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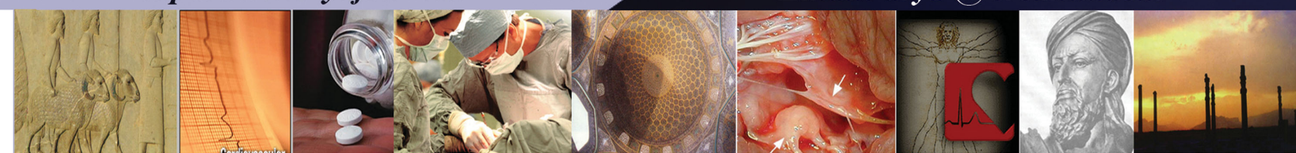

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2. Bonow RO, Mann DL, Zipes DP, Libby P. Braunwald's Heart Disease E-Book: A Textbook of Cardiovascular Medicine. 7th ed. Philadelphia, PA: Elsevier Health Sciences; 2007. p. 1976, 1981, 1982.

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

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Long-term clinical outcomes of the left ventricular thrombus in patients with ST elevation anterior myocardial infarction

Mahmoud Ebrahimi[(1)], Afsoon Fazlinezhad[(2)], Masoomeh Alvandi-Azari[(3)], Morteza Abdar Esfahani[(4)]

Original Article

Abstract

BACKGROUND: This study was performed to determine the size of left ventricular thrombus (LVT), risk of systemic embolization and response to medical treatment during 18 months of follow up in the patients with anterior-ST elevation myocardial infarction (aSTEMI).

METHODS: This cross-sectional study was performed on thirty-five patients with anterior myocardial infarction (MI), in Emam Reza Hospital and Ghaem Hospital, Mashhad, Iran, from August 2008 to January 2011. Warfarin was prescribed for all the patients. Transthoracic echocardiographic study was performed on the 1st, 2nd, 4th, 6th, 12th and 18th months. Outcomes included rate of death, MI, stroke, systemic embolization, major bleeding and change in thrombus size following treatment.

RESULTS: The resolve rate of clot on the 2nd, 4th, 6th, 12th and 18th months was 64.7, 86.6, 81.4, 81.4 and 100 percent, respectively. In five patients with complete clot resolution, clot reformation occurred after warfarin discontinuation. In these patients, left ventricular ejection fraction (LVEF) improvement was poor. During the study period, five patients died due to severe heart failure. One patient developed hematuria whereas non-experienced thromboembolic events. The mean LVEF at study initiation was 30.8 ± 0.92%, which improved to 42 ± 0.84% ($P < 0.05$) at the end.

CONCLUSION: All LVT was resolved with a combination therapy of antiplatelet and warfarin without any thromboembolic event. In patients with a poor improvement in the LV function, due to the risk of LVT reformation, lifelong warfarin therapy was recommended.

Keywords: Echocardiography, Left Ventricular Thrombosis, Myocardial Infarction

Date of submission: 27 Aug 2013, ***Date of acceptance:*** 27 Sep 2014

Introduction

Left ventricular thrombus (LVT) is a known complication of anterior ST-elevation myocardial infarction (aSTEMI), developing a median of 5 days after the acute event.[1] In the Pre-thrombolytic era, the incidence of LVT has been reported to range from 20 to 56% after aSTEMI. In the reperfusion era, despite aggressive reperfusion treatment and anti-aggregant use, the incidence of LVT remained high after anterior ST-elevation anterior myocardial infarction (AMI) (23.5%).[2-5] Post myocardial infarction (MI) LVT increases the risk of embolization significantly,[6] particularly if anticoagulation treatment is not used.[7] For these patients choosing the best treatment strategy for thrombus [Coronary artery bypass graft with surgical thrombectomy or percutaneous coronary intervention (PCI) with medical follow-up] has always been challenging. A major goal of our study was to identify the risks and benefits of anticoagulant therapy in patients with left ventricular (LV) mural thrombi during the 18 months follow-up period.

Materials and Methods

This cross-sectional study was performed on 35 patients with AMI, in Emam Reza Hospital and Ghaem Hospital, Mashhad, Iran, from August 2008 to January 2011. The demographic and clinical characteristics of patients were (88.57%) male, (34.28%) smoker, (45.71%) hypertension, (37%)

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diabetes, and (44%) dyslipidemia. Inclusion criteria were history of aSTEMI that accompanied visible clot in LV. patients with any contraindications for anticoagulant therapy or history of a previous thromboembolic event was excluded from the study. Transthoracic echocardiographic follow-up was performed on the 2nd, 4th, 6th, 12th and 18th months after admission. For all the patients warfarin was administered for at least 4 months. Patients undergoing PCI received clopidogrel as well. The studied outcomes included the rate of death, MI, stroke, systemic embolization, major bleeding and change in thrombus size following treatment. The patients' demographic data, clinical findings, cardiac risk factors and echocardiographic data [including primary ejection fraction (EF) and EF at the end of the follow-up period, localization of the clot and presence of aneurysm] were analyzed descriptively.

Results

From the 35 patients with the eligible criteria, 16 (45.71%) had been previously reperfused with PCI, 3 (8.58%) had only received streptokinase whereas 16 (45.71%) had not received any kind of reperfusion therapy before. Clinical and laboratory characteristics of the cases are presented in table 1. According to electrocardiographic (ECG) criteria, the location of MI was anterior in 31.43% (11), anteroseptal in 28.57% (10), whereas 40% (14) had extensive AMI. In total 21 (60%) patients had a true aneurysm. The primary mean LV systolic ejection fraction (LVEF) was 30.8 ± 0.92% and the mean clot area size was 3.73 ± 2.1 cm^2. The location of the clot in all patients was in the LV apex. The proportion of patients with a persistent thrombus after 2, 4, 6, 12 and 18 months were 35.3% (12 from 34), 13.3% (4 from 30), 18.5% (5 from 27), 18.5% (5 from 27) and 0%, respectively. The dropping number of patients in each month was due to surgery or death. Most thrombi resolved during the 2nd month, whereas lifelong continuation of warfarin therapy was required in five patients due to the reformation of the LVT after discontinuing warfarin administration. The important predicting factor for LVT occurrence after stopping warfarin therapy was severe LV dysfunction with akinesia or aneurysm of the apex. However, no thromboembolic events took place. Nineteen patients showed systolic function improvement (15-25%) and nine of them were re-vascularized by PCI. After 18 months of follow-up, the mean LVEF raised to 42 ± 0.84% and none of the cases experienced any thromboembolic events. One patient developed gross hematuria on the 6th month of treatment due to warfarin overdose.

Table 1. Demographic and clinical characteristics of patients

Characteristics	Percent (%)
Mean age (year)	44.22
Gender (male)	31 (88.57)
Smoking	12 (34.28)
Hypertension	16 (45.71)
Diabetes	13 (37.00)
Dyslipidemia	15 (44.00)
Mean LVEF	30.8
Clot size	1.2-9.88 cm^2 (mean 3.73 ± 2.1 cm^2)
True aneurysm	21 (60)

LVEF: Left ventricular ejection fraction

Discussion

LVT are the major sources of embolic stroke after ST segment elevation MI.[6-10] At present, despite the routine use of early revascularization and dual antiplatelet therapy, LVT is a common complication of aSTEMI.[11]

Weinreich et al. followed 43 patients with LVT for a mean duration of 15 months with serial echocardiography. None of the 25 patients who received anticoagulation treatment experienced an embolic event. Embolization occurred only in 7 of the 18 patients who had not received anticoagulation treatment. All embolic events occurred within four months of infarction. This quite remarkable outcome point that in patients with AMI especially in those with a low EF, serial echocardiography will be necessary for the diagnosis, immediate treatment and follow-up of ventricular thrombi.[12] Transthoracic echocardiography has a very high sensitivity and specificity in LVT diagnosis possibly even higher than 92% and 86-88% respectively.[4]

Nihoyannopoulos et al. determined that within 12 weeks of follow-up, patients with a thrombus had severe LV dysfunction compared with the patients without thrombus.[1]

In our study, all LVTs with any size (between 1.2 and 9 cm^2) were resolved by warfarin and aspirin therapy within 6 months, none of the patients experienced embolic events under anticoagulant therapy, which is consistent with other studies. Reformation of clot in 18.51% (5 from 27 remained patients) necessitates the readministration of warfarin therapy for a longer duration.

Clot reformation is accompanied by sever regional wall motion abnormality of the apex (apical

akinesia or aneurysm) and severe LV dysfunction (LVEF < 35%). Therefore, it seems that in patients with AMI in order to reducing the rate of clot formation and also clot reformation, the level of LVEF and regional wall motion abnormalities should be improved. These would best achieved by early reperfusion and intensive ischemic heart failure therapy.

In our study, the administration of aspirin plus warfarin did not increase the incidence of a major bleeding event in an international normalized ratio (INR) range of 2-3, even when clopidogrel was added.

Limitation

Contrast and the harmonic echocardiography which could have a higher sensitivity for the main purpose of the current study[13] were not used. Optimum time duration of anticoagulation therapy in patients with reforming clot after warfarin cessation is not clear. Furthermore, the authors recommend that in order to obtain more promising results, longer follow up periods are required.

Conclusion

In patients with AMI especially in those with a low EF, the application of serial echocardiography for the early detection and immediate administration of anticoagulant therapy of ventricular thrombi is vital in the prevention of thromboembolic complications. In this study, all LVTs resolved following combination therapy of aspirin and warfarin without any thromboembolic events or major bleeding.

Due to the probable risk of LVT reformation in patients with poor LV function, despite primary resolution, the continuation of warfarin therapy is highly recommended.

Effective ischemic treatment (early coronary reperfusion) is also essential for preventing ischemic heart failure and decreasing the rate of clot formation.

Acknowledgments

Hereby, we acknowledge personnel's of Echocardiography Wards in Ghaem and Emam Reza Hospitals, Mashhad University of Medical Sciences, Iran.

Conflict of Interests

Authors have no conflict of interests.

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Comparison of N-acetylcysteine and angiotensin converting enzyme inhibitors in blood pressure regulation in hypertensive patients

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Original Article

Abstract

BACKGROUND: Hypertension (HTN) is the most prevalent non-infectious disease worldwide and can lead to mortality. This trial aimed to compare the effect of N-acetylcysteine (NAC) and angiotensin-converting enzyme inhibitors (ACEIs) on controlling blood pressure in hypertensive patients.

METHODS: This cross-sectional clinical trial was conducted in Hajar Hospital, Shahrekord, Iran, in 2009. A sample of 126 patients with HTN was selected and randomly divided into 2 groups (group A and group B). First, group A was treated with ACEI alone and group B with ACEI + NAC for 2 months. Blood pressure of all patients was evaluated each week. After a 2 week period of washout, the drugs were changed. In the second period of the trial, group A was treated with ACEI + NAC and group B with NAC alone and their blood pressure was evaluated in the same manner as the previous period. The data were analyzed using SPSS.

RESULTS: A significant reduction was observed in systolic and diastolic blood pressure of patients ($P < 0.050$). However, during both periods of the trial, the group receiving NAC + ACEI experienced a more significant reduction in blood pressure compared with the ACEI group ($P < 0.050$).

CONCLUSION: NAC accompanied with ACEI decreased the patients' systolic and diastolic blood pressure significantly; however, ACEI alone did not have any significant effects on blood pressure. Systolic blood pressure decreased 7 mmHg on average and fluctuated during the trial.

Keywords: **N**-acetylcysteine, Angiotensin-Converting Enzyme Inhibitors, Hypertension

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Introduction

Hypertension (HTN) (high blood pressure) is a risk factor which leads to renal failure, peripheral vascular disease, retinopathy, stroke, and heart attacks.[1,2] Some research studies have indicated that oxidative stress and reactive oxygen species participate in the pathogenesis of cardiovascular diseases, including HTN and atherosclerosis.[3,4]

The relevant literature indicates the stability of or decrease in HTN prevalence in developed countries and increase in its prevalence in developing countries. In addition, no significant cross-sectional association was observed between developed and developing countries regarding the prevalence of awareness, treatment, and control of HTN. The mean level among men in developed countries was higher than that in developing countries. Prevalence of HTN varies worldwide, with the lowest prevalence in rural India (3.4% in men and 6.8% in women) and the highest prevalence in Poland (68.9% in men and 72.5% in women).[5,6]

The purpose of treating this disease is to regulate blood pressure; lower than 140/90 in healthy individuals and lower than 130/85 in patients suffering from diabetes or kidney disease. In most cases, HTN treatment has various side-effects, and thus, results in patients' non-cooperation. Hence,

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administration of a drug that is effective in reducing cardiovascular disease risk factors (decrease in cholesterol, homocysteine, and plasma lipoprotein a, and increase in high-density lipoprotein) will lead to the progress of HTN treatments and increase of these patients' prognosis. According to the investigations conducted on anti-HTN drugs, angiotensin-converting enzyme inhibitors (ACEIs) are the first choice in treating HTN. These drugs are useful especially in patients with kidney HTN, renovascular HTN, diabetes, as well as accelerated and malignant HTN. In mild and uncomplicated HTN, these drugs are as effective as beta-blockers and thiazides. Individuals afflicted with bilateral artery stenosis also suffer from acute renal failure.[7,8] Several lines of evidence have shown the antihypertensive role of cysteine. Some reports using dietary supplementation of the cysteine analog N-acetylcysteine (NAC) have indicated that it prevents or attenuates increased blood pressure in animal models of HTN.[9-20] It has also been demonstrated that the cysteine precursor methionine results in increasing of the cardiovascular risk factor and homocysteine results in increasing of blood pressure in normal rats.[21-23] Homocysteine has been shown to lower blood pressure in hypertensive rats.[24,25] In addition, in human studies, using NAC as an adjunct to other antihypertensive therapies resulted in a decrease in blood pressure.[26,27]

No research has been performed using NAC as a monotherapy in humans suffering from HTN. However, in a study including six hypertensive participants with good blood pressure control (mean: 139/93 mmHg) with the ACE inhibitor lisinopril, the increasing of NAC by 1.2 g/day for 1 week resulted in a significant decrease in both systolic and diastolic blood pressure.[28] In another study, the participants consisted of 18 hypertensive smokers whose blood pressure was not controlled with ACE inhibitor monotherapy (enalapril or captopril). These participants received 1.8 g/day NAC for 21 days. This treatment resulted in a decrease in 24 hour ambulatory and daytime systolic and diastolic blood pressure.[29] Another study assessed the influence of a combination of equal doses of NAC and arginine [the substrate of nitric oxide (NO) synthase], 1.2 g/day, in a group of 12 type 2 diabetic patients with HTN.[30]

One of the pathophysiologic mechanisms suggested in HTN is reduction in the vasodilating factor derived from endothelial cell (such as NO). Moreover, NAC, as an antioxidant, causes an increase in NO derived from endothelial cells due to its mechanism on NO. NAC can decrease homocysteine and lipoprotein and protect the heart against ischemic and perfusion damages on the myocytes through replenishing group of sulfhydryl. Its other effects are increasing the nitroglycerin activity, doubling the anti-platelet effect, dilating coronary veins, and reducing the ratio of tolerance to the hemodynamic effects of nitroglycerine.[27,28,31] Considering the abovementioned effects, this drug can lead to blood pressure reduction. Many studies examining the effect of NAC (based on the mechanism dependent on NO) in combination with ACEI in patients with HTN have shown contradictory results.[29,32] Due to the daily increase in the worldwide death toll due to HTN, and some damages due to this disease, which affect the whole society, and because no research similar to the present one existed in Iran or worldwide, this clinical trial was conducted to compare the effect of NAC and ACEIs on controlling blood pressure in hypertensive patients.

Materials and Methods

This clinical trial with ethics code 89-2-1 was conducted in Hajar Hospital in Shahrekord, Iran, in 2009-2010. The population studied included all patients of 18 years and older with HTN referring to this hospital. The inclusion criteria consisted of age above 18 years, systolic blood pressure of 140 mmHg or higher, diastolic blood pressure of 90 mmHg or higher in spite of taking ACEI, isolated systolic or diastolic HTNs, and diagnosis of HTN by a cardiologist. In addition, patients with HTN who took ACEI (enalapril or captopril) with doses determined by the respective physician and not changed during the trial, and did not take any other antihypertensive drugs, were also allowed to enter the study. Individuals with cystinuria, kidney stones, especially cysteine stones, and severe sensitivity to ACEI and NAC (such as coughing, digestive disorder, and etc.), and also patients who needed other antihypertensive drugs besides ACEI to control their blood pressure were excluded from the trial.

The sampling method was based on convenience sampling. The sample size was calculated based on a 95% confidence and a power of 80% to see a difference equal to 50% of standard deviation in the mean of blood pressure between two groups. The estimated sample size was 126 patients (63 patients in each group). At the beginning of the study, a consent form was filled by the patients and the ethical principles were taken into consideration.

Finally, 126 patients with HTN were entered into the study, and then, randomly divided into two

groups (A and B). ACEI alone was administered to group A and NAC tablets with the doses of 600 mg/12 hours in combination with ACEI was prescribed for 2 months for group B. In addition, NAC treating dose did not change during the trial. During these 2 months, blood pressures of both groups were measured every 5-7 days in the clinic. After this period, none of the two groups received NAC for 2 weeks and only received ACEI (washout period). Then, the two groups' programs were exchanged, and hence, for 2 months the group that received NAC+ACEI received ACEI alone and the group that received ACEI alone received NAC and ACEI. Subsequently, similar to the previous 2-month period, the blood pressure (systolic and diastolic) of all patients was measured by two observers every 5-7 days using the same manometer (Riester, Jungingen, Germany) and stethoscope (Welch Allyn, Tycos Instruments Inc., Skaneateles Falls, NY, USA) in the clinic. Finally, the results were reported as the mean decrease in blood pressure. Every equipment in this study was calibrated once a month.

Data collection was conducted using the questionnaire and measuring the patients' blood pressures. The questionnaire asked about the patients' age, gender, place of residence, duration of HTN history, antihypertensive drugs (enalapril or captopril), and duration of drug taking, blood pressure, diabetes, and smoking (Figure 1).

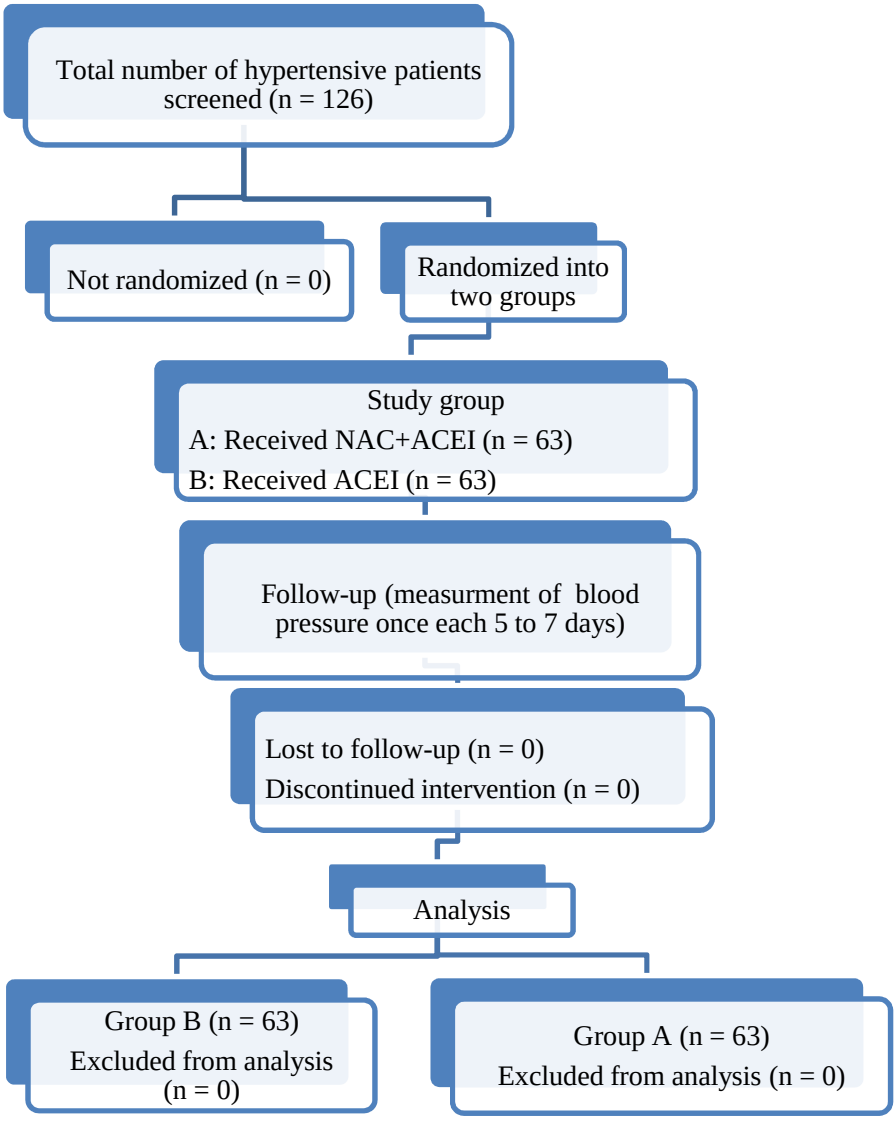

Figure 1: Number of subjects involved at each stage of the study (Flowchart)

For continuous variables, data were presented as means ± standard deviation (SD) and for categorical variables, as number with frequency. Because the sample size was moderately high in each group, the parametric test was used. A repeated measures analysis of variance (ANOVA) was used to compare the blood pressures of the two groups. The multivariate F-tests of Greenhouse-Geisser were used within the subject analysis because of the violation in sphericity assumptions. The comparisons of other variables of interest between the two groups were made using the chi-square or Fisher's exact test for categorical variables and independent t-test for continuous variables. Statistical analysis was performed using SPSS (version 11.5, SPSS Inc., Chicago, IL, USA). All P values below 0.050 were considered statistically significant.

Results

There were 65 patients in each group at the beginning of the study, 4 of whom from group A were excluded due to not referring or following the treatment. Therefore, 61 and 65 individuals continued drug-taking until the completion of the study in the first and second groups, respectively. The mean (± SD) of age in groups A and B were 58.9 ± 12.4 and 57.1 ± 9 years, respectively, with no significant difference between the two groups (P = 0.340). Among all studied patients, 42 and 84 individuals (33.3 vs. 66.7%) were male and female, respectively. There were 17 and 25 men in groups A and B (27.9 vs. 38.5%), respectively. Furthermore, there was no significant difference between the two groups in terms of gender (P = 0.210). Out of the 126 patients studied, 22(17.5%) had diabetes, 9 and 13 (14.8 vs. 20%) of whom were in groups A and B, respectively. In addition, 6 patients smoked, 2 and 4 of whom were in groups A and B, respectively. Moreover, 25 and 32 participants (41 vs. 49.2%) of groups A and B, respectively, took Enalapril. There was no significant difference in the frequency of diabetes, smoking, and the type of drug taken between the two groups (P > 0.050).

The mean systolic blood pressure during the study is shown in table 1 and the mean diastolic blood pressure in table 2. Furthermore, the trend of systolic and diastolic blood pressures of the two groups for the two periods is illustrated in figures 2 and 3, respectively.

No difference was observed in the mean systolic and diastolic blood pressure at the beginning of the study. The comparison of mean systolic and diastolic blood pressures during the study showed that the blood pressure of the group receiving NAC + ACEI (group A) was lower than the group receiving ACEI (group B). Based on the repeated measure analysis of variance, a significant reduction trend exists in systolic and diastolic blood

Table 1. Mean and standard deviation (SD) of systolic blood pressure in the two groups

Time	Group time	A	B	P
		Mean ± SD	Mean ± SD	
The first 2 month	Beginning of the study	12.0 ± 156.1	12.1 ± 157.2	0.610
	At the end of 1st week	10.0 ± 150.9	14.0 ± 147.9	0.170
	At the end of 2 week	10.2 ± 151.9	13.6 ± 145.3	0.003
	At the end of 3 week	10.6 ± 151.6	14.3 ± 142.1	< 0.001
	At the end of 4 week	10.5 ± 149.0	12.1 ± 140.4	< 0.001
	At the end of 5 week	8.7 ± 150.7	10.9 ± 138.8	< 0.001
	At the end of 6 week	10.4 ± 151.6	13.3 ± 138.2	< 0.001
	At the end of 7 week	9.0 ± 148.7	12.0 ± 137.4	< 0.001
	At the end of 8 week	10.1 ± 152.0	11.5 ± 138.7	< 0.001
The second 2 month	At the initiation to inter the second treatment month	8.8 ± 149.2	9.9 ± 152.6	0.420
	At the end of 1st week	10.1 ± 143.0	12.4 ± 151.7	< 0.001
	At the end of 2 week	11.0 ± 141.0	12.5 ± 150.8	< 0.001
	At the end of 3 week	10.0 ± 137.9	11 ± 150.3	< 0.001
	At the end of 4 week	11.0 ± 138.7	11.5 ± 149.9	< 0.001
	At the end of 5 week	9.6 ± 138.3	12.2 ± 151.1	< 0.001
	At the end of 6 week	10.3 ± 138.5	12.3 ± 151.7	< 0.001
	At the end of 7 week	8.7 ± 137.0	11.3 ± 149.5	< 0.001
	At the end of 8 week	9.7 ± 4139.4	10.2 ± 151.3	< 0.001

Group A: the first treatment 2 months with ACEI alone and the second with NAC + ACEI; Group B: the first treatment 2 months with NAC + ACEI and the second with ACEI alone; SD: Standard deviation; ACEI: Angiotensin converting enzyme inhibitor; NAC: N-acetylcysteine

Table 2. Mean and standard deviation (SD) of diastolic blood pressure in the two groups

Time	Group time	A	B	P
		Mean ± SD	Mean ± SD	
The first 2 month	Beginning of the study	9.8 ± 100.5	18.3 ± 96.8	0.170
	At the end of 1st week	8.6 ± 96.9	10.0 ± 92.2	< 0.005
	At the end of 2 week	9.5 ± 96.4	10.6 ± 89.7	< 0.001
	At the end of 3 week	9.0 ± 96.7	10.4 ± 86.8	< 0.001
	At the end of 4 week	9.6 ± 94.9	8.8 ± 85.5	< 0.001
	At the end of 5 week	7.7 ± 96.1	8.0 ± 84.5	< 0.001
	At the end of 6 week	9.2 ± 97.5	10.2 ± 84.4	< 0.001
	At the end of 7 week	8.2 ± 94.4	7.7 ± 82.6	< 0.001
	At the end of 8 week	8.3 ± 97.4	8.0 ± 38.8	< 0.001
	At the initiation to inter the second treatment month	7.4 ± 95.4	8.3 ± 86.3	0.520
The second 2 month	At the end of 1st week	9.4 ± 91.1	10.1 ± 95.3	0.016
	At the end of 2 week	10.0 ± 87.7	10.0 ± 94.5	0.001
	At the end of 3 week	8.7 ± 85.4	8.7 ± 94.3	< 0.001
	At the end of 4 week	10.0 ± 86.1	13.8 ± 92.8	< 0.001
	At the end of 5 week	8.8 ± 86.1	9.0 ± 94.7	< 0.001
	At the end of 6 week	6.8 ± 85.4	9.9 ± 94.8	< 0.001
	At the end of 7 week	7.8 ± 85.2	8.5 ± 93.6	< 0.001
	At the end of 8 week	8.0 ± 84.5	7.3 ± 95.0	< 0.001

Group A: the first treatment 2 months with ACEI alone and the second with NAC + ACEI; Group B: the first treatment 2 months with NAC + ACEI and the second with ACEI alone; SD: Standard deviation; ACEI: Angiotensin converting enzyme inhibitor; NAC: N-acetylcysteine

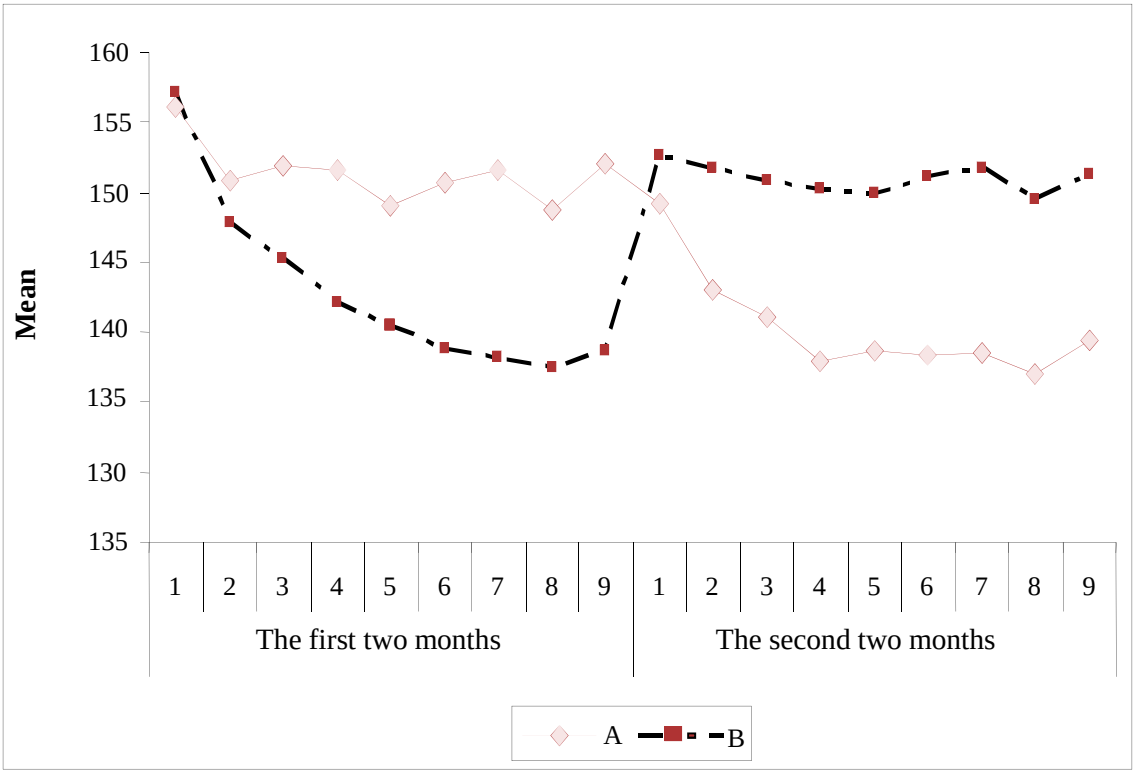

Figure 2. The mean trend of systolic blood pressure in the two groups **[**Group A: the first 2 months of treatment with angiotensin converting enzyme inhibitors (ACEI) alone and the second with N-acetylcysteine (NAC) + ACEI; Group B: the first 2 months of treatment with NAC + ACEI and the second with ACEI alone**]**

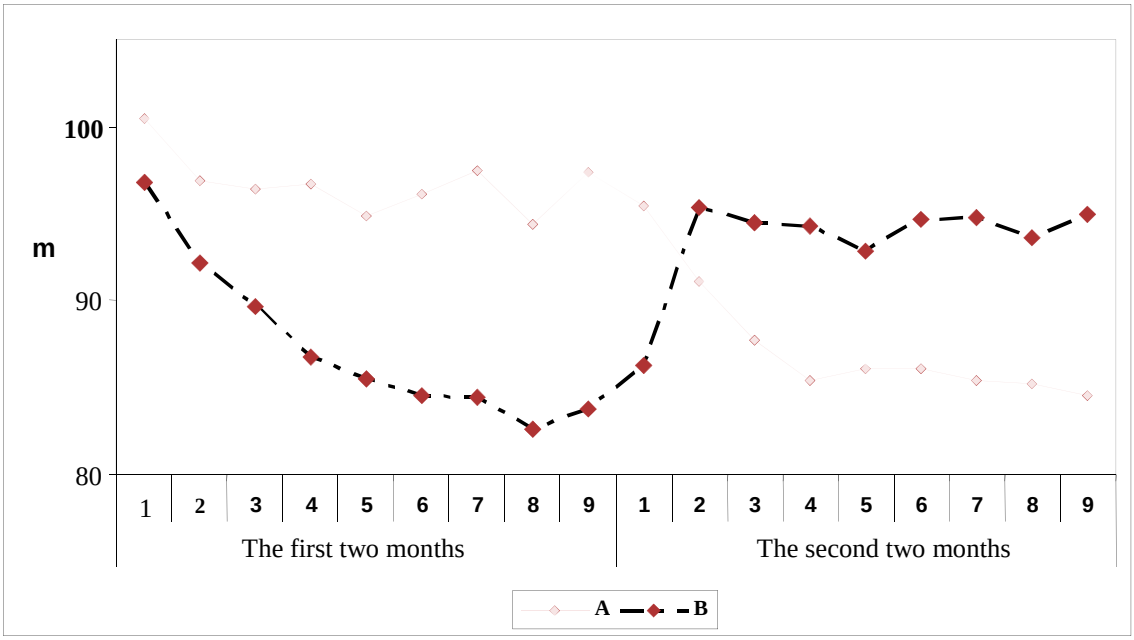

Figure 3. The mean trend of diastolic blood pressure in the two groups [Group A: The first 2 months of treatment with angiotensin converting enzyme inhibitors (ACEI) alone and the second with N-acetylcysteine (NAC) + ACEI; Group B: The first 2 months of treatment with NAC + ACEI and the second with ACEI alone]

Table 3. The result of repeated measure analysis of variance for the blood pressures factor

Blood pressure	Period	Source of variation	df	F	P
Systolic	First	Time	6.76	44.4	< 0.001
		Time × group	6.76	16.0	< 0.001
		Error	838		
	Second	Time	6.88	14.2	< 0.001
		Time × group	6.88	7.2	< 0.001
		Error	853		
Diastolic	First	Time	5.08	26.1	< 0.001
		Time × group	5.08	9.3	< 0.001
		Error	630		
	Second	Time	6.06	14.6	< 0.001
		Time × group	6.06	6.9	< 0.001
		Error	752.00		

Df: Degree of freedom

pressures of patients during the study in the two periods ($P < 0.050$). However, during the two periods, group A had a more significant reduction in systolic and diastolic blood pressures compared to group B ($P < 0.050$). Furthermore, the result of repeated measure ANOVA for the blood pressures is shown in table 3.

Discussion

The purpose of this study was to compare the effects of NAC (group A) plus ACEIs with ACEIs alone (group B) in controlling the patients' blood pressure. Based on the obtained results, NAC accompanied with ACEIs can decrease the patients' systolic and diastolic blood pressure (group A) significantly. However, ACEIs (group B) did not have any significant effects on their blood pressures. Systolic blood pressure decreased 7 mmHg on average, and fluctuated during the study. It is ACEIs accompanied with NAC that can have a quite significant effect on the reduction trend of the patients' systolic blood pressure. Systolic blood pressure reduction in these patients was 18.5 mmHg on average; in other words, taking NAC could decrease the patients' systolic blood pressures by more than two times. In addition, the rate of diastolic blood pressure reduction in patients who received ACEIs alone (group B) decreased 3.1

mmHg on average, while the group A patients' blood pressures reduced by 13 mmHg on average. On the other hand, the fluctuations of diastolic blood pressure in these patients were less than the patients who used ACEI alone (group B).

Regarding the effect of NAC on blood pressure, there have so far been numerous studies on animals, most of which have obtained positive results regarding the reduction of blood pressure. In the study conducted by Barrios et al., the heart ward of Madrid Ramony Cajal Hospital, NAC was presented as a receptor of the sulfhydryl group which can strengthen the antihypertensive effect of the drugs acting through NO mechanism. The studied participants with HTN who smoked consisted of 15 men and 3 women with the mean age of 69 ± 5 years. A considerable reduction (about 7%) was observed in the daily and 24 hour systolic and diastolic blood pressure of patients who took NAC accompanied with ACEI, comparable with ACEI alone. According to the mentioned studies, adding NAC to ACEI strengthens their antihypertensive effects in smoking patients with HTN. This effect can be dependent on NO mechanism and NAC causes an increase in it through the protective effect from NO oxidation.[28] In another study conducted by Bernatova et al., it was concluded that in the blood pressure dependent on NO shortage, the patients will improve more significantly through treatment by antioxidants due to the increase in NO production.[31] In the study by Ruiz et al., NAC was presented as a sulfhydryl group giver which automatically strengthened the reaction to captopril and enalapril treatment in rabbits with hypertension, and this effect was implemented by the mechanism dependent on NO and NAC-increased level of NO.[11] In the study by Martina et al. the decrease in systolic blood pressure was associated with type 2 diabetes in hypertensive patients.[29] Pharmacological analysis of the underlying mechanisms indicated voltage-gated potassium channels engagement in vasodilatory effect of NAC.[32] In another study, NAC was shown to prevent HTN, insulin resistance, and oxidative stress in rats chronically fed with glucose.[33] Renke et al. reported that the effect of NAC on kidney function, kidney damages, and blood pressure in HTN sensitive to salt was examined. In this study, 44 rabbits of 7-8 weeks of age that received high doses of sodium for 5 weeks underwent treatment by NAC with the dose of 4 g/kg/day. While mean arterial pressure had gone up to 1183 mm Hg, NAC treatment caused the arterial pressure to decrease to 4121 mmHg. In addition, NAC caused a 91 and 83% reduction in glomerular necrosis and tubulo-interstitial nephritis, respectively. NAC strengthens the kidney system, decreases kidney function disorder and arterial blood pressure, and thus, leads to the improvement of kidney damage.[34] In a study, NAC was not effective on blood pressure and surrogated markers of cardiovascular injury among non-diabetic patients suffering from a chronic kidney disease.[14] Ozaydin et al. concluded that NAC decreased the incidence of postoperative atrial fibrillation.[35] In the research conducted by Krug et al. in Australia, the effect of NAC on HTN resulting from adrenocorticoids was examined and the results were indicative of blood pressure reduction following taking NAC. In this study, the effect of NAC on HTN resulting from dexametazone usage was examined. In their study, 60 patients receiving dexametazone received 10 g/l NAC for 4-11 days and the patients' blood pressure reduced. Since dexametazone decreases the level of NO in plasma, which is a blood vessels tone setter, and increases blood pressure, NAC structure decreases the level of free radicals due to its antioxidant property, elevates the level of NO, and thus, causes the relative reduction in blood pressure and in fact its setting.[36] In their study, Girouard et al. concluded that increase in NO-mediated vasodilator tone and the possible decrease in adrenergic vasoconstriction induced by NAC treatment in SHR could explain the hypotensive effect of NAC in this model of HTN.[14] Meanwhile, in the study by Martina et al.[29] on patients with diabetic nephropathy and HTN, the effect of the combination of l-arginine and NAC was examined on the level of the patients' blood pressures. Free radicals can decrease NO, so it is possible to keep the level of NO unchanged through administration of NAC as an antioxidant and also l-arginine as an NO setter. In these patients with HTN, 1200 mg l-arginine and 600 mg NAC in the case group and placebo in the control group were prescribed. At the end of the study, the mean diastolic and systolic blood pressure in the case group decreased.[17] The results of several studies are consistent with our study results and show that NAC is effective in reducing blood pressure. Perhaps more noticeable and reliable results were obtained by our study than other studies due to our study time duration.

Conclusion

A patient with HTN with the accurate indications and no contradictions for drug usage, especially

patients with resistant HTN, can be treated with NAC plus ACEIs.

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Conflict of Interests

Authors declare no conflict of interests.

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Association between opium use and metabolic syndrome among an urban population in Southern Iran: Results of the Kerman Coronary Artery Disease Risk Factor Study (KERCADRS)

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Original Article

Abstract

BACKGROUND: Along with the established effects of opium on metabolic parameters, stimulatory or inhibitory effects of opium on metabolic syndrome are also predictable. This study aimed to examine the association of opium use with metabolic syndrome and its components.

METHODS: This study was conducted on 5332 out of 5900 original sample participants enrolled in a population-based cohort entitled the Kerman Coronary Artery Disease Risk Study in Iran from 2009 to 2011. The subjects were divided into three groups of "non-opium users" (NOUs = 4340 subjects), "former opium users" (FOUs = 176 subjects), and dependent and occasional people named "current opium users" (COUs = 811 subjects). Metabolic syndrome was defined according to two International Diabetes Federation (IDF) and National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition criteria.

RESULTS: The overall prevalence of IDF defined-metabolic syndrome among NOUs, FOUs, and COUs was 36.4%, 27.3%, and 39.0%, respectively; which was significantly higher in the COUs group (P = 0.012). However, no significant difference was revealed across the three groups in prevalence of NCEP defined-metabolic syndrome (NOUs = 37.2%, FOUs = 30.1%, and COUs = 39.6%, P = 0.058). The odds for IDF defined-metabolic syndrome was higher in both COUs [odd ratio (OR) = 1.28, P = 0.028)] and FOUs (OR = 1.57, P = 0.045) compared with NOUs as the reference adjusting gender, age, body mass index, and cigarette smoking. However, the appearance of NCEP defined-metabolic syndrome could not be predicted by opium use.

CONCLUSION: Opium use can be associated with an increased risk for metabolic syndrome based on IDF criteria and thus preventing the appearance of metabolic syndrome by avoiding opium use can be a certain approach to preventing cardiovascular disease.

Keywords: Metabolic Syndrome, Opium, Substance Abuse, Addictive Behavior

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Introduction

Very long years, it was believed to the effects of opium use on preventing traditional risk factors for cardiovascular diseases, as well as equilibrating metabolic systems. Particularly, a preventive role of this substance use on diabetes mellitus, insulin resistance, and lipid profile disturbances was common among physicians and healthcare incumbents.[1] This disbelief led to spreading the opium addition in some traditional societies such as Iran so that the common use of this substance has estimated 11-69 per 1000 general population.[2,3] The use of this agent has been even accounted notable among those with high educational level that a representative sample of college students in Iran found 4.4% reporting ever use of opium and out of this 0.8% reported currently using opium.[4]

The stimulating or inhibiting role of opium on metabolic regulatory systems is now challenging. Some recent studies on animal models have shown that opium addiction had profound effects on some biochemical parameters, including fasting blood sugar, low-density lipoprotein (LDL), serum triglyceride (TG), liver enzyme[5] and it had also a

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significant influence on the thyroid function so that increased serum level of total T3 and decreased serum level of T3 resin uptake (T3RU) and serum level of free T4.[6] However, some clinical studies have also revealed that the total cholesterol level in the opium addicts is less than that in the non-addict group; there was, however, no difference in terms of LDL, high-density lipoprotein, and TG between the opium addicts and non-addicts.[7] It seems that the different effects of opium on metabolic parameters may be related to the variety of 70 known components of this substance. Moreover, duration of use, route of consumption, and even being pure or impure can be responsible for contradictory effects of opium on metabolic indices.[8]

Metabolic syndrome is a cluster of clinical conditions including increased blood pressure, increased level of blood sugar, excess body fat around the waist and abnormal cholesterol levels increasing the risk of developing cardiovascular disease.[9,10] According to the established role of opium use on some metabolic parameters individually, stimulatory or inhibitory effects of opium on metabolic syndrome are also predictable. Hence, this study was designed to examine the association of opium use with metabolic syndrome.

Materials and Methods

This cross-sectional study was conducted on 5332 out of 5900 original sample participants aged more than 15-75 years that were enrolled in a population-based cohort entitled the Kerman Coronary Artery Disease Risk Study in Iran between 2009 and 2011 to determine the state of cardiovascular and metabolic risk factors among general population.[11,12]

All participants underwent a standardized interview to completely validated questionnaires containing questions on demography, socioeconomic status, smoking behavior, opium use, physical activity, and nutritional habits. A complete clinical examination for cardiovascular evaluation and its risk factors including systolic blood pressure (SBP), diastolic blood pressures (DBP), weight, height, body mass index (BMI), and waist circumference (WC) was done. All subjects gave informed consent, and procedures followed were in accordance with the Ethical Committee of the Kerman University of Medical Sciences and complied with the recently revised Declaration of Helsinki.

Height, weight, and WC were measured on the day of the visit to the outpatient clinic. BMI was calculated as weight divided by height squared (kg/m^2). Blood pressure was measured twice in the left arm by an examining physician using a mercury column sphygmomanometer (Korotkoff Phases I and V) after the subject had been at rest in the seated position for 5 min. Hypertension was defined as an SBP of ≥ 140 mmHg or a DBP of ≥ 90 mmHg or those who were receiving antihypertensive therapy at the time of the examination. Smoking status was also considered as smoking ≥ 1 cigarette/day in the year preceding the examination. Blood was drawn after an 8-12 h overnight fasting period in the morning after completion of the 24 h urine collection. Plasma biochemical indices were measured by standard laboratory procedures.

In this study, opium use was defined as self-reported use of opium. In this regard, the subjects were divided into three groups of non-opium users (NOUs = 4340 subjects), former opium users (FOUs = 176 subjects), and current opium users (COUs) (occasionally and dependency people based on DSM-IV) (COUs = 811).

Metabolic syndrome was defined according to two definition criteria including International Diabetes Federation (IDF) Worldwide Definition[9] and The US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition.[10] According to IDF definition, a participant has the metabolic syndrome if she/he had central obesity (defined as a WC ≥ 102 cm (40 inches) in men and 88 cm (35 inches) in women) and any two of the following: high-density lipoprotein (HDL) < 40 mg/dl in men and < 50 mg/dl in women or specific treatment for this lipid abnormality; TGs ≥ 150 mg/dl in men and women or specific treatment for this lipid abnormality; SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg in men and women or treatment of previously diagnosed hypertension; and fasting glucose ≥ 100 mg/dl in men and women. Furthermore, definition of metabolic syndrome according to NCEP definition requires at least three of the following: central obesity: WC ≥ 102 cm for men and ≥ 88 cm for women, serum TG ≥ 150 mg/dl, serum HDL level < 40 mg/dl for men and < 50 mg/dl for women, SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg in men and women or treatment of previously diagnosed hypertension, and fasting plasma glucose ≥ 110 mg/dl for both genders. The study endpoint was to examine differences in metabolic syndrome (according to two definitive criteria) and also its components across the three groups of NOUs, FOUs, and COUs.

Results were presented as mean ± standard deviation for quantitative variables and were summarized by absolute frequencies and

percentages for categorical variables. Continuous variables were compared using one-way analysis of variance and/or non-parametric or Kruskal–Wallis test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the three groups. Categorical variables were, on the other hand, compared using the chi-square test. The univariate and multiple logistic regression modeling were employed to assess the association of using self-reportedly opium and the metabolic syndrome after adjusting for gender, age, BMI, and cigarette smoking. Adjusted odds ratios (AOR) were reported. For the statistical analysis, the statistical software SPSS for Windows (version 19.0, SPSS Inc., Chicago, IL, USA) and the statistical package SAS for Windows (version 9.1, SAS Institute Inc., Cary, NC, USA) were used. P values of 0.050 or less were considered as statistically significant.

Results

Comparing the NOUs, FOUs, and COUs groups in terms of baseline characteristics (Table 1) showed significant differences. Male to female ratio was significantly higher in FOUs or COUs than in non-users as well as the COUs were significantly older than other groups. Furthermore, regarding central obesity state, the BMI value was significantly higher in NOUs compared with other two groups. The duration of opium use among FOUs was [mean ± standard error (SE): 11.0 ± 0.66 years; median (range): 8 (0.8-40) years], and among COUs was [mean ± SE: 11.8 ± 0.34 years; median (range): 10 (0.8-50) years].

According to IDF criteria, the overall prevalence of metabolic syndrome was 36.4% in NOUs, 27.3% in FOUs, and 39.0% in COUs that was significantly higher in the COUs group (P = 0.012) (Table 2). However, based on NCEP ATP III definitive criteria, no significant difference was revealed across the three groups in prevalence of metabolic syndrome (37.2% in NOUs, 30.1% in FOUs, and 39.6% in COUs, P = 0.058). Among various components of metabolic syndrome, abnormal serum fasting blood sugar and TG as well as high blood pressure were more prevalent in COUs than in NOUs. Regarding the prevalence of central obesity, abnormal WC was totally higher in NOUs than in other groups. In this context, currently addicted women had higher WC than non-addicted women (Table 2).

Based on the univariate logistic regression, the odds of developing metabolic syndrome among FOUs and COUs was 0.65 [95% confidence interval (CI): 0.46, 0.91] and 0.86 (95% CI: 0.73, 1.01) in comparison to NOUs in IDF definition. These results based on the NCEP definition was respectively 0.72 (0.52, 1.01) and 1.10 (0.94, 1.28). According to the multiple logistic regression model, the odds for metabolic syndrome (defined on IDF criteria) was higher in both COUs (AOR = 1.28, P = 0.028) and FOUs (AOR = 1.57, P = 0.045) compared with NOUs as the reference (Table 3) adjusting gender, age, BMI, and cigarette smoking. However, the appearance of metabolic syndrome defined based on NCEP ATP III criteria could not be predicted by opium use.

Table 1. Baseline characteristics of study population

Variables	NOUs (n = 4345)	FOUs (n = 176)	COUs (n = 811)	P
Sex				
Male	1568 (36.1)	156 (88.6)	642 (79.2)	< 0.001
Female	2777 (63.9)	20 (11.4)	169 (20.8)	
Age categories (year)				
≤ 30	1013 (23.3)	26 (14.8)	44 (5.4)	
31-40	809 (18.6)	57 (32.4)	112 (13.8)	< 0.001
41-50	853 (19.6)	37 (21.0)	185 (22.8)	
51-60	863 (19.9)	38 (21.6)	230 (28.4)	
> 60	807 (18.6)	18 (10.2)	240 (29.6)	
Mean age	45.08 ± 15.6	43.8 ± 12.6	52.5 ± 13.1	< 0.001
BMI				
< 25	1776 (41.2)	106 (60.2)	434 (53.8)	
25-29.99	1660 (38.5)	50 (28.4)	273 (33.8)	< 0.001
30-34.99	683 (15.8)	16 (9.1)	79 (9.8)	
≥ 35	195 (4.5)	4 (2.3)	21 (2.6)	
Mean BMI	26.25 ± 5.06	24.03 ± 4.7	24.8 ± 5.04	< 0.001

NOUs: Non-opium users; FOUs: Former opium users; COUs: Current opium users; BMI: Body mass index

Table 2. Prevalence of metabolic syndrome and its components

Variables	NOUs (n = 4345) (%)	FOUs (n = 176) (%)	COUs (n = 811) (%)	P
Abnormal WC (according to IDF)				
Only men	523 (33.5)	48 (31.0)	205 (32.0)	0.670
Only women	1702 (61.7)	12 (60.0)	126 (75.0)	0.002
Total sample	2225 (51.5)	60 (34.3)	331 (40.9)	< 0.001
Abnormal WC (according to NCEP ATP III)				
Only men	193 (12.4)	17 (11.0)	66 (10.3)	0.370
Only women	1024 (37.1)	6 (30.0)	85 (50.6)	0.002
Total sample	1217 (28.2)	23 (13.1)	151 (18.7)	< 0.001
Abnormal HDL cholesterol				
Only men	1116 (71.6)	104 (67.1)	457 (71.7)	0.480
Only women	2304 (83.4)	16 (84.2)	148 (88.6)	0.200
Total sample	3420 (79.1)	120 (69.0)	605 (75.2)	0.001
Abnormal FPG	1516 (35.0)	56 (32.2)	363 (45.1)	< 0.001
Abnormal TG	1637 (37.8)	79 (45.4)	343 (42.7)	0.007
Abnormal SBP	1217 (28.1)	40 (22.7)	290 (35.8)	< 0.001
Abnormal DBP	887 (20.5)	22 (12.5)	189 (23.3)	0.005
Abnormal blood pressure	1411 (32.6)	46 (26.1)	316 (39.0)	< 0.001
Metabolic syndrome (IDF)	1581 (36.4)	48 (27.3)	268 (33.0)	0.012
Metabolic syndrome (NCEP ATP III)	1618 (37.2)	53 (30.1)	321 (39.6)	0.058

NOUs: Non-opium users; FOUs: Former opium users; COUs: Current opium users; WC: Waist circumference; IDF: International Diabetes Federation; NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III; HDL: High-density lipoprotein; FPG: Fasting plasma glucose; TG: Triglyceride; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Table 3. Odds for metabolic syndrome adjusted for gender, age, body mass index (BMI), and cigarette smoking

Indicator variables	AOR (95% CI)	P
According to IDF definition		
NOUs	Ref	-
Opium ex-users	1.57 (1.01, 2.4)	0.045
COUs	1.28 (1.03, 1.6)	0.028
Cigarette	0.81 (0.62, 1.05)	0.120
Age (year)		
≤ 30	Ref	-
31-40	2.09 (1.6, 2.7)	< 0.001
41-50	3.52 (2.7, 4.6)	< 0.001
51-60	6.01 (4.6, 7.8)	< 0.001
> 60	8.70 (6.6, 11.3)	< 0.001
Sex (female)	1.83 (1.5, 2.15)	< 0.001
BMI		
< 25	Ref	-
25-29.99	10.90 (9.1, 13.1)	< 0.001
30-34.99	24.80 (19.7, 31.1)	< 0.001
≥ 35	33.80 (23.3, 48.9)	< 0.001
According to NCEP definition		
NOUs	Ref	-
Opium ex-users	1.02 (0.70, 1.5)	0.890
COUs	1.03 (0.84, 1.25)	0.760
Cigarette	0.99 (0.79, 1.24)	0.950
Age (year)		
≤ 30	Ref	-
31-40	2.10 (1.6, 2.7)	< 0.001
41-50	3.70 (2.9, 4.8)	< 0.001
51-60	7.30 (5.7, 9.3)	< 0.001
> 60	10.20 (8.0, 13.1)	< 0.001
Sex (female)	0.96 (0.83, 1.1)	0.640
BMI		
< 25	Ref	-
25-29.99	3.80 (3.2, 4.4)	< 0.001
30-34.99	8.90 (7.3, 10.9)	< 0.001
≥ 35	15.10 (10.6, 21.4)	< 0.001

AOR: Adjusted odds ratio; CI: Confidence interval; IDF: International Diabetes Federation; NOUs: Non-opium users; COUs: Current opium users; NCEP: National Cholesterol Education Program; BMI: Body mass index

Discussion

To the best of knowledge, the present study was the first to assess the effect of opium use on metabolic syndrome. The findings of our study can be very helpful particularly in the countries with commonly use of this substance such as Iran to prevent progression of cardiovascular disorders because of triggering effects of both opium addiction and metabolic syndrome in developing cardiac ischemic events. According to our first result, those who commonly used opium suffered more from metabolic syndrome because of higher prevalence of some metabolic components including increased serum blood sugar, serum TG, and also blood pressure. On the other hand, it can be an important hypothesized that opium consumption can mediate appearance of metabolic syndrome through its effect on blood glucose, lipid profile, and also blood pressure regulatory systems. In fact, our study could refuse preventive role of opium use on metabolic disorders such as diabetes or hyperlipidemia. Similar to our finding, some evidences have emphasized elevation of blood sugar following opium consumption. In some reports blood glucose had been increased, although this effect has been shown to be directly dose dependant.[8,13,14] It seems that the effects of opium on glucose metabolism can be mediated by the effects of opiate receptors so that these receptors may influence distribution volume and gluconeogenesis but do not play a major role in either insulin or glucagon secretion or in glucose disposal.[15,16] In addition, insulin resistance with opiate use may be coupled with β-cell dysfunction. After an intravenous glucose load, opium addicts were found to have a 42% lower acute insulin response than control subjects, accompanied by an 80% lower glucose disappearance rate.[17,18] Although, taken together, these findings suggest an association between opiate use and abnormal glucose metabolism, their clinical significance remains uncertain. Moreover, evidence from both preclinical and clinical studies demonstrates that chronic opioid exposure is associated with increased sugar intake. In this regard, elevating the role of opium on serum lipids has been also revealed in other studies that can be due to lipolytic effect of opium.[19,20] The effects of opium on blood glucose and lipids have been especially shown in diabetic patients so that opium addiction in non-insulin dependent diabetic subjects suffered increasing level of serum glucose and decreasing level of HDL-C leading metabolic disorders in these patients.[3] In total, a combination of stimulatory effects of opium on serum glucose, TG, and blood pressure can make the persons susceptible to metabolic syndrome.

Another important finding was that opium use results in different scenarios regarding its effects on weight changes so that the use of this substance led to weight gain only in women, but adversely associated with weight loss in total population. On the other hand, the pattern of weight changes after opium use may be different in men and women probably due to hormonal differences between the genders. The effects of opium addiction on weight change as well as on food intake have been widely studied. Reviews of the preclinical and clinical literature demonstrate a trend of increased eating following opiate agonist intake, with decreased eating after opiate antagonist intake in animals under acute food deprivation or stress, but not those that are chronically food deprived.[21,22] However, gender-dependent pattern of weight change following opium consumption should be more studied. In total, in light of the growing body of evidence linking the opioid system to food intake and risk of obesity, clinicians should reinforce proper exercise and dietary habits with opium users.

Another important point in our survey was obtaining different findings by employing two definitive criteria fir metabolic syndrome including IDF and NCEP criteria. In fact, by using IDF criteria, metabolic syndrome was strongly associated with opium use, while this association was not found by using NCEP criteria for defining metabolic syndrome. It seems that the rate of metabolic syndrome might be overestimated based on NCEP criteria leading incorrect estimation of the prevalence of metabolic syndrome especially in opium users. Hence, using the modified pattern of these criteria is preferred in this population.

Multiple studies have shown that metabolic syndrome has a strong association with socio-economic status of the people. In the current study, we could not to control the effect of such variables on the line of association of opium and metabolic syndrome, because the SES variables were not completely gathered, especially for economic section like income. Another limitation of the current study is that, about less than 600 cases due to having a lack in dependent or independent variables were removed from the study. Another limitation is that we could not define the time for cleaning from the addiction for those people who were classified as former users; however, we think this point cannot have a misleading effect on the results. With consideration of having such

information, we could not control the effect of these durations because this type of variable did not exist among other groups.

In conclusion, opium use can be associated with higher prevalence of metabolic syndrome. This association is explained by triggering effects of opium on serum levels of blood sugar and TG as well as on blood pressure. According to the observed relationship between metabolic syndrome and opium use and due to this fact the two pointed arms have been identified as potential risk factors for coronary artery disease, preventing appearance of metabolic syndrome by avoiding opium use can be a certain approach to prevent these diseases.

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Conflict of Interests

Authors have no conflict of interests.

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High-cocoa polyphenol-rich chocolate improves blood pressure in patients with diabetes and hypertension

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Original Article

Abstract

BACKGROUND: The aim was to examine the effects of high-cocoa polyphenol-rich chocolate on lipid profiles, weight, blood pressure, glycemic control, and inflammation in individuals with Type 2 diabetes and hypertension.

METHODS: Sixty individuals [32 in dark chocolate group (DCG) and 28 in white chocolate group (WCG)] with Type 2 diabetes on stable medication were enrolled in a randomized, placebo-controlled double-blind study. Subjects were randomized to consume 25 g DCG or WCG for 8 weeks. Changes in weight, blood pressure, glycemic control, lipid profile, and high sensitive C-reactive protein (hsCRP) were measured at the beginning and end of the intervention. This clinical trial was registered at the Iranian registry of clinical trials.

RESULTS: In DCC group, compared with baseline, serum levels of Apo A-1 (P = 0.045) was increased and fasting blood sugar (FBS) (P = 0.027), hemoglobin A1c (HbA1c) (P = 0.025), Apo B (P = 0.012) and Log of hsCRP (P = 0.043) levels were decreased at the end of study. No changes were seen within the WCG in studied parameters. High polyphenol chocolate consumption compared to white chocolate resulted in significant decrease in of systolic (−5.93 ± 6.25 vs. −1.07 ± 7.97 mmHg, P = 0.004) and diastolic blood pressure (−6.4 ± 6.25 vs. 0.17 ± 7.9 mmHg, P = 0.002), FBS (−7.84 ± 19.15 vs. 4.00 ± 20.58 mg/dl, P = 0.019) over the course of 8 weeks of daily chocolate consumption neither weight nor body mass index and TG levels altered from baseline.

CONCLUSION: High polyphenol chocolate is effective in improving TG levels in hypertensive patients with diabetes and decreasing blood pressure and FBS without affecting weight, inflammatory markers, insulin resistance or glycemic control.

Keywords: Chocolate, Polyphenols, Type 2 Diabetes, Cardiovascular Risk, Lipid Profile, High Density Lipoprotein Cholesterol, Apolipoprotein

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Introduction

The prevalence of Type 2 diabetes mellitus is rising worldwide, accompanied by an increasing risk of hypertension, cardiovascular disease, and mortality.[1] According to the result of the recent survey on the risk factor of chronic disorders in Iran, indicated that 7.8% of adult with age 25-64 years have Type 2 diabetes mellitus.[2] In diabetes, hypertension (defined as a blood pressure ≥ 140/90 mmHg) is a common comorbid condition affecting ~20-60% of diabetic patients, depending on obesity, ethnicity, and age. In observational studies, patients with both diabetes and hypertension have approximately twice the risk of cardiovascular disease as nondiabetic patients with hypertension. Patients with diabetes and hypertension have also increased the risk of specific complications, including retinopathy and nephropathy.[3]

Intense pharmacologic treatment regimens are necessary, but often remain inadequate to prevent incidence and complications of Type 2 diabetes

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mellitus.[4] Observational studies have shown that physical activity, weight loss, and diet can prevent diabetes and its complications.[4]

Diet is a major lifestyle factor that can greatly influence the incidence and the progression of chronic diseases such as cancer, cardiovascular disease, and diabetes.[1] Recently, flavanols, a subgroup of plant-derived phytochemicals called flavonoids, have gained increasing attention, because epidemiological investigations revealed an inverse correlation between the dietary intake of flavanols and the mortality of cardiovascular disease,[5] and the incidence of diabetes.[6] In the context of human nutrition, flavanols are found in fruit, vegetables, tea and red wine and especially with high concentrations can be present in cocoa and cocoa products.[7] Dietary interventions with flavanol-containing cocoa products in humans indicate beneficial effects of flavanols on low-density lipoprotein oxidation,[8] platelet aggregation,[9] insulin sensitivity,[10] endothelial function and blood pressure.[11]

It has been hypothesized that flavonoid compounds found in foods, including epicatechin found in high-cocoa-solid chocolates, decrease the risk of death from coronary heart disease, cancer and stroke.[12] Short-term administration of dark chocolate was followed by a significant increase in insulin sensitivity and a decrease in blood pressure in healthy subjects.[13] Therefore, we hypothesized that daily consumption of chocolate (25 g daily) containing polyphenol-rich; high-cocoa solids for 8 weeks would improve cardiovascular risk factors in patients with diabetes and hypertension.

Materials and Methods

This randomized, placebo-controlled, double-blind study was undertaken in the endocrinology and metabolism Institute of Tehran University of Medical Sciences, Iran, located at Firoozgar Hospital and the study was funded by the Tehran University of Medical Sciences. The study was approved by the Tehran University Ethics Committee, and written consent was obtained from all subjects prior to enrollment.

This study was conducted on 35-70 years old patients with diabetes and hypertension Type 2 referred to Firoozgar Hospital from March 2011 to February 2012. Sixty-eight subjects [4 in dark chocolate group (DCG) and 34 in white chocolate group (WCG)] with established Type 2 diabetes (age for DCG = 58.71 ± 9.07 and for WCG = 57.17± 7.86 years) were enrolled by blocked randomization method. During the study 2 cases because of insulin use in DCG and 6 cases from WCG because of insulin use (n = 2) and other supplement consumption (n = 4) were excluded. Whom 60 patients (32 in DCG and 28 in WCG) completed the study. The mean diagnosis duration of diabetes was (mean ± standard deviation for DCG = 7.46 ± 4.62 and for WCG = 7.92 ± 3.92) months. Inclusion criteria were diagnosis of Type 2 diabetes based on the World Health Organization guidelines [fasting blood sugar (FBS) > 126 mg/dl or 2h BS > 200 mg/dl][14] and systolic blood pressure ≥ 140 and diastolic blood pressure ≥ 90.[15] Exclusion criteria included hemoglobin A1c (HbA1c) > 9.0%, treatment with insulin, any change in use of medication in the previous 2 months, having any kind of special diets such as vegetarian, lactation, pregnancy, congestive heart failure, malignancies, chronic kidney disease, severe cardiac arrhythmias and inflammation. All participants were either life-long nonsmokers or reported smoking abstinence of at least 5 years before study inclusion. All of the subject's chronic medications such as lipid reducing and blood pressure reducing drugs were maintained at stable doses for at least 2 months prior to the start of the study. The subjects were given chocolate bars containing either dark chocolate or white chocolate in the same package by blind person. The chocolates delivered as a monthly manner and compliance were assessed by asking for how many of the chocolate bars were used. Individual's adherence after 8 weeks intervention was determined by total chocolate number to consumed chocolate. The individuals with < 80% consumption were excluded. Subjects were advised not to consume any other chocolate during the period of the study. In addition, subjects were instructed to make no further changes to their diet, lifestyle, and physical activity. Flow of participants through each stage of the study is available in figure 1.

The chocolate for the study was provided by Farmand Co. The active product was high-polyphenol chocolate containing 83% cocoa solids compared with iso-caloric white chocolate, and was packaged to the same color and shape as high polyphenol chocolate. 25 g foil-wrapped bars were provided individually, and subjects were asked to consume one bar every day. Chocolate bars in the aluminum foil administered in dated, sequentially numbered, nontransparent boxes not labeled about content. Involved physicians and staff were unaware of the group assignment. Patients did not receive information regarding the chocolate and were instructed not to disclose their assigned group to

investigators. To avoid changes in body weight during the intervention, participants were carefully instructed how to make proportional reductions in energy from their habitual diet to substitute for that supplied by chocolates. This amount of dark chocolate would provide a total of 143 kcal daily, with 450 mg flavonoids in comparison with the same amount of calories without flavonoids in white chocolate.

Weight was measured in fasting state using calibrated weighing scales in light clothing and bare feet with nearest of 0.1 kg. Height was measured by un-stretched tape with the nearest of 0.5 cm without shoes and standing position near to the wall. Body mass index (BMI) was calculated as the weight (kg) divided by height (m^2).

To obtain information about dietary intake and to confidence none change calorie consumption in baseline and endpoint of study, participants were asked to 24 h record dietary intakes using 3 days dietary records (one for weekend and 2 for week days) in the baseline and end of the study. Dietary intake data was processed using Nutritionist IV software (First Databank, San Bruno, Calif., USA) modified for Iranian food. International Physical Activity Questionnaire was used for evaluating physical activity levels before and after of the study. 10 ml fasting venous blood samples were separated by centrifugation at 3000 g and stored at -80 °C. Systolic and diastolic blood pressure was reported on average of two properly measured in the right or left arm supported at the heart level of seated position after 10 min of rest by a trained nurse using a mercury sphygmomanometer (Model Gamma G-7; Heine).[16] Fasting plasma glucose was measured by the glucose oxidize method (Pars Azmoon kit). HbA1c was measured by high-performance liquid chromatography method (Menarini Diagnostics, Florence, Italy). Insulin was measured by immunoradiometric assay (IRMA) method (Immunotech Co. Kit). Serum concentrations

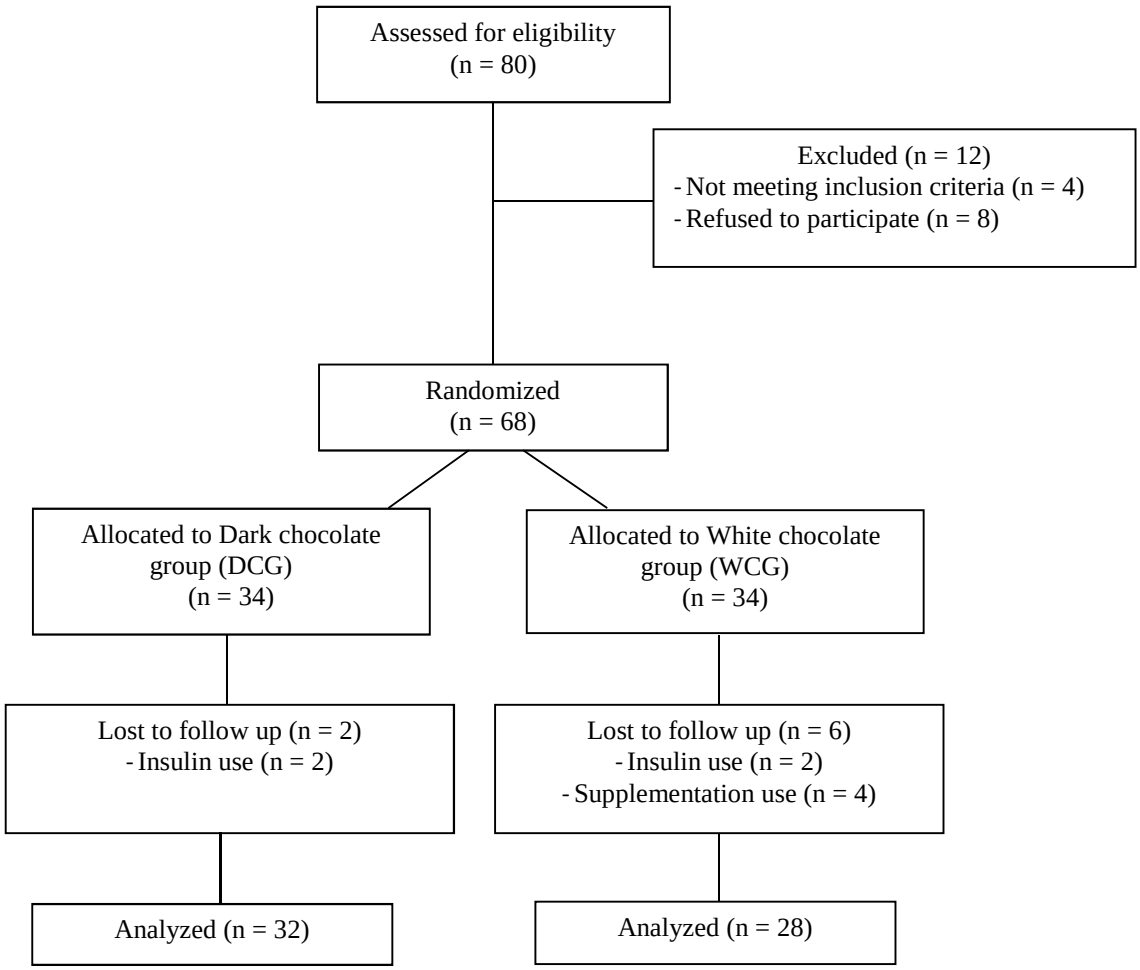

Figure 1. Study participants flow chart

of Triglyceride and total cholesterol were measured using the GPO-PAP kit and the CHOD-PAP kit, respectively (Pars Azmoon kit). High-density lipoprotein (HDL) cholesterol was measured by a direct colorimetric enzymatic method (Greiner). Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula. (TG levels of all patients were under 400 mg/dl). Apo-lipoproteins AI and B were measured by immunoturbidimetry method by using auto-analyzer Cobas (Pars Azmoon kit) and highly sensitive C-reactive protein (hsCRP) is measured by particle enhanced turbid metric immunoassay (Roche Products, Germany).

We used Kolmongrov-Smirnove test for normal distribution assessment of data. Normally distributed data within groups were compared using paired-samples t-test and between groups by independent-samples t-test. Log of non-normally distributed variables was used for changing their distribution to normal. Continues data are presented as mean ± standard deviation. Discrete variables are presented as n (%) and compared between two groups using chi-square test. Data adjusted for age, sex, energy intake and ANCOVA test used for comparing means between intervention groups. We used the SPSS software (version 17.0, SPSS Inc., Chicago, IL, USA) for all the statistical analyzes. $P < 0.050$ was considered significant.

Results

As shown in table 1, baseline characteristics of the participants did not differ between DCG and WCG. At the baseline of the study, comparison of dietary intakes of energy, carbohydrate, protein, fat, fiber and micronutrients including vitamin C, vitamin E, vitamin A, selenium and zinc showed no significant differences between two groups. Also, within group differences of dietary intake were not significant. Thus, there is not confounder at the baseline (Table 2).

Table 1. Clinical baseline characteristics of the study population*

Variable	DCG (n = 32)	WCG (n = 28)	P
Age (year)	58.71 ± 9.07	57.17 ± 7.86	0.650
Weight (kg)	77.62 ± 11.40	76.58 ± 11.33	0.770
Gender			
Men (%)	37.50 (n = 12)	42.90 (n = 12)	0.200†
BMI ($kg.m^2$)	30.12 ± 4.18	29.42 ± 4.58	0.540
Duration of diabetes	7.46 ± 4.62	7.92 ± 3.92	0.360

P values refer to comparisons mean between groups (Independent t-test); * Data are means ± SD or percentage; † Chi-square test used for comparing; DCG: Dark chocolate group; WCG: White chocolate group; SD: Standard deviation; BMI: Body mass index

Table 2. Baseline and after intervention energy and selected nutrient intake of participants assigned to dark chocolate group (DCG) and white chocolate group (WCG)

Diet ingredient	Intervention group	Before (mean ± SD)	After (mean ± SD)	Mean difference (mean ± SD)	P
Energy (Calories)	DCG	1880.80 ± 495.93	1844.72 ± 51.18	-36.290 ± 327.33	0.120
	WCG	1981.01 ± 504.61	1923.03 ± 468.72	-57.980 ± 364.88	
Carbohydrate (g)	DCG	255.60 ± 72.58	253.20 ± 76.15	-2.400 ± 66.34	0.430
	WCG	264.45 ± 81.50	258.87 ± 76.60	-5.570 ± 84.67	
Protein (g)	DCG	81.33 ± 26.46	78.47 ± 26.63	-2.860 ± 19.12	0.320
	WCG	90.10 ± 40.14	81.28 ± 21.01	-8.820 ± 43.26	
Fat (g)	DCG	62.48 ± 24.95	60.69 ± 21.95	-1.780 ± 23.56	0.560
	WCG	69.75 ± 27.17	66.85 ± 25.82	-2.900 ± 34.86	
Fiber (g)	DCG	12.21 ± 5.92	13.32 ± 5.82	1.110 ± 7.68	0.540
	WCG	14.90 ± 11.71	15.02 ± 6.19	2.640 ± 14.04	
Vitamin A (micro g)	DCG	945.27 ± 742.54	980.10 ± 704.38	34.830 ± 695.50	0.430
	WCG	1067.98 ± 800.76	1022.31 ± 709.27	-45.670 ± 840.37	
Vitamin C (mg)	DCG	87.59 ± 83.30	93.57 ± 85.47	5.980 ± 114.69	0.320
	WCG	92.65 ± 73.37	87.02 ± 85.71	-5.620 ± 14.01	
Vitamin E (mg)	DCG	33.07 ± 63.19	29.82 ± 57.34	-3.240 ± 78.19	0.410
	WCG	43.13 ± 84.22	43.03 ± 82.74	-0.090±123.27	
Zinc (mg)	DCG	7.89 ± 4.06	7.78 ± 2.98	-0.100 ± 3.69	0.320
	WCG	9.26 ± 4.66	8.39 ± 3.03	-0.870 ± 5.91	
Selenium (mg)	DCG	0.10 ± 0.05	0.10 ± 0.05	0.004 ± 0.06	0.340
	WCG	0.11 ± 0.05	0.12 ± 0.05	0.008 ± 0.08	

P values refer to comparisons mean difference between intervention groups (Independent t-test); SD: Standard deviation; DCG: Dark chocolate group; WCG: White chocolate group

Table 3 shows the fasting plasma glucose concentrations, HbA1c, serum lipids and other biochemical variables and the corresponding differences of these variables for the WCG and DCG. Compared to baseline, consumption of dark chocolate resulted in a significant decrease in fasting blood glucose (FBG) (-7.84 ± 19.15 mg/dl, P = 0.027), diastolic blood pressure (-5.93 ± 6.25 mmHg, P = 0.001), systolic blood pressure (-6.4 ± 6.25 mmHg, P = 0.001), HbA1c (-0.14 ± 0.34%, P = 0.025), Apolipoprotein B (-4.46 ± 9.44 mg/dl, P = 0.012) and hsCRP levels (-7.88 ± 17.98 nm/l, P = 0.043) and significant increase in Apo-lipoprotein A-1 level (4.56 ± 12.36 mg/dl, P = 0.045) in DCG. Despite major changes in mentioned variables, no such effects were observed in the WCG. Comparison of the two intervention groups showed that dark chocolate intake resulted in significant decrease in diastolic blood pressure (-5.93 ± 6.25 vs. -1.07 ± 7.97 mmHg, P = 0.002), systolic blood pressure (-6.4 ± 6.25 vs. 0.17 ± 7.99 mmHg, P = 0.004), FBS (-7.84 ± 19.15 vs. 4.00 ± 20.58 mg/dl, P = 0.019) compared to white chocolate consumption. We did not observe any significant effect of dark chocolate consumption on fasting insulin, HbA1c, triglyceride, LDL-cholesterol, HDL-cholesterol, Apo-lipoproteins AI and Apo-lipoproteins B levels comparing to white chocolate consumption.

Discussion

Cocoa has been claimed to protect the vascular endothelium by augmenting nitric oxide (NO) availability and thereby improving Endothelium-dependent vasorelaxation.[17] The results of our study showed that high cocoa chocolate consumption decreased blood pressure among diabetic patients. We did not observe any significant effect of dark chocolate intake on serum triglyceride, FBG, fasting insulin, HbA1c, Apo-lipoprotein B, hsCRP and Apo-lipoprotein A-1 level compared to the WCG. Also, dark chocolate consumption did not affect triglyceride, total cholesterol, HDL-cholesterol and LDL-cholesterol levels in comparing with WCG.

The low cardiovascular mortality observed in Kuna Indians has been hypothesized to be consequences of high consumption of cocoa-rich beverages.[18] Studies showed that flavanols, subclass of flavonoids is richly represented in natural cocoa beans, increased NO production in cultured human vascular endothelial cells[19] and improved NO depended endothelium vaso relaxation in finger and brachial arteries of healthy humans.[20] Because insulin sensitivity is dependent on NO availability, we hypothesized that dark chocolate containing polyphenols in addition to the decreasing effect on blood pressure, it might improve insulin sensitivity.[21]

To best of our knowledge, our study was the first study done on the diabetic patients with hypertension. Results of our study showed that feeding of high-polyphenol chocolate for 8 weeks decreased systolic and diastolic blood pressure. A previous report from a prospective study showed a significant inverse relationship between total flavonoid intake and coronary heart disease mortality over a 5 years follow-up period in elderly men.[22] Similarly, the Stockholm Heart Epidemiology Program, assessing the long-term chocolate effects among patients with established coronary heart disease, showed that chocolate consumption had a strong inverse association with cardiac mortality.[23]

Previous studies have suggested that polyphenols could show lipid-lowering effects through different mechanisms including; slowing triacylglycerol absorption via pancreatic lipase inhibitors, increasing fecal excretion of cholesterol,[24] decreasing of hepatic B100 secretion[25] and activation of AMP-activated protein kinase.[26]

The common lipid abnormality in diabetes mellitus is change in plasma triglyceride levels which certainly contribute to the development of cardiovascular disease.[27]

In insulin-deficient diabetic rats, lipoprotein lipase is not activated and hypertriglyceridemia was happened, Mokhtar Ruzaidi et al.[28] Suggested that the chocolate extract increased insulin secretion and hypotriglyceridemic effect of chocolate extract is due to an increase in insulin secretion.

In the agreement to our study, results of Mellor et al. showed that high polyphenol chocolate did not have a significant effect on TG level compared with low polyphenol in diabetic patients.[29]

In other study, daily consumption of dark chocolate did not show a significant effect on TG compared with consumption of white chocolate in healthy subjects.[17] It seems that the dark chocolate has not hypotriglyceridemic impact in diabetic patients and this effect also was not observed in healthy subjects. Inconsistent with our findings, two other studies[13,17] did not observe the effect of chocolate consumption on lipid profiles. In our study, lipid profiles of subjects did not change adversely following the intervention. Thus, the stearic acid in cocoa butter may be an explanation for neuter the beneficial effects of chocolate consumption.

Table 3. Biochemical and anthropometric measurements and mean differences ± standard deviation (SD) at baseline and after the intervention period

	DCG (n = 32)				WCG (n = 28)				P**
	Before	After	Differences	P*	Before	After	Differences	P*	
Diastolic blood pressure (mmHg)	85.15 ± 8.56	79.21 ± 8.89	-5.93 ± 6.25	0.001	86.96 ± 8.08	87.14 ± 8.09	-1.07 ± 7.97	0.920	0.002
Systolic blood pressure (mmHg)	137.03 ± 10.61	130.62 ± 11.19	-6.40 ± 6.25	0.001	137.32 ± 8.55	136.25 ± 8.34	0.17 ± 7.99	0.470	0.004
FBS (mg/dl)	138.06 ± 26.99	130.21 ± 23.67	-7.84 ± 19.15	0.027	134.89 ± 34.46	138.89 ± 30.04	4.00 ± 20.58	0.312	0.019
Fasting insulin	9.77 ± 6.29	9.36 ± 4.70	-0.40 ± 4.68	0.625	10.37 ± 4.63	11.45 ± 5.98	1.04 ± 6.19	0.572	0.141
HbA1c (%)	7.24 ± 1.02	7.10 ± 0.83	-0.14 ± 0.34	0.025	7.55 ± 0.94	7.45 ± 1.19	-0.10 ± 0.78	0.504	0.552
Triglyceride (mg/dl)	118.84 ± 46.02	112.37 ± 41.65	-6.46 ± 19.91	0.110	140.57 ± 47.94	143.57 ± 44.07	3.00 ± 17.82	0.331	0.055
Total cholesterol (mg/dl)	155.65 ± 35.23	153.15 ± 31.35	-2.50 ± 15.55	0.370	158.64 ± 40.33	152.42 ± 37.49	-6.21 ± 19.49	0.103	0.454
LDL cholesterol (mg/dl)	90.59 ± 29.31	87.53 ± 22.44	-3.06 ± 20.56	0.406	95.03 ± 38.75	94.35 ± 35.02	-0.67 ± 9.52	0.709	0.340
HDL cholesterol (mg/dl)	41.87 ± 8.73	42.21 ± 9.17	0.34 ± 7.66	0.802	38.53 ± 9.24	38.57 ± 8.00	0.03 ± 4.63	0.968	0.414
Apo-lipoproteins AI (mg/dl)	149.81 ± 17.89	154.37 ± 16.02	4.56 ± 12.36	0.045	152.14 ± 25.61	150.46 ± 25.56	-1.67 ± 12.19	0.472	0.060
Apo-lipoproteins B (mg/dl)	86.53 ± 20.11	82.06 ± 17.94	-4.46 ± 9.44	0.012	87.96 ± 23.79	85.46 ± 21.05	-2.50 ± 11.70	0.268	0.354
hsCRP (nm/l)	26.71 ± 34.66	18.82 ± 23.72	-7.88 ± 17.98	0.043	18.59 ± 20.70	17.21 ± 15.53	-1.38 ± 14.90	0.831	0.276

DCG: Dark chocolate group; WCG: White chocolate group; FBS: Fasting blood glucose; HbA1c: Hemoglobin A1c; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; hsCRP: Highly sensitive C-reactive protein; Data adjusted for age, sex, energy intake; * Values refer to variation from week 0 to week 8 within groups (Paired t-test); ** Values refer to comparisons between groups with adjusting for age, sex, energy intake (ANCOVA test)

Unlike some proposed mechanisms for glucose lowering effect of polyphenols including; synthesis of glucose transporter isoform 1 and activation of phosphatidylinositol 3-kinase,[17] the results of our study indicate that dark chocolate with 450 mg of polyphenols is not effective on improvement of FBG, insulin and HbA1c levels in hypertensive diabetic subjects. Similarly, Mellor et al. did not observe a significant effect of polyphenols-rich chocolate consumption on fasting glucose, and insulin levels.[29]

In other study, daily consumption of dark chocolate (6.3 g) for 18 weeks, did not demonstrate significant improvement in glucose and insulin levels.

In contrast to our findings, consumption of flavones (902 mg) for 12 weeks resulted in a decrease of insulin resistance in overweight and obese subjects.[30] Together, regarding these findings, we suggest that a higher dose of polyphenols with longer duration may result in a reduction of glucose and insulin.

To the best of our knowledge, there are few data about anti-inflammatory property of DCG. We examined the effect of cocoa consumption on hsCRP as an inflammatory marker.

In our study, despite significant decrease of hsCRP within DCG, we did not observe a significant difference between dark and WCGs. Similar to our findings, the study by Mathur et al. showed that cocoa consumption (36.9 g of dark chocolate bar and 30.95 g of cocoa powder drink) for 6 wk did not affect hsCRP level.[31]

There were a few limitations in the present study. First, serum polyphenols concentrations were not measured at the baseline and end point that may affect the results in both groups. In addition, our study design has not the possibility to double blinding, and patients were aware of the intervention grouping kind. Another limitation might be the financial restrictions that unpowered the follow-up time and more biochemical assessments such as polyphenol levels, that may need more time and investigation to show maximum results on changes in principle outcomes measured. Moreover, monitoring adherence to the intervention monthly may be another limitation in the present study; a close supervision of all participants has to be carried out through personal contact daily or weekly. Finally, we find that may be better this study conducted again with one more group as placebo to compare with previous groups (DCG and WCG) to provide better controlling.

Conclusion

Consuming high-polyphenol chocolate and not white chocolate over an 8 weeks period improved cardiovascular risk indices by decreasing systolic and diastolic blood pressure in patients with diabetes and hypertension without a detrimental effect on triglyceride, weight, insulin resistance, BMI. Our study clearly establishes improvements of blood pressure after regular consumption of flavanol-containing cocoa in patients with Type 2 diabetes, highlighting the potential of flavanol-containing diets, and underscoring their potential health care benefit for reducing the risk of cardiovascular events in diabetic patients.

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Conflict of Interests

Authors have no conflict of interests.

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Electrocardiographic characteristics of posterior myocardial infarction in comparison to angiographic findings

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Original Article

Abstract

BACKGROUND: Myocardial infarction (MI) is a cardiac cell death following the imbalance of supply and demand. Electrocardiography (ECG) is a diagnostic test for MI and can help the clinicians to estimate the severity and size of infarction, to suggest the artery related to the infarct and localize the pathology. The aim of this study is to evaluate the diagnostic value of ECG in posterior MI (PMI) compared with angiographic findings.

METHODS: In a prospective observational study, using simple sampling patients with diagnosis of PMI (ST elevation in at least two consecutive leads V7, V8, and V9) were enrolled and all standard 12 leads and also V7, V8, V9 and right leads, including V3R and V4R were recorded and angiography was performed. ECG changes were recorded and compared with angiography findings.

RESULTS: In this study, totally 138 patients were enrolled (mean ± standard deviation age of 65.00 ± 12.97 and 76.8% male). Left circumflex artery (LCX), right coronary artery (RCA) and left anterior descending artery (LAD) occlusions occurred in 65.9, 50.7, and 29 percent respectively. Patients with LCX occlusion had a significantly higher frequency of ST elevation in V5, V6, I and AVL ($P \leq 0.001$). Patients with RCA occlusion had a significantly higher frequency of ST elevation in V1, V3R, and V4R and also ST depression in V5 and V6 ($P \leq 0.001$).

CONCLUSION: In PMI, there is a relationship between ECG findings and different coronary artery occlusions. Hence that ECG is a useful tool to predict the LCX or RCA occlusion in PMI.

Keywords: Angiography, Coronary Artery, Electrocardiography, Posterior Myocardial Infarction

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Introduction

Cardiovascular diseases (CVD) are one of the most common causes of morbidity and mortality. Coronary artery disease (CAD) is a common form of CVD and is responsible for 22% of early and 15% of late deaths in patients with CVD.[1] Decrease in coronary artery flow has a wide range of symptom according to the severity of obstruction. It may be asymptomatic or symptomatic after exercise or at rest or may be more severe and causes myocardial infarction (MI).[2] MI is a cardiac cell death following the imbalance of supply and demand.[3] Posterior MI (PMI) is infarction of posterior wall resulting from occlusion of left circumflex artery (LCX) or right coronary artery (RCA) and is occurred in 15-20% of acute MIs.[4] It is hard to diagnose PMI and it is associated with a high 6 months mortality rate, especially if present with other myocardial wall ischemia.[5-7]

Different methods and criteria for diagnosis of MI such as considering the sign and symptoms, serological biomarkers, electrocardiography (ECG) and imaging are used.[8] ECG can help the clinicians to estimate the severity and size of infarction, to suggest the artery related to the infarct and localize the pathology.[9] It is mentioned that ECG is the most frequently used, a cost-benefit method and also most misinterpreted diagnostic test in cardiology.[10] It is clear that better tests and also development of the current methods in the diagnosis of MI are required. Hence, the aim of this study was to evaluate ECG characteristics of PMI compared to angiographic findings. This will prepare more information about the diagnostic characteristics of ECG in the diagnosis of PMI. There are some data and study about relationship between ECG and posterior wall MI and it is useful to find that because ECG is a diagnostic test 6-10.

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Materials and Methods

This was a prospective observational study conducted on a sample of 138 consecutive patients with evidence of acute coronary syndrome referred to Shahid Chamran and Noor Hospitals of Isfahan, Iran, in 2012. The inclusion criteria were as follow; (a) diagnosis of PMI according to ECG findings, (b) no streptokinase injection, (c) informed consent for performing angiography and (d) no contraindication for angiography. Patients with no net final diagnosis (not ruling out other diagnosis) and also with no regional wall motion abnormality (RWMA) of posterior wall (according to echocardiography) were excluded from the study. The study sample was selected using simple sampling.

Demographic characteristics including age and sex were recorded. Furthermore, past medical history, including hypertension (HTN), diabetes mellitus (DM), stroke, hyperlipidemia (HLP) and history of smoking were asked. All patients were undergone transthoracic echocardiography to determine the RWMA of posterior wall. Angiography was done using the standard technique, and the occluded arteries were defined. Before angiography ECG evaluation was performed for all participants. The ECGs were recorded at a speed of 25 mm/s and at a calibration of 1 mV = 10 mm using a Schiller Cardiovit recorder. All standard 12 leads and also V7, V8, V9 and right leads including V3R and V4R were recorded and were evaluated by two investigators blinded to angiography findings. PMI was assessed in all leads. PMI was defined as ≥ 1 mm ST elevation at least two consecutive leads of V7, V8 and V9. Also, other ECG changes including ST elevation in other leads, ST depression (> 1 mm), T change (T wave inversion > 3 mm) and pathological Q wave (Q-waves wider than 0.04 s or deeper than one-quarter of the R-wave) in all leads and R wave in V1 and V2 (R/S > 1 mm) were evaluated and recorded.[7,10,11]

Statistical analysis was performed using SPSS for Windows (version 16.0, SPSS Inc., Chicago, IL, USA). For categorical variables, chi-square test was used. Statistical significance was considered at the 0.05 probability level in all analyses, and the data are given as mean ± Standard deviation (SD) or number (%). Sensitivity, specificity, positive (PPV) and negative predictive value (NPV) were calculated according to the table 1.

The research protocol was approved by the Ethical committee of the Isfahan University of Medical Sciences in Iran, and an informed consent was obtained from all participants.

Table 1. Diagnostic power of the test electrocardiography (ECG)

ECG	Angiography (gold standard)		Total
	Positive	Negative	
Positive	TP	FP	TP + FP
Negative	FN	TN	FN + TN
Total	TP+FN	FP+TN	TP + FP + FN + TN

ECG: Electrocardiography; Sensitivity = TP/(TP + FN); Specificity = TN/(TN + FP); Positive predictive value = TP/(TP + FP); Negative predictive value = TN/(FN + TN); TP: True positive; FP: False positive; TN: True negative; FN: False negative

Results

In this study, 138 patients were enrolled. The mean age (± SD) of the participants was 65.00 ± 12.97 and 106 (76.8%) were male. Of the participants, 65 (47.1%), 55 (39.9%), 25 (18.1%), 58 (42%) and 55 (40.1%) had positive history of HTN, DM, stroke, HLP and smoking, respectively. Results of angiography showed that none of the participants had occlusion in left main coronary artery, 70 (50.7%) had RCA occlusion, 40 (29%) had left anterior descending artery (LAD) occlusion and 91 (65.9%) had LCX occlusion. Of the participants 35 (25.4%) had only RCA occlusion, 55 (39.9%) had only LCX occlusion, 13 (9.4%) had LCX and LAD occlusion, 8 (5.8%) had LCX and RCA occlusion, 12 (8.7%) had LAD and RCA occlusion and 15 (10.9%) had three-vessel (LCX, LAD and RCA) occlusion.

All patients had ST elevation in at least two consecutive leads of V7, V8 and V9 as it was the criteria to be included in this study. Tables 2 and 3 are reporting the frequencies of different ECG abnormalities and findings in all leads in patients with different types of coronary artery occlusions. According to table 2 and 3, patients with LCX occlusion had a significantly higher frequency of ST elevation in V5, V6, I and AVL (P ≤ 0.001). Also, they had a higher frequency of T changes in V3R and V4R (P = 0.011 and 0.004, respectively). Patients with RCA occlusion had a significantly higher frequency of ST elevation in V1, V3R and V4R (P ≤ 0.001). Also, they had a significantly higher frequency of ST depression in V5 and V6 (P ≤ 0.001) and T change in V6 (P = 0.046). Patients who had LAD occlusion in addition to LCX or RCA had a significantly higher frequency of ST elevation in V2, V3 and V4 (P ≤ 0.001) and ST depression in AVF (P = 0.028). In 81.9% and 84.1% of all patients ST elevation was recorded in leads II and III respectively. There was no significant difference between different artery

occlusions in ST elevation in leads II and III (P = 0.733 and 0.398, respectively) (Table 2). There were no significant differences between different types of coronary occlusions for R in V1 and V2 (P = 0.109 and 0.111 respectively).

According to the table 2 and 3, some criteria for diagnosis of the occluded coronary artery based on ECG findings are reported in table 4. As table 4 is reporting, if ST elevation in lead V5 or V6 be added to ST elevation in at least two consecutive leads of V7, V8 and V9, diagnostic power of ECG in LCX occlusion is as follow: sensitivity of 71.42% and specificity of 89.26%. If ST elevation in lead I or AVL be added to the mentioned criteria, specificity will increase to 97.87%, but sensitivity will decrease to 56.04%. For RCA occlusion, if ST elevation in lead V1 e added to ST elevation in leads of V7, V8 and V9, sensitivity and specificity of ECG in diagnosis of RCA occlusion will be 67.14% and 85.29%, respectively. If ST elevation in V3R or V4R is added to the mentioned criteria, sensitivity will be 60.00% and specificity will be 94.11%. Adding ST depression in V5 or V6 will decrease the sensitivity to 11.42%, but increase the specificity to 98.52%. Positive predictive value (PPVs) and negative predictive value (NPVs) are also reported in table 4.

Table 2. Frequency of different electrocardiographic findings of limb leads in patients with different coronary artery occlusions after posterior myocardial infarction

ECG change	ECG Leads					
	I	II	III	AVR	AVF	AVL
ST elevation						
Only RCA	3 (8.6)	28 (80.0)	31 (88.6)	1 (2.9)	33 (94.3)	3(8.6)
Only LCX	34 (61.8)	44 (80.0)	48 (87.3)	0 (0.0)	48 (87.3)	29 (52.7)
LCX + LAD	7 (53.8)	10 (76.9)	11 (84.6)	1 (7.7)	6 (46.2)	8 (61.5)
LCX + RCA	5 (62.5)	6 (75.0)	7 (87.5)	0 (0.0)	8 (100.0)	7 (87.5)
LAD + RCA	1 (8.3)	11 (91.7)	9 (75.0)	1 (8.3)	10 (83.3)	1 (8.3)
Three vessels	4 (26.7)	14 (93.3)	10 (66.7)	12 (80.0)	11 (73.3)	5 (33.3)
P	< 0.001	0.751	0.381	< 0.001	0.003	< 0.001
ST depression						
Only RCA	9 (25.7)	3 (8.6)	2 (5.7)	14 (40.0)	1 (2.9)	8 (22.9)
Only LCX	8 (14.5)	10 (18.2)	6 (10.9)	26 (47.3)	7 (12.7)	14 (25.5)
LCX + LAD	2 (15.4)	1 (7.7)	1 (7.7)	9 (69.2)	5 (38.5)	2 (15.4)
LCX + RCA	1 (12.5)	2 (25.0)	1 (12.5)	6 (75.0)	0 (0.0)	0 (0.0)
LAD + RCA	2 (16.7)	0 (0.0)	1 (8.3)	3 (25.0)	2 (16.7)	2 (16.7)
Three vessels	8 (53.3)	1 (6.7)	4 (26.7)	2 (13.3)	3 (20.0)	4 (26.7)
P	0.064	0.377	0.409	0.013	0.027	0.717
T change						
Only RCA	13 (37.1)	3 (8.6)	2 (5.7)	25 (71.4)	1 (2.9)	11 (31.4)
Only LCX	12 (21.8)	8 (14.5)	6 (10.9)	45 (81.8)	7 (12.7)	18 (32.7)
LCX + LAD	5 (38.5)	1 (7.7)	0 (0.0)	9 (69.2)	4 (30.8)	3 (23.1)
LCX + RCA	2 (25.0)	1 (12.5)	1 (12.5)	5 (62.5)	0 (0.0)	0 (0.0)
LAD + RCA	2 (16.7)	1 (8.3)	3 (25.0)	9 (75.0)	1 (8.3)	2 (16.7)
Three vessels	6 (40.0)	1 (6.7)	3 (20.0)	4 (26.7)	2 (13.3)	4 (26.7)
P	0.424	0.965	0.229	0.004	0.122	0.475
Pathological Q wave						
Only RCA	6 (17.1)	1 (2.9)	1 (2.9)	21 (60.0)	2 (5.7)	3 (8.6)
Only LCX	9 (16.4)	6 (10.9)	5 (9.1)	32 (58.2)	5 (9.1)	8 (14.5)
LCX + LAD	3 (23.1)	2 (15.4)	1 (7.7)	9 (69.2)	3 (23.1)	3 (23.1)
LCX + RCA	1 (12.5)	0 (0.0)	0 (0.0)	6 (75.0)	0 (0.0)	0 (0.0)
LAD + RCA	2 (16.7)	1 (8.3)	1 (8.3)	9 (75.0)	2 (16.7)	4 (33.3)
Three vessels	5 (33.3)	3 (20.0)	6 (40.0)	7 (46.7)	1 (6.7)	3 (26.7)
P	0.757	0.328	0.015	0.622	0.413	0.174

Data are given as frequency (percentage) of positive patients; ECG: Electrocardiography; LAD: Left anterior descending artery; LCX: Left circumflex artery; RCA: Right coronary artery

Table 3. Frequency of different electrocardiographic findings of precordial, posterior and right leads in patients with different coronary artery occlusions after posterior myocardial infarction

ECG change	ECG Lead										
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V3R	V4R
ST elevation											
Only RCA	24 (68.6)	2 (5.7)	1 (2.9)	1 (2.9)	1 (2.9)	3 (8.6)	29 (82.9)	33 (94.3)	31 (88.6)	30 (85.7)	29 (82.9)
Only LCX	4 (7.3)	0 (0.0)	0 (0.0)	18 (32.7)	28 (50.9)	34 (61.8)	51 (92.7)	46 (83.6)	44 (80.0)	7 (12.7)	7 (12.7)
LCX + LAD	6 (46.2)	10 (76.9)	8 (53.8)	9 (69.2)	11 (84.6)	10 (76.9)	11 (84.6)	13 (100)	10 (76.9)	2 (15.4)	1 (7.7)
LCX + RCA	7 (87.5)	0 (0.0)	0 (0.0)	6 (75.0)	8 (100)	8 (100)	7 (87.5)	7 (87.5)	8 (100)	6 (75.0)	8 (100)
LAD + RCA	8 (66.7)	8 (66.7)	9 (75)	4 (33.3)	2 (16.7)	1 (8.3)	7 (58.3)	11 (91.7)	11 (91.7)	9 (75.0)	11 (91.7)
Three vessels	8 (53.3)	7 (46.7)	7 (53.8)	8 (53.3)	5 (33.3)	7 (46.7)	11 (73.3)	12 (80.0)	12 (80.0)	11 (73.3)	11 (73.3)
P	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.048	0.363	0.629	< 0.001	< 0.001
ST depression											
Only RCA	3 (8.6)	7 (20.0)	5(14.3)	7 (20.0)	7 (20.0)	6 (17.1)	3 (8.6)	2 (5.7)	3(8.6)	1 (2.9)	1 (2.9)
Only LCX	9 (16.4)	11 (20.0)	11 (20.0)	7(12.7)	6 (10.9)	4 (7.3)	2 (3.6)	10 (18.2)	8 (14.5)	8 (14.5)	8 (14.5)
LCX + LAD	3 (23.1)	1 (7.7)	2 (15.4)	2 (15.4)	1 (7.7)	2 (15.4)	1 (7.7)	0 (0.0)	3 (23.1)	1 (7.7)	1 (7.7)
LCX + RCA	0 (0.0)	4 (50.0)	3 (37.5)	1 (12.5)	0 (0.0)	0 (0.0)	1 (12.5)	1 (12.5)	0 (0.0)	2 (25.0)	0 (0.0)
LAD + RCA	1 (8.3)	2 (16.7)	2 (16.7)	3 (25.0)	4 (33.3)	5 (41.7)	4 (33.3)	1 (8.3)	0 (0.0)	2 (16.7)	0 (0.0)
Three vessels	4 (26.7)	5 (33.3)	3 (20.0)	4 (26.7)	6 (40.0)	6 (40.0)	2 (13.3)	3(20.0)	3 (20.0)	3 (20.0)	2 (13.3)
P	0.399	0.268	0.778	0.718	0.044	0.005	0.053	0.291	0.365	0.191	0.355
T change											
Only RCA	5 (14.3)	9 (25.7)	13 (37.1)	15 (42.9)	16 (45.7)	16 (45.7)	3 (8.6)	1 (2.9)	3 (8.6)	1 (2.9)	2 (5.7)
Only LCX	18 (32.7)	19 (34.5)	24 (43.6)	15 (27.3)	14 (25.5)	12 (21.8)	2 (3.6)	10 (18.2)	8 (14.5)	16 (29.1)	17 (30.9)
LCX + LAD	6 (46.2)	3 (23.1)	6 (46.2)	5 (38.5)	2 (15.4)	3 (23.1)	2 (15.4)	1 (7.7)	4 (30.8)	4 (30.8)	4 (30.8)
LCX + RCA	0 (0.0)	3 (37.5)	4 (50.0)	2 (25.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (12.5)	0 (0.0)	2 (25.0)	0 (0.0)
LAD + RCA	4 (33.3)	3 (25.0)	0 (0.0)	4 (33.3)	5 (41.7)	5(41.7)	4 (33.3)	1 (8.3)	0 (0.0)	2 (16.7)	0 (0.0)
Three vessels	4 (26.7)	3 (20.0)	3(20.0)	2 (13.3)	6 (40.0)	3 (20.0)	2(13.3)	2 (13.3)	1 (6.7)	0 (0.0)	1 (6.7)
P	0.086	0.851	0.030	0.380	0.058	0.054	0.045	0.312	0.214	0.004	0.003
Pathological Q wave											
Only RCA	2 (5.7)	4 (11.4)	7 (20.0)	6 (17.1)	6 (17.1)	8 (22.9)	2 (5.7)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
Only LCX	7 (12.7)	8 (14.5)	9 (16.4)	6 (10.9)	4 (7.3)	3 (5.5)	2 (3.6)	6 (10.9)	6 (10.9)	12 (21.8)	12 (21.8)
LCX + LAD	4 (30.8)	2 (15.4)	4 (30.8)	4 (30.8)	2 (15.4)	2 (15.4)	0 (0.0)	0 (0.0)	2 (15.4)	1 (7.7)	1 (7.7)
LCX + RCA	1 (12.5)	1 (12.5)	2 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
LAD + RCA	2 (16.7)	2 (16.7)	2 (16.7)	3 (25.0)	2 (16.7)	3 (25.0)	4 (33.3)	1 (8.3)	1 (8.3)	1 (8.3)	0 (0.0)
Three vessels	5 (33.3)	4 (26.7)	3 (20.0)	3 (20.0)	6 (40.0)	5 (33.3)	1 (6.7)	1 (6.7)	2 (13.3)	3 (20.0)	2 (13.3)
P	0.085	0.829	0.861	0.315	0.046	0.022	0.035	0.644	0.157	0.017	0.015

Data are given as frequency (percentage) of positive patients; ECG: Electrocardiography; LAD: Left anterior descending artery, LCX: Left circumflex artery, RCA: Right coronary artery

Table 4. Evaluation the diagnostic power of electrocardiography in differentiation of coronary artery types occlusion on in patients with posterior myocardial infarction

Criteria	Angiography finding				Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	Occluded		Not occluded					
	TP	FN	TN	FP				
LCX								
ST elevation in two consecutive leads of V7, V8, V9 (diagnosis of PMI by ECG)								
AND ST elevation in lead V5 or V6	65 (47.1)	26 (18.8)	42 (30.4)	5 (3.6)	71.42	89.36	92.85	61.76
AND ST elevation in lead I or AVL	51 (37.0)	40 (29.0)	46 (33.30)	1 (0.7)	56.04	97.87	98.07	53.48
RCA								
ST elevation in two consecutive leads of V7, V8, V9 (diagnosis of PMI by ECG)								
AND ST elevation in lead V1	47 (34.1)	23 (16.7)	58 (42.0)	10 (7.2)	67.14	85.29	82.45	71.60
AND ST elevation in lead V3R or V4R	42 (30.4)	28 (20.3)	64 (46.4)	4 (2.9)	60.00	94.11	91.30	69.56
AND ST depression in V5 or V6	8 (5.8)	62 (44.9)	67 (48.6)	1 (0.7)	11.42	98.52	88.88	51.93

TP: True positive; FN: False negative; TN: True negative; FP: False positive; PPV: Positive predictive value; NPV: Negative predictive value; LCX: Left circumflex artery; RCA: Right coronary artery; ECG: Electrocardiography; PMI: Posterior myocardial infarction; AND means plus all above

Discussion

Standard leads of ECG are insensitive tool in identifying the PMI because they don't directly view the posterior wall.[7] As there are limited studies conducted on ECG properties of patients with PMI, the aim of the current study was to evaluate ECG characteristics of PMI in comparison to angiographic findings.

Our results showed that in patients with PMI, LCX occlusion was the most frequent occlusion (LCX > RCA > LAD). No left main coronary artery occlusion was defined. Previous reports have shown that PMI is usually caused by occlusion of LCX.[11,12] In addition, our results revealed that patients with LCX occlusion had a significantly higher frequency of ST elevation in V5, V6, I and AVL and T changes in V3R and V4R. According to previous studies, LCX supplies a small ventricular area, and ST elevation will occur in less than half cases. However when ST elevation happens, it is more often seen in leads II, III and AVF and also V5, V6 and AVL in patients with PMI. Also, it is reported that ST elevation in leads V5 and V6 are associated with LCX occlusion.[13,14] Kim et al. showed that patients with PMI diagnosed as having LCX occlusion have significantly higher frequency of ST elevation in leads I, AVL, V5 and V6 than patients with LAD and RCA occlusions.[15] Study conducted by Bairey et al. showed that patients with LCX occlusion had ST elevation in one or more lateral leads including AVL, V5 or V6 and it was significantly different from patients with RCA occlusion.[16] Also another study has reported the same results and revealed that patients with LCX lesion have most often ST elevation in V6.[17] In the current study, patients with RCA occlusion had a significantly higher frequency of ST elevation in V1, V3R and V4R and ST depression in V5 and V6 and T change in V6. Study of Birnbaum et al. showed that ST depression in leads V4 to V6 associated with higher probability of RCA occlusion.[18] By considering ST elevation in leads V5 or V6, LCX occlusion will be diagnosed with sensitivity of 71.42% and specificity of 89.26%. If ST elevation in leads I or AVL is added to the mentioned, sensitivity and specificity will be 56.04% and 97.87% respectively. According to our results, if ST elevation in lead V1 is considered, sensitivity and specificity of ECG in the diagnosis of RCA occlusion in patients with PMI will be 67.14 and 85.29% respectively. If ST elevation in V3R or V4R is added to the mentioned criteria, sensitivity will be 60.00%, and specificity will be 94.11%.

Conclusion

According to our results in PMI, there is a relationship between ECG findings and different coronary artery occlusions. So that ECG is a useful tool to predict the LCX or RCA occlusion in PMI. Also our results are suggestive of paying more attention and record posterior leads (V7, V8 and V9) when ECG changes such as ST elevation in lead V5 or V6 in addition to ST elevation in leads I or AVL or ST elevation in lead V1 in addition to ST elevation in lead V3R or V4R occurs during acute coronary syndromes.

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Conflict of Interests

Authors have no conflict of interests.

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The effect of pioglitazone on circulating interleukin-10 and tumor necrosis factor-alpha levels in a patient with metabolic syndrome: A randomized, double-blind controlled trial

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Original Article

Abstract

BACKGROUND: This study aimed to evaluate the effect of pioglitazone as an insulin sensitizer on circulating interleukin-10 (IL-10) as an anti-inflammatory factor and tumor necrosis factor-alpha (TNF-α) as main proinflammatory factor in non-diabetic metabolic syndrome (MetS) patients in Caucasians race of Middle East area in Iran.

METHODS: We conducted a randomized double-blind controlled study of 68 non-diabetic patients with MetS. Patients were randomly divided into two groups including intervention group received pioglitazone 30 mg daily for 24 weeks, and the control group received placebo pills for the same duration. Circulating levels of TNF-α and IL-10 were assessed as a primary goal. Lipid profile, liver enzymes, blood pressure (BP), waist circumference, and body mass index (BMI) also were measured.

RESULTS: Lipid profile and fasting blood sugar had non-significant changes after treatment by pioglitazone, but BMI was increased significantly ($P = 0.002$). BP and waist circumference had a significant decrease in both groups ($P < 0.050$). Aspartate transaminase and alanine transaminase were decreased significantly in the pioglitazone group ($P = 0.002$). TNF-α decreased non-significantly in both groups ($P > 0.050$). IL-10 increased in intervention group non-significantly ($P = 0.971$); whereas in placebo group decreased to a little extent ($P = 0.401$). C-reactive protein was also decreased insignificant after receive pioglitazone ($P = 0.333$). There was no significant difference in all variables between the two groups ($P > 0.050$) except liver enzymes ($P < 0.050$).

CONCLUSION: This study indicates that the pioglitazone has no positive effect on improving inflammatory status in the non-diabetes patients with MetS.

Keywords: Pioglitazone, Interleukin-10, Tumor Necrosis Factor Alpha

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Introduction

Metabolic syndrome (MetS) with increasing prevalence is one of the most important health and medical problems in developed and developing countries.[1] Metabolic or X syndrome includes a set of metabolic risk factors such as abdominal obesity, dyslipidemia, impaired glucose homeostasis and hypertension associated with an increase of cardiovascular disease and its resulting mortality. In fact, cardiovascular disease is the most important consequence of X syndrome and mortality factor among this population.[2]

Recently, several studies propose elevated serum levels of inflammatory biomarkers as an emerging risk factor for many chronic diseases such as diabetes and MetS and consider inflammatory processes as the overt factor leading to cardiovascular diseases progression.[3] In fact, systemic inflammation plays the main role in the pathogenesis of MetS and the role of intermediary in development of cardiovascular events in these patients.[4,5] The production of proinflammatory factors such as interleukin-1 (IL-1), IL-6, tumor

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necrosis factor-α (TNF-α) and C-reactive protein (CRP) due to homeostasis in adipose tissue in MetS plays an important role in atherosclerotic disturbances and diabetes by affecting endothelial function of vessels and making resistance against insulin.[6,7] Thus, overcoming insulin resistance could be a main step in prevention and treatment of patients suffering from MetS. Having agonist effect on peroxisome proliferator-activated receptor-gamma (PPAR-γ) and reducing inflammatory biomarker, thiazolidine (TZD) improves insulin sensitivity and has a little effect on the function of beta cells and liver.[8-11] Furthermore, TZD improves endothelial function, reduces vascular inflammation, free fatty acids and low-density lipoprotein cholesterol (LDL-C).[12] Among these, various studies have also investigated the effect of this drug category on the level of inflammatory biomarkers and vascular function of diabetic and non-diabetic patients, which besides anti-inflammatory effect of drug; they show contradictory results especially in various ethnicities.[13-16] On the other hand, there are a few studies investigating the effect of this drug on plasma level of anti-inflammatory cytokines like IL-10.[17] As far as we know, this study investigates the effect of pioglitazone (as a TZD) on plasma level of IL-10 as an anti-inflammatory factor and TNF-α as main proinflammatory factor in nondiabetic patients with MetS in Caucasians race of Middle East area in Iran, for the first time. The main reason for selection of patients suffering from MetS rather than one of its components like hypertension is that the resistance against insulin is a common pathophysiology between all different parts of MetS. The presence of all these components severely increases the cardiovascular risks. Hence, we assessed the effects of Pioglitazone as an insulin sensitizer on circulating IL-10 and TNF-α in the noted population (primary aim); and also we evaluated the metabolic risk factor including lipid profile, glucose serum level, body weight, blood pressure (BP) and other inflammatory makers like CRP as secondary aim.

Materials and Methods

This is a randomized; double-blind controlled trial study that approved by the Ethics Committee of the Isfahan University of Medical Sciences, Iran. The study was carried out on 89 men and women referring to Sedigheh Tahereh Medical Clinic (Isfahan Cardiovascular Research Institute) in 2012 to 2013. Inclusion criteria include age range of 35-65 years with non-diabetic MetS criteria. The updated Adult Treatment Panel III guideline of the National Cholesterol Education Program definition was used for MetS detection. It was defined as the presence of 3 or more of the following components: (1) serum triglycerides (TG) ≥ 150 mg/dl; (2) high-density lipoprotein-cholesterol (HDL-C) < 40 mg/dl for men and < 50 mg/dl for women; (3) glucose ≥ 100 mg/dl fasting or on treatment; (4) BP ≥ 130/85 mmHg or antihypertensive medication use, and (5) waist circumference ≥ 102 cm in men and ≥ 88 cm in women.[18]

Taking TZD medicine in the past 6 months, consumption of immunosuppression or anti-inflammatory drugs at the time of entrance to study, approved autoimmune disease, major cardiovascular events (like myocardial infarction), cerebrovascular disorders (stroke, transient ischemic attack), heart failure (Grade III or IV), liver enzyme abnormalities (liver enzymes level more than 2.5 times of normal), kidney dysfunction (creatinine higher than 1.8 mg/dl), pregnant women, breastfeeding women or women in childbearing age who do not have a good method of contraception were the exclusion criteria. Furthermore, in case of severe side effects associated with drugs that may require to stop drug consumption such as increased hepatic enzymes (2.5 times more that the base amount or higher), causing jaundice, making symptoms associated with heart failure, impaired vision, etc. the patients were excluded from the study. Conscious consent forms were completed by all participants.

Patients were divided into two 34-member groups receiving pioglitazone and placebo drugs by the use of table of randomized numbers. For the intervention group one tablet of 30 mg pioglitazone (Sajad Darou Pharmaceutical Co., Iran) per day was used.[19,20] Patients in the placebo group consumed placebo pills daily (produced by Isfahan School of Pharmacy) similar to pioglitazone pills in terms of shape, size, and color. The treatment period was 24 weeks and in this period, patients were given advises on diet and physical activity based on the available guidelines.[21] Patients were visited by residents of cardiovascular diseases within 6 weeks with the interval of every 2 weeks at the beginning and then monthly. In these visits, vital signs and drug side-effects were investigated and drugs were replaced by new one (Figure 1).

A volume of 10 cc venous blood sample was taken in the fasting state (12 h, between 8 and 9 AM) and serum was isolated by centrifugation 3000 ×*g* for 20 min at a temperature of around 4 °C. Circulating levels of IL-10 and TNF-α were measured using enzyme-linked immunosorbent

assay kit (Boster Biological Technology, China) in all patients before and after intervention. Fasting blood glucose, levels of total cholesterol, TG and HDL-C were measured through enzymatic method (Pars Azmoon Inc., Iran) by autoanalyzer (Hitachi 902, Japan). Concentrations of LDL-C was determined by Friedwald equation in individuals whose TG was < 400 mg/dl. Complete blood count (CBC) was done by Sysmex KX-21N (Japan) counter. High sensitive CRP, alanine transaminase (ALT) and aspartate transaminase (AST) levels were also measured by Hitachi 902 autoanalyzer using Pars Azmoon analytical kits. All tests were conducted in a laboratory (laboratory of Isfahan Cardiovascular Research Institute) with the same laboratorial kits. BP, waist circumference were measured before and after intervention. Demographic data including age, sex, hypertension and obesity were also recorded.

According to previous studies via inflammatory factors values and TNF-α standard deviation[15] with first type error $\alpha = 0.05$ and study power = 0.8 the sample size was calculated as 27 individuals for each group. To compare the variables between two groups independent t-test was used. To compare the changes in quantitative variables in each group, Paired t-test was used. All data had a normal distribution by Shapiro–Wilk test. Analysis was performed through SPSS software (version 16.0, SPSS Inc., Chicago, IL, USA). Data are in the form of mean ± standard deviation, and a significant level was considered as < 0.05.

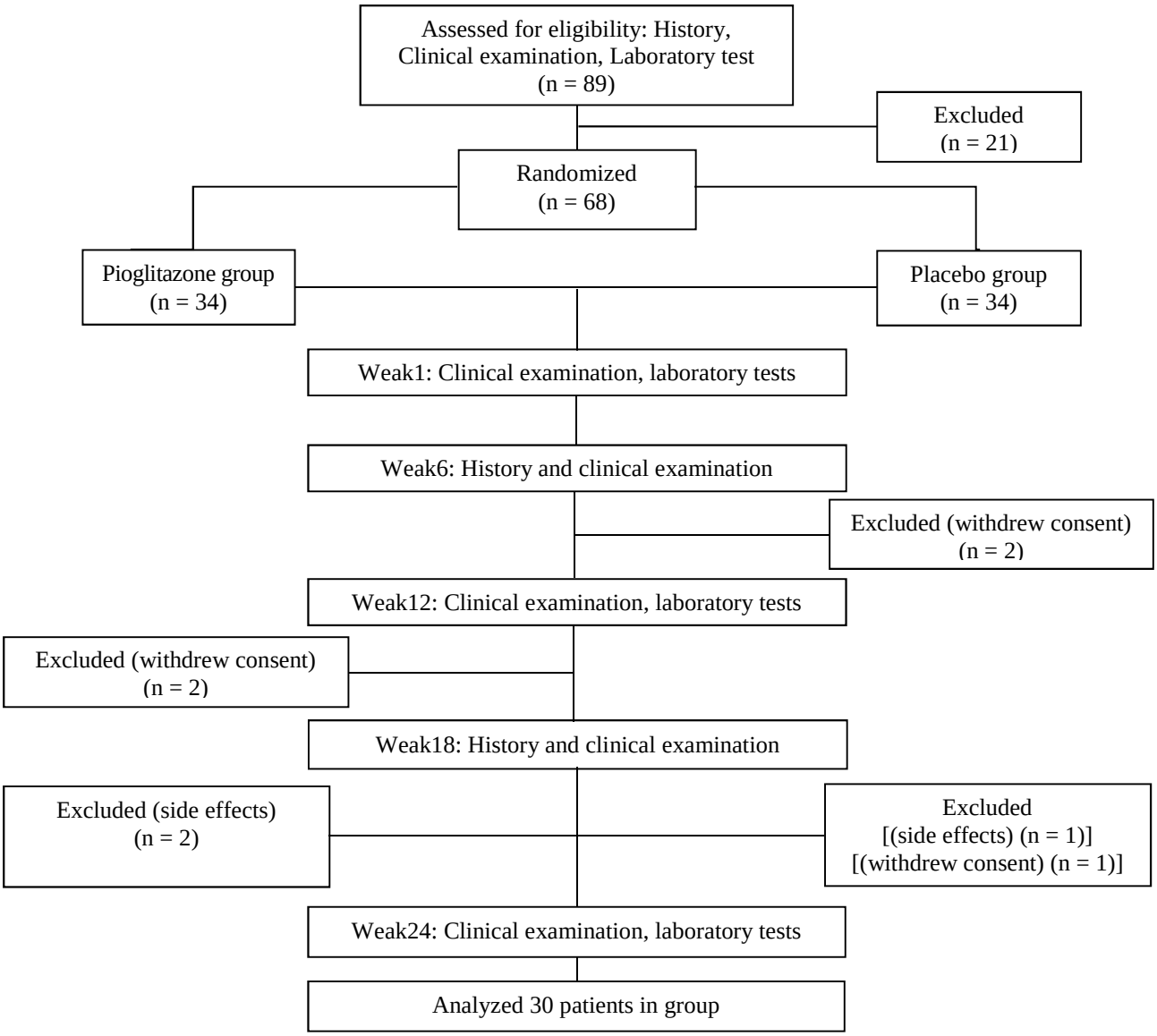

Figure 1. The chart of study process

Results

Eighty-nine patients participant in the study initially. Twenty-one of them excluded, and 68 patients including 32 female (54%) and age between 20 and 70 were eligible and randomized between to group (each one 34 patients). There were no significant differences between groups in demographic and primary metabolic information of patients that summarized in table 1. After 24 weeks of receiving pioglitazone, we saw different non-significant changes in lipid profile and fasting blood sugar. Total cholesterol, LDL-C, and HDL-C were increased non-significantly in the intervention group, while decreased in the placebo group. Serum TG level decreased in both groups non-significantly too (Table 2). Our patients had meaningfully higher increase of body mass index (BMI) after treatment by pioglitazone versus placebo (P = 0.002) (Table 2). In both group waist circumference decreased significantly (P = 0.003). Fasting blood glucose had no meaningful change within and between groups.

Both systolic and diastolic BP showed significant improvement in the pioglitazone and placebo group (Table 2).

Table 1. Demographic and primary metabolic data

Variable	Pioglitazone group (n = 30)	Placebo group (n = 30)	P
Age (mean ± SD)	47.7 ± 7.2	47.4 ± 7.6	0.904
Gender (male) [n (%)]	17 (56)	11 (36)	0.121
Hypertension and Prehypertension [n (%)]	27 (90)	27 (90)	0.932
Dyslipidemia [n (%)]	21 (70)	23 (76)	0.771
Obesity [n (%)]	19 (63)	17 (56)	0.601

SD: Standard deviation

Table 2. Changes and comparison in metabolic factors and cytokines levels after 24 weeks treatment within and between groups

Variable	Pioglitazone group (n = 30)			Placebo group (n = 30)			Between groups	
	Baseline	After treatment	P*	Baseline	After treatment	P*	Corrected difference (95% CI)	P**
FBS (mg/dl)	98.03 ± 13.26	95.60 ± 18.52	0.484	95.53 ± 10.87	96.42 ± 11.71	0.673	+3.32 (-4.72-11.36)	0.411
Total cholesterol (mg/dl)	202.92 ± 34.46	210.17 ± 36.85	0.252	226.48 ± 61.41	211.40 ± 40.56	0.172	46.93 (-2.28-22.32)	0.075
Triglyceride (mg/dl)	241.42 ± 173.78	200.53 ± 117.54	0.093	231.53 ± 155.29	228.92 ± 112.86	0.927	+38.28 (-35.06-111.63)	0.300
HDL-cholesterol (mg/dl)	41.89 ± 10.64	44.03 ± 11.28	0.168	42.71 ± 9.50	42.85 ± 11.47	0.916	-2.00 (-6.05-2.05)	0.327
LDL-cholesterol (mg/dl)	107.10 ± 21.78	116.96 ± 25.41	0.074	119.29 ± 35.22	119.33 ± 31.36	0.995	-9.82 (-25.62-5.98)	0.218
Systolic BP (mmHg)	128.89 ± 14.55	117.43 ± 10.35	0.001	140.22 ± 20.11	123.78 ± 14.56	0.001	-3.83 (-10.63-2.96)	0.263
Diastolic BP (mmHg)	82.12 ± 8.31	78.01 ± 4.13	0.002	85.44 ± 10.10	81.12 ± 7.35	0.004	-0.61 (-4.81-3.58)	0.770
BMI (kg/m^2)	30.16 ± 3.30	31.13 ± 4.05	0.002	30.20 ± 4.10	30.63 ± 4.20	0.091	-0.53 (-1.28-0.21)	0.160
Waist circumference (cm)	102.44 ± 9.01	101.95 ± 10.23	0.003	101.55 ± 10.11	99.32 ± 10.20	0.003	1.31 (-4.03-1.41)	0.340
AST (U/l)	27.89 ± 7.72	22.60 ± 5.10	0.002	25.25 ± 6.10	24.37 ± 6.93	0.497	+4.39 (0.31-8.48)	0.035
ALT (U/l)	29.78 ± 11.94	24.57 ± 9.60	0.032	26.92 ± 13.30	30.96 ± 15.91	0.033	+9.25 (3.37-15.12)	0.003
White blood cell (10^3/ml)	6.11 ± 1.54	5.80 ± 1.02	0.23	10.59 ± 16.60	6.56 ± 1.42	0.330	-3.71 (-11.91-4.47)	0.361
hs-CRP (mg/l)	2.50 ± 1.54	2.00 ± 1.03	0.333	1.88 ± 0.96	2.61 ± 1.53	0.120	+1.22 (-0.13-2.57)	0.075
TNF-α (pg/ml)	12.10 ± 11.81	10.70 ± 4.82	0.581	10.43 ± 6.12	10.24 ± 5.23	0.901	+1.55 (-4.05-7.17)	0.580
IL-10 (pg/ml)	14.21 ± 12.01	14.30 ± 10.52	0.971	14.82 ± 5.01	13.72 ± 5.63	0.401	-1.10 (-7.05-4.85)	0.713

Data presented by mean ± SD; Significant level was considered as < 0.05; * Paired t-test for compare variables in each group; ** Independent t-test for compare variables between groups; CI: Confidence interval; SD: Standard deviation; FBS: Fasting blood sugar; HDL-C: High density lipoprotein-cholesterol; LDL-C: Low density lipoprotein-cholesterol; BP: Blood pressure; BMI: Body mass index; AST: Aspartate transaminase; ALT: Alanine transaminase; hs-CRP: High-sensitivity-C reactive protein; TNF-α: Tumor necrosis factor-alpha; IL-10: Interleukin-10

In the investigation of inflammatory status, there was not prominent change after treatment of pioglitazone, although we observed a non-significant decrease of hs-CRP and TNF-α serum levels in pioglitazone group versus placebo. IL-10 increased in the intervention group; however, this increase was not significant. This is while this anti-inflammatory cytokine in the placebo group decreased to a little extent. WBC count was decreased in both group, but no significant (Table 2). There was no significant difference in all variables between the two groups ($P > 0.050$) except liver enzymes (Table 2). Generalized edema and rise in liver enzyme (more than 2.5 times of the upper limit of normal) was seen in pioglitazone group and excluded from study (one of each cases); but on the average, ALT serum levels were significantly decreased in pioglitazone group ($P = 0.032$) and increased in placebo group ($P = 0.033$) (Table 2). Serum AST levels only decreased significantly in the pioglitazone group ($P = 0.002$). Changes in serum level of liver enzymes were in normal range. One patient discontinues the study of severe headache complaint in the placebo group.

Discussion

This study indicated that the treatment with pioglitazone has no positive impact on improving inflammatory status in non-diabetic MetS patients. Despite most previous studies, pioglitazone has no significant impact on the reduction of TNF-α in blood circulation. Martens et al. also found the changes in TNF-α plasma levels due to pioglitazone as insignificant.[16] Plasma IL-10 level showed no significant increase in the pioglitazone group. In another study, the reverse effect of TZD (rosiglitazone) on the inflammation trend was seen with a decrease of this anti-inflammatory cytokine and effect on IL-1 function.[17] The previous studies (without consideration of glycemic control) obtained different results concerning lipid profile and obesity status the same as inflammatory cytokines. Moreover, most studies didn't report a positive effect of TZD on lipid profile status.[14-16] We showed non-significant increasing of total cholesterol, HDL-C, LDL-C and decreased in TG level after 24 weeks consumption of PPAR-γ agonist. Although the result of a meta-analysis study have shown an improving effect of pioglitazone on serum HDL-C and TG levels.[22] BMI was increased significantly in patients receiving pioglitazone due to increasing appetite and body fat and fluid retention mechanism probably.[23] In this trial, the improvement of BP in both group patients was significant that it is attributed to the regular blood pressure management and lifestyle modification advice given to the participants.[24] Liver enzyme had a significant decrease in the pioglitazone group in our non-diabetic patients, which it unexpected effect needed more detailed studies. In comparison to previous studies, McCoy et al. showed that there is strong relation between sensitivity to insulin and plasma level of inflammatory and coagulation cytokines like CRP, TNF-α and plasminogen activator inhibitor type 1 (PAI-1) as risk factors for cardiovascular diseases in diabetic and pre-diabetic patients. However, this change was not significant concerning IL-6 and fibrinogen level. In this study, sensitivity to insulin had no effect on weight and blood pressure of individuals; however it leads to 10% increase in HDL-C and 11.9% decrease in TG. The final result of this study indicated that combined treatment of metformin and pioglitazone (metformin 1000 mg/d + pioglitazone 45 mg/d, for 12 weeks) can lead to improvement of inflammatory and coagulation factors in groups at high risk like Asian-Indians race by creating sensitivity to insulin and at the end leads to reduction of occurrence and mortality of cardiovascular disease in these individuals.[13]

Raji et al. study showed that the resistance to insulin is more in Asian-Indian race rather than European Caucasians in non-diabetics. Furthermore, in this study, 16 weeks treatment with pioglitazone (30 mg/d) significantly improved insulin sensitivity and insulin-dependent vasodilation in the Asian-Indian race. At this intervention, CRP and PAI-1 plasma level meaningfully decreased in Asian-Indian group and Adiponectin level increased which lead to risk reduction of cardiovascular disease emergence in this population. Lipid profiles in both populations did not change; however, increase of BMI in Caucasian individuals was significant after treatment.[14] Shimizu et al. showed that in poor control Japanese diabetic patients, pioglitazone (pioglitazone 15-30 mg/d vs. voglibose 0.6-0.9 mg/d, for 12 weeks) significantly increases adiponectin level and decreases TNF-α level in addition to control of blood glucose. Reduction of systolic and diastolic pressure and weight reduction was the other findings of treatment with pioglitazone.[15] In a 4 weeks study, Martens et al. showed that pioglitazone (pioglitazone 30 mg/d vs. placebo) can reduce cardiovascular disease in

diabetic patients by blocking direct effect of TNF-α on vascular endothelial, however, CRP, IL-6 and TNF-α plasma level and lipid profile didn't significantly decreased in this study.[16] On the other hand, Halvorsen et al. showed that treatment with rosiglitazone (rosiglitazone 4-8 mg/d vs. placebo, for 12 weeks) leads to meaningful reduction of IL-10 level and IL-1 antagonist receptor in individuals suffering from MetS which indicates the inflammatory effects of this drug. This finding contradicts with anti-inflammatory effect of this drug in reduction of CRP, IL-6 and monocyte chemotactic protein-1 and uric acid in this study or comparing with other studies.[17]

As seen, TZD and especially pioglitazone leads to increase of sensitivity to insulin in most studies, however, their effects on reduction of level and type of inflammatory cytokine differed in various races and populations. It is obvious that the effect difference of treatment with TZD in blood circulation of inflammatory and anti-inflammatory cytokines in most studies and this study can be due to investigated population and race, method and duration of intervention and the type of patients. Furthermore, concerning different findings, it is not possible to definitely speak of the positive role of these drugs in improving of the effect of lipid profile, obesity status and blood pressure of individuals.

Failure to assess the response to insulin sensitivity and the lack of measurement of other inflammatory and anti-inflammatory cytokines in the population can be regarded as limitations of this study. Furthermore, it is also suggested that future studies with larger sample focus on reassessment of anti-inflammatory cytokines, particularly IL-10 in various population of races.

Conclusion

This study showed that pioglitazone has no effect on reduction of TNF-α as a proinflammatory cytokine and increase of IL-10 as an anti-inflammatory cytokine in non-diabetic individuals with MetS in Caucasians race of Middle East in Iran.

Conflict of Interests

Authors have no conflict of interests.

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Comparison between theophylline, N-acetylcysteine, and theophylline plus N-acetylcysteine for the prevention of contrast-induced nephropathy

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Original Article

Abstract

BACKGROUND: Few studies compared the efficacy of theophylline with N-acetylcysteine or evaluated the efficacy of combination therapy in the prevention of contrast-induced nephropathy (CIN). We compared the efficacy of theophylline, N-acetylcysteine, and the combination of these agents in the prevention of CIN.

METHODS: This randomized controlled trial was conducted on 96 patients referring consecutively to the Shahid Chamran University Hospital in Isfahan, Iran, for elective coronary angiography (with our without angioplasty). Patients with at least moderate risk for CIN were included and were randomized to receive theophylline (200 mg), N-acetylcysteine (600 mg), or theophylline + N-acetylcysteine, twice a day, from 24 h before to 48 h after administration of the contrast material. A non-ionic, low-osmolar contrast material was used. Serum creatinine was measured before and 48 h after contrast material injection.

RESULTS: Serum creatinine was increased by 6.83 ± 15.32% with theophylline, 13.09 ± 14.63% with N-acetylcysteine, and 5.45 ±1 3.96% with theophylline + N-acetylcysteine after contrast material injection (between group P = 0.072). Controlling for Mehran risk score, baseline serum creatinine, and contrast volume, the change in serum creatinine level was lower with theophylline compared with N-acetylcysteine (F = 4.79, P = 0.033), and with theophylline + N-acetylcysteine compared with N-acetylcysteine (F = 5.78, P = 0.020). CIN (increase in creatinine of ≥ 0.5 mg/dl or ≥ 25% from the baseline) was occurred in 20%, 21.9%, and 7.1% of patients in the theophylline, N-acetylcysteine, and theophylline + N-acetylcysteine groups, respectively (P = 0.260).

CONCLUSION: Theophylline is superior to N-acetylcysteine in preventing contrast-induced renal dysfunction, but the combination with N-acetylcysteine is not superior to theophylline alone in this regard. Further trials with larger sample of patients are warranted.

Keywords: Acute Kidney Injury, Theophylline, Acetylcysteine, Coronary Angiography, Contrast Media

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Introduction

Contrast-induced nephropathy (CIN) is the third most common cause of acute renal failure in hospitalized patients.[1] It is defined as an impaired kidney function after administration of intravascular contrast agent within 48-72 h of contrast injection, in the absence of other cause.[1] Previous studies showed that the incidence of CIN in patients who have no risk factor for CIN is < 2%, but the incidence in patients who are at a high risk for CIN is increased to 90%.[2] CIN is associated with morbidity, mortality, and high medical care costs.[2-4] Therefore, screening for high-risk patients and taking appropriate preventive measures have an important role in reducing the incidence and burden of CIN.

Previous studies proposed some preventive strategies for CIN including appropriate hydration before angiography, minimizing the dose of contrast material, using non-ionic contrast medium with low osmolarity, and administration of some medications

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such as sodium bicarbonate, N-acetylcysteine, theophylline, and high-dose statins.[5-7] Theophylline and N-acetylcysteine are among the most common studied agents in this regard.[8] Theophylline is shown to have a protective effect for kidney by increasing renal blood flow through selective renal adenosine antagonism and increasing the glomerular filtration rate (GFR).[9] N-acetylcysteine is an antioxidant and may also induce renal vasodilation by increasing intrarenal prostaglandin E2 level.[10] Meta-analyses have shown that N-acetylcysteine[8], and theophylline[11] are effective in the prevention of CIN, though controversy on the efficacy of N-acetylcysteine is still exist.[12]

Despite several randomized trials on the preventive efficacy of theophylline and N-acetylcysteine for CIN, only few studies on a head-to-head comparison between these drugs or the efficacy of combination therapy with these agents are available.[13-15] Considering different mechanisms of N-acetylcysteine and theophylline in preventing CIN, combination therapy with these two agents may be beneficial. Accordingly, we aimed to compare the efficacy of combined oral theophylline and N-acetylcysteine with theophylline and N-acetylcysteine alone in the prevention of CIN. We hypothesized that (1) the efficacy of theophylline and N-acetylcysteine in preventing CIN is different, and (2) combination of theophylline and N-acetylcysteine is more effective than each medication alone in preventing CIN.

Materials and Methods

This study was conducted on patients referring for elective coronary angiography (with or without angioplasty) from September 2013 to January 2014 to Shahid Chamran Hospital in Isfahan, Iran. This University Hospital is a cardiac specialized and referral center affiliated to the Isfahan University of Medical Sciences and includes two elective angiography units. Patients with at least moderate risk for CIN as defined by the Mehran risk score were included in the study.[16] Patients with the following characteristics were not included in the study; unstable angina, myocardial infarction, cardiac arrhythmias, acute or chronic renal failure, intravascular administration of contrast material in the past month, using theophylline or N-acetylcysteine in the past month, and known hypersensitivity to theophylline or N-acetylcysteine. The study was approved by the Ethics Committee of the Isfahan University of Medical Sciences and informed consent was obtained from patients before entering the study.

The study was designed as a randomized, double-blind, comparative trial with three parallel arms including theophylline, N-acetylcysteine, and theophylline plus N-acetylcysteine. An alphabetical code was assigned for each of the study arms (A, B, C). Using the Random Allocation Software,[17] a set of sequential numbers was generated in one block among which the study arms were randomly distributed. An independent investigator placed drugs in sequentially numbered, opaque and stapled, drug pockets. Patients were consecutively entered into the study and were assigned an order number and received the intervention based on the allocation sequence. The allocation sequence was concealed from the investigators who enrolled patients into the study. Blinding the attending physicians and patients was achieved by administering a placebo tablet identical in appearance with theophylline into the N-acetylcysteine arm and a placebo tablet identical in appearance with N-acetylcysteine into the theophylline arm. The trial was registered in clinicaltrials.gov (ID: NCT02088502). Sample size was calculated using the G*Power software (version 3.1.7, Universität Kiel, Germany). Considering the effect size of 0.3,[11] significance level of 0.05, and study power of 0.8, a total sample of 32 patients in each group was required.

Patients in the theophylline group received200 mg slow-release theophylline tablet (Darupakhsh Co., Tehran, Iran) plus placebo, and patients in the N-acetylcysteine group received600 mg non-effervescent N-acetylcysteine tablet (Shafa Co., Tehran, Iran) plus placebo, twice daily, from 24 h before to 48 h after administration of contrast material. Patients in theophylline plus N-acetylcysteine group received both drugs in the same order. All patients were hydrated with 0.9% sodium chloride (1 ml/kg/h) for 24 h, started 12 h before operation. Patients with left-ventricular ejection fraction of less than 40% or New York Heart Association functional class of III-IV were hydrated at rate of 0.5 ml/kg/h. Angiography ± angioplasty was done according to the clinical standards, by trans-femoral or trans-radial approach. In all cases, Iodixanol (Visipaque™, Amersham Healthcare, Cork, Ireland) was used as a non-ionic contrast media with low contrast osmolality.

Before the operation, all the patients underwent a detailed history and physical examination by a cardiologist. Age, gender, and history of hypertension, diabetes mellitus, dyslipidemia, and

smoking were recorded, and weight was measured. Cardiopulmonary examination was done for the evaluation of heart failure and systolic/diastolic blood pressure. Complete blood count was checked for anemia before operation. The volume of contrast material used was recorded for each patient. Serum creatinine was measured before and 48 h after contrast material injection in a hospital laboratory and the amount of change was considered as the study outcome. CIN was defined as an increase in serum creatinine level of ≥ 0.5 mg/dl or ≥ 25% of the baseline creatinine after 48 h of contrast material injection.[18]

Data were analyzed using the SPSS software for Windows (version 16.0, SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard deviation or number (%). The chi-square test was applied for comparison of qualitative data between groups. Quantitative data were checked if normally distributed in each group using the Kolmogorov–Smirnov Test. If data were normally distributed, the ANOVA test (with Tukey post-hoc) was applied for comparisons among the three study groups. If data was not normally distributed, the Kruskal-Wallis test was applied, followed by the Mann–Whitney U-test for comparisons between each two pairs. The Wilcoxon test was applied for within-group comparisons. Furthermore, the ANCOVA test was done for controlling the effects of covariates. $P < 0.050$ was considered as significant.

Results

A total of 436 candidates of coronary angiography with and without angioplasty were evaluated during the study period. One hundred patients were eligible for the study. Four patients were unwilling to participate. Ninety-six patients were equally randomized into the three study groups. All patients received the assigned intervention, but six patients did not refer for the post medication evaluation (Figure 1). Demographic data and baseline characteristics of the patients are summarized in table 1. There was some difference between the study groups regarding frequency of diabetes and heart failure, but the Mehran risk score for CIN was the same among the three groups.

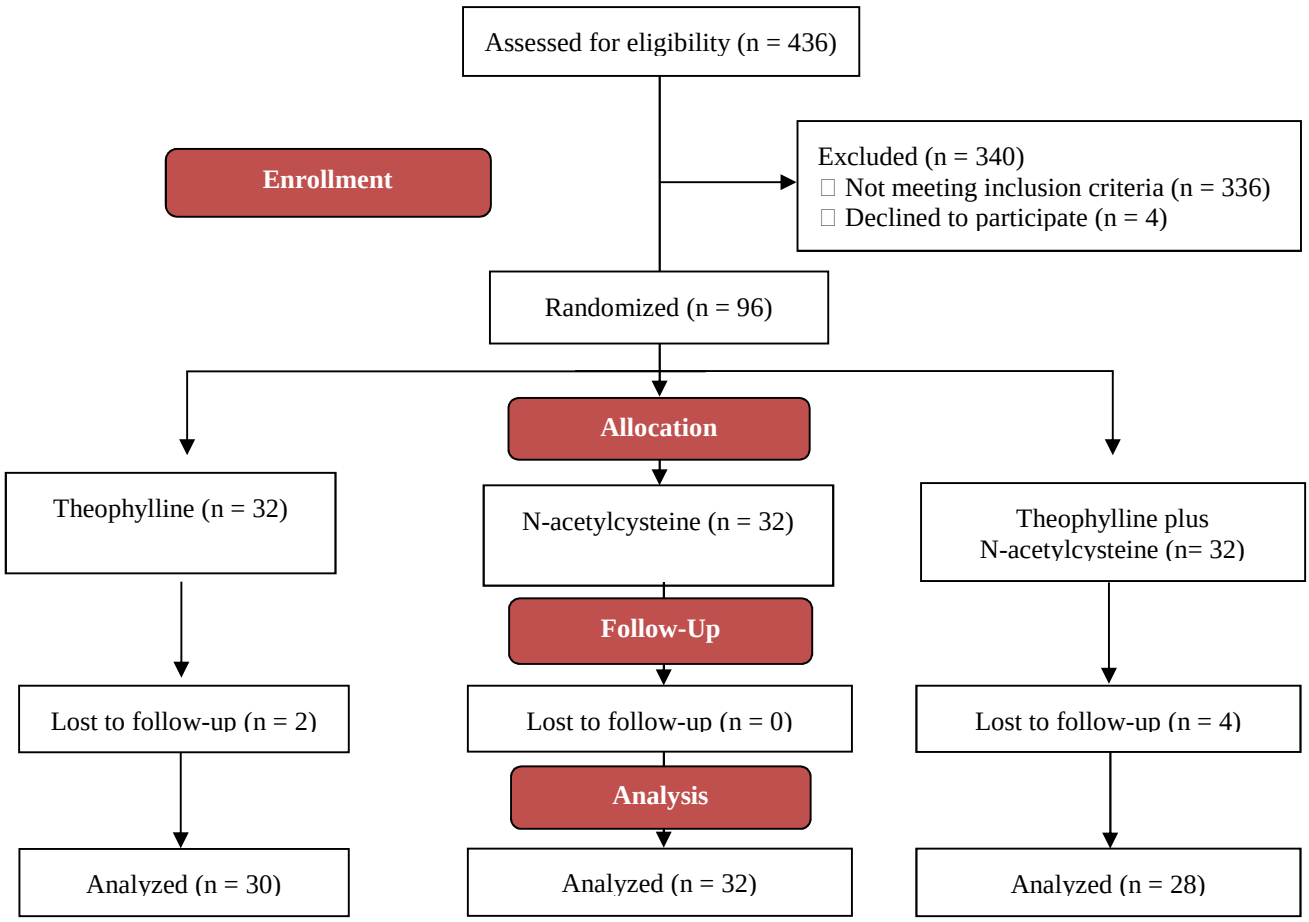

Figure 1. Patients' flow diagram

Table 1. Demographic data and baseline characteristics of the patients

Variables	Theophylline (n = 30)	N-acetylcysteine (n = 32)	Theophylline plus N-acetylcysteine (n = 28)	P
Male/Female	13 (43.3)/17 (56.7)	15 (46.9)/17 (53.1)	11 (39.3)/17 (60.7)	0.839*
Comorbidity				
Hypertension	19 (63.3)	16 (50.0)	13 (46.4)	0.390*
Diabetes	17 (56.7)	27 (84.4)	17 (60.7)	0.041*
Dyslipidemia	13 (43.3)	18 (56.3)	9 (32.1)	0.171*
Heart failure	18 (60.0)	9 (28.1)	12 (42.9)	0.041*
Anemia	14 (46.7)	18 (56.3)	17 (60.7)	0.544*
Smoking	8 (26.7)	9 (28.1)	5 (17.9)	0.615*
CIN risk				
Moderate	23 (76.7)	27 (84.4)	24 (85.7)	0.647*
High	6 (20.0)	5 (15.6)	4 (14.3)	
Very high	1 (3.3)	0	0	
Weight	68.9 ± 8.7	71.0 ± 11.4	70.6 ± 7.8	0.655†
Age	65.0 ± 9.5	59.7 ± 13.3	64.5 ± 12.0	0.153†
Contrast volume (cc)	124.0 ± 115.2	155.6 ± 114.9	128.9 ± 89.4	0.318‡
Hemoglobin (g/dl)	13.0 ± 1.2	12.6 ± 1.2	12.9 ± 1.2	0.424†
Hematocrit (%)	39.0 ± 3.9	37.8 ± 3.9	38.8 ± 3.7	0.426†
SBP (mmHg)	136.5 ± 18.2	125.4 ± 16.7	128.8 ± 21.3	0.066†
DBP (mmHg)	82.0 ± 10.5	80.2 ± 10.3	80.0 ± 9.9	0.720†
eGFR (ml/min/1.72 m^2)	61.6 ± 18.4	71.1 ± 27.7	65.8 ± 25.9	0.312†
Risk score	9.4 ± 2.9	8.2 ± 2.5	8.8 ± 2.4	0.332‡

Data are presented as mean ± SD or number (%); CIN: Contrast-induced nephropathy; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SD: Standard deviation; GFR: Glomerular filtration rate

* Chi-square test; † ANOVA (with Tukey post-hoc); ‡ Kruskal–Wallis test

There was no difference among the study groups regarding baseline creatinine level (Table 2). Creatinine level significantly increased in all groups after 48 h (all P < 0.050). The Kruskal-Wallis test showed a difference among the study groups regarding the amount of changes in creatinine level after 48 h (P = 0.048). In pair-wise comparisons, there was no significant difference between the theophylline group compared with N-acetylcysteine group (Mann–Whitney test, P = 0.117) or compared with theophylline plus N-acetylcysteine group (Mann–Whitney test, P = 0.604) regarding the amount of change in serum creatinine level after angiography. More increase was observed in serum creatinine level in the N-acetylcysteine group compared with the theophylline plus N-acetylcysteine group after angiography (Mann–Whitney test, P = 0.025) (Figure 2). Frequency of CIN was 20, 21.9, and 7.1% in the theophylline, N-acetylcysteine, and theophylline plus N-acetylcysteine groups, respectively, but the difference was not significant (P = 0.260).

Considering some differences among the study groups in baseline characteristics, ANCOVA was conducted controlling for the Mehran risk score, baseline serum creatinine concentration, and contrast volume used as covariates. The amount of change in creatinine level was considered as the dependent variable. Compared with theophylline, those who received N-acetylcysteine experienced more increase in creatinine level after contrast injection [95% confidence interval (CI) of delta Cr = 0.009 to 0.196, F = 4.79, P = 0.033]. Compared with N-acetylcysteine, receiving theophylline plus N-acetylcysteine resulted in less increase in creatinine level after contrast injection (95% CI of delta Cr = -0.168 to -0.015, F = 5.78, P = 0.020). No difference was observed between the theophylline and theophylline plus N-acetylcysteine groups in this regard (95% CI of delta Cr = −0.105 to 0.088, F = 0.03, P = 0.862).

Discussion

Various interventions are evaluated for the prevention of CIN. Among the most studied medications, theophylline and N-acetylcysteine are shown to be effective in this regard,[8] with controversy on the efficacy of N-acetylcysteine.[12] Our study was aimed to compare the efficacy of theophylline, N-acetylcysteine, and their combination therapy in the prevention of CIN in patients with at least moderate risk. In overall, we found that theophylline is superior to N-

Table 2. Change of serum creatinine level among the study groups

	Theophylline (n = 30)	N-acetylcysteine (n = 32)	Theophylline plus N-acetylcysteine (n = 28)	P
Baseline Cr (mg/dl)	1.14 ± 0.40	1.08 ± 0.22	1.08 ± 0.22	0.987*
48 h Cr (mg/dl)	1.21 ± 0.46	1.22 ± 0.28	1.14 ± 0.23	0.457*
Delta Cr (%)	6.83 ± 15.32	13.09 ± 14.63	5.45 ± 13.96	0.072*
Delta Cr (mg/dl)	0.06 ± 0.20	0.14 ± 0.14	0.05 ± 0.15	0.048*
P†	0.003	< 0.001	0.020	
Occurrence of CIN	6 (20)	7 (21.9)	2 (7.1)	0.260‡

Data are presented as mean ± SD or number (%); CIN: Contrast-induced nephropathy; Cr: Creatinine; SD: Standard deviation
* Kruskal–Wallis test; † Wilcoxon test; ‡ Chi-square test

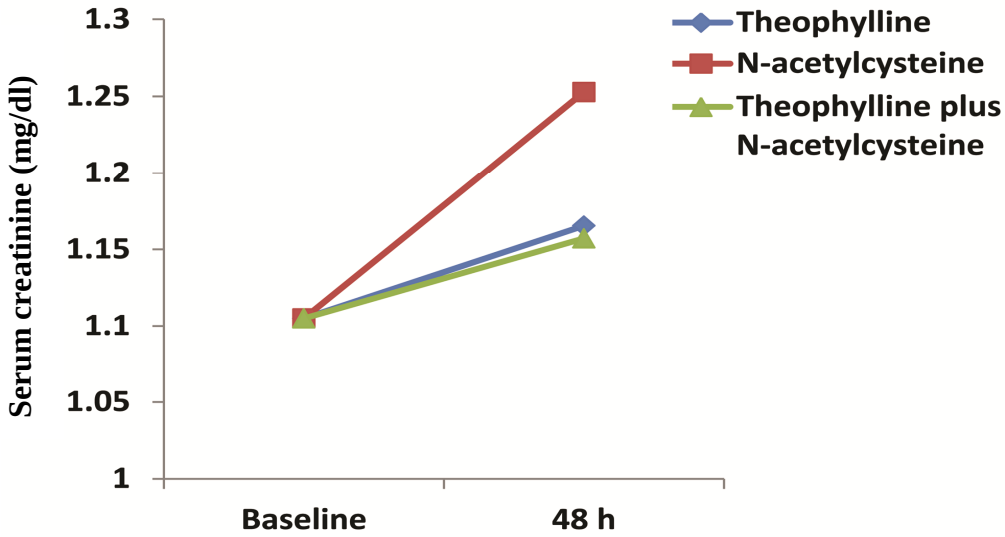

Figure 2. Changes in serum creatinine concentration from baseline to 48 h after angiography

acetylcysteine in preventing CIN, in terms of less increase in serum creatinine level after contrast material injection. Furthermore, we found that the combination of theophylline plus N-acetylcysteine is superior to N-acetylcysteine alone but not theophylline alone in this regard. However, we found no difference among the study groups in the incidence of CIN.

Few studies are conducted on head-to-head comparisons between theophylline and N-acetylcysteine or on combination therapy with these agents. Baskurt et al. compared the efficacy of N-acetylcysteine, N-acetylcysteine plus theophylline, and hydration alone. Considering the incidence of CIN, author found no benefit for N-acetylcysteine over hydration alone (9.6 vs. 6.9%). However, the incidence of CIN in those who received N-acetylcysteine plus theophylline (0%) was significantly lower than those who received N-acetylcysteine or hydration alone. Also, eGFR at 48 h after contrast material injection was higher with N-acetylcysteine plus theophylline compared with other interventions.[14] Huber et al. compared the preventive efficacy of acetylcysteine, theophylline, and their combination in an intensive care unit. Authors reported CIN in 2, 12, and 4% of patients who received theophylline, acetylcysteine, and combination therapy, respectively, revealing superiority of theophylline over acetylcysteine.[13] In another study, Bilasy et al. compared the efficacy of N-acetylcysteine plus hydration with N-acetylcysteine plus hydration and intravenous theophylline in patients with at least moderate risk for CIN. Authors found decreased serum creatinine and increase eGFR at 72 h after contrast administration with combination therapy that shows additional benefits of intravenous theophylline in preventing CIN when added to N-acetylcysteine.[15] These studies, as well as ours, suggest the superior efficacy of theophylline over N-acetylcysteine, which can also justify the beneficial effects of theophylline when added to N-acetylcysteine in preventing CIN. However, adding N-acetylcysteine to theophylline does not seem to increase the efficacy of theophylline.

While most of the previous trials, as well as meta-analyses, have supported the preventive efficacy of theophylline,[7,8,11] there is controversy on

the efficacy of N-acetylcysteine in the prevention of CIN. Recent meta-analyses focusing on more qualified studies do not support the efficacy of N-acetylcysteine to prevent CIN.[12,19] Also, a recent large randomized trial on N-acetylcysteine which included about 2308 patients (1400 patients with diabetes mellitus) undergoing coronary and peripheral vascular angiography found no significant benefit for N-acetylcysteine in preventing CIN in all[20] or in diabetic patients.[21] According to the recent mete-analyses and large trials, it seems that N-acetylcysteine is not highly effective in preventing CIN. Therefore, as we also found in our study, N-acetylcysteine has no additional effects in combination therapy with theophylline.

Our study has some limitations. First, the trial was a single-center study, which may reduce its generalizability. Second, our study sample size was small, and we were not able to show statistical significant effects of the medications in terms of CIN incidence that is a clinical important outcome. Post-hoc power calculation showed that to achieve a study power of 0.8 we required at least 59 cases in each group. Finally, we monitored our patients for 48 h. Longer follow-ups can provide more information on the efficacy of preventive measures.

Conclusion

The results of this study showed that, in patients undergoing coronary angiography (with or without angioplasty) with at least moderate risk for CIN, theophylline is superior to N-acetylcysteine in preventing contrast-induced renal dysfunction, in terms of less increase in serum creatinine level after contrast material injection. Also, we found that the combination of theophylline plus N-acetylcysteine is superior to N-acetylcysteine alone but not theophylline alone in this regard. These results should be interpreted cautiously considering the study limitations. Further trials including larger sample of patients and longer follow-ups are warranted in this regard.

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Conflict of Interests

Authors have no conflict of interests.

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A rare presentation of late right coronary artery spasm following aortic valve replacement

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Case Report

Abstract

BACKGROUND: Coronary artery spasm (CAS) is defined as a reversible, sudden epicardial coronary artery stenosis that causes vessel occlusion or near occlusion.

CASE REPORT: In this article, we present a clinical case of CAS in a 48-year-old woman undergoing elective aortic valve replacement surgery for aortic stenosis. On the 3rd post-operative day, the patient suffered from chest pain and dyspnea. Emergent coronary angiography demonstrated a significant spasm of the ostium portion of the right coronary artery.

CONCLUSION: This case shows that delayed coronary spasm should be considered as a cause of hemodynamic instability after valvular surgery.

Keywords: Aortic Valve Replacement, Coronary Artery Vasospasm, Coronary Artery Disease, Postoperative Complication

Date of submission: 8 Sep 2013, ***Date of acceptance:*** 16 Apr 2014

Introduction

Coronary artery spasm (CAS) is defined as a reversible, sudden, intense epicardial coronary artery stenosis that causes vessel occlusion or near occlusion and therefore limits coronary blood flow.[1]

The occurrence of CAS is mostly after coronary artery bypass surgery. However, its incidence after valve replacement is uncommon.[2,3]

We report a case of delayed right coronary artery (RCA) vasospasm, after aortic valve replacement (AVR).

Case Report

A 48-year-old woman with symptomatic severe aortic stenosis [New York Heart Association (NYHA class II)] was admitted for elective AVR. There was a history of patent ductus arteriosus closure by catheterization and coarctation stenting 7 years before. However; there was no history of angina pectoris in the past. Preoperative cardiac catheterization confirmed important aortic stenosis with left ventricular ejection fraction (LVEF): 60%. It also revealed dilated aortic root, ascending aorta and aortic arch. Coronary angiography was normal (Figure 1). Aortic valve was replaced by a 23 mm mechanical prosthesis (St. Jude Medical); aortic cross-clamping lasted 55 min. The early post-operative period in critical care unit (ICU) was uneventful. The electrocardiogram showed normal sinus rhythm and no any ischemic changes (Figure 2).

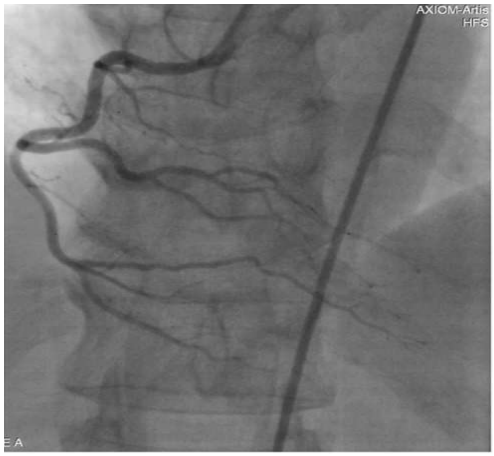

Figure 1. Pre-operative right coronary artery angiography

On admission at ward (3 days after surgery), the patient suffered from typical chest pain and dyspnea. New onset ST segment elevation occurred in inferior leads, and ST-T dynamic changes were also occurred in pericardial leads (Figure 3) with hemodynamic

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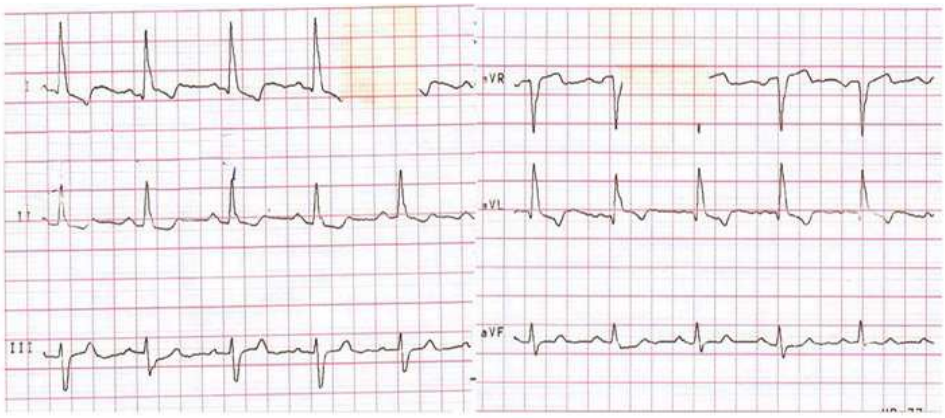

Figure 2. Early post-operative electrocardiogram

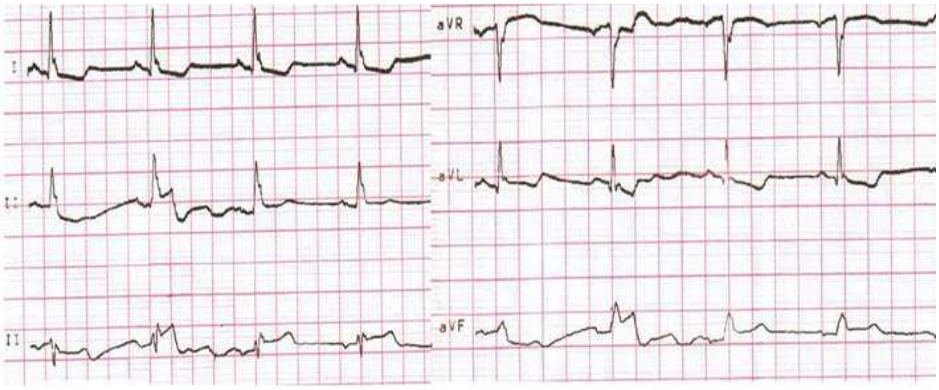

Figure 3. Electrocardiogram at the time of chest pain 3 days after the surgery

instability but no ventricular arrhythmia. Laboratory test showed troponin I: 0.46 μg/l and creatine phosphokinase-MB: 13 IU/l. Therefore, the patient underwent emergent trans- the thoracic echocardiography (TTE) and catheterization. Emergent TTE showed no signs of mechanical prosthesis dysfunction, dissection, pulmonary embolism or evidence of myocardial impairment. Since marked hemodynamic instability persisted, coronary angiography was performed. Non-selective aortic root injection and selective RCA angiography showed a pronounced spasm of the ostium portion of RCA with aortic gradient in coarctation site: 15-20 mmHg (Figure 4). Intravenous trinitroglycerin (TNG) was promptly administered. Coronary artery was relieved of vasospasm (Figure 5) and intravenous TNG was maintained for 24 h.

The remainder of the post-operative course was uneventful. There was no evidence of myocardial infarction [electrocardiogram (ECG), Enzymes]. Pre-discharge evaluation (TTE) showed normal aortic prosthesis, left ventricular functions and coronary perfusion. The ST-T change returned to normal (Figure 6), there was no evidence of myocardial infarction or even dysfunction (LVEF: 55%, mean pressure gradient: 17 mmHg and peak pressure gradient: 31 mmHg).

The patient was discharged on the 6th post-operative day under warfarin therapy.

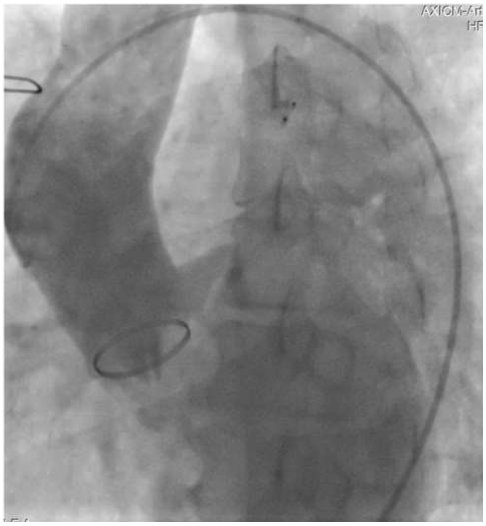

Figure 4. Non-selective aortic root injection angiography

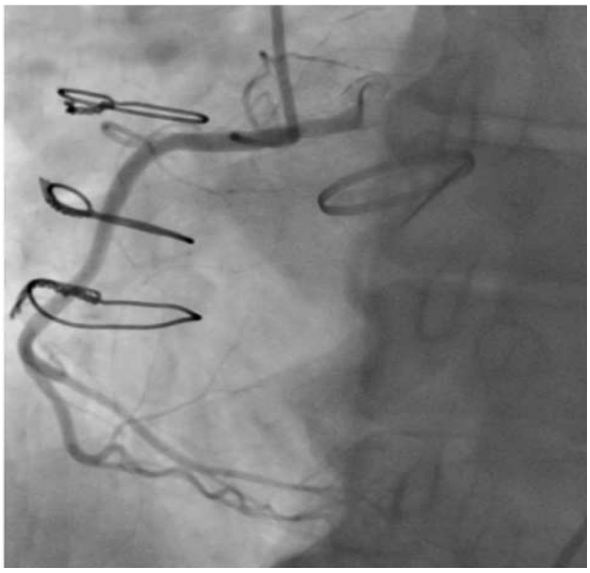

Figure 5. Selective right coronary artery angiography after infusion of intravenous trinitroglycerine

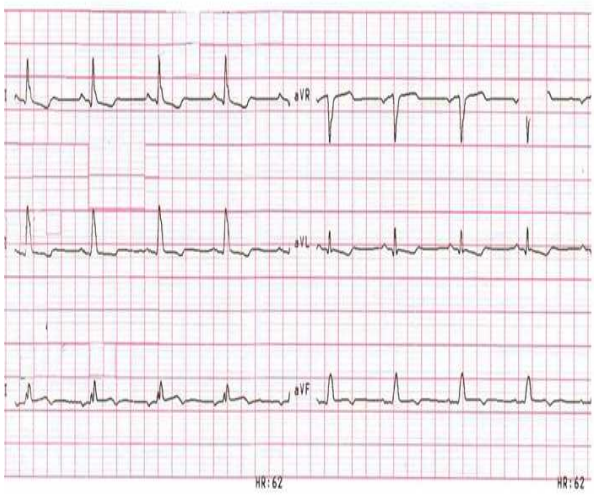

Figure 6. Electrocardiogram after transient right coronary artery spasm

Discussion

CAS is an abnormal transient and intense constriction of a segment of an epicardial artery resulting in myocardial ischemia. There are different but uncertain mechanisms of CAS including the autonomic nervous system, platelet aggregation, and vascular endothelium.[1,3] Endothelin, isosorbide dinitrate, and concomitant administration of calcium-channel blockers, have been implicated in the control of vascular tone and may be able to relieve patients from CAS during and after cardiac operations.[4,5] Post-operative coronary arterial spasm may be due to trauma during surgical manipulation, compression by chest drain tubes and hypothermia and vasoconstrictor factors during cardiopulmonary bypass released by platelets.[6] There are different manifestations of CAS range from asymptomatic ST elevation to hemodynamic instability. Therefore, CAS must be considered as a differential diagnosis of acute post-operative chest pain and circulatory instability. Most of the previously reported CAS cases were during and after coronary artery bypass graft, and there are few reports of post-operative coronary spasm after valve replacement procedure.[3,5]

In this case, emergency coronary angiography was performed since hemodynamic instability was not apparently related to mechanical prosthesis dysfunction or worsened ventricular function and the suspicious diagnosis was RCA occlusion by sewing ring of prosthesis or local dissection or RCA orifice tension by prosthesis. Finally, right CAS was evidenced. We speculate that the trauma during surgical manipulation may have had some influence in the development of spasm. Therefore, intracoronary nitrates were immediately infused and coronary artery was relieved of vasospasm In conclusion, this case shows that delayed coronary spasm should be considered as a cause of unexplained hypotension, circulatory collapse and hemodynamic instability after valvular surgery and proper attitudes should be promptly performed.

Acknowledgments

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Conflict of Interests

Authors have no conflict of interests.

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Effect of vitamin D therapy on endothelial function in ischemic heart disease female patients with vitamin D deficiency or insufficiency: A primary report

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Short Communication

Abstract

BACKGROUND: Vitamin D deficiency is associated with vascular endothelial dysfunction. We evaluated endothelial function in ischemic heart disease (IHD) patients with vitamin D deficiency or insufficiency before and after vitamin D therapy.

METHODS: An uncontrolled before-after study was conducted in Isfahan, Iran on consecutive sample of female IHD patients who had undergone percutaneous coronary intervention in the preceding 6 months and/or referred with chronic stable angina. Forty patients with vitamin D deficiency or insufficiency (serum 25-hydroxy vitamin D < 20 or 20-30 ng/ml, respectively) were included and received two intramuscular injections of 300,000 IU cholecalciferol with 1 month interval. Endothelial function, assessed by measuring flow-mediated dilatation (FMD), and serum 25-hydroxy vitamin D level were measured at baseline and 1 month after the second dose of cholecalciferol.

RESULTS: A total of 30 patients completed the study, age = 59.4 ± 8.7 years; serum 25-hydroxy vitamin D = 19.0 ± 6.5 ng/ml. After treatment, serum 25-hydroxy vitamin D was reached to > 30 ng/ml in all patients. Brachial artery diameter (mm) after ischemia increased significantly, statistically but not clinically (4.55 ± 0.37 to 4.67 ± 0.38, P < 0.001). Furthermore, FMD (%) was increased from 1.96 ± 1.65 to 4.65 ± 1.27 (P < 0.001). The amount of change in FMD was not significantly correlated with serum 25-hydroxy vitamin D (r = 0.038, P = 0.858).

CONCLUSION: Endothelial function was improved after vitamin D therapy in IHD patients with low serum vitamin D. Controlled studies with larger sample size are required to confirm if vitamin D therapy has effects on endothelial function.

Keywords: Cardiovascular Diseases, Coronary Artery Disease, Endothelium, Vitamin D Deficiency

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Introduction

Cardiovascular diseases (CVDs) are the most common causes of morbidity and mortality in developed and developing countries.[1] Coronary artery disease (CAD) is a common form of CVD, and it is reported that more than 4.5 million deaths occur in developing countries due to CAD.[2] According to estimations, mortality rate of CAD will double from 1990 to 2020.[3] Different risk factors are mentioned to be associated with CVDs. It is reported that vitamin D deficiency plays a role in developing of CVDs and CAD risk factors such as hypertension, diabetes, and metabolic syndrome.[4,5]

Vitamin D deficiency is a common health problem, and it is estimated that about 1 billion people are suffering from vitamin D insufficiency or deficiency.[6] Vitamin D deficiency is associated with endothelial vascular dysfunction and will increase the risk of CVD.[7] Also, peripheral arterial disorders are reported to be associated with low serum vitamin D levels.[8]

It is not well-known whether vitamin D therapy

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in patients with vitamin D deficiency causes a reduction in CVD.[9] Some studies have reported that vitamin D supplementation will improve vascular health markers such as endothelial function in type 2 diabetes mellitus patients and asymptomatic vitamin D deficient subjects.[10,11] Considering the limited data on this subject, especially in patients with CADs, the aim of this study was to evaluate the effect of vitamin D therapy on the endothelial function in CAD patients with vitamin D deficiency/insufficiency.

Materials and Methods

This was an uncontrolled before-after study conducted on a consecutive sample of ischemic heart disease (IHD) patients referred to the cardiology clinic of the Sina Hospital in Isfahan, Iran, in 2013. The Sina Hospital is a general private medical center with a specialized unit for care of heart disease patients including interventional and cardiac care units. Inclusion criteria were as follow; (a) female subjects, (b), having chronic stable angina or had performed percutaneous coronary intervention during preceding 6 months, and (c) having vitamin D deficiency (serum 25-hydroxy vitamin D level < 20 ng/ml) or insufficiency (serum 25-hydroxy vitamin D level = 20-30 ng/ml).[4] Patients with uncontrolled hypertension, osteomalacia, and taking of vitamin D supplements were not included. Those who developed unstable angina or myocardial infarction and undergone coronary artery bypass grafting after the beginning of the study were excluded from the study. Considering Type I error (alpha) = 0.05, study power = 0.8, and expecting at least 5% increase in flow-mediated dilatation (FMD) after intervention, the required sample size was calculated as 30 cases. The Ethics Committee of the Isfahan University of Medical Sciences approved the study protocol and informed consent was taken from all enrolled patients.

Age was asked, weight and height were measured, and body mass index was calculated as weight divided by height squared. Medical history of hypertension, diabetes mellitus, hyperlipidemia and smoking and drug history for the treatment of the mentioned diseases were recorded. All participants were examined for systolic and diastolic blood pressure. All measurements were performed with calibrated equipment. Examinations and interviews were done by a single cardiologist.

Serum vitamin D concentration: Five ml of venous blood was taken from the patients before and 1 month after the intervention. The samples were centrifuged to separate the serum and were kept in −70 °C until measurement. Samples were measured for plasma levels of 25-hydroxy vitamin D using a chemiluminescent immunoassay kit (“25 OH vitamin D total assay, DiaSorin LIAISON) by LIAISON analyzer.

FMD analysis: The FMD was measured to assess the vascular endothelial function. Participants rested for 10 min on a plain surface to reach a stable status of the heart rate and blood pressure. Participants were asked not to use caffeine and fat-rich meals, do exercise or smoke 4-6 h before the measurements. Brachial artery diameter was assessed using a high-resolution B-mode sonogram (Vivid 3, General Electric, 7.5 MHz transducer) by placing the probe at 5 cm above the anterior Cubital cavity of the non-dominant arm. Forearm ischemia was induced by inflating a sphygmomanometer cuff to 50-100 mmHg more than systolic blood pressure for 5 min. Brachial artery diameter before ischemia was assessed as baseline brachial artery diameter. Sixty seconds after deflation the same assessment was done to measure the brachial artery diameter after ischemia. Measurement of arteries was performed during the diastolic phase, measuring the distance between outermost limit of one side of the artery to the other. The FMD% was calculated according to the following formula;[12] FMD% = [(maximum diameter−baseline diameter)/baseline diameter] × 100. FMD was assessed before the intervention and also 1 month after the final dose of vitamin D injection by a single cardiologist.

All participants who had the criteria to be enrolled in the study received two doses of intramuscular injection of 300,000 IU of cholecalciferol (vitamin D3) with an interval of 1 month (the second dose was administrated 1 month after the first injection).[4] The Study Protocol has shown in figure 1.

Statistical analysis was performed using SPSS software for windows (version 16.0, SPSS Inc., Chicago, IL, USA). Quantitative data are presented as mean ± standard deviation and qualitative data are presented as number (%). Quantitative data were checked for being normally distributed with the Kolmogorov–Smirnov test, all were normally distributed. A paired t-test was used to compare variables before and after the study. Pearson correlation coefficient was applied for evaluating the correlation between variables. Statistical significance was assessed at the 0.05 probability level in all analyses.

Results

A total of 73 IHD female patients were evaluated during the study period. There were 40 patients with low serum vitamin D levels (< 30 ng/ml), from them 10 patients left the study, and final study sample consisted of 30 patients. Baseline characteristics of the patients are reported in table 1.

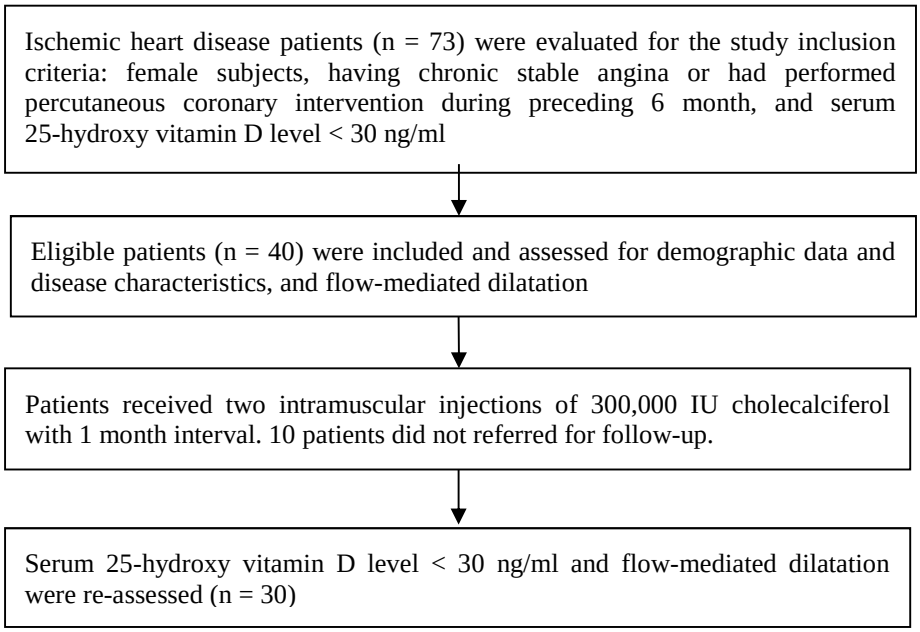

Figure 1. Study protocol

Table 1. Baseline characteristics of the participants (n = 30)

Variables	Mean ± SD	n (%)
Age (year)	59.4 ± 8.7	-
Height (cm)	161.4 ± 3.6	-
Weight (Kg)	66.7 ± 6.2	-
BMI (Kg/m^2)	25.5 ± 1.9	-
SBP (mmHg)	131.2 ± 17.5	-
DBP (mmHg)	80.0 ± 8.6	-
Serum vitamin D level (ng/ml)	19.0 ± 6.5	-
Serum vitamin D level		
< 20 ng/ml	-	18 (60.0)
20-30 ng/ml	-	12 (40.0)
Comorbidities		
Previous MI	-	5 (16.7)
Hypertension	-	20 (66.7)
Heart failure	-	4 (13.3)
Diabetes mellitus	-	17 (56.7)
Dyslipidemia	-	22 (73.3)
Drug history		
Aspirin	-	30 (100)
Beta blocker	-	22 (73.3)
Statins	-	28 (93.3)
ACE inhibitor	-	18 (60.0)
Plavix	-	11 (36.7)
Angiography results		
SVD	-	12 (40.0)
2VD	-	12 (40.0)
3VD	-	6 (20.0)
History of PCI	-	21 (70.0)

Data are presented as mean ± SD or numbers (%)

SD: Standard deviation; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MI: Myocardial infarction; ACE: Angiotensin-converting-enzyme; SVD: Single vessel disease; 2VD: Two vessel disease; 3VD: Three vessel disease; PCI: Percutaneous coronary intervention

Table 2. Comparison of endothelial function parameters before and after receiving vitamin D supplements in patients with vitamin D deficiency and stable angina

Endothelial function parameters	Before intervention	After intervention	P*
Serum vitamin D level (ng/ml)	19.00 ± 6.50	53.20 ± 17.50	< 0.001
Baseline brachial artery diameter (mm)	4.47 ± 0.37	4.47 ± 0.38	> 0.999
Brachial artery diameter after ischemia (mm)	4.55 ± 0.37	4.67 ± 0.38	< 0.001
FMD (%)	1.96 ± 1.65	4.65 ± 1.27	< 0.001

Data are presented as mean ± SD; FMD: Flow-mediated dilatation; SD: Standard deviation; * Paired t-test

There was no significant correlation between baseline vitamin D level and brachial artery diameter before (r = 0.333, P = 0.078) or after ischemia (r = 0.286, P = 0.132) or with baseline FMD (r = 0.193, P = 0.355). Serum vitamin D level was increased by 34.0 ± 15.0 ng/ml and reached to > 30 ng/ml in all patients after the intervention (table 2). Analysis of brachial artery diameters showed that the mean of baseline diameters did not statistically change after the intervention (P > 0.999). Brachial artery diameter after ischemia increased significantly, statistically but not clinically, after the intervention (P < 0.001). FMD analysis showed that after vitamin D injection, FMD was significantly increased (P < 0.001) (table 2). Split analysis of patients with vitamin D deficiency and those with insufficiency provided the same results; FMD was improved in both groups (P < 0.001). There was no significant correlation between the amount of change in FMD and vitamin D after the intervention (r = 0.038, P = 0.858).

Discussion

The aim of this study was to evaluate the effect of vitamin D therapy on vascular endothelial function in IHD patients with vitamin D deficiency/insufficiency. Our results revealed that two single intramuscular injection of vitamin D (300,000 IU) with 1-month interval can correct vitamin D deficiency in these patients. The increase in vitamin D level (though with no significant correlation) was accompanied with improvement of FMD as a marker of endothelial function in these patients, although, due to the uncontrolled design of the study, we cannot confirm that such improvement was exactly the result of vitamin D therapy.

Vitamin D deficiency is associated with a higher incidence of cardiovascular events and is treatable by vitamin D supplements that are inexpensive and available.[13] According to previous studies, low vitamin D level is associated with endothelial dysfunction.[14] Chitalia et al. have reported that patients with lower vitamin D levels had lower FMD. They have reported an independent association between low serum vitamin D level and endothelial dysfunction.[13] Similar to that study, Yiu et al. has reported that serum vitamin D status was significantly associated with brachial artery FMD and vitamin D deficiency might contribute to endothelial dysfunction.[15] Another study revealed that vitamin D insufficiency is associated with arterial stiffness and endothelial dysfunction.[16] Ertek et al. showed that serum vitamin D level is associated with better endothelial function by comparison of normal and vitamin D deficient subjects.[17] In contrast, we found no clear relationship in this regard that might be related to the small sample of our patients. The exact mechanisms in which vitamin D can influence the CVDs are not completely elucidated. However, there are some mechanisms that can be the explanation for the effect of vitamin D on the endothelial function. Vitamin D can decrease blood pressure and improve endothelial function by suppressing rennin system, decreasing vascular resistance, and by its effect on vascular calcifications.[10,18,19]

The effect of vitamin D supplements on CVDs is not well demonstrated. It has been reported that vitamin D therapy is associated with better survival of patients with CVD, especially in those with documented vitamin D deficiency.[20] Matias et al. have reported that 6 months oral cholecalciferol (a form of vitamin D) improves cardiac function in patients with chronic kidney disease.[21] There are limited studies on the effect of vitamin D supplements on endothelial function. Sugden et al. showed that a single large dose of vitamin D improves endothelial function in type 2 diabetes mellitus and vitamin D insufficient patients.[10] In contrast to Sugden et al.[10] study and also in contrast to our study, Yiu et al. has reported that 12 weeks oral supplementation of vitamin D does not significantly affect vascular function in patients with diabetes mellitus and suboptimal vitamin D levels.[22] Another study conducted by Tarcin et al. on asymptomatic vitamin D deficient subjects showed that mean FMD in deficient patients was significantly lower than normal controls, and also vitamin D supplements causes improvement of

FMD.[11] Similar to these studies, Stricker et al. showed that most of the patients with peripheral artery disease are vitamin D deficient. However, these investigators coul not find any association between vitamin D supplementation and improvement of endothelial function.[23] Witham et al. in a study on stroke patients showed that although high-dose oral vitamin D supplementation does not improved blood pressure status, but it causes an improvement of endothelial function in a short-term period.[24] We found no relationship between the amount of increase in vitamin D level and change in FMD after intervention. The change in serum level of vitamin D measured shortly after treatment may not exactly be correlated with its clinical consequences, and longer follow-up measurement is required in this regard.

The most important limitation of our study was its uncontrolled design accordingly we cannot confirm that the observed improvement in endothelial function was exactly the result of vitamin D therapy. It was unethical to not to treat vitamin D deficiency in IHD patients and consider them as controls. However, comparison with a control group of IHD patients without vitamin D deficiency would provide more reliable results by controlling for the clinical course of the disease. Furthermore, the study sample was selected consecutively from a single center and the sample size was small.

Conclusion

Our results showed that vitamin D therapy (with a total dose of 600,000 IU intramuscular injection of cholecalciferol) is associated with improvement in endothelial function in IHD patients with vitamin D deficiency or insufficiency. We cannot confirm that the observed improvement in endothelial function was exactly the result of vitamin D therapy due to uncontrolled design of the study. According to these findings and the fact that vitamin D supplements are available and are inexpensive, vitamin D may be useful for prevention of more cardiovascular events in IHD patients especially in vitamin D deficient subjects. Controlled studies with larger sample of patients are required to confirm this study results.

Conflict of Interests

Authors have no conflict of interests.

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