Isfahan Cardiovascular Research Institute

ARYA Atherosclerosis

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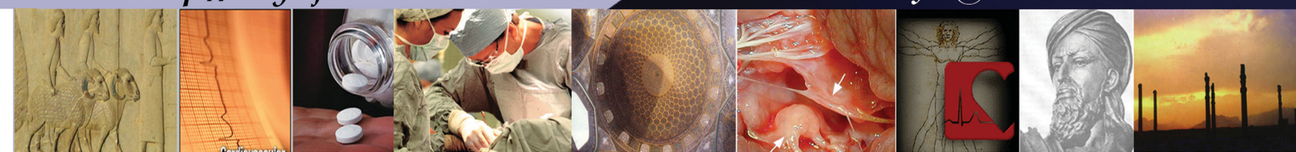

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The effects of coenzyme Q10 supplementation on cardiometabolic markers in overweight type 2 diabetic patients with stable myocardial infarction: A randomized, double-blind, placebo-controlled trial

Seyyed Mehdi Mirhashemi[(1)], Vajiheh Najafi[(2)], Fariba Raygan[(3)], Zatollah Asemi[(2)]

Original Article

Abstract

BACKGROUND: Limited data are present that have assessed the effects of coenzyme Q10 (CoQ10) intake on cardiometabolic markers in type 2 diabetic patients with coronary heart disease (CHD). This study was done to determine the effects of CoQ10 administration on cardiometabolic markers in overweight diabetic patients with stable myocardial infarction.

METHODS: This randomized double-blind placebo-controlled clinical trial was done among 60 diabetic patients with CHD aged 45-75 years old. Subjects were randomly allocated into two groups to receive either 100 mg/day CoQ10 supplements (n = 30) or placebo (n = 30) for 8 weeks.

RESULTS: Compared with the placebo, CoQ10 intake led to a significant reduction in serum interleukin 6 (IL-6) (-1.7 ± 1.6 vs. 0.8 ± 1.7 ng/l, P < 0.001) and protein carbonyl (PCO) levels (-0.2 ± 0.3 vs. 0.1 ± 0.2 nmol/mg protein, P < 0.001). Supplementation with CoQ10 did not affect serum lipoprotein(a), advanced glycation end-products and thiol concentrations compared with the placebo.

CONCLUSION: Overall, this study indicated that CoQ10 intake after 8 weeks among diabetic patients with the stable CHD had beneficial effects on serum IL-6 and PCO levels, but did not alter other cardiometabolic markers.

Keywords: Coenzyme Q10, Supplementation, Cardiometabolic Markers, Type 2 Diabetes Mellitus, Coronary Heart Disease

Date of submission: 22 Jan 2016, ***Date of acceptance:*** 28 May 2016

Introduction

Type 2 diabetes mellitus (T2DM) is associated with increased lipid concentrations, inflammation and oxidative stress, which greatly increase the risk of coronary heart disease (CHD) compared with people without diabetes.[1] Moreover, advanced glycation end-products (AGEs) are proposed to contribute to myocardial stiffness in diabetes by cross-linking myocardial proteins such as collagen and elastin.[2] Previous studies have reported that 50%-80% of populations with diabetes die of cardiovascular disease including CHD, stroke and other vascular diseases, making it the major cause of morbidity and mortality in diabetic patients.[3]

Coenzyme Q10 (CoQ10) is localized in cellular membranes and participates in electron transport, protects against oxidative stress and regenerates active forms of the antioxidant vitamin E.[4] Prior studies have exhibited that CoQ10 deficiency may increase inflammation and oxidative stress,[5] and mitochondrial adenosine triphosphate production.[6] Our previous study in subjects with metabolic syndrome indicated that 100 mg CoQ10 intake after 8 weeks had beneficial effects on markers of insulin metabolism and total antioxidant capacity, but did not alter lipid concentrations, nitric oxide and high sensitivity C-reactive protein levels.[7] In addition, 300 mg CoQ10 intake per day increased antioxidant enzymes activities and decreased inflammation in subjects with coronary artery disease (CAD) during statins therapy.[8] However, 200 mg CoQ10 intake daily after 12 weeks did not change biomarkers of inflammation and oxidative stress in obese persons.[9]

CoQ10 intake may exert anti-inflammatory effects through suppressing the expression of tumor necrosis factor alpha (TNF-a) gene[10] and inhibit the

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activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappa B1).[11] Moreover, CoQ10 can decrease reactive oxygen species (ROS) by a direct reduction back to the tocopherol.[12] We hypothesized that CoQ10 supplementation might affect cardiometabolic markers among T2DM patients with CHD. The current study was performed to evaluate the effects of CoQ10 supplementation on cardiometabolic markers in these participants.

Materials and Methods

This research was a randomized double-blind placebo-controlled trial that was recorded in the Iranian registry of clinical trials (registration number www.irct.ir: IRCT2014111920007N1). The study population consisted of T2DM subjects with CHD recruited from those who attended medical cardiology outpatient clinic affiliated to Kashan University of Medical Sciences (KUMS), Kashan, Iran, between May-July 2015. We used a formula where type one (α) and type two error (β) were 0.05, and 0.20 (power = 80%), respectively. According to a previous randomized double-blind placebo-controlled trial,[13] we used 36.0 pg/ml as standard deviation (SD) and 30.0 pg/ml as the change in mean (d) of interleukin 6 (IL-6) as a main variable. Based on the formula, we needed 25 participants in each group; after considering of 5 dropouts in each group, the final sample size was 30 participants in each group.

Inclusion criteria were T2DM patients with stable CHD condition aged 45-75 years old. According to the criteria of American Diabetes Association, the diagnosis of T2DM is based on having either of fasting plasma glucose (FPG) ≥ 126 mg/dl, blood glucose 2-h pp ≥ 200 mg/dl, and had HbA1c ≥ 6.5%.[7] Subjects who had one or more of the following were considered to have CHD: participants with renal insufficiency, on CoQ10 or antioxidant supplements.[14] Those most likely to change their course of medications within 3 months and those who had cardiac surgery within the past 3 months were excluded from the study. The ethical committee of KUMS confirmed the trial. The study was done after taking informed consent from all participants.

At first, subjects were matched one-by-one according to age, body mass index (BMI), gender, dosage and type of medications. Then the matched subjects were randomly assigned into 2 groups of receiving CoQ10 supplementation (n = 30) or placebo (n = 30). Participants in the CoQ10 group took 100 mg per day for 8 weeks as capsule. Due to lack of document about the proper dosage of CoQ10 in type 2 diabetic subjects with CHD, we used the above-mentioned dose based on a prior study in rheumatoid arthritis patients.[15] Subjects in the placebo group received one capsule (cellulose) daily which was similar in shape and size to the CoQ10 capsule. CoQ10 supplement and placebo were produced by Nature Made Pharmaceutical Company (Nature's Plus, New York, USA) and Barij Essence Pharmaceutical Company (Kashan, Iran), respectively. The researcher and subjects were blinded to randomization and allocation until the main analyses were completed. Compliance to the consumption of supplements and placebos was controlled by asking the patients to bring the containers back and counting unused capsules. All participants completed three dietary records and three physical activity records at study baseline, week 2, 4 and 6 of the trial and at the end of trial. To take nutrient intakes of subjects according to 3-day food records, we used Nutritionist IV software (First Databank, San Bruno, CA).[16] Physical activity was described as metabolic equivalents (METs) in hours per day.[17]

Assessment of anthropometric measures: Body weight was determined with a digital balance (Seca, Hamburg, Germany) at the onset and the end of the study in the cardiology clinic by a trained staff. BMI was determined as weight in kg divided by height in meters squared.

Ten milliliter of blood samples was taken from participants after overnight fasting at study baseline and after 8-week intervention at the KUMS reference laboratory.[16] Serum lipoprotein(a) [Lp(a)] levels were quantified using enzyme-linked immunosorbent assay (ELISA) kit (Bioassy Technology Laboratory, Shanghai, China) with inter- and intra-assay coefficient variances (CVs) of 8.5 and 9.6%, respectively. Serum IL-6 concentrations were determined by the use of ELISA kit (Bioassy Technology Laboratory, Shanghai, China) with inter- and intra-assay CVs of 7.5 and 9.1%, respectively. Serum AGEs were quantified by the fluorometeric method with inter- and intra-assay CVs of 3.5 and 4.4%. Serum protein carbonyl (PCO) and thiol were quantified using spectrophotometric method with inter- and intra-assay CVs of lower than 5%.

To evaluate if the variables in the study were normally distributed or not, we applied the Kolmogrov-Smirnov test. We carried out analyses based on intention-to-treat (ITT) principle. Missing values were treated based on last observation carried forward method (LOCF).[18] To detect

differences in anthropometric measures as well as in daily macro- and micro-nutrient intakes between the two groups, we applied independent samples Student's t-test. Pearson chi-square test was used for comparison of categorical variables. To assess the effects of CoQ10 administration on cardiometabolic markers, we used independent samples Student's t-test. To compare within-group differences (before and after treatment), we used paired-samples t-tests. Analysis of covariance (ANCOVA) assessed differences between groups at the end of the study after adjustment for baseline values of biochemical parameters, age and BMI at baseline. The P-value of less than 0.05 was considered statistically significant. Data analysis was done using SPSS software (version 18.0, SPSS Inc., Chicago, IL, USA).

Results

Among participants in the CoQ10 group, 2 subjects [withdrawn due to personal reasons (n = 2)] and in the placebo group, 2 subjects [withdrawn due to personal reasons (n = 2)] were excluded (Figure 1). Finally, 56 subjects [CoQ10 (n = 28) and placebo (n = 28)] completed the trial. However, we did the analysis based on ITT principle and all 60 participants (30 in each group) were included in the final analysis.

Distribution of gender, mean age, height and BMI at baseline and at the end of the trial, and BMI change of study participants were not statistically different between the two groups (Table 1).

Based on the 3-day dietary records obtained at study baseline, week 2, 4, 6 and at the end of trial, we found no significant difference in mean dietary macro- and micro-nutrient intakes (data not shown).

After 8 weeks of intervention, compared with the placebo, CoQ10 supplementation resulted in a significant reduction in serum IL-6 (-1.7 ± 1.6 vs. 0.8 ± 1.7 ng/l, $P < 0.001$) and PCO levels (-0.2 ± 0.3 vs. 0.1 ± 0.2 nmol/mg protein, $P < 0.001$) (Table 2). Supplementation with CoQ10 did not affect serum Lp(a), AGEs and thiol concentrations compared with the placebo. Within-group changes revealed significant decreases in serum IL-6 ($P < 0.001$), PCO ($P < 0.001$) and a significant rise in thiol concentrations ($P = 0.03$) in the CoQ10 group. In addition, within-group change indicated a significant increase in IL-6 concentrations ($P = 0.01$) in the placebo group.

Adjustments for baseline values of biochemical parameters did not affect our findings (Table 3).

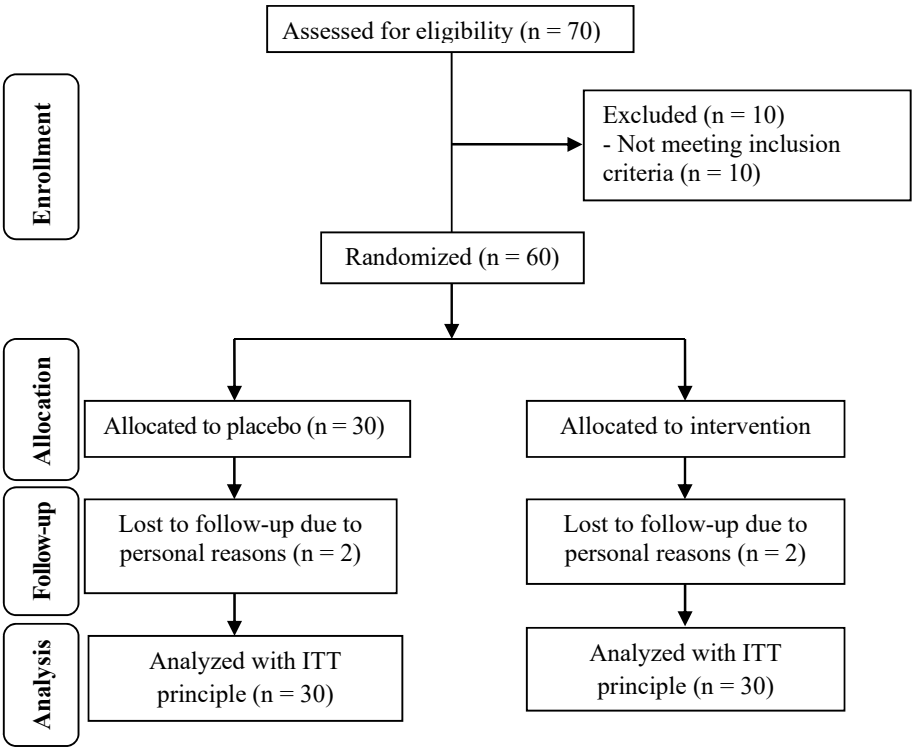

Figure 1. Summary of patient flow diagram

Table 1. General characteristics of study participants

Variable	Placebo group (n= 30)	CoQ10 group (n= 30)	P*
Age (year) (mean ± SD)	59.9 ± 13.1	65.9 ± 12.5	0.070
Height (cm) (mean ± SD)	162.0 ± 9.3	160.0 ± 9.8	0.430
BMI at study baseline (mean ± SD)	30.7 ± 5.9	28.2 ± 5.2	0.080
BMI change (kg/m^2) (mean ± SD)	-0.0 ± 1.0	0.1 ± 0.3	0.620
Gender [n(%)]			
Male	19 (63.3)	19 (63.3)	>0.999†
Female	11 (36.7)	11 (36.7)	
Smoking [n(%)]	2 (6.7)	2 (6.7)	> 0.999†
Aspirin 80 mg [n(%)]	30 (100)	30 (100)	> 0.999†
Statin [n(%)]	30 (100)	30 (100)	> 0.999†
Insulin therapy [n(%)]	7 (23.3)	6 (20.0)	0.750†
Antidiabetic drugs [n(%)]			
Monotherpy	17 (73.9)	17 (70.8)	0.810†
Combination therapy	6 (26.1)	7 (29.2)	
Hypertension [n(%)]	21 (70.0)	22 (73.3)	0.770†
ACEI/ARB drugs [n(%)]	30 (100)	30 (100)	> 0.999†
Blocker drugs [n(%)]			
β-blocker	28 (93.3)	29 (96.7)	0.550†
Calcium channel blocker	2 (6.7)	1 (3.3)	

* Obtained from independent t test; † Obtained from Pearson chi-square test

CoQ10: Coenzyme Q10; BMI: Body mass index; ACEI: Angiontensin converting enzymes inhibitors; ARB: Aldosterone receptor blockers

Discussion

In this trial, we assessed the effects of CoQ10 supplementation on cardiometabolic markers among T2DM patients with CHD. We observed that CoQ10 intake after 8 weeks among T2DM subjects with CHD had beneficial effects on serum IL-6 and PCO levels, but did not affect other cardiometabolic markers.

Patients with T2DM are susceptible to increased atherogenic lipid profiles and increased risk of CHD.[1] This trial exhibited that CoQ10 use among T2DM individuals with CHD after 8 weeks led to a significant decrease in IL-6 levels compared with the placebo, but unchanged levels of Lp(a). Supporting with this study, administration of 100 mg CoQ10 per day among rheumatoid arthritis subjects for 8 weeks decreased inflammatory cytokines.[15]

In addition, Sanoobar et al.[19] exhibited that 500 mg/day CoQ10 intake among subjects with multiple sclerosis for 12 weeks decreased serum levels of TNF-a and IL-6, but other anti-inflammatory cytokines such as transforming growth factor-beta and IL-4 remained unchanged. In another study, a 12-week supplementation of a nutritional supplement containing 270 mg/day CoQ10 and 2250 mg/day L-carnitine in patients with heart failure was also associated with reduced levels of both TNF-a and IL-6, but did not influence IL-10 concentrations.[20]

However, Lee et al. [21] indicated that taking 60 mg/day CoQ10 supplements did not lower plasma IL-6 in patients with CAD after 12 weeks. The same findings were seen following the supplementation of 100 mg CoQ10 per day in sedentary men for 8 weeks.[13] A possible mechanism by which CoQ10 exerts inhibitory effects on IL-6 secretion may be attributed to its capability in inhibition of NF-kB signaling pathways.[11]

In addition, a possible mechanism of protective effect of CoQ10 on inflammatory cytokines can be attributed to its ability to inhibit the activation of the transcription of nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) and inducible nitric oxide synthase genes.[22]

We have shown that the use of CoQ10 supplements after 8 weeks among T2DM subjects with CHD decreased serum levels of PCO compared with the placebo, but did not alter AGEs and thiol concentrations.

In accordance with our study, administration of 200 mg/day CoQ10 after 4 weeks among elderly men and women led to a significant reduction in PCO levels.[23]

Table 2. Cardiometabolic markers at study baseline and after 8-week intervention in type 2 diabetic patients with coronary heart disease that received either coenzyme Q10 (CoQ10) supplements or placebo*

Variable	Placebo group (n = 30)				CoQ10 group (n = 30)				P‡
	Baseline	End of trial	Change	P†	Baseline	End of trial	Change	P†	
Lp(a) (ng/ml)	45.3 ± 5.3	45.8±12.7	0.5 ± 12.8	0.820	46.3 ± 4.3	45.6 ± 8.7	-0.7 ± 7.5	0.610	0.650
IL-6 (ng/l)	12.2 ± 1.4	13.0 ± 1.6	0.8 ± 1.7	0.010	13.1 ± 1.5	11.4 ± 1.4	-1.7 ± 1.6	< 0.001	< 0.001
AGEs (AU)	13.5 ± 1.4	14.0 ± 2.2	0.5 ± 2.2	0.270	14.0 ± 2.4	14.0 ± 2.1	0.0 ± 1.6	0.970	0.380
PCO (nmol/mg protein)	1.4 ± 0.2	1.5 ± 0.1	0.1 ± 0.2	0.110	1.3 ± 0.2	1.1 ± 0.2	-0.2 ± 0.3	< 0.001	< 0.001
Thiol (nmol/mg protein)	13.5 ± 3.3	14.9 ± 2.6	1.4 ± 3.9	0.050	14.4 ± 2.9	15.9 ± 3.0	1.5 ± 3.6	0.030	0.970

* Data are means ± Standard deviation (SDs); † Obtained from paired-samples t-tests; ‡ P-values represent independent samples Student's t test
CoQ10: Coenzyme Q10; AGEs: Advanced glycation end-products; IL-6: Interleukin 6; Lp(a): Lipoprotein(a); PCO: Protein carbonyl

Table 3. Mean adjusted changes in metabolic variables in type 2 diabetic patients with coronary heart disease that received either CoQ10 supplements or placebo*

Variable	Placebo group (n= 30)	CoQ10 group (n= 30)	P†
Lp(a) (ng/ml)			
Model 1‡	0.3 ± 1.9	-0.5 ± 1.9	0.750
Model 2§	-0.1 ± 1.9	-0.1 ± 1.9	0.990
IL-6 (ng/l)			
Model 1	0.5 ± 0.3	-1.4 ± 0.3	< 0.001
Model 2	0.5 ± 0.3	-1.4 ± 0.3	< 0.001
AGEs (AU)			
Model 1	0.4 ± 0.3	0.1 ± 0.3	0.540
Model 2	0.4 ± 0.3	0.1 ± 0.3	0.480
PCO (nmol/mg protein)			
Model 1	0.1 ± 0.1	-0.2 ± 0.1	< 0.001
Model 2	0.1 ± 0.1	-0.2 ± 0.1	< 0.001
Thiol (nmol/mg protein)			
Model 1	1.1 ± 0.5	1.9 ± 0.5	0.280
Model 2	1.0 ± 0.5	2.0 ± 0.5	0.190

* All values are means± standard errors (SEs); † Obtained from analysis of covariance; ‡ Adjusted for baseline values; § Additionally adjusted for age and baseline body mass index (BMI)
CoQ10: Coenzyme Q10; AGEs: Advanced glycation end-products; IL-6: Interleukin 6; Lp(a): Lipoprotein(a); PCO: Protein carbonyl

Moreover, CoQ10 treatment in male New Zealand white rabbits for 2 weeks significantly attenuated protein carbonylation and nitration.[24] In another study, dietary supplementation with CoQ10 in mice for one month significantly decreased brain PCO concentrations.[25] However, CoQ10 at a daily dose of 10 mg/kg of body weight in adult male Wistar rats for 6 weeks did not affect PCO levels.[26] Chronic exposure of biomolecules like lipids and proteins to higher levels of ROS may result in peroxidation and glycoxidation reactions that lead to PCO production, oxidation of thiol groups and advanced oxidation protein products generation in diabetic patients.[27] Previous studies have demonstrated that increased levels of carbonyl compounds can act as a biomarker of insulin resistance in T2DM.[28] Furthermore, increased levels of PCO in diabetic patients with poor glycemic control may contribute to development of diabetic complications.[29] CoQ10 is a potent antioxidant that can decrease ROS and free radicals produced by the reaction with lipid or oxygen radicals through a direct reduction back to the tocopherol,[12] which in turn would result in a decreased oxidative stress and a decreased generation of PCO.

This study had some limitations. Firstly, the sample size was small in the current study. Secondly, due to limited funding, we did not evaluate the effects of CoQ10 supplementation on serum CoQ10 levels, HbA1c, signaling pathway and receptors of AGEs.

Conclusion

Overall, this study indicated that CoQ10 intake after 8 weeks among diabetic patients with the stable CHD had beneficial effects on serum IL-6 and PCO levels, but did not alter other cardiometabolic markers.

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Conflict of Interests

Authors have no conflict of interests.

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Stress as a risk factor for noncompliance with treatment regimens in patients with diabetes and hypertension

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Original Article

Abstract

BACKGROUND: We have assessed the role of stress on compliance of patients with diabetes mellitus (DM) and hypertension (HTN) with taking prescribed medications and following dietary and exercise regimens.

METHODS: A total of 9544 individuals more than 19 years of age were selected from three counties in central Iran. The presence of DM and HTN were asked from participants. We defined treatment adherence (compliance) based on agreement of individual's self-report behavior with recommendations from a physician.

RESULTS: Awareness about DM and HTN was 82.6% and 49.9%, respectively. Multivariate analysis showed that odds ratio (OR) of high to low stress level was lower than one for both "usage of medication" and "following exercise regimen" in diabetics even after adjustment for either "age and sex" or "age, sex and education". In hypertensive patients, OR of high to low stress level was lower than one for "usage of medication" even after adjustment for either "age and sex" or "age, sex and education" and also lower than one for "following exercise regimen" only as crude index.

CONCLUSION: Cases with higher stress level had lower compliance for accepting either medication or exercise as a treatment option for their DM or HTN.

Keywords: Stress, Patient Compliance, Risk Factors, Exercise, Diabetes Mellitus, Hypertension

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Introduction

The new era of disease control is obviously about chronic diseases that need long term management programs to be followed by either health systems or patients. In this dilemma, several factors play important roles to ensure effective and efficient service provision for the Management of Chronic Diseases (MCD); among them, patients' adherence to treatment and compliance with medications are considered important factors.[1,2]

Adherence was defined as "the extent to which the patient follows medical instructions"[3] or more extensively as "the extent to which a person's behavior such as taking medication, following a diet, and/or following lifestyle changes, corresponds with agreed recommendations from a health care provider".[4,5] Compliance can be defined as "taking medications as prescribed",[6] and has deep impact on MCD.[7,8] Previous studies have reported the rate of good compliance with medication in patients with hypertension (HTN) to be between 9.6%-74%,[9-12] and compliance with modifications in cardiovascular risk factors was between 39.3%-62.8%[13] and in patients with diabetes mellitus (DM) between 38%-79%.[7]

Many factors (including psychological factors) are proposed to affect compliance in chronic diseases such as anxiety, depression, age, race and perceived social support.[14-16] The role of depression

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has been studied extensively[17-21] but despite the proposed role of stress and anxiety in the development and management of DM,[17,22-25] little is known about the role of stress in etiology of HTN and its impact on patient's compliance with treatment. The role of anxiety and stress on factors affecting MCD especially following treatment regimens is still an issue.

The aim of this study was to assess the role of stress on the compliance of patients with DM and HTN with treatment programs such as taking prescribed medications and following dietary and exercise regimens.

Materials and Methods

Data of this study was part of the "Isfahan Healthy Heart Program" (IHHP), a community-based program designed to prevent and control cardiovascular diseases in Iran. The main goal of IHHP was promotion of healthy nutrition and increasing physical activity and conducting stress management and tobacco control activities. The IHHP design was described in detail elsewhere.[26,27]

Multistage cluster random sampling was used to stratify the study population based on living area (urban or rural) according to the national census in the last survey of the IHHP in 2007. In total, 9544 men and women over 19 years old from three counties in central Iran (Isfahan, Najafabad and Arak), were selected for this study. To achieve adequate sample size, those who declined to participate in the study were replaced by their neighbors.

The total number of participants for this study was determined according to their sex, age, and area of residence compared with the entire population. Approximately 5%-10% of households within these clusters were randomly selected for inclusion.

According to the 2006 national census, the population was 1986542 in Isfahan and 282430 in Najafabad, a county neighboring Isfahan. Arak, with a population of 615702 is located 375 km northwest of Isfahan.[27,28]

Individuals who were pregnant, mental retard or physically disabled (all according to medical history by cases or their families) were excluded from the study.

After clarifying the study protocol and study process, written informed consent was obtained. Data on demographic and socioeconomic characteristics and lifestyle behaviors were recorded by a trained interviewer at baseline. We also collected some data about the presence of DM, HTN, type of medication, patient's compliance and lifestyle habits. The study protocol was reviewed and approved by the Ethics Committee of Isfahan University of Medical Sciences, Iran.

Demographic factors included age, sex, and education level (classified as 0–5 years, 6–12 years, and > 12 years).

Psychological distress was assessed by 12-item General Health Questionnaire (GHQ-12), a self-administered well established screening tool.[29] This questionnaire is a consistent and reliable instrument for using in general population studies.[30] The questionnaire consists of 12 items with four-point scale (less than usual, no more than usual, fairly more than usual, or much more than usual). The 0-0-1-1 method was used to score the GHQ-12 questionnaires in this study. Using this method, a participant could score between 0 and 12 points; with a score of 4 or more identified as high stress level.

After at least 12 hours fasting, all individuals were referred to the nearest health center to their home for taking a blood sample to measure their fasting blood sugar (Pars Azmon, Tehran, Iran). Before blood sampling from the veins of the anti-cubital region, blood pressure was measured for all participants in the sitting position twice with an interval of 5-10 minutes. Prevalence of DM and HTN, patients' awareness of their diseases and the difference between their awareness of their disease and the actual prevalence according to physical examination and laboratory data were evaluated in this study. For calculating the exact prevalence of DM and HTN, we used either self-reports of the disease related medications or laboratory examination results since cases under treatment for these conditions (medical or non-medical) may have normal values of fasting blood glucose (FBS) or blood pressure. On the other hand, there were cases with abnormal FBS or blood pressure that were not aware of their diseases.

In this study, we defined treatment compliance based on whether patients took their medications properly and followed dietary and exercise recommendations or not. Self-reported responses to three separate questions were based on yes/no scale. "Yes" answers were considered good compliance.

The SPSS software for Windows (version 15.0, SPSS Inc., Chicago, IL, USA) was used for analyzing data. Quantitative variables were expressed as mean ± standard deviation (SD). To compare continuous variables between subjects with high and low stress level, Student's t-test was used. Categorical variables were compared between these two groups using chi-square. Logistic regression analysis (Enter method) was used to

determine the effect of independent variables such as DM and HTN, usage of medications for these two diseases according to the physician's advice (medical compliance), and non-medical advices such as diet and exercise (non-medical compliance) on stress level of the cases in the treatment of the DM and HTN. Age, gender and education level were considered for adjustment. Analyses of medication, diet or exercise were done in cases that were aware of their diseases. A P-value < 0.05 was considered statistically significant.

Results

Mean age of the participants was 38.7 ± 15.5 years and 4772 (50%) were male. Subjects with higher stress level were significantly older (39.5 ± 16.2 vs. 38.4 ± 15.2, P = 0.001), were more likely female (57.9% vs. 45.9%, P < 0.001) and had lower education level. The prevalence of diabetes was 404 (6.5%) and 238 (7.8%) in low and high stress individuals (P = 0.113), respectively. Also, the prevalence of hypertension was 1055 (17.1%) in low stress and 619 (19.3%) in high stress individuals (P = 0.08) (Table 1).

Table 1. Characteristics of all individual according to stress level*

Indicator	Low stress n = 6289	High stress n = 3260	P
Age (mean ± SD)	38.41 ± 15.19	39.51 ± 16.24	0.001
Sex (Male) [n(%)]	3402 (54.1)	1375 (42.1)	<0.001
Education (Year)			<0.001
0-5	2677 (42.6)	1619 (49.7)	
6-12	2699 (43.0)	1278 (39.2)	
> 12	901 (14.4)	363 (11.1)	
Diabetes [n(%)]	404 (6.5)	238 (7.8)	0.113
Hypertension [n(%)]	1055 (17.1)	619 (19.3)	0.008

*Data are expressed as mean ± standard deviation (SD) for continuous variables and number (percentage) of participants for categorical variables

As table 2 shows, only 325 cases among 404 (82.6%) with low stress and 205 cases among 238 (86.1%) with high stress were aware of their DM. According to table 3, 510 (48.3%) individuals with low stress and 326 (52.7%) with high stress were aware of their HTN.

Patients with either HTN or DM in the high stress group had a significantly lower percentage of medication usage (P = 0.018 and P < 0.001, respectively) and were less likely to follow recommended exercise regimen (P = 0.039 and P = 0.032, respectively) Following dietary restrictions was not significantly different between cases with low and high stress levels (Tables 2 and 3).

Table 2. Treatment regimens of individuals who were aware of their diabetes

Treatment [n(%)]	Low stress n = 325	High stress n = 205	P
Medication	307 (94.6)	177 (86.5)	0.018
Diet	222 (68.3)	144 (70.1)	0.665
Exercise	73 (22.5)	36 (17.5)	0.039

Multivariate analysis showed that the odds ratio (OR) of high stress to low stress level was lower than one for both usages of medication and following exercise regimen in diabetics as crude index and even after adjustment for either age and sex or age, sex and education (Table 4). In hypertensive patients, OR of high stress to low stress level was lower than one for usage of medication as crude index and even after adjustment for either age and sex or age, sex and education and was also lower than one for following exercise regimen only as crude index (Table 4). It means lower compliance of cases with high stress level in comparison with patients with low stress level to accepting either medication or exercise as a treatment option for their DM or HTN.

Table 3. Treatment regimens of individuals who were aware of their hypertension

Treatment	Low stress [n(%)] n = 510	High stress [n(%)] n = 326	P
Medication	478 (93.6)	279 (85.7)	< 0.001
Diet	317 (62.2)	213 (65.3)	0.088
Exercise	130 (25.6)	61 (18.8)	0.032

Discussion

This study was a part of IHHP that was designed to assess the impact of community-based programs in prevention and control of cardiovascular diseases and their risk factors.[31,32] Our findings showed that higher levels of stress in patients with HTN or DM had independent impact on compliance with medication and exercise, but not for dietary recommendations; the level of stress regardless of age, sex and education level had an independent effect on compliance, specially taking medication in both hypertensive and diabetic patients.

There are many sophisticated models of interaction between stress and chronic diseases such as HTN and DM, mostly emphasizing a biopsychosocial model. In this model, stress has

Table 4. Crude and adjusted odds ratio (95% confidence interval) of treatment regimens of diabetes and hypertension with stress level

Variable	Unadjusted	Adjusted (age and sex)	Adjusted (age, sex and education)
Prevalence of diabetes	1.14 (0.97, 1.35)	1.05 (0.88, 1.25)	1.04 (0.88, 1.24)
Treatment regimens of diabetes			
Medication	0.41 (0.29, 0.87)	0.41 (0.29, 0.88)	0.41 (0.29, 0.90)
Diet	1.09 (0.74, 1.59)	0.96 (0.65, 1.42)	0.91 (0.61, 1.36)
Exercise	0.70 (0.64, 0.76)	0.76 (0.70, 0.83)	0.77 (0.70, 0.84)
Prevalence of hypertension	1.16 (1.04, 1.30)	1.09 (0.96, 1.23)	1.09 (0.96, 1.23)
Treatment regimens of hypertension			
Medication	0.41 (0.35, 0.67)	0.45 (0.37, 0.74)	0.45 (0.37, 0.88)
Diet	1.10 (0.71, 1.73)	1.12 (0.75, 1.94)	1.13 (0.65, 1.94)
Exercise	0.67 (0.47, 0.97)	0.75 (0.52, 1.09)	0.76 (0.52, 1.11)

biological effects such as changes in endocrine stress modulating systems including hypothalamus-pituitary-adrenal (HPA) axis. Stress has also impacts on illness behavior, on modifying risk factors and therapeutic recommendation. All of them would result in initiation and continuation of chronic diseases through a multi-factorial model.[33,34] There are several reports claiming stress and other psychological factors as etiologies of DM.[22,35] In our study, there was no difference in stress level between subjects with or without HTN/DM and based on our findings, we were unable to show the role of stress in the pathogenesis of HTN or DM. However, it may be involved in the management of these disorders. This contradiction could be attributed to the design of our study that only evaluated patients' current stress level and did not consider the chronic stress state.

Interestingly, less than half of the subjects were aware of their high blood pressure; while in the case of DM about 82.6% were aware of their condition. Comparing with the previous IHHP survey that reported awareness rates of HTN and DM to be 40.3% and 54.6%, respectively,[36] it seems that as the project proceeded, there was a significant increase in awareness for DM. On the other hand, awareness of HTN showed no significant change from previous phase of IHHP. This may be related to differences in subjective and cultural believes about DM and HTN as IHHP targets both conditions with similar goals,[31,36] and may denote need for establishment of new strategies regarding increasing awareness of HTN. In assessment of compliance to medications, diet and exercise, we were limited to include only subjects who were aware of their disease, so we did not have access to data about possible medication/diet/exercise adherence of non-aware subjects in relation to stress level. In another IHHP report in 2007, investigators found negative impact of high stress level on diet but not on exercise and physical activity. That study enrolled all target population from the community regardless of having HTN and or DM.[37] We found no relationship between stress and diet in patients with HTN and or DM, which may indicate that stress shows its effect on life style factors of chronic diseases in at risk but not diseased population. This may have implications in prevention strategies and interventions to implement programs with target to manage stress levels in at risk populations.

While there are no established etiologic pathways,[16] it seems that stress and other psychological attributes play important role in compliance of patients with HTN and DM.[19-21,38-40] So, they can be considered as targets for HTN and DM management and control programs.[41] Addressing depression and anxiety in compliance improving programs would provide better chance to deal with management of chronic medical conditions such as DM and HTN. This effect would possibly act via several hypothetical pathways such as modification of monoamines implicated in stress and depression as well as other medical and psychological conditions that encounter disease and health, providing more adequate treatment regimens to subjects. These assumptions need to be studied deeply in further studies.

A limitation to this study is lack of information about long term stress levels in subjects and lack of differentiating stress trait and state. If such data was gathered, it might have contributed to more comprehensive understanding of the relationship between stress and HTN/DM. It is suggested to use inventories in further studies to overcome this

issue. Another limitation is that the assessment of compliance about medication was based on self-report by cases.

Conclusion

Management of depression and anxiety symptoms generally experienced as stress by the patient could be an efficient method in management of DM and HTN and possibly other chronic diseases. Addressing stress in clinical and community management of these chronic medical conditions would improve health status of patients via several routs such as improving compliance to medications, exercise and diet.

Acknowledgments

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Conflict of Interests

Authors have no conflict of interests.

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Are the price patterns of cardioprotective vs. unhealthy foods the same? A report from Iran

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Original Article

Abstract

BACKGROUND: Although several studies have assessed the price of different food groups in developed countries, there is scarce evidence regarding developing countries. Also, there is no report regarding the price of cardioprotective compared with unhealthy foods. The aim of this study was to determine the trend of food cost across different food groups (cardioprotective vs. unhealthy) and to assess the association between food cost and nutritional quality of foods in Iran.

METHODS: A list of foods consumed frequently by Iranian population was provided. Nutritional quality of foods was assessed by energy density and nutrient rich foods (NRF) index. Food groups were defined according to the US Department of Agriculture (USDA) MyPlate food groups. The price of food groups was reported as kcal/price and price/serving.

RESULTS: Although a positive association between different types of nutrient rich foods, nutrient content of foods and food price was observed, there was an inverse relationship between food price and energy density. The kcal/price of "oils" was less than "whole grains" and "refined grains". "Sugar, sweets and beverages" and "beans and legumes" food groups had equal kcal/price media. Among healthy foods for cardiovascular system, nuts had the highest price/serving. On the other hand, among unhealthy foods for cardiovascular system, processed meat had the highest price/serving. The price/serving of healthy oils was similar to saturated and *trans* fatty acids rich oils. Also, the price/serving of low-fat (healthy) vs. high fat (unhealthy) dairy was not different. Similar finding was observed for white meat vs. red meat.

CONCLUSION: Our findings revealed that the pattern of food price in Iran is different from developed countries. Also, we found that Iranians can consume a cardioprotective diet without any economic pressure.

Keywords: Food Price, Nutritional Quality, Cardioprotective Agents, Unhealthy Foods, Developing Country

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Introduction

Socioeconomic status (SES) is inversely associated with risk behaviors for chronic diseases[1] including cardiovascular diseases,[2] diabetes,[3] hypertension,[4] kidney disease,[5] and dental caries.[6] The risk of dying due to ischemic heart disease is higher among subjects with lower SES.[7] On the other hand, dietary intakes have an important role in incidence and progression of chronic diseases.[8] Reports from western populations revealed that there was a direct association between SES and diet quality.[9] Moreover, a strong relationship between income and micronutrient content of the diet was observed in a developing country.[10] Investigators have suggested that such direct association between SES and diet quality may be mediated by the food price.[11] Studies reported that there was an inverse association between diet cost and dietary energy density in a western population.[12]

Evidence showed that food price crisis might result in increased food insecurity and decreased intake of vegetables, fruits, meat products and dairy in a low-income country.[13] Also, it was predicted that zinc intake was significantly influenced by rise in food price

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in a developing country.[10] Previous studies from developed countries reported that diet cost was inversely related to intake of total fat and saturated fatty acids, and was directly associated with vitamin A and vitamin C intake.[14] It was also revealed that the cost of an unhealthy diet rich in added sugar, added fat and refined grain was lower in the US.[15] A favorable relationship between higher diet cost and dietary risk factors of cardiovascular diseases such as quality of diet, unhealthy food consumption, and obesity was observed among US adolescents.[16] Although several studies assessed the relationship between economy and diet quality in developing countries,[10,13,17] scarce data were reported regarding the association between economy and nutrient content of foods.

It was observed that high intake of several food groups such as refined grains,[18] saturated and trans fatty acid rich oils,[19] red meats,[20] processed meats,[21] high-fat dairy[22] and sugar sweetened foods[23] was unfavorably associated with the risk factors and mortality of cardiovascular diseases. Nevertheless, the price of unhealthy foods for cardiovascular system in comparison with healthy foods was not assessed in previous studies.

As reported by The World Bank (Middle East and North Africa Region), the food price change had a different pattern in Middle Eastern and North African countries[24] and it had significantly higher increase in Iran.[24] Therefore, the aim of present study was to compare the food cost across different food groups based on their effect on cardiovascular system and to assess the association between food cost and nutritional quality of foods in Iran.

Materials and Methods

A list of the names and foods extracted from different dietary assessment tools (i.e. food frequency questionnaire, food diary and dietary recall) consumed in different provinces of Iran was checked by expert nutritional epidemiologists in several meetings to provide a list of foods consumed frequently by Iranian population. Finally, 160 food items were selected (Table 1). Nutrient content of the foods was extracted using Nutritionist IV software (N-Squared Computing, Salem, OR). Data regarding the added sugar required to calculate the food quality indices was extracted from food labels.

The food price was obtained from licensed retail sale outlets in which sale price was approved by central government and was constant among all provinces. The food price was corrected for edible portion and food weight changes due to cooking. The price of foods was presented as per 100 kcal (price/100 kcal) and per serving (price/serving).

The US Department of Agriculture (USDA) MyPlate serving sizes were used to calculate food cost per serving.[25] According to the USDA MyPlate food categories, following food groups were defined: whole grains (n = 2), refined grains (n = 13), beans and legumes (n = 8), red meats (n = 12), white meats (n = 4), processed meats (n = 4), dairy products (n = 16), oils (n = 9), vegetables (n = 21), fruits (n = 35), fruit juices and canned fruits (n = 6), nuts (n = 7), sugar, sweets and beverages (n = 19) and miscellaneous (n = 4).

Table 1. Macronutrients, vitamins and minerals to encourage and nutrients to limit used to calculate different versions of nutrient rich food (NRF) index

Version of nutrient rich food (NRF) Index	Nutrients to encourage	Nutrient to limit
NRF 6.3	Protein, fiber, vitamin A, vitamin C, calcium, iron	Saturated fatty acid, added sugar and sodium
NRF 9.3	Protein, fiber, vitamin A, vitamin C, calcium, iron, vitamin E, magnesium, potassium	Saturated fatty acid, added sugar and sodium
NRF 11.3	Protein, fiber, vitamin A, vitamin C, vitamin E, vitamin B-12, calcium, iron, zinc, magnesium, potassium	Saturated fatty acid, added sugar and sodium
NRF 15.3	Protein, fiber, monounsaturated fat, vitamin A, vitamin C, vitamin E, vitamin D, vitamin B-12, thiamin, riboflavin, folate, calcium, iron, zinc, potassium	Saturated fatty acid, added sugar and sodium

Nutritional quality of foods was evaluated by energy density and Nutrient Rich Food (NRF) index. Energy density of each food was calculated by dividing energy content (kcal) of food by unit weight (gram). Nutritive value of each food was assessed by NRF calculated by following formula:[26]

$$NRF = [\sum\left(\frac{\text{nutrients to encourage}}{\text{reference daily value}}\right) - \sum\left(\frac{\text{nutrientsto limit}}{\text{maximum recommended values}}\right)] \times 100$$

Nutrients to encourage and nutrients to limit used to calculate different versions of NRF are presented in table 1. Different macronutrients, vitamins and minerals as nutrients to encourage were considered in different versions of NRF. Nutrients to limit were constant in all versions and were saturated fatty acids, added sugar and sodium.[26] Reference daily values and maximum recommended values were based on the recommendations of Institute of Medicine.[27] The definition of healthy and unhealthy food groups were based on previous studies.[18-23]

We analyzed data using SPSS software for windows (version 20.0, SPSS Inc., Chicago, IL, USA). Food price variable was presented as tertiles by following cut-points: ≤ 2630, 2631-6460 and ≥ 6461 Rials for food price/serving, and ≤ 3290, 3291-8470 and ≥ 8471 Rials for price/100 kcal. The results of the Kolmogorov–Smirnov test and histogram showed that the distribution of dependent variables was not normal. Therefore, we used nonparametric tests. Kruskal-Wallis H test was performed to compare the mean ranks of NRFs and energy density across tertiles of food price. The association between prices of foods and nutrients were also tested using Spearman correlations. $P < 0.05$ was determined as level of statistical significance.

Results

The trend of different versions of NRF (presented per serving and per 100 kcal) across tertiles of food price is presented in table 2. Foods in the last tertile of the food price/serving had significantly higher NRF/serving in comparison to the first tertile. This finding was observed for all versions of NRF/serving. Similar result was found for the NRFs/100 kcal in the tertiles of the price/100 kcal (Table 2).

Results regarding the Spearman correlation between food price and nutrient content of the foods are displayed in table 3. There was a significant direct association between food price and protein, potassium, iron, calcium, magnesium, zinc, selenium, vitamin A, β-carotene, thiamin, riboflavin, niacin, vitamin B6, folate, vitamin C, poly-unsaturated fatty acids, mono-unsaturated fatty acids and dietary fiber content of foods ($P < 0.05$ for all). Added sugar, a cardiovascular risk factor, was inversely related to the food price ($P < 0.01$). Two other dietary cardiovascular risk factors (i.e. saturated fatty acids and cholesterol) had no significant association with the food price.

Energy density mean ranks of foods across tertiles of food price are illustrated in figure 1. As shown in the figure, the price of foods with lower energy density was more than foods with higher energy density ($P = 0.01$).

Table 2. The of different versions of Nutrient Rich Food (NRF) index across tertiles of food price

Variables	Tertile 1 (n = 54)	Tertile 2 (n = 54)	Tertile 3 (n = 55)	P*
Price per serving (Iranian Rials)	**≤ 2630**	**2631-6460**	**≥ 6461**	
NRF 6.3/serving	5.5 (-9.2, 18.3)†	21.5 (-5.3, 70.3)	20.8 (8.1, 55.7)	0.02
NRF 9.3/serving	10.8 (-7.9, 29.5)	33.0 (-0.8, 88.7)	36.7 (17.6, 82.7)	< 0.01
NRF 11.3/serving	11.8 (-6.4, 31.5)	43.2 (3.4, 100.0)	57.7 (37.5, 98.5)	< 0.01
NRF 15.3/serving	19.5 (1.5, 42.5)	58.3 (23.9, 122.0)	75.8 (51.9, 133.0)	< 0.01
Price per 100 kcal (Iranian Rials)	**≤ 3290**	**3291-8470**	**≥ 8471**	
NRF 6.3/100 kcal	3.61 (-13.6, 17.6)	24.2 (-2.9, 88.2)	53.3 (23.0, 157.0)	< 0.01
NRF 9.3/100 kcal	13.7 (-10.4, 28.5)	38.0 (2.0, 97.0)	75.5 (31.5, 190.0)	< 0.01
NRF 11.3/100 kcal	18.9 (-7.3, 34.0)	52.2 (14.6, 110.0)	86.7 (45.6, 214.0)	< 0.01
NRF 15.3/100 kcal	37.3 (6.7, 53.1)	76.8 (32.9, 141.0)	105.0 (61.0, 242.0)	< 0.01

* P value was calculated by Kruskal-Wallis H test
† All values are medians (interquartile range)
NRF: Nutrient Rich Foods Index

Table 3. Spearman correlation between food price and nutrient content of the foods

Nutrient	Spearman's rho	P	Nutrient	Spearman's rho	P
Protein	0.208	< 0.01	Vitamin A	0.283	< 0.01
Carbohydrate	0.118	0.13	β-carotene	0.159	0.04
Fat	0.030	0.70	Thiamin	0.226	< 0.01
Cholesterol	0.034	0.67	Riboflavin	0.394	< 0.01
SFA	0.035	0.76	Niacin	0.383	< 0.01
Potassium	0.544	< 0.01	Vitamin B6	0.369	< 0.01
Iron	0.279	< 0.01	Folate	0.306	< 0.01
Calcium	0.285	< 0.01	Vitamin B12	0.032	0.68
Magnesium	0.386	< 0.01	Vitamin C	0.509	< 0.01
Zinc	0.311	< 0.01	Dietary fiber	0.247	< 0.01
Selenium	0.231	< 0.01	Added sugar	-0.225	< 0.01
Sodium	0.042	0.60	MUFA	0.403	< 0.01
PUFA	0.359	< 0.01			

MUFA: Mono-unsaturated fatty acid; PUFA: Poly-unsaturated fatty acid; SFA: Saturated fatty acid

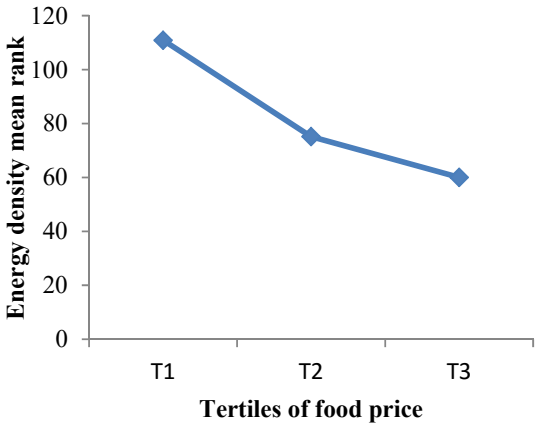

Figure 1. Energy densities mean ranks of foods across tertiles of food price

The food price in different food groups was assessed by two variables, i.e. kcal per price (kcal/price) and price per serving (price/serving). Medians of kcal/price in fourteen defined food groups are shown in figure 2. The results revealed that "whole grains" had the highest kcal/price median. The kcal/price of "oils" was less than "whole grains" and "refined grains". "Sugar, sweets and beverages" and "beans and legumes" food groups had equal kcal/price median. Similar finding was observed for "nuts" and "vegetables" food groups. Among animal sources of protein (i.e. "dairy products", "red meats", "white meats" and "processed meats"), "dairy products" had the lowest kcal/price.

Medians of price/serving are illustrated in figure 3. The findings showed that the highest price/serving was in "nuts" food group. "whole grains" and "refined grains" had lower price/serving than "oils". Although "sugar, sweets and beverages" and "vegetables" food groups had equal price/serving median, this value was lower in "beans and legumes" food group. Similarly, the price/serving in "fruit juices and canned fruits" and "white meats" was equal and higher than "fruits". The price/serving of "red meats" food group was sharply increased compared with "white meats" food group.

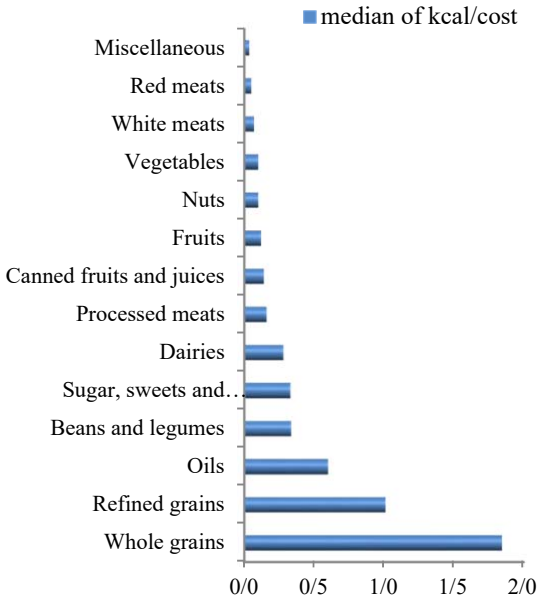

Figure 2. Medians of kcal/price in fourteen defined food groups

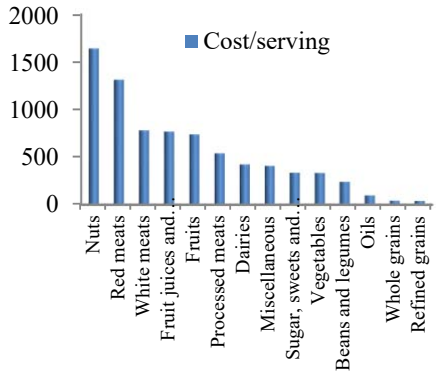

Figure 3. Price/serving medians in fourteen defined food groups

Figure 4 shows the price/serving of healthy and unhealthy foods for cardiovascular system. Among healthy foods for cardiovascular system, nuts had the highest price/serving. On the other hand, among unhealthy foods for cardiovascular system, processed meat had the highest price/serving. The price/serving of healthy oils was similar to saturated and *trans* fatty acid rich oils. Also, the price/serving of low fat (healthy) vs. high fat (unhealthy) dairy was not different. Similar finding was observed for white meat vs. red meat.

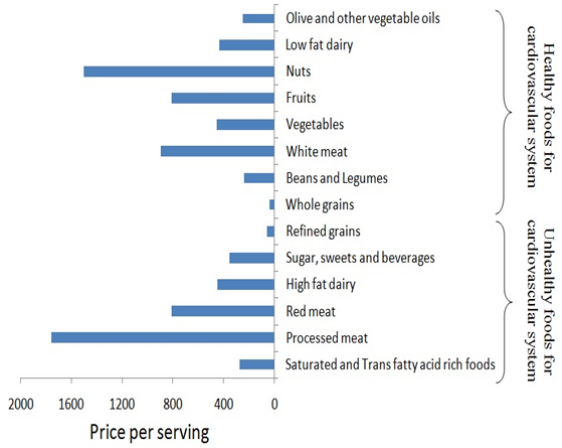

Figure 4. Price/serving of healthy and unhealthy foods for cardiovascular system

Discussion

The findings showed that higher food price had a favorable association with nutritional quality, nutrient content and energy density of foods. Moreover, results revealed that in this developing country, the price of healthy food groups was equal to unhealthy food groups in several cases. To the best of our knowledge, this study is the first study from Middle East which reports food price in different food groups.

We found that foods in the last tertile of the food price/serving had significantly higher NRF in comparison with the first tertile. This finding was observed for all versions of NRF/serving and NRF/100 kcal. NRF index is a valid tool which scores foods on the basis of their healthy and unhealthy nutrients content (Table 1).[26] It is a useful scoring system to identify affordable foods.[28] NRF index can be calculated for individual foods and food groups.[29] A previous study reported that food groups with higher NRF (i.e. vegetables and fruits) were more expensive in the US.[28] We could not find any study regarding the association between food price and NRFs of individual foods. Therefore, it seems that this is the first study which assessed foresaid relationship.

A significant direct association between food price and several important nutrients was observed in the present study. Direct association between food price and NRF was expected because NRF was calculated based on nutrient content of foods. Townsend et al. reported that energy adjusted diet cost was directly related to intake of potassium, vitamin A, vitamin C and dietary fiber in the US.[14] Evidence from a non-developed country revealed that there was a positive association between per capita expenditure and intake of iron, zinc, vitamin A, vitamin B12 and folate.[10] Therefore, results of previous studies confirmed our findings. Also, we found that there was no association between food price and cholesterol and saturated fatty acid content of foods. It means that unhealthy foods for cardiovascular system rich in cholesterol and saturated fatty acids are not more expensive than healthy foods. Therefore, higher consumption of unhealthy foods for cardiovascular system rich in cholesterol and saturated fatty acids is not due to lower price of these foods and education has an important role in choosing a cardioprotective food.

It was observed that more expensive foods had higher energy density. The study by Monsivais et al. conducted in the US reported similar result.[30] Previous study showed that the cost of low-energy density diet was high in a developed country.[12] Low energy density diet was associated with several cardiometabolic risk factors and disorders such as obesity,[31] dyslipidemia[32] and metabolic syndrome.[33]

We found that the kcal/price of "oils", the main source of dietary fat, was less than the main carbohydrate rich food groups, i.e. "whole grains" and "refined grains". It shows that in Iran,

carbohydrate, as a source of energy, is more affordable than fat. Evidence form the US showed that grain products had lower kcal/dollar than fats.[28] Also, it was observed that "sugar, sweets and beverages" and "beans and legumes" food groups had equal kcal/price median. Therefore, we can educate Iranians to provide their required energy from "beans and legumes" rather than "sugar, sweets and beverages" without any economic pressure. In contrast, it was reported that the kcal/price median of sugars food groups was greater than beans and legumes in a developed country.[28] "Dairy products" food group has lower kcal/price than other sources of animal protein because it is the only source of animal protein to receive a government subsidy in Iran. The price of other sources (i.e. "red meats", "white meats" and "processed meats") is determined by supply and demand system. Observed equal kcal/price medians for "nuts" and "vegetables" food groups in our study is due to lower calorie content of "vegetables". According to the results from the US, the kcal/price median of fruits and vegetables was higher than different types of meat in this country.[28] Nevertheless, the findings of present study showed that the kcal/price median of meats were higher than fruits and vegetables in Iran.

As shown in the results, "whole grains" and "refined grains" had the lowest price/serving. The "whole grains" food group consists of two types of bread available in all provinces of Iran. Nevertheless, there are several whole grain products only available in affluent areas of metropolises of Iran. These products are more expensive than frequently consumed whole grain products included in our analysis.

Our results revealed that "whole grains" and "refined grains" had lower price/serving than "oils". In contrast with this finding, Drewnowski et al. reported that the price/serving median of oils was greater than grain products in the US.[34] According to the findings of the current study, the price/serving of healthy food groups such as "vegetables" and "beans and legumes" were less or equal to price/serving of unhealthy food group i.e. "sugar, sweets and beverages". This finding is in contrast with reported results from the US.[34] We could not find any evidence regarding price/serving of food groups from developing countries. Nevertheless, the comparison between findings of the present study and reported results from the developed countries disclose the importance of nutritional education in Iran because Iranians can replace several unhealthy foods with healthy ones without any economic pressure.

We found that the price/serving of healthy foods for cardiovascular system was similar to unhealthy foods. This finding shows that education of healthy nutrition has important role in dietary pattern of Iranian population and individuals can consume a healthy diet for cardiovascular system without economic pressure.

The limited number of food items included in the current study may be considered as a limitation because we did not include local foods consumed in an ethnic group. This study focused on the frequently consumed foods and therefore food items only available in metropolises were not assessed. Also, the differences in the price of several foods in areas with thriving agriculture and livestock were not considered. We could not find evidence from different countries. Therefore, we did not compare our findings with reports from several countries.

There are scarce data regarding food cost in different food groups in developing countries. Therefore, the main strength of the present research is study location. Moreover, the association between food price and nutritional quality of foods was presented by several indices.

Conclusion

Our findings revealed that the pattern of food price in Iran is different from developed countries. Also, we found that Iranians can consume a cardioprotective diet without any economic pressure.

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Conflict of Interests

Authors have no conflict of interests.

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Effects of digoxin on cardiac iron content in rat model of iron overload

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Original Article

Abstract

BACKGROUND: Plasma iron excess can lead to iron accumulation in heart, kidney and liver. Heart failure is a clinical widespread syndrome. In thalassemia, iron overload cardiomyopathy is caused by iron accumulation in the heart that leads to cardiac damage and heart failure. Digoxin increases the intracellular sodium concentration by inhibition of Na^+/K^+-ATPase that affects Na^+/Ca^{2+} exchanger (NCX), which raises intracellular calcium and thus attenuates heart failure. The mechanism of iron uptake into cardiomyocytes is not exactly understood.

METHODS: We assessed the effect of different concentrations of digoxin on cardiac iron content in rat model of iron overload. Digoxin had been administrated intraperitoneally (IP) for one week before main study began to assure increased digoxin levels. Group 1 received four IP injections of iron-dextran (12.5mg/100g body weight) every 5 days evenly distributed over 20 days. Groups 2-4 received 0.5, 1 and 5 mg/kg/day IP digoxin, respectively. Last three groups 5-7 received iron-dextran as group 1 and digoxin concentrations 0.5, 1 and 5 mg/kg/day, respectively.

RESULTS: Cardiac iron contents were significantly higher in iron overload groups that received different concentrations (0.5, 1 and 5 mg/kg/day) of digoxin than their counterparts in control groups and this pattern was also observed in pathology assessment.

CONCLUSION: It seems that digoxin plays an important role in iron transport into heart in iron overload state but exact mechanism of this phenomenon is not clear. L-type Ca^{2+} channels are good candidates that probably could be involved in iron accumulation in cardiomyocytes. Thus it would be better to reconsider digoxin administration in thalassemia and iron overload conditions.

Keywords: Iron Overload, Digoxin, Iron Dextran Complex, Cardiac Iron Content

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Introduction

Iron is an essential trace element that has many biological and biochemical functions. Iron is an important component of hemoglobin, myoglobin, cytochrome p450 system and many other proteins. Iron levels are precisely regulated under normal physiological conditions via complex mechanisms.[1] In some clinical conditions such as hemochromatosis, bone marrow failure and massive transfusion, there is an intensive load of iron in serum and subsequent accumulation in tissues.[1] In such conditions, iron metabolism is disturbed and results in increased mortality. Iron plays a pivotal role in generation of reactive oxygen species (ROS) and therefore causes many disorders such as ischemia-reperfusion injury, atherosclerosis and problems in other tissues.[2]

Iron accumulation in heart and liver damages these tissues.[3] Iron overload cardiomyopathy results from increased cardiac iron deposits. Iron accumulation in cardiac muscle cells is the leading cause of heart failure in iron overload conditions which increases mortality in affected patients.[4] Patients with thalassemia, especially thalassemia major need massive transfusions. Hence, they are predisposed to iron overload and there is no physiological mechanism to get rid of iron load in this group. Cardiomyopathy is common in patients with thalassemia and leads to left ventricle dysfunction, heart failure and death.[5,6]

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Digoxin increases the intracellular sodium concentration by interfering with Na^+/K^+-ATPase (NKA) activity. Intracellular sodium increment affects Na^+/Ca^{2+} exchangers (NCX) that subsequently leads to an increase in intracellular calcium concentration.[7,8] The exact mechanism of iron uptake into cardiomyocytes is still not fully and clearly understood. Many studies suggest that L-type Ca^{2+} channels (LTCCs) are likely to be involved in iron uptake into cardiomyocytes.[7,9,10] These channels primarily transport Ca^{2+} and also other cations such as Fe^{2+}, Zn^{2+}, Co^{2+}, Ba^{2+} and Mn^{2+} into cardiac muscle cells.[9,11,12] Digoxin inhibits NKA activity, and that probably activates LTCCs involved in divalent cations transport, therefore digoxin indirectly activate LTCCs. According to these information, we designed this study to investigate the effect of digoxin administration on iron transport into cardiomyocytes in iron overloaded rat model.

Materials and Methods

Study was performed on 56 male Sprague Dawley rats obtained from Kerman Physiology Research Center, Kerman, Iran (weight = 200-230 g). Animals were kept in standard condition and were provided with rat chow and water ad libitum. Iron content of serum and heart tissue were measured by iron assay kit (BioVision, Catalog #K390-100) and digoxin levels of serum and heart tissue were measured by digoxin assay enzyme-linked immunosorbent assay (ELISA) kit (Digoxin AccuBind ELISA Kits, 925-300). Iron-dextran (Sigma, D8517) and digoxin were also prepared from Sigma-Aldrich.

This study was approved by the Ethic Committee, Kerman University of Medical Sciences. Iron overload was induced by iron-dextran. Fifty six male Sprague-Dawley rats were randomly divided in 7 groups as below. At first digoxin had been administrated intraperitoneally (IP) daily for a 7-days period before main study began to assure high digoxin levels in groups receiving digoxin in main study. Digoxin was administrated daily and iron dextran was administrated every 5 days.

Group 1 (iron overload): received 12.5 mg/100g body weight iron-dextran every 5 days.

Group 2 (digoxin control 0.5): received 0.5 mg/kg/day digoxin.

Group 3 (digoxin control 1): received 1 mg/kg/day digoxin.

Group 4 (digoxin control 5): received 5 mg/kg/day digoxin.

Group 5 (iron + digoxin 0.5): received 12.5 mg/100g body weight iron-dextran every 5days + 0.5 mg/kg/day digoxin.

Group 6 (iron + digoxin 1): received 12.5 mg/100g body weight iron-dextran every 5 days + 1 mg/kg/day digoxin.

Group 7 (iron + digoxin 5): received 12.5 mg/100g body weight iron-dextran every 5 days + 5 mg/kg/day digoxin.

Group 1 received four IP injections of iron-dextran (12.5 mg/100g body weight) every 5 days evenly distributed over a period of 30 days. Groups 2-4 received 0.5, 1 and 5 mg/kg/day IP digoxin injections, respectively. Last three groups (5-7) received iron-dextran as group 1 and also 0.5, 1 and 5 mg/kg/day IP digoxin injections.[13,14]

At the end of the study, animals were anesthetized by ether and sacrificed, blood sample were collected and serum were separated. Then, after an abdominal incision, the heart was removed and rinsed with 0.9% NaCl to remove excess blood. A sample of the heart tissue was collected for iron and digoxin assessment. Tissues were homogenized in cold sample buffer by Hielscher homogenizer and centrifuged at 15000 rpm for 15 minutes. Supernatant was used for further evaluations. A small sample of heart was fixed immediately in 10% formalin for histological processing. Sections (4 mm) were cut and stained for histopathological evaluation. Prepared slides after Prussian blue staining were evaluated and scored 0-4 based on severity by two pathologists that were blinded to animal grouping.[15]

Statistical analyses were performed via SPSS software for Windows (version 16.0, SPSS Inc., Chicago, IL, USA). All the results are presented as mean ± standard deviation (SD). Group differences were examined for significance using one-way analysis of variance (ANOVA) followed by the Tukey's post hoc test.

Results

Data is shown in table 1. Serum digoxin levels in groups 3-4 and 6-7 were significantly higher than group 1. Serum digoxin levels in groups that receive 1 and 5 mg/kg/day digoxin were significantly higher than digoxin 0.5 control group.

Heart digoxin levels were significantly lower in iron control group compared to all other groups.

Heart iron levels were significantly higher in groups that received combination of digoxin and iron (groups 5-7) than their counterpart control groups (groups 2-4); this pattern was also observed in pathology assessment (Figure 1, A-G).

Table 1. Biochemical and pathological parameters in studied groups

Groups	Iron	Digoxin 0.5	Digoxin 1	Digoxin 5	Iron + digoxin 0.5	Digoxin 5	Iron + digoxin 5
Serum digoxin (ng/ml)	4.8 ± 2.0‡§	10.8±4.3§	50.5±30.0*†‡§	140.0 ± 30.0*†‡	5.5 ± 1.7‡§	140.0 ± 30.0*†‡	125.0±37.0*†‡
Heart digoxin (ng/mg) tissue	0.2 ± 0.0§	24.4±9.2§	14270±14010§	511400±362110*†‡	1066±850§	511400±362110*†‡	431230±240250*†‡
Serum iron (nmolar)	18.6±3.0†‡§	6.5 ± 1.6*	7.0 ± 1.5*	7.8 ± 2.4*	8.8 ± 2.0*	7.8 ± 2.4*	11.2 ± 2.0*†‡
Heart iron (nM/mg) tissue	0.2 ± 0.1	0.3 ± 0.1	0.4 ± 0.1	0.4 ± 0.8	0.7±0.2*†‡§	0.4 ± 0.8	1.0 ± 0.1*†‡§
Pathology score	3.2 ± 0.4†‡§	0.0 ± 0.0*	0.5 ± 0.5*	0.4 ± 0.5*	3.2 ± 0.4†‡§	0.4 ± 0.5*	3.9 ± 0.5†‡§

Values are mean ± SD; n = 8 rats/group; data were analyzed using one-way ANOVA
* Statistically significant compared to iron group (P < 0.05)
† Statistically significant compared to digoxin 0.5 group (P < 0.05)
‡ Statistically significant compared to digoxin 1 group (P < 0.05)
§ Statistically significant compared to digoxin 5 group (P < 0.05)

Discussion

Massive and long term transfusion in patients with thalassemia or bone marrow failure is considered as a life protecting therapy.[1] Following transfusions, iron levels rise in the body and iron overload condition occurs. Iron overload leads to some complications such as ROS generation and also iron deposition in many tissues including heart and liver.[2] Cardiac cellular damage and heart failure by iron known as iron overload cardiomyopathy occurs under iron overload condition and is the main cause of death in thalassemia major patients.[5,6] Digoxin has an indirect effect on intracellular calcium levels. Digoxin therapy to maintain cardiac function leads to increased intracellular sodium concentration that subsequently increases the intracellular calcium concentration by affecting NCX.[7,8] However, it is suggested that LTCCs also play a part in divalent cations transport into cardiomyocytes.[10] We have shown that digoxin administration in digoxin control groups (groups 2-4) and iron overloaded groups (groups 5-7) caused iron accumulation in the heart tissue. There was a dose dependent increase in iron content of cardiomyocytes by different concentrations of digoxin.

Several findings support the role of LTCCs in myocardial iron transport. Tsushima et al.[10] showed that myocardial iron uptake was driven by LTCCs and suggested that LTCCs blockers could be a useful treatment in iron overload condition. Compared to our data, it seems reasonable to account LTCCs as a major player in iron transport into cardiomyocytes.

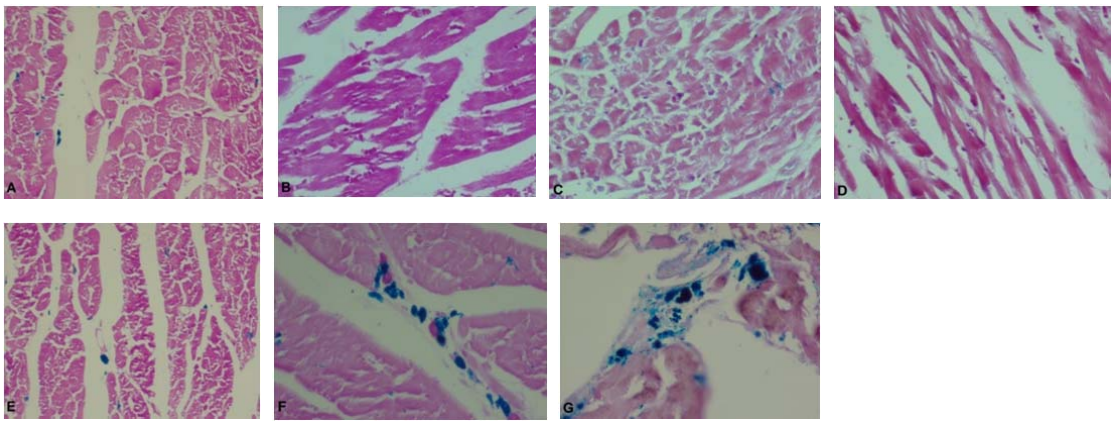

Figure 1. Prussian blue staining of heart. Groups respectively received A. Iron-dextran (12.5 mg/100g body weight), B. 0.5 mg/kg digoxin, C. 1 mg/kg digoxin, D. 5 mg/kg digoxin, E. Iron-dextran as group A and 0.5 mg/kg digoxin, F. Iron-dextran as group A and 1mg/kg digoxin, G. Iron-dextran as group A and 5 mg/kg digoxin

Efonidipine is a T-type Ca^{2+} channels (TTCCs) and LTCCs blocker but it blocks TTCCs greater than LTCCs.[16] It has been reported that efonidipine prevented iron uptake into cultured thalassemic cardiomyocytes in iron overload conditions.[17] On the other hand, verapamil (a LTCCs blocker) could not prevent iron uptake but efonidipine prevented iron uptake. These findings from previous studies suggested that TTCCs also play a significant role in iron uptake into cardiomyocytes.[18] A rat heart in iron loaded condition showed that iron uptake was increased by the LTCCs agonist, Bay K 8644, and iron uptake was inhibited by the LTCCs blocker, nifedipine.[10] In other study, Oudit et al.[18] have demonstrated that treatment with LTCCs blockers such as amlodipine and verapamil led to LTCCs inhibition in cardiomyocytes; hence reduced myocardial iron accumulation.

Xu et al.[7] showed that NKA inhibition by ouabain-induced Ca^{2+} influx. They also provided direct evidence that KB-R7943 (NCX blocker) and nifedipine both could halt ouabain-induced Ca^{2+} influx, indicating that both LTCCs and NCX contributed to the rise of intracellular Ca^{2+} levels. The exact mechanism of iron transport into cardiomyocytes is not fully and properly understood but according to Xu et al. observations, it seems that LTCCs along with NCX are involved in this phenomenon especially in iron overload conditions.[7] But digoxin role in this process is not investigated and needs to be clarified. Digoxin elevates intracellular Ca^{2+} levels and probably maximizes its effect on Ca^{2+} elevation by elevating LTCCs activity that could increase iron transport into cardiomyocytes.[8,18]

LTCC activity is increased by iron elevation under iron overload condition.[9] In our groups that received same iron concentrations (groups 5-7), there was a digoxin dependent iron transport into the cardiomyocytes. Findings from previous studies are controversial and are challenging about LTCCs probable role in iron transport into cardiomyocytes. We showed that digoxin in digoxin control groups (groups 2-4) raised iron content in cardiomyocytes but in iron overloaded group (group 1) despite presence of iron overload condition, there was lower iron content in heart tissue compared to other groups. Considering digoxin role in Ca^{2+} (and probably other divalent cations such as Fe^{2+}) transport by LTCCs into cardiomyocytes,[7,9,10] our findings support this hypothesis that digoxin has a pivotal role in activation of LTCCs and helps iron entrance into cardiomyocytes in iron overload condition. On the other hand, digoxin also has an iron overload independent effect on LTCCs to enter iron into cardiomyocytes.

Conclusion

If we accept that digoxin increases the flow of ions (other divalent cations except Ca^{2+}) through LTCCs, as Xu et al. have shown in their study,[7] it seems that it has an important role in iron entrance into cardiomyocytes especially in thalassemic and other iron overload conditions, and digoxin administration in these patients must be reconsidered or must be administrated with caution. Also the direct effect of digoxin needs to be further investigated in animal models and it is necessary to administer digoxin chronically in iron overload models and investigate gene expression and protein levels of LTCCs in heart tissue in order to prove the effect of digoxin on these channels.

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Conflict of Interests

Authors have no conflict of interests.

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Transition in public knowledge of risk factors of cardiovascular disease in an Iranian general population: A latent transition analysis (LTA) on a longitudinal large community-based educational prevention program

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Original Article

Abstract

BACKGROUND: Cardiovascular diseases (CVD) are the second leading cause of death, after accidents, in Iran. This study was performed to assess the change in levels of knowledge about 8 risk factors of CVD and its associated determinants the Iranian general population.

METHODS: The current repeated cross-sectional study included 3014 people in 2004, 3012 in 2005, and 4719 in 2007, aged older than 19 years. Knowledge about 8 risk factors (high blood pressure, nutrition, physical inactivity, smoking, diabetes, heredity, stress, and obesity) as the major causes of CVD was evaluated using latent transition analysis (LTA).

RESULTS: The most widely known CVD risk factors were nutrition and physical inactivity followed by stress. In addition, old age, low level of education, male gender and low socioeconomic status (SES) level were the significant determinants of low knowledge levels of CVD risk factors. Besides, individuals' knowledge of CVD risk factors increased across the time.

CONCLUSION: Public knowledge of CVD risk factors has increased; however significant gaps continue to exist, particularly among the elderly, less-educated people, people in low socioeconomic status level and men. Future intensified educational efforts by policymakers are necessary for improving knowledge of CVD, particularly among high-risk groups.

Keywords: Cardiovascular Disease, Risk Factors, Prevention, Knowledge, Latent Transition Analysis

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Introduction

Cardiovascular diseases (CVD) are the leading cause of mortality and morbidity all over the world.[1,2] According to World Health Organization (WHO) reports, it is estimated 17.3 million people became dead from CVDs in 2008 and it is predicted that almost 23.3 million people will die annually from CVDs, by 2030.[3] CVD remains the first cause of preventable death globally and continues to grow in prominence, because of attendant burden, inequalities, and costs.[2] CVD is responsible for a considerable proportion of mortality and morbidity among Iranian general population; in which according to Iran ministry of health, CVD is the second leading cause of mortality and morbidity after accident and WHO is predicted that 44.8% of incidence of mortality will be related to it by 2030.[3,4]

Prevention of CVD is the most effective way of combating the CVD epidemic in the less-developed and developing nations. Knowledge of modifiable risk factors of CVD particularly in life style domain has been identified as a prerequisite for change in behaviour and is often targeted by prevention programs.[5,6] Although, knowledge alone is not sufficient, it is assumed to be a key component of behavioural change decision making, and provides cues for action. Earlier studies have revealed that the education programs were effective in improving health promotion knowledge and behaviours.

It is clear that the knowledge and identification of risk factors for CVD, with early detection, can play an important role in controlling the symptoms, complications, and deaths, and decrease their health burden.[5,7]

Although the level of knowledge of risk factors for CVD varies among different populations over the world; however the majority of the studies conducted in this area has reported low levels of knowledge.[8-16]

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Some limited studies carried out in Iran about the levels of knowledge of the CVD and its risk factors among Iranian general or specific population showed that the knowledge levels are poor.[17-23]

In Iran, there is lack of large population-based studies on evaluating the distribution of knowledge levels about major risk factors of CVD and its determinants. Due to the expansion of CVD and its large burden, in a developing society such as Iran, implementing such monitoring study can provide effective perquisites for change, conducting and improving the prevention programs. Therefore, the present study was conducted to assess not only the current but also the trend of changes over the 2004-2007 in levels of knowledge about CVD risk factors and related determinants in large samples of general public in Isfahan city and suburbs, using data obtained from a large-population, community-based intervention follow-up study, i.e. Isfahan Healthy heart program (IHHP),[24,25] using an advanced statistical method i.e. latent transition analysis (LTA).[26] To our knowledge, the current study is not only the first large community-based study in Iran but also all around the world that examines the impact of a health-promotion educational intervention community-based program longitudinally using a relevant and comprehensive statistical modelling approach. LTA enables us to examine sequential stage movements in levels of knowledge and LTA with covariates also can provide the capability for examining the effects of potential determinants of participant's status in terms of knowledge levels about CVD risk factors. Estimating the level of knowledge of the population can help to promote the public health programs especially those directed towards reducing modifiable risk factors of CVD.

Materials and Methods

This panel or cross-sectional time-series study was conducted in an explanatory and correctional setting among general population living in Isfahan, the biggest province in central Iran, within the framework of IHHP.[25,26] IHHP is a comprehensive integrated community-based intervention program targeted toward prevention of CVD risk factors and heart diseases was conducted in 4 phases started from 2001. Tree cities (Isfahan, Najafabad and Arak), all located in central Iran, were contained in the study. Five independent cross-sectional surveys, in 2002, 2003, 2004, 2005 and 2007, were performed in three areas at the same time, addressing mainly the community knowledge, attitude and practice of CVD risk factors. In a multistage cluster sampling method, individuals aged ≥ 19 years were randomly selected. Inclusion criteria were as aged 19 years and over and Iranian citizenship that at least 6-month residence in the area of the study. Exclusion criteria were as pregnant, prior history of mental disorders, mental retardation and physical disability. Written informed consent was obtained from individuals, prior to participating in the study. The Ethics Committee of the Isfahan University of Medical Sciences approved the IHHP study. More details about IHHP study design, sampling strategy and studied variables can be found elsewhere.[24,25]

In current study, the data obtained from Isfahan in 2004, 2005 and 2007 were used. The studied sample sizes for Isfahan were 3014, 3012, and 4719 in those three sections (2004, 2005 and 2007), respectively. Despite the studied samples in this study were independent, however considering the IHHP as the community-based intervention program, we considered them as the same sample that their levels of knowledge sequentially were evaluated over the study periods.

To assess the knowledge of CVD risk factors, a questionnaire consisted of 8 questions regarding "knowledge of people about well-known risk factors of CVD" was used. Respondents were asked to indicate which one of the following items is a risk factor for CVD "high blood pressure", "nutrition", "physical inactivity", "smoking", "diabetes", "heredity", "stress", and "obesity". The response categories for the questions were as "correct", "wrong", and "I don't know". Each question was assigned a score of 0 for wrong answer (individual marked "I don't know" or marked "wrong" options) and 1 for correct answer (individual marked "correct"). Our questionnaire was structured according to well-known CVD risk factors identified by American Heart Association and content validity of questionnaire items was examined by the clinical experts via peer reviewing.[13]

Other studied variables in the current study that played the role of potential determinants of status of participants in terms of knowledge levels were as gender, age, education [three categories i.e. not-educated, less than diploma or diploma (12 years formal education) and university graduated], marital status (married and single), and socioeconomic status (SES). SES was considered as a latent variable, and was constructed using latent class analysis techniques,[26] with two classes (high or low SES) based on four indicator variables i.e.

ownership of a house, car, personal computer, and health insurance support. Membership in each constructed class showed the status of SES.

To analyse the level of "knowledge" about the CVD risk factors and changes over time as well as its determinants, LTA was used. LTA is a version of atent class analysis (LCA) used in longitudinal data to model transitions in latent class membership over time. LTA enables the investigator to address an additional set of questions about changes between latent classes across time, how can this change be characterized, the probability that the individual will remain in the same latent class at time t + 1, and the probability that the individual will be in a different latent class at the next time.

As an application of LTA, in this study, the overall knowledge about the risk factors of CVD as the categorical latent class variable was constructed based on multiple dichotomous observed indicators including being aware of high blood pressure, diabetes, obesity, physical inactivity, heredity, stress, smoking, and nutrition. LTA with covariate approach was used to determine the impact of potential determinants including age, gender, education level, marital status and socioeconomic status on knowledge level. All descriptive and analytical analyses in the present study were performed in R free statistical software, version 3.1.3 (R Foundation for Statistical Computing, Stanford University, CA, USA).

Results

Sociodemographic characteristics

Respondents in this study included 3014 people in first, 3012 in second, and 4719 in the third stage, aged 19 years or more. The average age of participants was 42.40 (± 0.31) years. Slightly more than half of the respondents (50.6-51.7 percent) were women and the rest (48.2-49.3 percent) were men. The majority of the respondents [77.0 percent (75.9-78.1)] were married. Most of the people included in the study [85.1 percent (80.2-90.4)] had diploma or less than 12 years of formal education and 32.0 percent (19.0-39.0) of individuals were in high socioeconomic status (according to results of latent class analysis).

Knowledge about the specific CVD risk factors

Table 1 shows the prevalence of correct answers to the questions about CVD risk factors in study sample. Among the 8 risk factors, the most widely known factors were nutrition and physical activity, followed by stress, blood pressure and obesity. In contrast, the knowledge about diabetes was low compared to other risk factors. Factors, such as heredity and smoking ranked between the high and low fractions. On average, the level of correct knowledge in both genders was comparable, and prevalence of correct answers increased across time.

Evaluation of the overall knowledge level about the CVD risk factors and its determinants

To analyse the overall level of knowledge about the CVD risk factors and its determinants, using LTA, we constructed latent statuses of the respondents based on knowledge about each of the8 dichotomous variables as having knowledge or lack of knowledge and evaluated transitions between statuses across the considered study periods. We first fitted a LTA model without covariates, with different number of statuses (2-5 statuses) to find the appropriate number of statuses to have the best fit and the most interpretability of the results. Accordingly, a model with three latent statuses

Table 1. Prevalence (%) of correct knowledge about the cardiovascular diseases (CVD) risk factors*

Risk factor	Time 1 (2004)				Time 2 (2005)				Time 3 (2007)			
	Women	Men	Total	95%CI	Women	Men	Total	95%CI	Women	Men	Total	95%CI
Blood pressure	71	66	68	67-70	70	71	70	69-72	82	80	81	80-82
Diabetes	39	36	38	36-39	35	35	35	34-37	40	39	39	38-41
Nutrition	83	82	83	81-84	79	80	80	78-81	89	88	89	88-90
Physical inactivity	82	81	82	80-83	81	81	81	80-82	88	89	89	88-90
Smoking	44	45	44	42-46	48	52	50	48-52	52	56	54	53-56
Heredity	50	46	48	46-50	56	52	54	52-56	71	68	70	68-71
Obesity	62	72	67	65-69	66	65	65	64-67	60	66	62	60-63
Stress	78	71	74	73-76	78	74	76	75-78	87	88	88	87-88

* The amounts are percentages of correct answers (knowledge).
95%CI: 95% confidence interval

Table 2. Item-correct response probabilities

Risk factor	Time 1 (2004)			Time 2 (2005)			Time 3 (2007)		
	Status 1	Status 2	Status 3	Status 1	Status 2	Status 3	Status 1	Status 2	Status 3
Blood pressure	0.0439	0.4895	0.9460	0.3265	0.6159	0.9064	0.3349	0.5433	0.9790
Diabetes	0.7499	0.2576	0.7409	0.8403	0.3216	0.7577	0.8947	0.5501	0.5649
Nutrition	0.9469	0.2883	0.9168	0.9114	0.4646	0.9195	0.9360	0.3457	0.9621
Physical inactivity	0.9469	0.2586	0.9081	0.9025	0.4590	0.9364	0.9597	0.4212	0.9581
Smoking	0.1244	0.2568	0.5914	0.0570	0.3609	0.7622	0.2071	0.3742	0.6860
Heredity	0.1891	0.2423	0.4697	0.0715	0.3288	0.5088	0.1385	0.3029	0.4729
Obesity	0.3543	0.1969	0.5884	0.7220	0.3254	0.5895	0.7492	0.3410	0.7128
Stress	0.6304	0.3131	0.8864	0.8659	0.4086	0.8923	0.9437	0.6257	0.9014
Latent status prevalence	0.21	0.15	0.63	0.22	0.27	0.52	0.17	0.11	0.71

was chosen (Log-likelihood:-44755.89, G-squared: 27889.69, AIC: 28061.69, BIC: 28617.19, and Degrees of freedom: 16777129).

Then, covariates were entered into the model. Table 2 shows the prevalence of correct answers to the questions on CVD risk factors in constructed statuses at each three evaluation times. Each status can be interpreted in terms of level of knowledge about the CVD risk factors. According to prevalence of correct responses reported in table 2, over the all study periods, status 3 can be considered as the high knowledge levels class; because as can be seen, this status included higher percentages of correct answers about all studied items in comparison with other statuses; while, status 2 can be considered as the class of people with poor knowledge levels about the majority of the studied risk factors. Status 1 is the class of persons who were knowledgeable about some special risk factors such as nutrition, physical activity, diabetes and stress.

In the lower part of table 2, the prevalence of latent status membership is shown. It can be seen that the prevalence of status 3 across all times are more than other statuses; it means that the most of individuals in this study had a high level of knowledge about CVD risk factors.

Changes in knowledge level about the CVD risk factors and its determinants

Table 3 shows the transition probabilities across the study periods. From time 1 to 2, two transition probabilities showed minor differences, while marked difference was observed from time 2 to the third stage in which it is more likely to transition into higher levels of knowledge class. According to transition probabilities, it can be inferred that the individuals' knowledge levels about risk factors of CVD have been increased across time.

Table 3. Latent transition probabilities

Probability of transitioning to…		…time 2 latent status		
		Status 1	Status 2	Status 3
Conditional on time 1 latent status	Status 1	0.2060	0.2751	0.5189
	Status 2	0.2295	0.3363	0.4342
	Status 3	0.2144	0.2490	0.5366
Probability of transitioning to…		**…time 3 latent status**		
		Status 1	**Status 2**	**Status 3**
Conditional on time 2 latent status	Status 1	0.1477	0.1179	0.7344
	Status 2	0.1678	0.1165	0.7157
	Status 3	0.1778	0.1099	0.7124

Table 4 shows the regression coefficients, odds ratios of covariates and their significant levels. Considering latent status 3 as the reference response category, it can be seen that the men (OR = 1.49), single individuals (OR = 1.91), individuals with low levels of SES (OR = 2.49), older people (OR = 1.02), and less-educated people (OR = 1.22 and 1.26), were more likely for being in lower levels of knowledge (i.e. being in latent status 2 and latent status 1).

Discussion

In this study, we assessed the level of knowledge about the CVD risk factors and its transitions across time and evaluated its association with some potential determinants in a general population of Isfahan and suburbs, using an advanced statistical analysis method i.e. LTA. Among the 8 risk factors, the most widely known CVD risk factors were nutrition and physical inactivity. The American Heart Association has recently focused on lack of physical activity as a major modifiable risk factor for heart disease.[27]

Table 4. Estimations of the covariates coefficient (factors associated with knowledge level) reflecting their impact on latent status of membership in time 1

Risk factor	B		Odd's ratio (OR)		P
	Status 1	Status 2	Status 1	Status 2	
Age	-0.0013	0.0246	0.9987	1.0249	0.000002
Sex (Reference: Women)	0.4928	0.4013	1.6369	1.4937	0.000043
Education (Reference: university graduation)					0.001597
Less than diploma or diploma (12-year formal education)	0.55535	0.1554	1.7393	1.1681	0.041221
Not educated	0.8416	0.2372	2.3201	1.2676	
Marital status (Reference: Married)	0.3897	0.6518	1.4766	1.9190	0.000198
Socio-economic status (Reference: high level)	0.8076	0.9163	2.2425	2.4999	< 0.000001

The next known risk factor in our study was stress. The relatively higher knowledge about stress as CVD risk factor in our society can be attributed, in part, to the increasing prevalence of stress.[27]

However, as can be seen from tables 1 and 2, the current study showed poor knowledge about some key risk factors of CVD such as diabetes, heredity and smoking among the studied population. In addition, for some other important risk factors such as high blood pressure and obesity the knowledge levels were moderate i.e. slightly more than 60% of study sample could correctly identify them as a CVD risk factor.

The lowest level of knowledge in our study was observed about diabetes. According to assessment of the American Heart Association about CVD risk factors, women with diabetes are classified as at high risk of developing CVD and in men, diabetes is correlated with a twofold to threefold increase in heart disease.[27]. This finding emphasizes the conducting community-based public educational programs on the raising knowledge and management of diabetes in order to prevent CVD.

About blood pressure, smoking and obesity, however our findings showed low levels of knowledge of majority of these pathogenic risk factors of CVD, that it can be linked to low rates of blood pressure and obesity control among the studied population.[28] These findings provide an implicit knowledge-based objective framework through implementation of effective public education programs in order to diminish CVD modifiable risk factors using change and modification in lifestyle.

To determine the predictors of status membership in terms of knowledge levels at the first stage of study, LTA with covariate was conducted. Men were less likely than women participants to have high levels of CVD risk factor knowledge, independent of education level. Besides, as it was anticipated, in the current study, we found that more-educated participants had higher knowledge about CVD risk factor than less-educated ones. The observed gender and educational attainment levels differences in terms of knowledge about CVD risk factors can be associated with more contributing in the prevention actions or getting more information in women and higher educated people. Therefore, considering these findings, substantial gap remains in prevention programs assessing specific cardiovascular knowledge in men and less educated people and preventive action taken.

Considering that the incidence of CVD increases rapidly with age, the knowledge disparity among elderly people needs to be addressed in programs aimed at helping them to recognize and take enhancement treatment-seeking action through simple and effective guidelines. Our study showed that lower levels of SES are positively associated with a lower CVD risk factors knowledge.

Conclusion

The findings of this survey, based on a reliable and comprehensive statistical modelling approach specified to evaluating the changes across time in knowledge levels, demonstrated that although the public knowledge of CVD risk factors relatively improved in the Isfahan region between 2004 and 2007; however, knowledge about some important risk factors such as smoking, diabetes, heredity and obesity remained relatively constant. Although, public knowledge of CVD risk factors has increased, that partly can be attributed to the impacts of IHHP public intervention education programs, but

significant gaps continue to exist, with lack of knowledge most apparent regarding key risk factors particularly among the elderly, men, less-educated and low-SES people. Future intensified educational efforts are necessary to promote knowledge of CVD, particularly among high-risk groups, by policymakers, as well as local and national organizations.

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Conflict of Interests

Authors have no conflict of interests.

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Multiple right coronary artery fistulas to coronary sinus: A case report and literature review

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Case Report

Abstract

BACKGROUND: Coronary arteriovenous fistula is a rare congenital or acquired abnormal connection between a coronary artery and any of the great vessels or any of the heart chambers. Most of them are diagnosed during routine coronary angiography.

CASE REPORT: This case report illustrates a successful surgical ligating of multiple right coronary artery and circumflex artery fistulas to coronary sinus.

CONCLUSION: According to our experience and literature review, it can be concluded that to prevent potential complications in various cases of coronary arteriovenous fistula, early surgical management, just after their condition has been diagnosed, is the best choice.

Keywords: Coronary Arteriovenous Fistula, Right Coronary Artery, Dilated Coronary Sinus

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Introduction

Coronary arteriovenous fistula (AVF) is an uncommon malformation.[1,2] Most fistulas are single communications, but multiple fistulas have been identified too. It has variable presentations, such as asymptomatic, acute onset or chronic progression of symptoms.[3] Most of the times patients do not have any significant signs and symptoms and are diagnosed during routine coronary angiography. The potential complications of coronary fistula include congestive heart failure, thrombosis, myocardial infarction and even sudden death.[4] Spontaneous closure is rare.[1]

Symptomatic patients or those with severe shunts may be treated with surgical closure, although percutaneous closure with coil embolization may also be tried.[3] This case report illustrates a successful surgical ligation of multiple right coronary artery and circumflex artery fistulas to coronary sinus.

Case Report

Our patient was a 42 year old man. He has been found to have a machinery murmur at the left lower sternal border during routine checkup by his family physician. The patient had experienced chest discomfort and dyspnea on exertion which was precipitated over the last two years. Laboratory tests were normal.

A mild right-heart border expansion was seen on chest x-ray. Electrocardiography was normal. Computed tomography angiographies showed dilated left circumflex and right coronary arteries and tortuosity in a whole course that was fistulized to the posterior and inferior aspects of coronary sinus respectively. Right coronary artery (dominant artery) was fistulized to inferior aspect of coronary sinus via posterior left ventricular (PLV) branch and coronary sinus, mid cardiac and greater cardiac veins were dilated. Left ventricular hypertrophy was noted and mild pericardial effusion was present. Left heart catheterization and selective coronary angiography showed large AVF from circumflex to coronary sinus and huge right coronary artery. The ejection fraction was 50%. Surgery was performed under cardiopulmonary bypass with separate bicaval cannulation. On direct observation, a large, dilated, tortuous right coronary artery on the surface of the heart was seen (Figures 1-3) which was draining to a dilated coronary sinus. Long time presence of multiple right coronary artery and circumflex artery fistulas to coronary sinus has led to severe dilatation of the coronary sinus (Figures 4 and 5).

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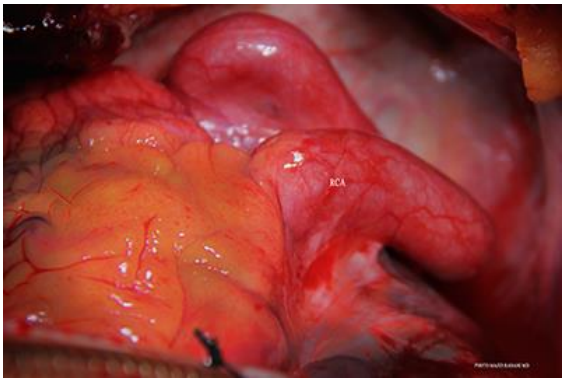

Figure 1. Large dilated right coronary artery due to congenital fistula to coronary sinuses

After the right coronary artery was opened, coronary sinus was unroofed and had a severely stenotic ostium. Two fistulas communications were ligated. The postoperative course was uneventful. Right after the surgery, the continuous murmur at the left sternal border could not be heard anymore.

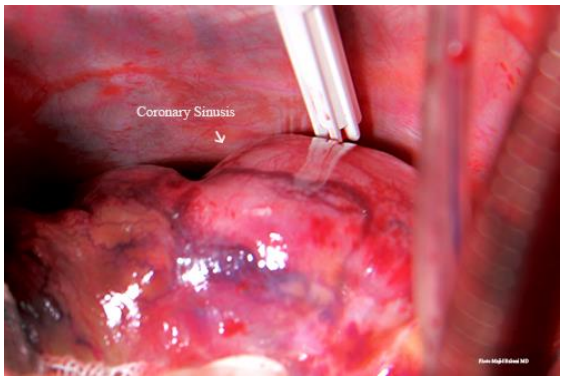

Figure 2. Large dilated right coronary artery due to congenital fistula to coronary sinuses

In follow-up visits 1 week and 1 month after the surgery, the patient's condition improved gradually so that in the second visit, he felt good and did not experience dyspnea on exertion anymore.

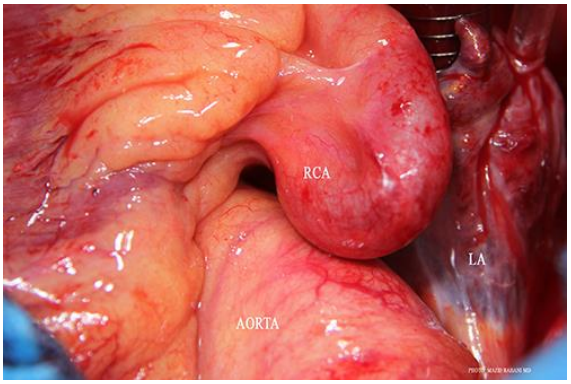

Figure 3. Large dilated right coronary artery due to congenital fistula to coronary sinuses

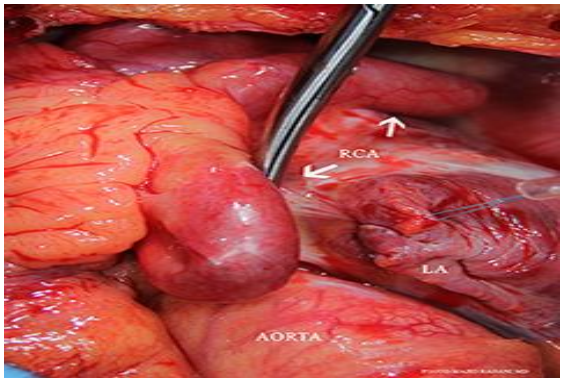

Figure 4. Coronary sinuses

Discussion

Coronary arteriovenous fistulas were first described by Krause in 1865.[5,6] These are rare congenital or acquired abnormal connections between a coronary artery and any of the great vessels or heart chambers that can bypass the myocardial circulation.[7,8] Most of coronary AVFs are diagnosed at routine coronary angiography.[4] The incidence of AVF in patients undergoing diagnostic cardiac catheterization has been reported to be 0.1%. Although both left and right coronary arteries are common origins, the right coronary artery involvement is more often (50%-55%).[6] Actually the right coronary artery is the most common origin and right ventricle is the most common distal connection site. Drainage to the coronary sinus has been found in seven percent of surgical cases. Multiple coronary artery fistulas have been found in five percent of patients.[7]

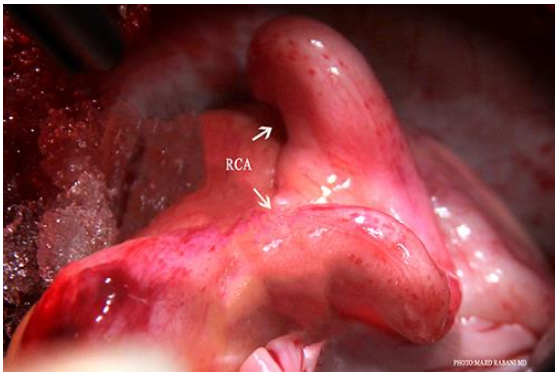

Figure 5. Large dilated right coronary artery due to congenital fistula to coronary sinuses

The course of this malformation is usually benign but significant complications can occur.[7] Clinical symptoms include angina, fatigue and dyspnea which are thought to be caused by a phenomenon known as coronary steal, where blood is drawn away from the distal coronary vasculature

by the fistulous connection.[8] Size of the fistula, degree of associated shunt and complications determine disease presentation. For example, the associated shunt can cause high output heart failure. Besides, arrhythmia, embolization, rupture, myocardial infarction, infective endocarditis, and sudden death are the other potential complications.[4,9] Because of these potential complications, timely intervention is indicated.[8] Direct ligation of the fistulous communication at the point of entry to the cardiac chamber is usually recommended. There is a 3.6% risk of postoperative myocardial infarction.[4] In this patient, a rare kind of multiple coronary AVFs was reported with an unroofed severely dilated coronary sinus that made it difficult to find the site of coronary sinus orifice.

El Watidy et al. reported a similar case of coronary AVFs in a patient which also developed mitral and tricuspid regurgitation due to longstanding left to right shunt with a 7-year interval between the diagnosis and the corrective surgery.[4] This time in our patient was around one year and there was no significant volume overload or mitral and tricuspid valves regurgitation. According to our experience and literature review, it can be concluded that to prevent potential complications in various cases of coronary AVFs, early surgical management, just after the condition has been diagnosed is the best choice.[4,7]

Acknowledgments

We would like to use this opportunity to show our gratitude to the staff of the Cardiac Surgery Unit and Intensive Care Unit of the Sina Hospital, Isfahan, Iran.

Conflict of Interests

Authors have no conflict of interests.

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Effect of intravenous midazolam on cardiac parameters in acute tricyclic antidepressants poisoning

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Short Communication

Abstract

BACKGROUND: Midazolam is commonly and safely used in poisoning management and intensive care for the control of agitated poisoned patients. Despite the introduction of newer and safer antidepressants, tricyclic antidepressants (TCAs) are still prescribed and used in many countries due to their cost-effectiveness. Severe morbidity and mortality associated with these drugs arises largely from their well-documented cardiovascular toxicity. In this study we aimed to investigate the probable effect of midazolam on some hemodynamic indices in TCAs-poisoned patients.

METHODS: In this clinical trial, we have evaluated some cardiovascular and hemodynamic indices of 100 TCAs-poisoned patients whom were randomly allocated for receiving midazolam with a first loading dose of 0.1 mg/kg (2 mg/minute) followed by a 6-hour maintenance infusion of 0.1 mg/kg/h of the drug in dextrose-saline (3.33% of dextrose and 0.33% of NaCl) or placebo (dextrose-saline infusion without midazolam). Pulse rate, systolic/diastolic blood pressure, respiratory rate, neurologic status and the outcome of therapy for all patients were recorded at the time of admission and hourly for the next 6 hours.

RESULTS: There was a statistically significant reduction in the heart rate of the midazolam treated group after the first hour of hospital admission. There were no significant differences in the respiratory rate, central nervous system manifestations and other indices between the two groups.

CONCLUSION: Midazolam may reduce tachycardia (and its fatal consequences) in the first hour of admission in TCAs-poisoned patients.

Keywords: Midazolam, Tricyclic antidepressants (TCAs) Poisoning, Tachycardia

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Introduction

Tricyclic antidepressants (TCAs) are still prescribed worldwide for some psychiatric conditions especially depressive disorders in spite of their serious side effects.[1] Despite the introduction of newer and safer antidepressants (e.g. selective serotonin reuptake inhibitors), TCAs are now used in many countries due to their cost-effectiveness.[2] Even though of this obvious benefit of lower price for TCAs treatments, they are still considered as an important cause of death in poisoning emergency wards and nearly most of TCAs-poisoned cases need intensive care support and intensive care unit (ICU) admission.[3,4] According to the National Poison Data System annual report of the American Association of Poison Control Centers, antidepressants were the eighth and seventh leading cause of toxic exposures in 2007 and 2008, respectively.[5]

In an analysis of deaths due to acute poisoning 20% were antidepressant-related, of which 95% were associated with TCAs.[6,7] TCA overdose is known to cause anticholinergic, cardiopulmonary and central nervous system (CNS) complications. Severe morbidity and mortality associated with these drugs arises largely from their well-documented cardiovascular toxicity.[7,8] In addition, the worldwide expansion in the use of benzodiazepines (BDZs) has led to their frequent and often inappropriate use, including an increase in their involvement in self-induced poisoning. Previous studies have also demonstrated the effect of benzodiazepines in the management of seizure.[9-11]

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In Iran more than one third of all emergency room admissions for drug intoxication are reported to be due to TCAs (especially amitriptyline and nortriptyline) which makes this type of poisoning as the second leading cause of death due to drug overdose in many Iranian hospitals.[12-14] Overdose with TCAs is also one of the most common causes of admission to our Poisoning Emergency Department in Isfahan, Iran.[15,16] In a study, which was performed in our poisoning department, it was revealed that signs of cardio toxicity were significantly less in patients who had ingested TCA and benzodiazepine.[11]

Fatality due to TCA poisoning is highly related to the refractory hypotension and hemodynamic changes.[17-20] High accessibility (in some cases even without providing a valid prescription to the pharmacies), the nature of disease in patients with major depression whom are not reluctant to suicide, the narrow therapeutic window of these drugs, seriousness and severity of the cardiovascular and neurologic consequences after TCA overdoses and finally the limitations for specific supportive therapies (e.g. in cases of refractory hypotension and seizures) are all considered to contribute for the occurrence and poor management of this type of intoxication.[21]

Midazolam is a relatively safe benzodiazepine which is widely used for anesthesia, sedation in mechanically ventilated patients, agitated critically ill patients and refractory status epilepticus patients.[22] Hemodynamic effects of this drug in human is discussed elsewhere.[23] In our referral poisoning and drug overdose emergency ward, we have noted that TCA overdosed patients who received midazolam for other reasons seem to have lower mortality rate and their hemodynamic indices were more near stable. To clarify the answer to this research question, and with taking to consideration that cardio toxicity is one of the common causes of death in TCA poisoning, we aimed to evaluate the effects of intravenous midazolam on the electrophysiological and hemodynamic indices in acute TCA-poisoned patients.

Materials and Methods

This clinical trial was done in 2011-2012 in Isfahan. Isfahan is the second largest city in Iran and is located in the center of Iranian plateau. This industrial city has a population of near two million. Poisoning emergency department of Noor and Ali Asghar (PBUH) University hospital is the main referral center for the central part of Iran and poisoned patients from at least 5 Iranian central provinces (including Isfahan) are referred there for poison management and supportive therapy.

The study protocol was approved by the Research Council and the Institutional Board of Ethics for Human Research of the Isfahan University of Medical Sciences. Informed consent was obtained from all study subjects (if conscious and oriented) or legally eligible companion after explaining the purpose of the study, the potential use of the collected information, and procedures. If the consent was signed by the legally eligible companion, the patient was also informed completely as soon as medically possible. For individuals who were unable to read, the informed consent was read aloud and then written consent was requested.

The study population was all poisoned patients with an evident and reliable history of TCA poisoning, whom were randomly selected by simple random sampling method from patients referred to the Noor and Ali Asghar University hospital. Eligible patients for the studies were symptomatic patients with TCA poisoning during the first 6 hours after oral drug intake whom were admitted with a documented tachycardia. TCA-poisoned patients who had received sodium bicarbonate before hospitalization, or patients who had ingested any drugs that affected entry criteria and patients who were transferred to other hospitals before completing and patients who were discharged with their own consent were excluded.

To detect at least 10% reduction in the heart rate of patients between the current standard therapy and midazolam treated group, assuming presence of tachycardia in 70% of the TCA-poisoned patients at the time of admission with an 80% power and a 5% type I error, 45 subjects were needed in each group (90 for both arms). To compensate for anticipated losses to follow-up, we inflated the sample size by 10%. Hence, the final sample size, rounded to the nearest 10 was 100 individuals with 50 individuals in each arm. Power analysis and sample size software (PASS 12, Jerry Hintze, Kayeville Utah) was used to calculate the required sample size.

Using random numbers table and patient's file number, all eligible patients were allocated randomly to two groups: cases whom received midazolam as an add-on to their normal routine medical care, and controls whom received normal supportive care without midazolam administration. Patients were matched in both groups in terms of age, gender, type of poisoning (accidental, intentional) and the route of access to TCA.

Routine supportive care according to the institutional protocol [including initial steps of basic life support e.g. airway, breathing, circulation

(ABC), administration of sodium bicarbonate] were done for all patients in both groups. Cases received a first loading dose of 0.1 mg/kg (2 mg/minute) of intravenous midazolam followed by a 6-hours maintenance infusion of 0.1 mg/kg/h of the drug in dextrose-saline (3.33% of dextrose and 0.33% of NaCl). Patients in control group received all routine supportive and specific therapies for TCA poisoning and also a 6-hours infusion of dextrose-saline (3.33% of dextrose and 0.33% of NaCl) without midazolam.

After obtaining informed consent and the questionnaires, basic demographic information and vital signs were recorded. All routine laboratory tests (complete blood count, serum creatinine, blood urea nitrogen, arterial blood gas, liver function tests, blood glucose and serum electrolytes) were performed for both groups as per our institutional protocol for supportive therapy of TCA-poisoned patients.

All data were collected by certified health care professionals and a medical toxicologist attending physician (NEM) supervised all clinical and medical processes of the study. Nurses were trained for clear and precise reporting of possible side effects of midazolam and its probable adverse drug reactions before the start of the study.

Descriptive data analysis was done on baseline characteristics of the study patients. For continuous variables mean and standard deviation (SD) were calculated and histograms were plotted to assess the distribution of the variables. Kolmogorov-Smirnov test was performed for evaluating the normal distribution of the continuous variables. Descriptive statistics were computed for midazolam and placebo infusion therapy groups separately. Mean values of continuous variables were compared between the two groups (cases and controls) by independent Student's t-test. Pearson's chi-square test was used for comparing the proportions. Categorical variables that had a cell count less than five, were analyzed using Fisher's exact test. All P values were based on two-sided tests and the significance was set at a P-value of less than 0.05. Statistical analyses were done using the SPSS software for Windows (version 13.0, SPSS Inc., Chicago, IL, USA).

Results

During the 20 months of the study period, 124 patients were recruited to the both arms of the study (50 cases, 50 controls) and 24 of them left the study either by their personal consent or incomplete data as per study protocol. A full set of 100 patients finished the study completely. An overview of the demographic and overall features of the study population (n = 100) revealed that in age, gender, mode of poisoning, marital status, and job career categories there was not any statistically significant difference between cases and controls (Table 1).

Table 1. Demographic characteristics of the study patients in midazolam treated (cases) and placebo (controls) groups

Characteristic	Cases [Midazolam, (n = 50)]	Controls [Placebo, (n = 50)]	P
Age (Year) [Mean ± SD]	29.1 ± 5.1	27.3 ± 6.2	0.120*
Gender			
Male	26 (52)	24 (48)	0.670**
Female	24 (48)	26 (52)	
Type of poisoning			
Suicide	6 (12)	2 (4)	0.430***
Accidental	44 (88)	48 (96)	
Route of access to TCAs			
Personal	34 (68)	37 (74)	0.003***
Family	9 (18)	0 (0)	
Accidental	7 (14)	13 (26)	
History of depression			
Positive	28 (56)	38 (76)	0.040**
Negative	22 (44)	12 (24)	

* Independent Student's t-test; ** Chi-squared test; *** Fisher exact test
SD: Standard deviation; TCAs: Tricyclic antidepressants

Table 2. Comparison of the mean difference (**Δ**) of the hourly vital signs of patients in the first hour until the sixth in midazolam treated (cases) and placebo (controls) groups (mean ± SD)

Variable		Time interval of statistical comparison (from n1 to n2 hours after admission)				
		$n_1 = 1^{st}$, $n_2 = 2^{nd}$ hour	$n_1 = 1^{st}$, $n_2 = 3^{rd}$ hour	$n_1 = 1^{st}$, $n_2 = 4^{th}$ hour	$n_1 = 1^{st}$, $n_2 = 5^{th}$ hour	$n_1 = 1^{st}$, $n_2 = 6^{th}$ hour
Δ Pulse rate	Controls	12.0 ± 1.9	17.0 ± 2.1	19.7 ± 2.1	17.7 ± 2.7	19.3 ± 2.7
	Cases	15.3 ± 2.6	16.7 ± 2.0	18.0 ± 2.0	20.6 ± 2.6	19.1 ± 2.8
	P†	0.03	0.08	0.79	0.33	0.31
Δ Systolic blood pressure	Controls	-3.7 ± 2.2	-2.9 ± 2.8	-1.5 ± 3.2	-3.7 ± 3.6	-1.9 ± 3.7
	Cases	2.1 ± 2.7	2.4 ± 2.4	1.7 ± 2.7	0.8 ± 2.6	3.6 ± 2.5
	P†	0.79	0.28	0.33	0.30	0.17
Δ Diastolic blood pressure	Controls	-4.1 ± 2.1	-6.7 ± 3.5	-2.1 ± 4.7	-0.2 ± 5.0	-0.4 ± 3.9
	Cases	0.1 ± 3.1	3.8 ± 3.0	2.5 ± 2.9	2.5 ± 3.0	2.2 ± 3.4
	P†	0.17	0.37	0.44	0.60	0.64
Δ Respiratory rate	Controls	-0.3 ± 0.5	-0.8 ± 0.5	-0.9 ± 0.3	-0.9 ± 0.8	-0.6 ± 0.8
	Cases	-0.1 ± 0.4	-0.1 ± 0.5	-0.7 ± 0.6	-0.5 ± 0.6	-0.6 ± 0.7
	P†	0.63	0.22	0.80	0.66	0.96

† Independent student's t-test
SD: Standard deviation

Comparison of the results of the frequency distribution of the main cardiovascular symptoms caused by tricyclic antidepressants poisoning demonstrated that no significant difference was observed between cases and controls in terms of blood pressure on admission (P = 0.11) and 6 hours later (P = 0.69), R/avR more than or equal to 3 mm in the beginning (P = 0.08) and 6 hours later (P = 0.98), prolonged QTc (greater than 0.44) on admission (P = 0.11) and 6 hours later (P = 0.75) (Table 2).

On the other hand, we found a statistically significant difference of the admission time QRS complex width between the two groups (P = 0.003) but after 6 hours this variable was not statistically significant between the cases and controls (P = 0.78).

Hourly evaluation of the results of vital signs in two groups from the time of admission for the next 6 hours revealed no statistical significance between cases and controls groups for the mean heart rate (P = 0.19), systolic blood pressure (P = 0.82), diastolic blood pressure (P = 0.42) in the first hour and every hour until the sixth hours. The mean respiratory rate at the time of arrival in control group was significantly different from the cases (P = 0.003) but both were in the normal range.

Comparison of mean vital signs of patients in the first hour until the sixth hour in two groups showed significant difference in pulse rate in first hours of admission (Table 2).

The comparison of the frequency distribution of the central nervous system symptoms showed that at the time of admission, no significant difference was observed in terms of the level of consciousness (P = 0.21), occurrence of seizure (P = 0.49) and agitation (P = 0.09) between the two groups.

Discussion

The purpose of this study was to evaluate the effects of intravenous midazolam on electrophysiological and hemodynamic indices in acute TCAs-poisoned patients.

We found a statistically significant reduced heart rate in the midazolam treated group (cases) compared with the control group within the first hours of admission. Fortunately, there were no significant differences in the respiratory rate and central nervous system manifestations between two groups, thus we think that benzodiazepines, such as midazolam may reduce the tachycardia and its fatal consequences in the first hour of admission in TCAs-poisoned cases.

Mechanism of the benzodiazepine such as midazolam on TCA-induced tachycardia is not clear yet. Some possible explanations might be central suppression of the release of cathecholamines or a direct effect on the benzodiazepine receptors on heart.[24]

We also have not found any statistically significant difference in the heart rate of the two groups at other times which could be related to the extent of drug metabolism in both groups, reduction in plasma levels and effects of midazolam,

and most importantly maybe due to our drug administration protocol for the patients. For example in cocaine poisoning, midazolam was infused 1 to 2 mg every 3 to 5 minutes (to control hypertension and tachycardia) until the patient became asymptomatic,[25] while in our study we used midazolam with a bolus dose of 0.1 mg/kg and also the infusion rate was very low.

As a limitation for our results and discussion, we think that our findings should be considered with caution because the results of measurements in different times after admission were analyzed pair-wise and due to some limitations for meeting the assumptions, we did not perform repeated measure test.[26]

Conclusion

Midazolam may have a positive role in preventing tachycardia in TCA-poisoned patients which can prevent the consequences of tachyarrhythmia and its complications in the poisoned patients.

We recommend further study with higher and more frequent doses of midazolam for these patients in future.

Acknowledgments

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Conflict of Interests

Authors have no conflict of interests.

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Prevalence of non-alcoholic fatty liver disease in patients with coronary artery disease

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Short Communication

Abstract

BACKGROUND: Several common metabolic risk factors contribute to development of both non-alcoholic fatty liver disease (NAFLD) and coronary artery disease (CAD). The aim was to determine prevalence of NAFLD in patients with CAD.

METHODS: This prospective study was carried out from December 2011 to June 2012. All patients with documented diagnosis of CAD with stenosis of one of the main coronary arteries or their branches were included in the study. Ultrasound examination of liver was performed in all patients to diagnose hepatic steatosis. Accordingly, the severity of steatosis was graded from 0 (absence of steatosis) to 3 (severe steatosis). Finally, prevalence of NAFLD was determined in the studied patients.

RESULTS: Among 170 patients with CAD included in the study, 63 and 17 had grade 1 and 2 hepatic steatosis in ultrasound examination, respectively, providing prevalence of 47% in studied population. There was no significant difference between patients with NAFLD and those without NAFLD regarding gender (P = 0.120), presence of diabetes mellitus (P = 0.270), hyperlipidemia (P = 0.210) and hypertension (P = 0.870). There was no association between involvement of left anterior descending artery and hepatic steatosis (P = 0.870).

CONCLUSION: The present study indicated a high prevalence of NAFLD in patients with documented CAD.

Keywords: Non-Alcoholic Fatty Liver Disease, Coronary Artery Disease, Ultrasound

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by triglyceride deposition in the liver exceeding 5% of the total liver weight in the absence of a history of heavy alcohol intake and other etiologies of liver disease.[1] Based on a report from Tehran, capital of Iran, steatosis was found in 31.6% (283 out of 896) of liver samples obtained during autopsy, which was the most common silent liver disease in the study sample.[2] In a school-based study on 966 school-aged children in Iran, NAFLD was detected in 7.1% of children.[3] In addition, in a recent population-based study conducted on 819 individuals in Shiraz, Iran, the prevalence of NAFLD was reported 21.5%.[4]

NAFLD is closely associated with metabolic syndrome and insulin resistance[5] which some of them contribute to development of coronary artery disease (CAD).[6] Thus, it was hypothesized that NAFLD correlates with CAD, which is one of the major causes of mortality worldwide.

Since CAD is usually symptomatic, finding significant relationship between CAD and NAFLD may indicate that patients who are diagnosed with CAD may benefit from screening for NAFLD to diagnose the disorder in early stages. Thus, the present study was designed and conducted to determine the prevalence of NAFLD in patients with CAD.

Materials and Methods

After approval of the Ethical Committee of Human Research of Lorestan University of Medical Sciences, Iran, this prospective study was conducted in Angiography Ward of Khorammabad Heart Center, Iran, from December 2011 to June 2012. All patients signed an informed consent before enrollment. Patients were selected among those

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underwent coronary artery angiography in Khorammabad Heart Center due to acute coronary syndrome, chest pain, or positive exercise test. Patients with or without any degree of stenosis in the coronary arteries or their branches in coronary angiography were included in the study, randomly. Patients with history of coronary artery bypass graft (CABG), excessive alcohol intake, any hepatic disorder, cor pulmonale, chronic renal disease, cancer, acute or chronic infections, positive serology for hepatitis B, C, human immunodeficiency virus (HIV) or syphilis, and heart failure were excluded from the study.

The Gensini scoring system was used to determine the severity of CAD.[7] In brief, the coronary artery tree was divided in 8 segments and in each segment the most severe stenosis scored based on the following classification: stenosis less than 25% was considered as score 0, 25%-49% scored 1, 50% to 74% scored 2, 75% to 99% scored 3, and 100% stenosis was considered as score 4. These score were then multiplied by a number indicating the importance of the lesion's location in the coronary artery tree. The number for the left main coronary artery was 5, for the proximal left anterior descending (LAD) or proximal left circumflex was 2.5, for the mid-part of the LAD was 1.5, and for the right coronary artery, distal LAD and mid-distal region of the left circumflex was 1.

Diagnosis of NAFLD was made based on the ultrasound findings. All ultrasound examinations were performed after 12 hours of fasting by one radiologist using the same device and criteria. Echogenicity of liver was compared to the echogenicity of the left kidney and using the following grading system: grade 0, no fatty liver; grade 1, mild disease; grade 2, moderate disease; and grade 3, severe disease. The method described by Saverymuttu et al.[8] was used to assess hepatic steatosis. The method works based on the abnormally intense, high level echoes from the hepatic parenchyma, liver–kidney difference in echo amplitude and echo penetration into the deep portion of the liver and clarity of vascular pattern of the liver.

Sample size was calculated based on the study by Acikel et al.[9] By considering the 38% frequency of fatty liver disease in patients with CAD, we determined 135 patients required to achieve an accuracy of 0.05 with a type I error of 0.05. However, we included 170 individuals in the study period.

Statistical analysis was performed utilizing the MedCalc software version 12.2.1.0 (Mariakerke, Belgium) and SPSS software for Windows (version 17.0, SPSS, Inc., Chicago, IL, USA). Fisher's exact test and Student's independent t-test were used to analyze categorical and continues variables respectively. P-values less than 0.05 were considered to be statistically significant.

Results

One hundred and seventy individuals including 93 females (54.7%) were enrolled in the study. Mean age of the patients was 58.1 ± 12.5 years. Mean body mass index (BMI) of the studied patients was 26.4 ranging from 19.2 to 42.2 kg/m^2. Table 1 demonstrates angiographic findings in studied patients.

Table 1. Angiographic findings of coronary artery in studied patients

Vessel stenosis / Coronary artery	25%-49% (Number)	50%-74% (Number)	75%-99% (Number)	100% (Number)
Proximal LAD	7	8	20	11
Mid-part LAD	11	15	24	3
Distal LAD	0	4	9	1
Diagonal arteries	2	8	21	3
Proximal left circumflex	3	7	8	3
Mid-part left circumflex	12	6	11	4
Distal left circumflex	2	3	3	0
Obtuse marginal	2	11	15	4
Proximal RCA	8	7	7	12
Mid-part RCA	12	10	8	5
Distal RCA	5	1	7	1
PDA	2	1	7	0
PLV	1	0	1	1

LAD: Left anterior descending; RCA: Right Coronary artery; PDA: Posterior descending artery; PLV: Posterior left ventricular branches

Table 2. Different study parameters in different degrees of non-alcoholic fatty liver disease

Characteristic	No NAFLD	Mild NAFLD (Grade 1)	Moderate NAFLD (Grade 2)	P
Gender				
Male	46 (59.7)	24 (32.1)	7 (9.1)	0.230
Female	43 (46.7)	39 (42.4)	10 (10.9)	
Age				
< 40 years	71 (55.9)	45 (35.4)	11 (8.7)	0.350
≥ 40 years	19 (44.2)	18 (41.9)	6 (14.0)	
Hypertension [n (%)]				
Yes	31 (51.7)	23 (38.3)	6 (10.0)	0.960
No	59 (53.6)	40 (36.4)	11 (10.0)	
Hyperlipidemia [n (%)]				
Yes	10 (41.7)	12 (50.0)	2 (8.3)	0.360
No	80 (54.8)	51 (34.9)	15 (10.3)	
BMI [n (%)]				
Normal	39 (63.9)	19 (31.1)	3 (4.9)	0.005*
Overweight	41 (50.6)	32 (39.6)	8 (9.9)	
Obesity	5 (21.7)	12 (52.2)	6 (26.1)	
CAD [n (%)]				
Yes	56 (50.9)	42 (38.2)	12 (10.9)	0.730
No	34 (56.7)	21 (35.0)	5 (8.3)	
Diabetes				
Yes	19 (44.2)	18 (41.9)	6 (14.0)	0.350
No	71 (55.9)	45 (35.4)	11 (8.7)	
Smoking				
Yes	27 (60.0)	15 (33.3)	3 (6.7)	0.470
No	63 (50.4)	48 (34.8)	14 (11.2)	

NAFLD: Non-alcoholic fatty liver disease; BMI: Body mass index; CAD: Coronary artery disease
* $P < 0.05$ significant

Forty-three patients (25.2%) were diabetic, 60 (35.2%) suffered from hypertension and 24 individuals (14.1%) mentioned hyperlipidemia as co-existing medical conditions. History of smoking was found in 45 patients (26.5%).

Sixty-three and 17 cases had grade 1 and 2 steatosis (NAFLD) in ultrasound examination respectively, providing prevalence of 47% (80 patients) NAFLD in studied population. Mean BMI was significantly higher in patients with fatty liver disease compared to those without (27.3 ± 4.4 kg/m^2 versus 25.6 ± 3.4 kg/m^2, $P = 0.005$). There were no significant differences between patients with NAFLD and those without NAFLD regarding gender ($P = 0.230$), age ($P = 0.350$), presence of diabetes mellitus ($P = 0.350$), hyperlipidemia ($P = 0.360$), hypertension ($P = 0.960$) and smoking ($P = 0.470$) (Table 2). There was no significant association between NAFLD and CAD in none of the coronary artery branches ($P = 0.730$). There was significant association only between NAFLD and BMI ($P = 0.005$). Multiple logistic regression model was used to remove confounding factors. Using this model, there was a significant association between NAFLD and CAD (odds ratio = 1.83; $P < 0.001$). The association between CAD and NAFLD changed to non-significant after adjustment for age, gender, hypertension, hyperlipidemia, BMI, diabetes and smoking ($P = 0.430$). There was only significant association between age and gender with CAD in regression analysis.

Discussion

The association between CAD and NAFLD has been investigated widely. Kim et al. enrolled 4023 subjects without known liver disease or a history of ischemic heart disease in their study.[10] They found that coronary artery calcification was associated with NAFLD independent of traditional risk factors for CAD including body visceral adiposity. They suggested that

NAFLD should be considered as an independent risk factor of CAD. In the present study, we found fatty liver disease in 47% of patients with CAD which is inconsistent with the aforementioned studies supporting a close association between NAFLD and CAD. In agreement with our study, Assy et al. demonstrated that 67% and 52% of patients with NAFLD had calcified and non-calcified coronary plaque respectively which was significantly higher than controls[11] and supports high prevalence of NAFLD in CAD patients and vice versa.

It seems that development of coronary artery atherosclerosis in patients with NAFLD is independent of traditional risk factors for CAD, though concomitant presence of these risk factors and metabolic syndrome components potentiates pathogenesis of NAFLD. There are also evidences indicating that NAFLD can cause endothelial dysfunction, elevate biomarkers of inflammation and result in subclinical atherosclerosis in carotid artery.[12,13] In the present study, we found that NAFLD developed more frequently in patients with higher BMI as has been previously reported.[1]

In the present study, we used ultrasound for detection of NAFLD that should be considered as one of the limitations of our study. The study by Foster et al. demonstrated that ultrasound can only detect 60% of patients with fatty infiltration of the liver.[14] The false positive rate was very low in this technique; however, the range of changes in cirrhosis and liver steatosis were similar and experience of the operator was the only tool to distinguish these two conditions.[14] Using liver-kidney contrast technique which was utilized in this study have been shown to improve the detection of fatty liver changes. Yajima et al. indicated that combination of liver-kidney contrast with vascular blurring and deep attenuation can be used for semi-quantitative assessment of liver steatosis.[15] When fatty change is over 30% in the hepatic lobule, using both liver-kidney contrast and vascular blurring will provide sensitivity of 83%, specificity of 100%, and an accuracy of 96% for diagnosis of fatty liver disease.[15] Similarly some other authors suggested that ultrasound can be used with good results for diagnosis of hepatic steatosis.[16] In brief, it is possible that prevalence of fatty liver disease in our study has been underestimated due to limitations of ultrasound in diagnosis of NAFLD.

Conclusion

Our findings indicated that NAFLD can be detected in high percentage of patients with documented CAD (47%) and BMI is significantly associated with NAFLD. The present study along with previous reports may indicate the importance of screening for NAFLD in patient with CAD and vice versa.

Acknowledgments

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Conflict of Interests

Authors have no conflict of interests.

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Efficacy and safety of Tornus catheter in percutaneous coronary intervention of hard or balloon-uncrossable chronic total occlusion

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Short Communication

Abstract

BACKGROUND: Balloon advancement and dilation through chronic total occlusion segment could be challenging in some cases after successful wire crossing. The purpose of this study was to evaluate efficacy and safety of Tornus catheter (Asahi Intecc; Aichi, Japan) in percutaneous coronary intervention of chronic total occlusion in hard or balloon-uncrossable chronic total occlusion.

METHODS: The present study is a retrospective and descriptive analysis of 14 hard or balloon-uncrossable chronic total occlusions treated percutaneously in our catheterization laboratory (cath lab). Tornus catheter was used to penetrate and eventually cross the chronic total occlusion segment. Procedure success was defined when Tornus penetrated at least partly into chronic total occlusion segment making possible the subsequent balloon dilatation and stent implantation achieving a final TIMI III angiographic result with residual stenosis less than 30%. Switch to other microcatheter was considered as an unsuccessful procedure. Complications associated with the Tornus use were analyzed in order to evaluate device safety.

RESULTS: The average age of patients was 65.2 ± 9.6 and 11 out of 14 (78.6%) were male. In 7 (50%) cases, Tornus was used after an unsuccessful balloon passage through occluded segment. In 11 (78.6%) out of 14 cases the procedure was successful and in 3 (21.4%) cases, the operator switched to another microcatheter to continue with the procedure. No complication occurred during all procedures.

CONCLUSION: Tornus catheter can be effectively and safely used in a subgroup of patients undergoing percutaneous coronary intervention of chronic total occlusion with hard or balloon-uncrossable lesions and could facilitate the treatment of this type of lesions.

Keywords: Percutaneous Coronary Intervention, Chronic Total Occlusion, Catheter

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Introduction

Chronic total occlusion (CTO) is defined as a coronary artery occlusion longer than three months standing with Thrombolysis in Myocardial Infarction (TIMI) flow grade of zero.[1] Around 30% of all coronary angiograms performed in patients with coronary artery disease show a CTO.[2,3] The presence of a CTO is one of the most common reasons for referring patients to coronary artery bypass grafting (CABG).[4,5] Successful recanalization of a CTO in the presence of viable myocardium has been demonstrated to reduce symptoms of angina, decrease the need for CABG and improve survival.[6-8] During the last 15 years we have seen a considerable improvement in the success rate of CTO-percutaneous coronary intervention (PCI) due to the operator expertise, advances in equipment and procedural techniques.[6,9,10] Despite advancement in techniques and instrumentation, success rate of CTO-PCI is lower than that of subtotal stenosis (70% vs. 98%),[11] and this kind of procedures is considered the last frontier in interventional cardiology.[12]

The most common cause of procedural failure in CTO recanalization is the inability to CTO segment wire crossing (80%-90%) and the other reasons are balloon-uncrossable lesion after successful wire crossing (2%-15%) or inadequate dilatation of the occlusion segment (2%-5%).[13] To overcome the problem of balloon-uncrossable CTO segment in

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calcified and hard lesions, a penetrating device, Tornus catheter has been designed and widely used for CTO-PCIs since 2004.[14] This catheter is made up of 8 braided steel wires along a longitudinal axis providing penetration through CTO segment with counter-clockwise rotation and device withdrawal by clockwise rotation. The Tornus catheter is able to penetrate and dilate the lesion getting a slightly larger channel.

The purpose of this study was to analyse efficacy and safety of the Tornus catheter in hard and balloon-uncrossable lesions in a single-centre with a growing experience in CTO program implemented since 2007.

Materials and Methods

One hundred fourteen CTO-PCIs were performed in our institution (Joan XXIII university hospital, Tarragona, Spain) between May 2007 and August 2012. The selection of patients was based on standard definition of CTO consisting of a coronary artery occlusion longer than three months standing with TIMI = 0. The chronic lesion definition was defined as either symptoms onset or coronary angiogram findings with more than three months standing.

We retrospectively analysed 14 out of 114 patients in whom Tornus catheter was used in antegrade approach to penetrate and/or cross the CTO segment. Tornus utilization was based on operator's criteria, basically when he assumed CTO as hard enough to be crossed by balloon or in cases of unsuccessful attempts to pass through the lesion with a small balloon (< 1.5 mm).

Procedure success was defined when Tornus either completely crossed the CTO segment or partly penetrated the lesion making possible the subsequent balloon predilatation of CTO segment and further stent implantation achieving a final angiographic result of TIMI III flow with less than 30% of residual lesion. Switching Tornus to another microcatheter was considered as procedural failure. The presence of any complication such as dissection, coronary artery perforation or device entrapment was analyzed as well in order to evaluate the device safety. Calcification was defined as none when no angiographic calcification was observed; severe when densely visible calcification existed and mild if calcification intensity was between none and severe. All patients were under double antiplatelet therapy with aspirin 100 mg and clopidogrel 75 mg daily.

Once the guidewire crossed the CTO segment, the distal wire position in true lumen was angiographically verified in two different orthogonal views. Then the Tornus catheter was used to cross antegradely the CTO segment with a maximum of 20 counter-clockwise rotations while the wire was held steadily (Figure 1).

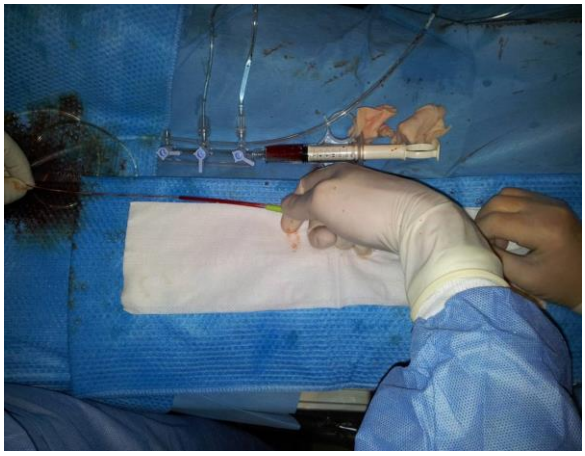

Figure 1. The operator is performing counter-clockwise rotation with Tornus in order to antegradely penetrate the chronic total occlusion (CTO) segment while an assistant fixes the guidewire

If Tornus successfully crossed the lesion, the specific wire for CTO was immediately exchanged for a floppy wire through the Tornus catheter in order to minimize the risk of distal vessel perforation. Tornus withdrawal was carried out by clockwise rotation and no more than 20 rotations were performed in order to prevent the breakage of the shaft at distal part.

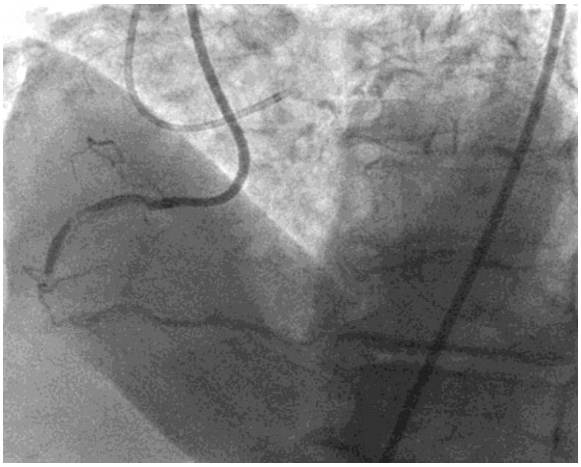

Figure 2-A. Chronic total occlusion of a right coronary artery visualized by a double injection coronary angiogram

Once Tornus was moved back, a 1.5 mm balloon was initially used to predilate the lesion and

after multiple balloon predilatations, one or more stent were implanted in all cases (Figure 2-A-D).

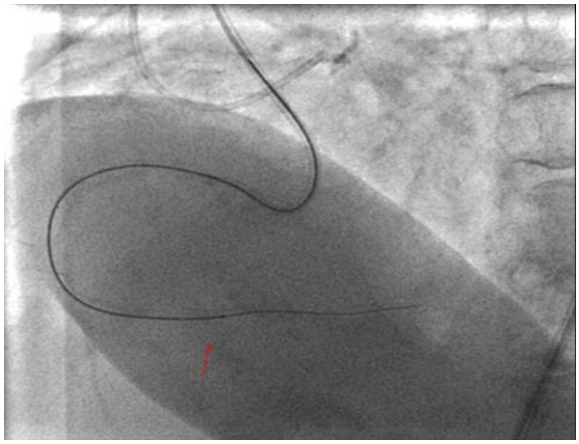

Figure 2-B. Tornus can successfully cross the chronic total occlusion (CTO) segment up to the right coronary artery distal segment over a Confianza Pro 9 guidewire (Asahi intecc, Japan)

If Tornus partly penetrated the CTO segment, multiple predilatations with a ≤ 1.5 mm balloon were performed in CTO proximal cap in order to gradually recanalize the whole CTO segment. Heparin in a 100 IU/kg was administered and activated clotting time (ACT) was checked every 30-45 minutes during all procedures for keeping a value of 250-300 seconds.

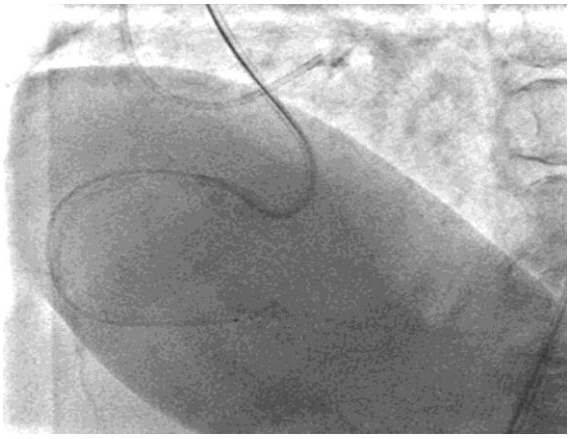

Figure 2-C. Guidewire withdrawal after Tornus advancement beyond chronic total occlusion (CTO) segment. After this step a floppy wire is advanced through the Tornus and the microcatheter is moved back in clockwise rotation

All data were introduced and analysed using SPSS software (version 19.0, SPSS Inc., Chicago, IL, USA). Continuous variables were reported as mean ± standard deviation, while categorical variables were expressed as frequencies.

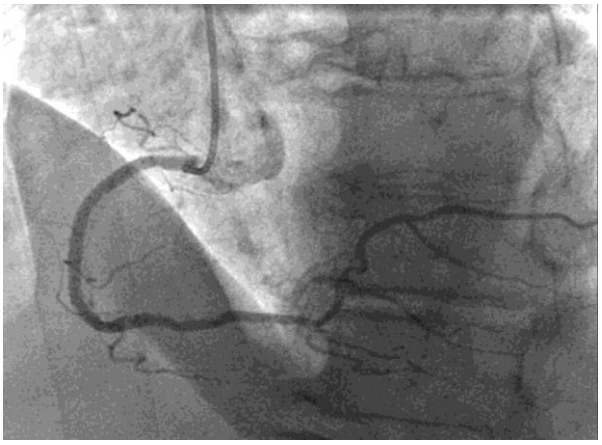

Figure 2-D. Final angiographic result after balloon predilatation and stent implantation

Results

Patients' average age was 65.2 ± 9.6 years and 11 (78.6%) out of 14 were men. 13 patients (92.9%) suffered from hypertension, 10 (71.4%) from hypercholesterolemia, 9 (64.3%) and from diabetes; 8 patients (57.1%) were smokers.

Baseline lesion characteristics and procedural results are shown in table 1. Tornus catheter was used in 14 cases. 12 (85.7%) patients presented with chronic stable angina, and 2 (14.3%) had suffered from recent acute coronary syndrome. Ten (71.4%) had normal ejection fraction, 3 (21.4%) had mild left ventricular dysfunction and 1 (7.1%) presented with moderate left ventricular dysfunction. In 11 (78.6%) patients femoral access was used to treat the occluded coronary artery and in 3 (21.4%) remaining cases radial access was utilized. Contralateral injection was utilized in 9 (64.3%) cases using radial access in 6 (66.7%) and femoral approach in 3 (33.3%), respectively. The distribution and segment of treated coronary artery were as follow: left anterior descending coronary artery (LAD) 2 (14.3%), both at mid-segment; right coronary artery (RCA) 10 (71.4%), 5 (50%) at proximal, 4 (40%) at mid and 1 (10%) at distal segment; left circumflex artery (LCX) 2 (14.3%), 1 (50%) at mid- and 1 (50%) at distal segment. CTO angiographic characteristics were as follow: length average value was 17.7 ± 9.5 mm. Four (28.6%) of all CTOs had no angiographic calcification whereas in 5 (35.7%) and 5 (35.7%) cases the artery revealed mild and severe angiographic calcification, respectively. One out of 14 (7.1%) cases had an ambiguous stump, 2 (14.3%) presented with vessel proximal tortuosity before the CTO, 7 (50%) had a side branch at proximal cap, 1 (7.1%) had ostial location, in 6 (42.9%) the vessel size was less than 2.5 mm, 2 (14.3%) had an inappropriate distal part visibility and finally 8 (57.2%) had multivessel disease.

Table 1. Baseline lesion characteristics and procedural results

Patient	Access	Vessel	Calcification	Prior balloon	GC (Fr)	Penetration	Switch	Complication	Success
1	F	LAD	Mild	Yes	EBU3.5 (8)	Complete	No	No	Yes
2	F	LAD	Mild	No	EBU3.5 (7)	Complete	No	No	Yes
3	F	RCA	Severe	Yes	AR2 (7)	Partial	No	No	Yes
4	F	LCX	None	No	XB3.5 (7)	Complete	No	No	Yes
5	F	RCA	None	No	JR4 (7)	Complete	No	No	Yes
6	F	RCA	None	No	AL1 (7)	Complete	No	No	Yes
7	F	RCA	Mild	Yes	AL0.75 (8)	No	Yes	No	No
8	F	RCA	Mild	Yes	AL1 (7)	Partial	No	No	Yes
9	F	RCA	Severe	Yes	AL1 (7)	Complete	No	No	Yes
10	R	RCA	Severe	No	AR2 (7)	Partial	Yes	No	No
11	F	RCA	Severe	No	AR2 (7)	Partial	Yes	No	No
12	R	LCX	None	Yes	XB3.5 (6)	Complete	No	No	Yes
13	R	RCA	Severe	Yes	AR2 (7)	Complete	No	No	Yes
14	F	RCA	Mild	No	JR4 (7)	Partial	No	No	Yes

LAD: Left anterior descending coronary artery; RCA: Right coronary artery; LCX: Left circumflex coronary artery; F: Femoral; R: Radial; GC: Guiding catheter

In 1 (7.1%) patient a 6 Fr guiding catheter was used for CTO recanalization and in 11 (78.6%) and 2 (14.3%), 7 Fr and 8 Fr guiding catheter were utilized, respectively. In 7 (50%) cases the Tornus catheter was employed after an unsuccessful passage of a small balloon through the lesion and in 7 (50%) procedures the operator decided to use Tornus as a first device to cross the lesion. In 8 (57.1%) cases, Tornus crossed the CTO segment into distal part of coronary artery and in 5 (35.7%), the proximal cap of CTO was penetrated by Tornus with subsequent balloon predilatation of CTO proximal cap achieving a successful final CTO recanalization in 3 cases; finally in 1 (7.1%) case, Tornus could not penetrate CTO segment. In 3 (21.4%) cases the operator switched to another microcatheter (Corsair: Asahi Intecc; Aichi, Japan) in order to continue with PCI and in all cases the procedure was unsuccessful. In 11 out of 14 cases (78.6%) the procedure was successful and no complication was associated with Tornus catheter. Successful procedure was obtained in 67% of remaining 100 patients in whom Tornus was not utilized although this difference was not statistically significant (P = 0.54; data not included in the tables). The 3 cases in which the procedure was unsuccessful, RCA was the treated vessel. Procedure mean time was 194 ± 59 minutes and contrast medium average value was 328 ± 132 ml.

Discussion

In our study the use of Tornus in a subgroup of CTO-PCI with hard or balloon-uncrossable lesion was associated with a high procedural success rate (78.6%) and did not present any complication which reveals its safety in this kind of procedures. These characteristics have been tested in other studies in which Tornus has been basically utilized after an unsuccessful attempt to cross a balloon through a CTO or severe calcified stenosis after successful guidewire crossing.[14,15] In Reifart et al.[15] study, Tornus contributed to success in 91% of a total 44 cases whereas in Tsuchikane et al.[14] experience in 14/14 cases Tornus successfully crossed the lesion. The discrepancy in results of these studies with our study can partly be explained by the fact that Rotational atherectomy was used in 3 cases in the former and in 7 cases in the latter study. At the same time, the lower success rate in our study can reflect the real scenario of a gradual experience in CTO-PCI techniques and instrumentations in our cath lab. In all the cases, we followed the recommendations of device use in terms of verifying the guidewire position into true lumen from angiographic point of view before Tornus advancement and the use of maximum 20 rotations in counter-clockwise and clockwise direction which we do believe is the main reason for the absence of any complication during all procedures. We considered the partial penetration of CTO segment as a contributing factor to CTO recanalization with subsequent CTO proximal part balloon dilatation. We included these cases as procedural success when TIMI III flow restoration was finally achieved after stent implantation. This inclusion criterion in our study was based on the fact that the gradual penetration of CTO proximal cap after Tornus partial penetration has previously been described by Ochiai[16] and our experience enhances this concept. Actually, in 5 cases

in our series Tornus partly penetrated the CTO segment making possible balloon predilatation in CTO proximal cap in 3 out of 5. Tornus could subsequently advance through CTO segment and after exchanging the specific wire with a floppy one, stent implantation was carried out achieving a successful final result.

The problem of balloon-uncrossable lesion after successful wire crossing in complex PCI like CTO has been tried to be solved with several techniques. Among these techniques, we can mention anchor balloon technique in order to increase the backup support and to facilitate the balloon advancement during PCI.[17] Takahashi et al.[18] described the five-in-six system technique inserting a 5 Fr guiding catheter (Heartrail, Terumo, Japan) into 6 Fr guiding catheter in order to increase the backup support after verifying the balloon was unable to cross the CTO segment. Another interesting tool for percutaneous treatment of very calcified and eventually uncrossable lesion is the use of rotational atherectomy. Fang et al.[19] compared the rotational atherectomy with Tornus in 77 patients with impassable CTO by the smallest balloon or microcatheter and they concluded that device success was significantly lower (77% vs. 95%) and mean procedural time was significantly longer (144 minutes vs. 115 minutes) in Tornus group. Although rotational atherectomy is very effective in some cases the important issue, as recognized by the authors in the previous study, was the ability for distal advancement of Rotawire through a microcatheter before rotablation application. Furthermore, rotational atherectomy is not available in all cath labs and training for Tornus use is much easier than that of rotational atherectomy.

There are several limitations in our study. This is a retrospective study and the use of Tornus was not limited to the group of uncrossable lesions and in 7 cases the device was used because the operator considered the CTO as a very hard or tight lesion "a priori". This aspect in our study may limit the real device efficacy in this kind of procedures. Another limitation of the study is that we did not distinguish between two different sizes of Tornus (2.1 Fr and 2.6 Fr). Actually, the 2.6 Fr Tornus has a superior torquability and can be advanced more easily through the lesion creating a larger lumen whereas 2.1 Fr is slightly better to penetrate and advance through tortuous vessels although strength of the device is weaker and may reduce the progression in hard calcified lesions.[20] These device characteristics should be taken into account in each particular case in order to increase the device efficacy.

Finally, although the purpose of our study was not to compare the procedure success rate in Tornus with the remaining CTO-PCI, the better outcome in Tornus group (78.6% vs. 67%) was not statistically significant. We cannot ensure whether this lack of significance could be related to small sample size of our study.

Conclusion

Tornus is a useful device for PCI in hard or balloon-uncrossable CTOs and could safely contribute to overcome some technical difficulties during PCI of this kind of lesions.

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Conflict of Interests

Authors have no conflict of interests.

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