21 months after renal sympathetic denervation. We have to acknowledge the investigation limitation due to the fact that inasmuch as, there are no other therapeutic strategies to be compared with renal sympathetic denervation, we are not capable to judge against the renal sympathetic denervation effectiveness with other remedy options. Another study limitation possibly will be the relatively little sample size.

Conclusion

Renal sympathetic denervation presents a modern and secure catheter-based method for sustained reduction hypertension in treatment-resistant cases. We demonstrate for the first time to our knowledge that triglyceride, HDL, and FBS are also controlled by renal sympathetic denervation.

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Conflict of Interests

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References

1. 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.
2. Sadeghi M, Talaei M, Oveisgharan S, Rabiei K, Dianatkhah M, Bahonar A, et al. The cumulative incidence of conventional risk factors of cardiovascular disease and their population attributable risk in an Iranian population: The Isfahan cohort study. Adv Biomed Res 2014; 3: 242.
3. Cutler JA, Sorlie PD, Wolz M, Thom T, Fields LE, Roccella EJ. Trends in hypertension prevalence, awareness, treatment, and control rates in United States adults between 1988-1994 and 1999-2004. Hypertension 2008; 52(5): 818-27.
4. Gharipour M, Khosravi A, Sadeghi M, Roohafza H, Hashemi M, Sarrafzadegan N. Socioeconomic characteristics and controlled hypertension: Evidence from Isfahan Healthy Heart Program. ARYA Atheroscler 2013; 9(1): 77-81.
5. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet 2005; 365(9455): 217-23.
6. Rippy MK, Zarins D, Barman NC, Wu A, Duncan KL, Zarins CK. Catheter-based renal sympathetic denervation: chronic preclinical evidence for renal artery safety. Clin Res Cardiol 2011; 100(12): 1095-101.
7. World Health Organization. Global health risks: mortality and burden of disease attributable to selected major risk [Online]. [cited 2009]; Available from: URL: http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf
8. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation 2008; 117(25):e510-26.
9. Gosain P, Garimella PS, Hart PD, Agarwal R. Renal sympathetic denervation for treatment of resistant hypertension: a systematic review. J Clin Hypertens (Greenwich) 2013; 15(1): 75-84.
10. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 2009; 373(9671): 1275-81.
11. Erdine S. Compliance with the treatment of hypertension: the potential of combination therapy. J Clin Hypertens (Greenwich) 2010; 12(1): 40-6.
12. di Bona G. Sympathetic nervous system and the kidney in hypertension. Current Opinion in Nephrology & Hypertension: 2002; 11(2): 197-200.
13. di Bona GF. Neural control of the kidney: past, present, and future. Hypertension 2003; 41(3 Pt 2): 621-4.
14. Schlaich MP, Hering D, Sobotka PA, Krum H, Esler MD. Renal denervation in human hypertension: mechanisms, current findings, and future prospects. Curr Hypertens Rep 2012; 14(3): 247-53.
15. Hoobler SW, Manning JT, Paine WG, Mcclellan SG, Helcher PO, Renfert H, et al. The effects of splanchnicectomy on the blood pressure in hypertension; a controlled study. Circulation 1951; 4(2): 173-83.
16. Vase H, Mathiassen ON, Kaltoft A, Pedersen EB, Christensen KL, Buus NH, et al. Catheter-based renal denervation for treatment of resistant hypertension. Dan Med J 2012; 59(6): A4439.
17. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Bohm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): A randomized controlled trial. Lancet 2010; 376(9756): 1903-9.
18. Dorenkamp M, Bonaventura K, Leber AW, Boldt J, Sohns C, Boldt LH, et al. Potential lifetime cost-effectiveness of catheter-based renal sympathetic denervation in patients with resistant hypertension. Eur Heart J 2013; 34(6): 451-61.
19. Katholi RE, Rocha-Singh KJ. The role of renal sympathetic nerves in hypertension: has percutaneous renal denervation refocused attention on their clinical significance? Prog Cardiovasc Dis 2009; 52(3): 243-8.
20. Gharipour M, Sarrafzadegan N, Sadeghi M, Khosravi A, Hoseini M, Khosravi-Boroujeni H, et al. The metabolic syndrome and associated lifestyle factors among the Iranian population. Adv Biomed Res 2015; 4: 84.
21. Esler MD, Krum H, Schlaich M, Schmieder RE, Böhm M, Sobotka PA. Renal sympathetic denervation for treatment of drug-resistant hypertension. One-year results from the symplicity HTN-2 randomized, controlled trial. Circulation 2012; 126(25): 2976-82.

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