Isfahan Cardiovascular Research Institute

ARYA Atherosclerosis

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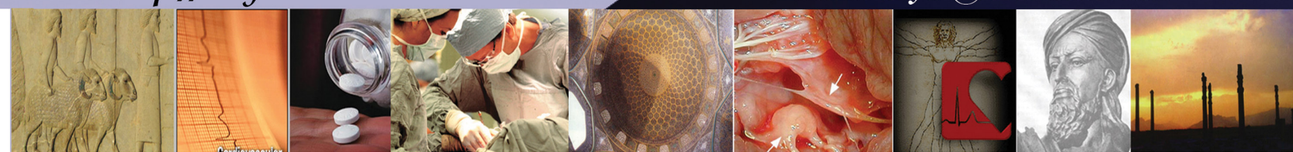

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The association between particulate matter 2.5 and hospitalization and mortality rates of heart failure: The CAPACITY study

Nafise Moein[(1)], Mohammad Garakyaraghi[(2)], Davood Shafie[(2)], Katayoun Rabiei[(3)], Sayed Mohsen Hosseini[(4)], Tohid Jafari-Koshki[(5)], Mojtaba Rahimi[(6)], Babak Sadeghian[(7)], Mahshid Givi[(2)], Nizal Sarrafzadegan[(3)]

Original Article

Abstract

BACKGROUND: Considering the high concentrations of pollutants in large cities of Iran and the high prevalence of heart failure (HF) among Iranians, especially with increasing life expectancy, this study investigated the relationship between airborne contaminants with a diameter < 2.5 µm or particulate matter 2.5 ($PM_{2.5}$) and hospitalization and mortality in patients with HF in Isfahan, Iran, during 2011.

METHODS: This ecological study was carried out on a part of data from the CAPACITY study. A total of 275 patients with HF were randomly selected from 840 subjects with International Statistical Classification of Diseases, 10th Revision (ICD-10) diagnosis code I50 in the CAPACITY study. Patients' records were evaluated and their clinical characteristics, disease history, and laboratory and echocardiographic findings were extracted. Air pollution and climatic data were extracted from the CAPACITY study. Poisson regression was used in crude and adjusted models to evaluate the association between $PM_{2.5}$ and study outcomes. All analyses were performed using crude models and models adjusted for temperature, dew point, and wind speed.

RESULTS: 54.9% (n = 151) were men with mean age of 70.4 ± 13.7 years. While most patients (85.8%) were discharged after recovery, 14.2% of the patients died in the hospital. Blood glucose, heart rate, and ejection fraction (EF) were significantly higher on unhealthy days than normal days. Regression analysis revealed no significant relationships between hospitalization and mortality rates and $PM_{2.5}$ concentrations on healthy days, unhealthy days for sensitive people, and unhealthy days.

CONCLUSION: The model used in our study revealed no significant relationships between $PM_{2.5}$ concentrations and hospital admission on healthy days, unhealthy days for sensitive people, and unhealthy days.

Keywords: Hospitalization, Mortality, Particulate Matter

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Introduction

In recent years, air pollution caused by motor vehicles and industrial activities has turned into a major public health threat and an important management challenge in various countries. Numerous studies have shown a direct association between air pollution and the incidence of

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cardiovascular and pulmonary diseases and related mortality.[1] Short-term exposure to air pollution has been reported to increase the risk of several complications such as hypertension (HTN),[2] arrhythmias,[3] exacerbation of heart failure (HF),[4] and acute ischemic and atherosclerotic cardiovascular complications.[5] Long-term exposure is also known to lead to cardiovascular events such as atherosclerosis and deep vein thrombosis (DVT).[6] These complications might be caused by either acute daily changes in air pollution levels or lifetime exposure to contaminants.[7]

Particulate matter (PM) is a mixture of solid and liquid particles with different compositions and sizes which suspend in the air. These particles are surrounded by various gases such as ozone (O_3), carbon monoxide (CO), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2). They are divided into three categories including coarse (PM_{10}, diameter: 2.5-10 μm), fine ($PM_{2.5}$, diameter < 2.5 μm), and ultra-fine (UFP, diameter < 0.1 μm) particles.[8] It is widely accepted that smaller particles offer a larger surface area and hence potentially larger concentrations of adsorbed or condensed toxic air pollutants per unit mass. Hence, $PM_{2.5}$ was taken to be more relevant as an exposure indicator than larger particles.[9]

Chronic HF (CHF) is one of the most common causes of mortality from cardiovascular diseases (CVDs) and its related hospitalization rates have remarkably increased during the past two decades.[10] The hospitalization and one-year mortality rates due to CHF are about 2% and 30%, respectively.[11] In patients with HF, hospitalization occurs following decompensation caused by various factors such as inadequate treatment, uncontrolled HTN, and arrhythmias.[12] PM contributes to the pathogenesis of HF through several biological mechanisms. Oxidative inflammation and endothelial dysfunction can increase the number and activity of platelets, elevate the levels of inflammatory and coagulation factors, and cause autonomic nerve disorders.[13] A combination of these factors intensifies ventricular remodeling and myocardial fibrosis and causes left ventricular dysfunction (LVD), increased pulmonary capillary wedge pressure (PCWP), and repeated decompensation attacks in the long-term.[14]

In Iran, as a developing country, the level of air pollutants has increased gradually since the beginning of industrialization in the 1970s, but it has reached a very harmful level in some megacities such as Tehran, Mashhad, Tabriz, Isfahan, Ahvaz, Arak, and Karaj, Iran, over the past two decades.[15] Isfahan is the second most polluted city in Iran and one of the most polluted cities in the world.[16] Various factors such as Isfahan's specific geographic location, the presence of industrial units and contaminating firms, and the large number of motor vehicles and related traffic problems increase the risk of exposure to air pollution in the residents of the city. Since air pollution and thus hospitalization and mortality rates due to HF are on the rise in Isfahan,[17] this study investigated the relationship between airborne contaminants (particularly $PM_{2.5}$) and hospitalization and mortality rates in patients with HF in Isfahan during 2011.

Materials and Methods

This study was a part of the CAPACITY study which focused on participants with HF and was carried out in Isfahan from March 20, 2011 to March 20, 2012. It sought to clarify the association between hospitalization caused by cardiovascular and respiratory diseases and air pollutants. The CAPACITY study collected data from all patients who had been diagnosed with and hospitalized for cardiovascular and respiratory diseases based on International Statistical Classification of Diseases, 10th Revision (ICD-10) codes in Isfahan. PM, SO_2, NO_2, CO, and O_3 levels measured by six fixed pollution monitoring stations were retrieved from Isfahan Department of Environment (DOE). The methodology of the CAPACITY study has been fully described elsewhere.[18]

HF had already been diagnosed by the patient's physician at the time of admission and the records were documented in the health information system (HIS) based on ICD-10 codes and ejection fraction (EF) of 40% or less as HF with reduced EF.[19] Of all patients with ICD-10 diagnosis code I50 in the CAPACITY study, 275 subjects who were hospitalized for acute HF (AHF) during March 20, 2011 to March 20, 2012 were randomly selected. The participants' records were evaluated by project executive and patient information including admission time, demographic information (e.g., age, gender, and place of residence), history of diabetes, HTN, ischemic heart disease (IHD), chronic obstructive pulmonary disease (COPD), smoking, and medication use, vital signs at the time of admission [i.e., systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, respiratory rate, and oxygen saturation], and troponin, blood urea nitrogen (BUN), creatinine (Cr), blood sugar, and hemoglobin (Hb) levels was recorded in a checklist. Echocardiographic data including left ventricular EF (LVEF), mitral and

tricuspid valve regurgitation (MR and TR, respectively), and systolic pulmonary arterial pressure (SPAP), as well as discharge/death dates were also recorded.

In the study year, only one station in the center of Isfahan measured hourly $PM_{2.5}$ concentrations. The station is located in one of the busiest areas of Isfahan near Naqshe-e Jahan Square (a historical site) and a specialty cardiac hospital (established in 2010). This station continuously monitored the concentrations of $PM_{2.5}$ and gas contaminants [sulfur oxides (SOX), nitrogen oxides (NOX), CO, and O_3] and recorded the data as mean hourly values. $PM_{2.5}$ concentrations were measured through beta attenuation monitoring (BAM) method. Considering the effects of weather conditions on air pollution, in order to eliminate their confounding effects on $PM_{2.5}$ concentrations, we adjusted dataset for climatic variables (wind speed, temperature, and humidity). The hourly average values, for 24 hours during March 20, 2011 to March 20, 2012 for temperature (in Fahrenheit), dew point (in percent), and wind speed [in meters per second (m/s)] were also collected from Isfahan Meteorological Organization and were compared with available satellite data (an archive of all climatic data recorded at meteorological stations since 1950).

All data were entered into SPSS software (version 23, IBM Corporation, Armonk, NY, USA) and data about $PM_{2.5}$ concentrations and anthropometric factors were merged with patient information based on the patient's hospitalization date. Data were shown as mean ± standard deviation (SD) for quantitative variables or frequency and percentage for qualitative variables. Before the analyses, the days of the year were categorized as "good or moderate", "unhealthy for sensitive people", and "unhealthy" or "hazardous" based on $PM_{2.5}$ levels and air quality index (AQI) classifications.[20] Hospitalization data and disease history in patients admitted on good or moderate ($PM_{2.5}$ < 40.5), unhealthy for sensitive people ($PM_{2.5}$ = 40.5-65.5), and unhealthy or hazardous ($PM_{2.5}$ > 66) days were compared by chi-square test and one-way analysis of variance (ANOVA).

Poisson regression model was performed to investigate crude and adjusted effect of $PM_{2.5}$ on mortality or hospitalization rate of HF. Age, temperature, dew point, and wind speed were added to model as adjustments also for hospitalization rate models were performed separately for each gender. Data analysis was conducted using SPSS and Stata (version 12, Stata Corporation, College Station, TX, USA) and P-values less than 0.05 were considered significant.

Results

Of 16990 patients with CVDs who were enrolled in the CAPACITY study during March 20, 2011 to March 20, 2012, 840 patients had HF. A total of 275 individuals with HF, including 151 men (54.9%) and 124 women (45.1%), were randomly selected from this population and included in the present research. The patients' mean age was 70.4 ± 13.7 years. Most patients (n = 236, 85.8%) were discharged from the hospital and 39 patients (14.2%) died. Table 1 presents the patients' history and clinical characteristics at the time of admission.

Table 1. Patients' history and clinical characteristics at the time of admission

Variable	Value
Gender	275 (100)
Male	151 (54.9)
Female	124 (45.1)
Viability	275 (100)
Alive	236 (85.8)
Died	39 (14.2)
Past history	
Diabetes	103 (37.5)
HTN	148 (53.8)
IHD	161 (85.5)
COPD	68 (24.7)
Smoking	59 (21.5)
Physical examination	
SBP (mmHg)	125.04 ± 30.34
DBP (mmHg)	76.07 ± 15.95
Heart rate (per minute)	87.96 ± 21.37
Respiratory rate (per minute)	23.03 ± 8.15
O_2 saturation (percent)	90.64 ± 68.46
Laboratory data	
Urea (mg/dl)	35.08 ± 62.36
Creatinine (mg/dl)	1.67 ± 1.21
Blood glucose (mg/dl)	160.32 ± 87.17
Hb (mg/dl)	14.82 ± 12.59
Positive troponin	21 (7.6)
Echocardiography	
EF (percent)	32.48 ± 13.76
SPAP (mmHg)	41.34 ± 17.69
MR	259 (94.2)
TR	255 (92.7)

Values are mean ± standard deviation (SD) for quantitative variables and number (%) for qualitative variables.
HTN: Hypertension; IHD: Ischemic heart disease; COPD: Chronic obstructive pulmonary disease; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; Hb: Hemoglobin; EF: Ejection fraction; SPAP: Systolic pulmonary artery pressure; MR: Mitral regurgitation; TR: Tricuspid regurgitation

As seen, over 90% of the patients had MR and TR, 85.5% had a history of IHD, and 53.8% had HTN. The patients' SBP, DBP, and blood glucose were within the acceptable ranges at the time of admission. Positive troponin, as an indicator of acute coronary event, was detected in 7.6% of the patients at the time of admission.

Table 2 shows the mean $PM_{2.5}$ concentrations, temperature, wind speed, humidity, and visibility for all days, as well as healthy, unhealthy for sensitive people, and unhealthy days. As seen, the largest number of admissions belonged to unhealthy days for sensitive people.

Table 2. Climatic variables and particulate matter 2.5 ($PM_{2.5}$) concentrations

Variable	Value
Wind speed (m/s)	5.55 ± 2.83
Temperature (Fahrenheit)	57.73 ± 19.35
Humidity (percent)	27.40 ± 9.19
Visibility (km)	4.52 ± 1.15
$PM_{2.5}$ concentrations (µg/m^3)	55.36 ± 32.12
Frequency of hospitalization	275 (100)
Good or moderate	68 (24.7)
Unhealthy for sensitive people	149 (54.2)
Unhealthy or hazardous	58 (21.1)

Values are mean ± standard deviation (SD) for quantitative variables and number (%) for qualitative variables.
PM: Particulate matter

Table 3 compares the study variables on healthy, unhealthy for sensitive people, and unhealthy days. According to the provided data, EF, blood glucose, and heart rate at the time of admission were significantly higher on unhealthy days than healthy days.

Table 4 presents the association between the mean $PM_{2.5}$ concentrations and hospitalization due to HF in the whole population and the two genders based on Poisson regression analysis (crude models and models adjusted for temperature, humidity, wind speed, and visibility). After adjustment for climatic variables (wind speed, temperature, visibility, and humidity), a positive relationship was observed between $PM_{2.5}$ concentration and hospitalization rate both in the whole population and in women. However, no significant relationships were found in good or moderate, unhealthy for sensitive people, and unhealthy or hazardous ranges.

Discussion

The results of this study showed no significant correlations between $PM_{2.5}$ concentrations and hospitalization due to HF on healthy days, unhealthy days for sensitive people, and unhealthy days.

Table 3. Comparison of patient characteristics at the time of admission in particulate matter 2.5 ($PM_{2.5}$) groups

Patient characteristics	Good or moderate	Unhealthy for sensitive people	Unhealthy or hazardous	P
HTN	40 (60.6)	80 (54.8)	28 (49.1)	0.441*
Diabetes	30 (46.2)	57 (39.6)	16 (28.1)	0.117*
IHD	42 (64.6)	91 (64.1)	28 (50.9)	0.195*
COPD	18 (28.6)	36 (25.7)	14 (25.9)	0.908*
Smoking	19 (30.6)	30 (22.2)	10 (18.2)	0.252*
Positive troponin	7 (10.1)	13 (9.8)	1 (2.0)	0.203*
Died	11 (16.2)	21 (14.1)	7 (12.1)	0.804*
Age (year)	72.22 ± 12.06	69.98 ± 14.12	69.36 ± 14.48	0.435**
SBP (mmHg)	125.94 ± 24.14	126.09 ± 31.43	121.40 ± 33.93	0.588**
DBP (mmHg)	74.89 ± 15.41	77.57 ± 16.14	73.64 ± 15.93	0.226**
Heart rate (per minute)	80.00 ± 21.48	88.81 ± 20.72	93.09 ± 20.73	0.002**
Creatinine (mg/dl)	1.45 ± 0.78	1.82 ± 1.46	1.53 ± 0.86	0.076**
Blood glucose (mg/dl)	134.48 ± 55.18	161.43 ± 86.12	180.81 ± 106.12	0.014**
Hb (mg/dl)	12.90 ± 2.15	14.78 ± 12.52	17.15 ± 18.37	0.175**
EF (percent)	28.32 ± 12.18	31.08 ± 14.42	35.00 ± 13.82	0.028**
SPAP (mmHg)	41.81 ± 17.52	40.35 ± 18.51	43.18 ± 15.94	0.598**

Values are mean ± standard deviation (SD) for quantitative variables and number (%) for qualitative variables.
* Chi-square test or Fisher's exact test were used where appropriate.
** One-way analysis of variance (ANOVA) was used.
HTN: Hypertension; IHD: Ischemic heart disease; COPD: Chronic obstructive pulmonary disease; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; Hb: Hemoglobin; EF: Ejection fraction; SPAP: Systolic pulmonary artery pressure

Table 4. Crude and adjusted effect of particulate matter 2.5 ($PM_{2.5}$) on mortality or hospitalization rate of heart failure (HF)

Events	$PM_{2.5}$ level	Crude model		Adjusted model*	
		OR (95% CI)	P	OR (95% CI)	P
Total	Good or moderate	1		1	
	Unhealthy for sensitive people	1.19 (0.69-2.08)	0.510	0.99 (0.56-1.79)	0.990
	Unhealthy or hazardous	1.25 (0.62-2.53)	0.530	1.08 (0.52-2.24)	0.830
Female	Good or moderate	1		1	
	Unhealthy for sensitive people	1.40 (0.64-3.06)	0.380	1.09 (0.46-2.59)	0.830
	Unhealthy or hazardous	1.76 (0.60-5.16)	0.300	1.18 (0.34-3.99)	0.780
Male	Good or moderate	1		1	
	Unhealthy for sensitive people	1.01 (0.46-2.23)	0.960	0.79 (0.33-1.87)	0.600
	Unhealthy or hazardous	0.94 (0.36-2.44)	0.910	0.64 (0.23-1.79)	0.400
Mortality	Good or moderate	1		1	
	Unhealthy for sensitive people	2.33 (0.40-13.45)	0.340	3.55 (0.46-27.30)	0.220
	Unhealthy or hazardous	1.00 (0.11-9.27)	0.990	1.63 (0.13-20.7)	0.700

* Adjusted for age, temperature (˚F), dew point (percent), and wind speed (m/s)
PM: Particulate matter; OR: Odds ratio; CI: Confidence interval

However, a comparison between patients' clinical characteristics at the time of admission revealed that heart rate and blood glucose levels of patients hospitalized on unhealthy days were significantly higher than those of patients admitted on healthy days. Likewise, significantly higher EF was observed in patients admitted on unhealthy days than those hospitalized on healthy days. This finding suggests that patients with more stable conditions experienced decompensation on more contaminated days.

Yang et al. investigated the long-term effects of air pollution on LV function during 2005-2009. They observed significant relationships between $PM_{2.5}$ and age, plasma glucose, prevalence of diabetes, and LV function variables (e.g., age-standardized EF and longitudinal strain rate).[21] Since EF does not change in the absence of an acute coronary artery attack within 24 hours and the reduction in this parameter is more pronounced over time,[22] long-term comparisons of EF would be possible if we followed the admitted patients. In Jackson Heart Study (JHS), echocardiography was performed on 4866 patients. The patients' exposure to pollutants was also evaluated according to their distance from highways. Various analyses did not show any significant differences in LVEF, E velocity, isovolumic relaxation time (IVRT), and left atrium size.[23]

Different biological studies have shown that circulating adhesion molecules [E-selectin (endothelium-derived), P-selectin (platelet-derived), vascular cell adhesion molecule (VCAM), and intercellular adhesion molecule (ICAM)] create a systemic inflammatory condition and play an important role in the development of adverse cardiovascular effects.[24] Through the release of the mentioned inflammatory mediators, the respiratory system triggers endothelial dysfunction, decreases NO-dependent vasodilation, promotes pulmonary arteriole remodeling, and ultimately increases pulmonary vascular resistance and decreases venous return to the left atrium. According to Frank-Starling Law, these hemodynamic changes in pulmonary circulation reduce atrial contraction and may exacerbate patients' dyspnea regardless of their EF.[25] Moreover, pulmonary inflammation caused by air pollution can stimulate vagal afferents in the lungs and cause autonomic dysfunction. The consequent transfer of inflammatory mediators from the lungs to the systemic circulation affects cardiac neurotransmission and changes the heart rate (i.e., decreases heart rate variability).[26]

This study presented evidence of a correlation between $PM_{2.5}$ levels and hospitalization and mortality rates due to HF. However, this relationship was not statistically significant. Milojevic et al. investigated the short-term effects of air pollution on hospitalization and mortality caused by cardiovascular events during 2003-2008. Consistent with our findings, they reported $PM_{2.5}$ concentrations to have no significant effects on 335000 hospitalizations and 37000 deaths caused by HF.[27] Nevertheless, a recent meta-analysis of 32 studies on the relationship between air pollution and HF concluded that every 10 $\mu g/cm^3$ increase in $PM_{2.5}$ concentration increased hospitalization and mortality rates in patients with HF by 12.2%.[28] The differences between various studies can be attributed to different methods of data analysis and disease diagnosis recording. In the present study, the relationship between air pollution and HF did not depend on the history of diabetes, HTN, and smoking. Similar findings were reported by Annesi-Maesano et al.[29]

One strength point of this study was collecting data from government departments (HIS from the Deputy of Treatment, air pollutant data from the DOE, and weather data from the Meteorological Organization) which reduced the cost of the research. Given the fact that almost all national data are currently collected and recorded online, research costs can be reduced by using different data recording systems. One of the limitations of this study was time-dependent confounding effects, including day, month, weather conditions, stress, and physical activity. In addition, due to the elimination of cases of deterioration and death at home or attribution of dyspnea to other respiratory diseases, the estimated values might be lower than the actual rates. Therefore, correct recording of the information and an accurate final diagnosis are highly important in determining the relationship between HF and air pollution. Nevertheless, air pollution seems to have greater impacts on patients with previously-diagnosed HF than the new cases of the disease.[30] Thus, further studies with this goal are recommended in the future. Furthermore, since we collected the data over a specific period of time, future studies are recommended to collect more information through longer follow-up of the patients.

Patients hospitalized for HF had significant differences in terms of echocardiographic EF, blood glucose, and heart rate at the time of admission. This finding can indicate that patients with more stable conditions experience decompensation events on more polluted days. However, an increase in 24-hour $PM_{2.5}$ concentrations was not significantly related to patients' hospitalization and mortality rates and no differences in the levels of moderating variables were observed in this regard. Considering the important role of air pollution in the incidence of cardiovascular and respiratory diseases, more effective strategies should be adopted to reduce these contaminants. Meanwhile, high-risk patients should be advised to take care of measures and avoid exposure to air pollution. According to the findings of the present study, case-crossover models, similar to that used in the CAPACITY study for the examination of all patients, are recommended for the elimination of the effects of many patient-related confounders. In addition, longitudinal studies on patients hospitalized for HF are warranted to investigate the long-term impacts of $PM_{2.5}$ on changes in heart function (including EF).

Conclusion

The model used in our study revealed no significant relationships between $PM_{2.5}$ concentrations and hospital admission on healthy days, unhealthy days for sensitive people, and unhealthy day.

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Conflict of Interests

Authors have no conflict of interests.

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Socioeconomic status, cardiac risk factors, and cardiovascular disease: A novel approach to determination of this association

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Original Article

Abstract

BACKGROUND: Socioeconomic inequality is one of the important issues in cardiovascular diseases (CVDs). The aim of this study was to investigate the distribution and relation between selected cardiac risk factors, type of CVD, and the socioeconomic status (SES) in the hospitalized patients with heart disease in Isfahan, Iran.

METHODS: This analytical and cross-sectional study was conducted in Isfahan in 2013. The population consisted of all patients with CVD admitted to the public and private hospitals. The sample size was 721. Data collection was conducted through one researcher-made questionnaire with three sections: demographic, disease, and SES questionnaires. To determine the SES of the patients, the indicators of income, housing status, occupation, family size, and education were used. Data analysis was conducted in two statistical levels of descriptive and inferential.

RESULTS: 69.1% of the patients were placed in the poor status, and there was no wealthy status within the subjects. The five most frequent CVDs were chronic ischemia, unstable angina, arrhythmia, congestive heart failure (CHF), and acute myocardial infarction (MI), respectively. The three highest frequent risk factors in the patients were hypertension (HTN) (47.2%), diabetes (33.6%), and hyperlipidemia (32.6%). Regression analysis of the risk factors and the type of heart disease on the SES revealed that there were statistically significant differences between patients who were smokers (P = 0.030) and those who had valve disease (P = 0.010), adjusted for age, gender, and marital status.

CONCLUSION: Our findings showed that the frequency of CVD risk factors were higher in lower SES groups and thus SES can be a strong predictor for the occurrence of the CVD risk factors as well as the CVDs.

Keywords: Risk Factors, Cardiovascular Diseases, Socioeconomic Factors

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Introduction

Cardiovascular diseases (CVDs) are the leading causes of death worldwide. They cause 17.5 million deaths in the world annually,[1] which accounts for 10% of the total deaths.[2] Out of these, 80% occur in middle or low-income countries.[1] The important point is that while the trend of CVD in developed countries is downward, it is upward in low and middle-income countries, so that about 85 percent of heart deaths occur in poor countries.[2]

Although it is well-recognized that CVD is a major and growing problem, less attention has been paid to the fact that this disease is the main cause of the widespread inequities in health status between the rich and the poor.[1,3] Evidence relating to the socioeconomic determinants of CVD, particularly in developing countries, indicates an inverse relationship between socioeconomic status (SES) and the occurrence of deaths by CVD. Although cardiovascular risk factors and diseases arose in higher SES groups first, but gradually the risk

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factors of the disease has spread to the lower SES groups over the last 50 years.[4-6]

Many studies have shown that cardiac patients with better SES receive treatments in more specialized hospitals with better-prescribed medicines in comparison to the lower SES groups.[7-9] Access to rehabilitation cares is also lower for the people with lower SES.[10]

In addition, socioeconomic factors, such as employment and income, also affect the death rate through the impact on risk factors related to the lifestyle before and after the heart attack.[11] After the heart attack, lower SES groups would face more serious health consequences in long run.[2] Socioeconomic inequities have been recorded in almost all western countries in the prevalence and occurrence of deaths from CVD.[12] Socioeconomic inequity is one of the major challenges in the CVD.[13] The aim of this study was to investigate the distribution and relationship between selected cardiac risk factors, type of CVD, and the SES of the hospitalized patients with heart disease. This study is one of the first studies which used cumulative indicators, calculated individual score for determining SES of the patients, and evaluated the relationship between SES and CVD risk factors.

Materials and Methods

This analytical and cross-sectional study was conducted in Isfahan, Iran, in 2013. The population consisted of all patients with CVD admitted to the public (8 hospitals) and private hospitals (3 hospitals) in Isfahan in all relevant wards, including cardiology, cardiac care unit (CCU), and post CCU. Cluster random sampling was done. The sample size was determined as 721 patients, taking into account the confidence level (CI) of 95%, the power of 80%, and the design effect of 1.8. The number of samples per hospital was determined through the sharing ratio, that is the number of patients with CVD who were admitted in previous year at each hospital was considered as a criterion for selecting the number of patients for the study.

Data collection was conducted through a researcher-made questionnaire. The questionnaires were completed in the first six months of 2013. As the questions were objective, preliminary studies were not needed to confirm the reliability. To determine the face and content validity, the questionnaire was given to 30 experts and cardiologists and after receiving their comments, the necessary amendments were made. The questions were divided into three sections: demographic, disease, and SES. The questions in demographic part included age, sex, and marital status. The disease part included the questions on the type of heart disease and associated risk factors. The patient's medical records were also reviewed to confirm the type of heart disease. These heart diseases included chronic ischemia, unstable angina, arrhythmia, congestive heart failure (CHF), acute myocardial infarction (MI), valve disease, and congenital heart defects (CHDs). Cardiac risk factors contained hypertension (HTN), diabetes, hyperlipidemia, family history of CVD, and smoking. The patients or their families completed the questionnaires.

To determine the SES of the patients, the indicators of income, housing status, occupation, family size, and education were assessed. Finally, 5 SES groups were considered. The first group was in the lowest level and the fifth one was in the highest level. These groups included extremely poor, poor, moderate, good, and wealthy. The method of SES determination and cut points of groups is described in more details elsewhere in the methodology article of authors.[14,15] A tripartite classification for occupations was used. Individuals in high rank included large and moderate landowners, top-level managers, and professionals. People in average rank were lower managers, semiprofessionals, vendors, and artisans. Low-wage industrial workers, officers, retail sellers, services workers, unemployed, and pensioners were placed in low SES group. The detailed method of calculation was described in Davari et al. paper.[14] Income classification was based on Isfahan poverty line (PL). The PL means the level of consumption (or income) required for a household to reach basic needs. The Isfahan PL for 2013 was received from experts of bank system and was applied to calculate the level of patient's income.

Data analysis was conducted in two statistical levels of descriptive and inferential, using SPSS software (version 16, SPSS Inc., Chicago, IL, USA). Categorical and continuous data were reported as frequency (percent) and mean ± standard deviation (SD), respectively. The inferential statistics level was done using chi-square test, analysis of variance (ANOVA), and multiple logistic regression model. P-value less than 0.05 was considered as a significant level. Bonferroni correction was used to adjust P-value. In this correction method, P-value was dependent on the numbers of all risk factors and CVDs. In multiple logistic regression model, the coefficient regression of SES on outcome (each risk factor or CVDs) was estimated with controlling for all other variables in the model to consider

confounding effect, for example, odds ratio (OR) of SES on HTN, controlling for other risk factors. All the variables except age were nominal in this study. SES was determined based on calculation of different scores of its variables and overall score was included as a continuous quantitative variable in the multiple logistic regression model. Final individual scores for SES were calculated from the sum of the detailed individual scores. As a result, the lowest possible score was 100 (when all detailed parameters were considered at their minimum scores) and the highest possible score was 720 (when all ones were at their highest value). These scores were categorized into 5 groups, from the lowest to the highest one, for finding the SES of individuals. These groups consisted of extremely poor (scores 100 to 224), poor (scores 225 to 348), moderate (scores 349 to 472), good (scores 473 to 596), and wealthy (scores 597 to 720). In addition, ordinal classification was defined for labeling patients in different groups of SES.

Results

The frequency distribution of the SES characteristic of hospitalized patients with CVD is presented in table 1. The ranking of the patients based on their education factors showed that most of them (81.3%) were in high school level. Likewise, the majority of them were in medium occupational level (73.9%), 5 or more in family size (33.4%), home owner (84.5%), and equal or less than PL in the income level (53.5%). The results of SES classification showed that status II (poor) had the highest frequency (69.1%) and there was no wealthy status within the subjects at all (Table 1).

Results showed that 54.8% of the samples were men. In terms of marital status, the highest frequency (82.1%) was for the married, divorced/widowed were 15.1%, and singles 2.8%. Among the samples, the five most frequent CVDs were chronic ischemia (33.2%), unstable angina (22.4%), arrhythmia (9.3%), CHF (8.6%), and acute MI (7.0%), respectively.

The data also showed that the most frequent risk factors in the patients were HTN (47.2%), diabetes (33.6%), hyperlipidemia (32.6%), family history of CVD (23.9%), and smoking (23%), correspondingly. Among the extremely poor, poor, and moderate SES groups, ischemia, and among good SES group, unstable angina were the most frequent diseases. HTN was the most common risk factor in extremely poor and poor SES groups. Likewise, family history of CVD in moderate SES group, and smoking and hyperlipidemia in good SES group were the most common risk factors, respectively.

Table 1. Frequency distribution of the socioeconomic characteristics of hospitalized patients with cardiovascular disease (CVD)

Socioeconomic characteristics		n (%) (n = 721)
Education	High school and lower	586 (81.3)
	Bachelor	129 (27.9)
	MSc and higher	6 (0.8)
Occupational level	Low	12 (1.7)
	Medium	533 (73.9)
	High	176 (24.4)
Family size	≤ 2	186 (25.8)
	3	180 (25.0)
	4	114 (15.8)
	≥ 5	241 (33.4)
Housing	Renting	112 (15.5)
	Property	609 (84.5)
Income level	≤ 1/2 PL	386 (53.5)
	½ PL	278 (38.6)
	PL	35 (4.9)
	2PL	11 (1.5)
	3PL	9 (1.2)
	4PL	2 (3.2)
SES	I (extremely poor)	43 (6.0)
	II (poor)	498 (69.1)
	III (moderate)	165 (22.9)
	IV (good)	15 (2.1)
	V (wealthy)	0 (0)

MSc: Master of Science; PL: Poverty line; SES: Socioeconomic status

There were statistically significant differences by age ($P < 0.001$), gender ($P = 0.006$), and marital status ($P = 0.040$) between different SES groups. Older individuals were placed mainly in the extremely poor and poor groups. In addition, a higher percentage of men were placed in higher SES groups comparing to women. Based on the age of participants, post-hoc test on SES showed that the extremely poor group was statistically significant comparing to good ($P = 0.039$) and moderate groups ($P = 0.017$); this means that the average age of the patients was higher in lower SES groups. HTN ($P = 0.005$) and hyperlipidemia ($P < 0.001$), among risk factors, were statistically significant in SES groups (Table 2). Besides, 10.3% of the patients had two or more diseases simultaneously.

Table 3 showed that smoking patients ($P = 0.030$) and patients with valve disease ($P = 0.010$) had statistically significant relationship with the SES groups, adjusted for age, gender, and marital status.

Table 2. Frequency and univariate analysis of demographic characteristics, risk factors, and cardiovascular disease (CVD) on socioeconomic status (SES) in hospitalized patients with CVD

Variable		Total [n (%)]	SES				P*
			Extremely poor [n (%)] 43 (6.0)	Poor [n (%)] 498 (69.1)	Moderate [n (%)] 165 (22.9)	Good [n (%)] 15 (2.0)	
Age (mean ± SD)		57.4 ± 12.5	61.2 ± 13.3	62.9 ± 12.8	54.6 ± 13.6	50.8 ± 12.1	< 0.001
Gender	Male	395 (54.8)	19 (44.2)	258 (51.8)	109 (66.1)	9 (60.0)	0.006
	Female	326 (45.2)	24 (55.8)	240 (48.2)	56 (33.9)	6 (40.0)	
Marital status	Married	592 (82.1)	33 (76.7)	399 (80.1)	147 (89.1)	13 (86.7)	0.040
	Single/ divorced/ widow	129 (17.9)	10 (23.3)	99 (19.9)	18 (10.9)	2 (13.3)	
Risk factors							
HTN		340 (47.2)	16 (37.2)	258 (51.8)	60 (36.4)	6 (40.0)	0.005
Diabetes		242 (33.6)	10 (23.3)	181 (36.3)	46 (27.9)	3 (33.3)	0.100
Hyperlipidemia		235 (32.6)	7 (16.3)	181 (36.3)	40 (24.2)	7 (46.7)	< 0.001
Family history of CVD		172 (23.9)	9 (20.9)	113 (22.7)	47 (28.5)	3 (20.0)	0.450
Smoking		166 (23.0)	9 (20.9)	121 (24.3)	32 (19.4)	4 (26.7)	0.590
CVDs							
Chronic ischemia		236 (33.2)	15 (34.9)	162 (33.1)	56 (34.4)	3 (20.0)	0.720
Unstable angina		159 (22.4)	9 (20.9)	113 (23.1)	32 (19.6)	5 (33.3)	0.580
Arrhythmia		66 (9.3)	3 (7.0)	47 (9.6)	14 (8.6)	2 (13.3)	0.870
CHF		61 (8.6)	3 (7.0)	43 (8.8)	15 (9.2)	0 (0)	0.640
Acute MI		50 (7.0)	1 (2.3)	32 (6.5)	14 (8.6)	3 (20.0)	0.100
Valve disease		19 (2.7)	3(7.0)	14 (2.9)	2 (1.2)	0 (0)	0.360
CHD		9 (1.3)	0 (0)	6 (1.2)	3 (1.8)	0 (0)	-

* Analysis of variance (ANOVA) test was used for age and chi-square test was used for other parameters

SES: Socioeconomic status; SD: Standard deviation; HTN: Hypertension; CVD: Cardiovascular disease; CHF: Congestive heart failure; MI: Myocardial infarction; CHD: Congenital heart defect

However, the Bonferroni method, which was used to adjust the P-value, suggested that smoking and valve disease would be significant if the P-values were < 0.006 and < 0.001, respectively. Our results also confirmed that the good status of SES reduced the risk of valve disease (72%) and the smoking (39%) significantly (Table 3).

Discussion

The aim of this study was to find out whether the cardiac risk factors and CVDs have any relations with the patients' SES. Our findings showed that most of the patients were placed in the poor SES and there were no patients in the wealthy SES.

Table 3. Multiple logistic regression analysis of the socioeconomic status (SES) on each of risk factors and type of cardiovascular diseases (CVDs) by controlling age, gender, and marital status

Variable		OR (95% CI)	P
Risk factors	Diabetes	1.34 (0.92-1.95)	0.120
	HTN	1.02 (0.70-1.49)	0.880
	Hyperlipidemia	1.17 (0.80-1.72)	0.400
	Smoking	0.61 (0.38-0.97)	0.030
	Family history of CVD	0.79 (0.52-1.18)	0.250
CVDs	Chronic ischemia	1.14 (0.82-1.60)	0.430
	Unstable angina	0.82 (0.57-1.20)	0.310
	Arrhythmia	1.13 (0.67-1.92)	0.640
	CHF	0.99 (0.57-1.71)	0.970
	Acute MI	1.18 (0.66-2.13)	0.580
	Valve disease	0.28 (0.10-0.76)	0.010
	CHD	1.61 (0.43-6.09)	0.470

Mean socioeconomic status (SES): 308.90 ± 67.37, minimum: 180, maximum: 549.50

OR: Odds ratio; CI: Confidence interval; CVD: Cardiovascular disease; HTN: Hypertension; CHF: Congestive heart failure; MI: Myocardial infarction; CHD: Congenital heart defect

This fact may primarily suggest that the SES of the society might be inappropriate. Although patients with CVD cannot be considered as an ample representative of the total population, other studies in Tehran, Iran,[16] and Rafsanjan, Iran,[17] also have shown that very small percentage of people belong to the wealthy SES. The second justification explaining this fact is that the wealthy group might have referred to better hospitals to get better and high-quality medical services, i.e., hospitals in Tehran or abroad. There is, however, no evidence to support this explanation. Many studies have drawn upon the relationship between different socioeconomic indicators and concluded that people in poor SES group had more health problems.[13,18-23] These findings led to the conclusion that the SES is a strong predictor for the occurrence of CVD and cardiovascular side effects. This theory could be applied to explain third possible justification for our findings. This justification is supported by numerous studies, which revealed that the occurrence of heart failure (HF) is very much related to the lower SES, both in the society and among the admitted patients in the hospitals.[13,18-23] Many studies have shown that the risk factors are more common in the lower SES group.[24-29]

Our results indicated that some demographic variables such as age and gender were associated with SES. Aging makes the SES of the people worse. Older patients usually are involved with CVD longer, which can affect their SES.[30,31]

Among the patients, smokers also had lower SES. Smoking habit inflicts a huge financial burden upon people that can make their SES worse. Another study also indicated that cardiac patients from lower SES group had higher rates of smoking. They also had higher rates of heart attacks.[32] Many studies have suggested that the most common risk factor among patients with CVD was smoking.[33-35]

Like the smokers, the women also were placed in lower SES group as compared to the men. It is obvious that some of the women were the heads of their households. It is obvious that men normally have better income than women. Nevertheless, the prevalence of CVD was higher among men. Other studies supported our findings and showed that CVD was more common among men than women.[33,36-38]

The findings showed that the most and the least frequent risk factors in patients with CVD were HTN and smoking, respectively. The prevalence of HTN is expressed variously in Iranian studies. For instance, HTN prevalence among Iranians under 65 years was 20.9%.[39-41] Though smoking was the least CVD risk factor in the patients, this habit in Iranian people has risen from 0.4% to 41.0% in various subpopulations during 1999-2007.[42]

Our results showed that SES groups were statistically significant between patients who smoked and those who had valve disease. Indeed, adjusting the P-value through Bonferroni method indicated that smoking and valve disease would be significant if the P-values changed. Also the good status of SES in contrast to poor status would decrease the risk of valve disease and smoking. Many studies showed that risk factors related to CVDs were more common in lower SES group of society.[24-29] As a result, by improving the level of SES, the frequency of cardiac risk factors such as smoking will be decreased.

This study has some strengths and limitations. The most important strength and novel approach of this study was using the SES model to determine the SES of the patients with heart disease. This model is selected as a more comprehensive approach to determine SES in Iran. Another strength of this study is the use of statistical methods such as Bonferroni correction to show the accuracy of the study that is referred to along with regression. The limitation of this study was the number of patients who eventually were in each group of SES. In fact, after sampling patients, according to the SES score, most of the patients were in the poor and moderate classes, which was due to the context of Iran economic status.

Conclusion

Our findings showed that the frequency of CVD risk factors was higher in lower SES groups and thus SES can be a strong predictor for the occurrence of CVD risk factors as well as CVDs. Our analysis of the risk factors and the type of heart disease on the SES revealed that smoking and valve disease could have significant relationship with each other if the sample size of target population was larger.

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Conflict of Interests

Authors have no conflict of interests.

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A clinical trial on the effect of a multifaceted intervention on blood pressure control and medication adherence in patients with uncontrolled hypertension

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Original Article

Abstract

BACKGROUND: Hypertension (HTN) is the key risk factor for cardiovascular diseases (CVDs). The purpose of this study was to determine the effect of a multifaceted intervention on blood pressure (BP) control and medication adherence (MA) among patients with uncontrolled HTN.

METHODS: A randomized controlled clinical trial study was conducted on 72 patients in the emergency ward who were selected through convenience sampling method. They were randomly divided into intervention and control groups. The studied multifaceted intervention includes motivational interviews and 90 minutes of training sessions, use of a drug reminder box, family support, and 4 phone call follow-ups. The8-Item Morisky Medication Adherence Scale (MMAS-8) was used before and after the intervention. BP was measured in both groups before and after the intervention and compared between them.

RESULTS: No significant difference existed between the two groups in terms of MA and systolic and diastolic BP before the study. The differences between the mean changes in post-intervention systolic (-25.75 ± 19.39 vs. -2.88 ± 11.92 mmHG; P < 0.001) and diastolic (-6.18 ± 8.87 vs. -1.06 ± 8.70 mmHg; P = 0.010) BP in the intervention and control groups were statistically significant. The mean changes in post-intervention MA in the intervention and control group was 2.91 ± 1.64 and -0.36 ± 1.15, respectively; this difference was statistically significant (P < 0.001).

CONCLUSION: The studied multifaceted intervention promoted MA and reduced systolic and diastolic BP. Thus, the use of this method as a supplementary treatment is recommended after patient discharge.

Keywords: Blood Pressure, Hypertension, Medication Adherence, Nursing, Iran

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Introduction

Cardiovascular diseases (CVD) are the first cause of death due to non-communicable diseases worldwide.[1] More than 22% of the urban and rural population in Isfahan, Iran, had hypertension (HTN) in 2014.[2] HTN is a key risk factor for increased mortality and morbidity of CVD. Hence, its management and treatment can significantly reduce the prevalence of CVD in societies.[3,4]

Managing and controlling HTN through lifestyle modification and adherence to drug therapy throughout life is feasible.[5] However, the lack of appropriate medication adherence (MA) is an obstacle for the healthcare team and also a major challenge of controlling this disease.[6]

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The role of drug therapy in controlling or non-controlling blood pressure (BP) is very important.[7] HTN-drugs not only control the disease, but also reduce mortality, side effects, and delayed complication of diseases in societies.[8] Despite the efforts of the healthcare team, many patients still refuse to treat HTN or have uncontrolled HTN, which may be due to side effects of medications. Nearly 85% of patients have experienced at least 1 medication side effect.[9] Moreover, some patients have no symptoms despite their lack of medication use. However, they may experience side effects after taking medications; therefore, they do not take their medications.[5,10] Regardless of the differences in the quality of medication adherence in different cultures and nationalities, about a quarter of hypertensive patients do not follow a suitable medical treatment.[11]

According to a study in Isfahan, over 40% of patients under medical treatment, especially men, have uncontrolled HTN.[12] Another study has shown that 60 out of 100 hypertensive patients under medical treatment suffered from the lack of disease control.[13] Accurate controlling of HTN cannot only improve the quality of life (QOL), but also reduce or eliminate acute and chronic complications.[14]

Various factors negatively affect medication adherence (MA) such as culture, educational facilities, and long-term use of medication and its resulting complications. Therefore, intervention and greater attention of the healthcare team is recommended in these areas so that better results can be achieved from the treatment and management of HTN.[15] Since the training of patients by the healthcare team has a great and constructive role in promoting and improving MA, and also because suitable MA requires high personal awareness, trust in treatment, and trust in the healthcare team, training should be considered as the main key to increasing patients' desire to use prescribed medication.[16,17]

In addition, medication training of patients by the healthcare team can provide satisfaction with medical therapy.[18] Negative consequences of BP control caused by discontentment with HTN treatment could lead to increased frequency of hospitalization.[19] Training provided for patients with HTN should be related to explaining the disease and treatment status, resolving any misunderstandings for patients, and encouraging patients to discuss their medication and schedule.[20,21]

According to a review study in 2012 by Noohi et al., utilizing patient capacities in training and creating satisfaction in using medication along with support from the healthcare team are some of the most manageable factors of this disease.[22]

However, the lack of HTN control in the patients cannot be solved only by training and assurance of promoting medical information. Another problem that causes patients to reduce MA is untimely medication intake, which is more pronounced due to the long-term medication intake, and therefore, using a reminder is the best way of solving this problem.[7,23] In addition, using a multi-part medication box embedded for daily medication can be beneficial.[23] Moreover, in order to improve treatment adherence in patients, we can use encouragements and persuasion through family support[24,25] and remote tracking of the patient by the healthcare team to improve MA and HTN control. Social support between the healthcare team, patient, and families not only result in patients' satisfaction, but also leads to elimination of negative factors such as untimely medication intake.[6,26]

Medical therapy alone cannot be successful in controlling HTN and one-dimensional interventions like training cannot be beneficial for promoting MA. Therefore, our aim is to determine the effects of new multifaceted strategies for improvement of MA by using encouragement interviews and training sessions and its positive feedback on adherence to the treatment by the patients and their families, and the healthcare team support.

Materials and Methods

This randomized clinical trial (RCT) was conducted from April to June 2018 in the emergency ward of Al-Zahra Hospital of Isfahan, Iran. This study was conducted with two groups of intervention and control. First, the study was explained to 72 patients referring to the emergency ward who had the inclusion criteria; those who were willing to take part in the study were asked to provide a written consent form. The participants were chosen based on the inclusion criteria and through convenience sampling. Next, each participant received a numbered card and based on the number, whether it was odd or even, they were randomly assigned to the control and experimental groups. Sample allocation continued until the sample size reached the predetermined number.

The inclusion criteria consisted of at least a 1-year history of HTN approved by the physician and undergoing HTN medical therapy, lack of a history of Alzheimer's disease, BP of higher than 140/90 mmHg at the time of reception in the

emergency ward, and accompaniment of 1 family member. The exclusion criteria consisted of death, any serious or life-threatening problems and any disability during the study, discontentedness or withdrawal from the study. The data were collected through reviewing of medical records and completion of the questionnaire by the researcher. Prior to the beginning of the study and 1 week after the last training session, the BP of the right hand in the intervention group was measured and recorded at 2 times with a 5-minute interval. Moreover, the same measurement was implemented in the control group at the beginning of the study and 1 month after. In addition, MA of both groups was measured and recorded at the beginning of the study and 1 month after the intervention. In order to collect data, a multi-section questionnaire containing questions on demographic information (age, gender, education, marital status, job, duration of the disease, and drug abuse), the type and number of daily medication, systolic and diastolic BP, and pulse. The second section of the questionnaire consisted of the 8-Item Morisky Medication Adherence Scale (MMAS-8), with yes (1)/no (0) answers for questions 1 to 7 and a 5-item Likert scale ranging from always (0) to sometimes (1) for question 8. A score of 8, 6-8, and 6 was considered as high MA, average MA, and low MA, respectively. The MMAS-8 was approved in 2008 by Morisky et al. with a Cronbach's alpha of 0.83 and a high validity in chronic diseases studies.[27] The Persian version was approved in 2015 by Moharamzad et al. for patients suffering from HTN.[28]

To determine the desired sample size, the following formula was used:

$$n = \frac{2(z_1+z_2)^2 s^2}{d^2}$$

where z_1 is the safety factor (95%), z_2 is the test power (80%), and d is the average of a minimum difference of BP score that is 0.7 S. N was equal to 32 which was increased to 36 individuals in each group with the consideration of a 10% dropout rate.

The intervention groups, 4 groups consisting of 10 patients each with a family member, participated in an encouragement interview and received a medication reminder box consisting of 7 parts used for 1 week of medication. Subsequently, in a class located at the entry of Al-Zahra Hospital, 3 training sessions (90 minutes) were held in 3 weeks and emphasis was placed on family support for taking medications. Moreover, a 10-minute phone call was made with the participants and their family member at the end of each week for 4 weeks. The content of the training sessions consisted of the nature and side effects of the disease, the consequences of not taking HTN medication, methods of controlling the disease via appropriate lifestyle changes, and etcetera (Table 1). The information was presented through lectures, PowerPoint, discussions between participants, and a training booklet. The content of the phone calls included question and answer sessions regarding the reinforcement of the content of the training sessions, techniques of strengthening family support, utilization of the medication reminder box, and answers to possible problems of the participants. However, only data collection was performed for the control group before and 1 month after the study. At the end of the study, in order to follow ethical codes, the subjects in the control group were given a medication reminder box and a training booklet with regard to discussions of the training sessions.

This study was implemented with the ethics license number IR.MUI.REC 1396.3.841 from Isfahan University of Medical Sciences, Isfahan, and a code from the Iranian Registry of Clinical Trials (IRCT20110821007391N6).

The numerical variables are reported as mean ± standard deviation (SD), and categorical variables are presented as frequencies and percentages. Using the Kolmogorov-Smirnov normality test, variables were normally distributed. For intra-group comparisons, the paired t-test was used, and for between-group comparisons, the independent t-test was used. The non-numerical values were compared between the two groups using the chi-squared test. For data analysis, chi-squared test, and paired and independent sample t-tests were applied in SPSS software (version 18; SPSS Inc., Chicago, IL, USA).

Results

No significant difference was observed between the two groups regarding age (P = 0.800), years of education (P = 0.170), and duration of the disease (P = 0.240). The average age of the participants in the intervention and control group was 59.17 ± 12.63 and 58.44 ± 12.59, respectively. The mean ± SD of the years of education was 8.78 ± 5.8 years in the intervention group and 7.8 ± 5.40 years in the control group. Moreover, the duration of HTN in the intervention and control group was 10.49 ± 8.91 and 8.42 ± 5.88 years, respectively. There was no significant difference between the two groups in terms of gender (P = 0.810), marital

Table 1. The content of the training sessions

Row	Content	The goal and expectation of the researcher	Training method	Time
First session				
1	Introduction of the researcher and explanation of the purpose of the research and its implementation to the participants	Building trust	Lecture +PowerPoint	10 min
2	Motivation for participation in the research and attention to disease	Encouraging knowledge and understanding about HTN and motivation for research participation	Question and answer	20 min
3	Distribution of drug reminder boxes among patients	Removing or reducing untimely medication intake	Personal	
4	Training of families to remind the patient of drug use	Reminding the patient of the timely intake of medicine by the family	Lecture	
Second session				
1	Explanation of the definition of HTN and its risk factors and risks of not controlling HTN	Increasing their understanding and correcting their perspective toward the conditions of their disease	Lecture +PowerPoint	15 min
2	Questions about the drug problems of patients	Motivating the recognition of a drug problem and trying to solve the problem	Question and answer	5 min
3	Explanation of how to control HTN and maintain a healthy lifestyle	Encouraging increased self-care in controlling HTN	Lecture +PowerPoint	10 min
Third session				
1	A review of the contents of the previous session	Removing or reducing forgetfulness among patients	Lecture	5min
2	Questions about the complications of uncontrolled BP and explaining the causes of not controlling the disease	Increasing their awareness and encouraging them to learn more about helping themselves to better control their illness and identify their own problems	Question and answer	5 min
3	Evaluation of non-drug intake factors	Informing patients about their condition in drug therapy	Lecture +PowerPoint	10 min
4	Questions and answers about medications	Increasing their knowledge of medicine	Question and answer	5 min
5	A brief explanation of the use of antihypertensive drugs	Increased patient satisfaction with treatment	Lecture +PowerPoint	5 min
Fourth session				
1	A review of the contents of the previous session	Removing or reducing forgetfulness among patients	Lecture	5 min
2	Questions about the complications of not controlling HTN	Increasing their awareness and encouraging them to learn more about helping themselves to better control their illness and identify their own problems	Question and answer	5 min
3	Study of the factors causing non-controlled HTN	Helping the patients to have an understanding about their treatment condition	Lecture +PowerPoint	10 min
4	Questions and answers about medications	Increasing their knowledge of medicine	Question and answer	5 min
5	An explanation of the use of antihypertensive drugs	Increasing patient satisfaction with medication therapy	Lecture +PowerPoint	5 min

HTN: Hypertension; BP: Blood pressure

status (P = 0.520), employment status (P = 0.280), cigarette, pipe, and hookah smoking (P = 0.120), diabetes (P = 0.200), and hyperlipidemia (P = 0.380). Of the intervention and control group participants, 19 (52.8%) and 18 (50%) were women. Most of the subjects in the intervention (n = 29; 80.6%) and control groups (n = 31; 86.1%) were married. In the intervention group, 13 (36.2%), 7 (19.4%), and 16 (44.4%) individuals were, respectively, employed, retired or unemployed, and housewives.

Table 2. Comparison of demographic and clinical characteristics between the intervention and control groups

Group		Intervention group (n = 36)	Control group (n = 36)	P*	P**
		Mean ± SD	Mean ± SD		
Age (year)		59.17 ± 12.63	58.44 ± 12.59	0.800	-
Years of education		8.78 ± 5.08	7.08 ± 5.40	0.170	-
Duration of the disease (year)		10.49 ± 8.91	8.42 ± 5.88	0.240	-
		n (%)	n (%)		
Sex	Female	19 (52.8)	18 (50.0)	-	0.810
	Male	17 (47.2)	18 (50.0)		
Marital status	Married	29 (80.6)	31 (86.1)	-	0.520
	Divorced or widowed	7 (19.4)	5 (13.9)		
Job	Employed	13 (36.2)	8 (22.2)	-	0.280
	Retired/unemployed	7 (19.4)	12 (33.3)		
	Housewife	16 (44.4)	16 (44.5)		
Smoking, pipe, and hookah	Yes	8 (22.2)	14 (38.9)	-	0.120
Diabetes	Yes	4 (11.1)	8 (22.2)	-	0.200
Hyperlipidemia	Yes	6 (16.7)	9 (25.0)	-	0.380

Values are presented as mean ± standard deviation (SD) or number (%).
* values of the independent t-test; ** values of the chi-square test

In the control group, 8 (22.2%), 12 (33.3%), and 16 (44.5%) individuals were, respectively, employed, retired or unemployed, and housewives. In the intervention and control group, respectively, 8 (22.2%) and 14 (38.9%) individuals used tobacco. The prevalence of diabetes and hyperlipidemia was 11.1% (n = 4) and 16.7% (n = 6) in the intervention group, and 22.2% (n = 8) and 25% (n = 9) in the control group, respectively (Table 2).

The mean ± SD of systolic and diastolic BP in the intervention group was, respectively, 162.79 ± 14.21 and 84.08 ± 10.79 before the intervention, and 137.04 ± 14.21 and 77.90 ± 8.74 1 month after the intervention, thus representing a significant decrease (P < 0.001). In the control group, the mean ± SD of systolic and diastolic BP was, respectively, 166.69 ± 15.29 and 81.84 ± 13.17 before the intervention, and 163.80 ± 14.90 and 80.77 ± 11.57 after the intervention, representing no significant difference. There was a significant difference in terms of average changes in systolic BP between the intervention group (-25.75 ± 19.39) and the control group (-2.88 ± 11.92) (P < 0.001). The average of variation in diastolic BP in the intervention and control group was -6.18 ± 8.87 and -1.06 ± 8.70, respectively; there was a statistically significant difference between the two groups (P = 0.010). The reduction of diastolic BP in the intervention group was greater than that in the control group (Table 3).

Before the intervention, no significant difference was observed between the two groups regarding MA score (P = 0.770). However, after the study, this difference was significant (P < 0.001). The pre-intervention and post-intervention mean ± SD of MA score in the intervention group was 3.86 ± 1.75 and 6.77 ± 1.39, respectively, which were significantly different (P < 0.001).

Table 3. The average of pre-intervention and post-intervention blood pressure in the intervention and control groups

BP		Intervention group	Control group	P*
		Mean ± SD	Mean ± SD	
Systolic BP	Before the intervention	162.79 ± 14.21	166.69 ± 15.29	0.260
	After the intervention	137.04 ± 14.21	163.80 ± 14.90	< 0.001
P**		< 0.001	0.150	
Mean changes in systolic BP		-25.75 ± 19.39	-2.88 ± 11.92	< 0.001
Diastolic BP	Before the intervention	84.08 ± 10.79	81.84 ± 13.17	0.430
	After the intervention	77.90 ± 8.74	80.77 ± 11.57	0.230
P**		< 0.001	0.460	
Mean changes in diastolic BP		-6.18 ± 8.87	-1.06 ± 8.70	0.010

Values are presented as mean ± SD.
* values of the independent t-test; ** values of the paired t-test
SD: Standard deviation; BP: Blood pressure

Table 4. Pre-intervention and post-intervention medication adherence score in the intervention and control groups

Medication adherence score	Intervention group	Control group	P*
	Mean ± SD	Mean ± SD	
Before the intervention	3.86 ± 1.75	3.75 ± 1.46	0.770
After the intervention	6.77 ± 1.39	3.38 ± 0.99	< 0.001
P**	< 0.001	0.060	P**
Mean changes of medication adherence score	2.91 ± 1.64	-0.36 ± 1.15	< 0.001

Values are presented as mean ± standard deviation (SD).
* values of the independent t-test; ** values of the paired t-test

Nevertheless, this difference was not significant in the control group (P = 0.060). Based on independent t-test, the mean changes in MA score between the pre-intervention and post-intervention in the intervention and control group was 2.91 ± 1.64 and -0.36 ± 1.15, respectively, and the difference was statistically significant (P < 0.001) (Table 4).

Discussion

Adherence to the drug regimen is important in controlling HTN. The purpose of this study was to determine the effect of a multifaceted intervention on MA and BP scores among 72 participants. Based on the results of various researches, factors such as gender, age, education, duration of HTN, and diseases such as diabetes and hyperlipidemia are effective factors impact BP management.[29] Thus, the two groups were compared in this regard and no significant difference existed, showing that they were similar in terms of these factors. Furthermore, the two groups were similar in terms of marital status, employment status, and smoking, with no statistically significant difference. In the intervention group, there was a significantly lower average of systolic and diastolic BP after the intervention compared to before the intervention. However, there was no significant difference in the post-intervention systolic and diastolic BP in the control group compared to pre-intervention. The systolic and diastolic BP of the two groups did not have a significant difference before the intervention. After the intervention, only the difference in systolic BP between the two groups was significant.

Leiva et al. reported a reduction in systolic and diastolic BP in the intervention group through a multifaceted intervention including self-control of BP, physician's visit, encouragement interview, drug reminder box, and family support during the first, third, and ninth months of intervention.[23] Their findings were in agreement to those of the present study. Moreover, Fakhri et al. performed 3 sessions of weekly training accompanied with stimulation interviews for 3 weeks, which led to a greater reduction in the systolic and diastolic BP of the intervention group than the control group.[30]

Changes in average systolic and diastolic BP from pre-intervention to post-intervention in the intervention group was -25.75 ± 19.39 and -6.18 ± 8.87, respectively. In a study by Williams et al., systolic BP in the intervention group decreased to 6.9 mm Hg and their diastolic BP to 2.25 mm Hg after the intervention.[31] Furthermore, MA in the intervention group was improved compared to the beginning of the study,[31] which is consistent with the results of the present study. Moreover, after performing 5 sessions of lifestyle education during 5 weeks, Babaei-Sis et al. reported an 8.3 mmHg decrease in the systolic BP and a 2.5-mmHg decrease in the diastolic BP of the intervention group. There was a significant difference between the two intervention and control groups after the intervention, although there was no statistical difference before the intervention.[32] The results of another study indicated that every 10 mmHg reduction in systolic BP significantly reduced the risk of major CVD events, coronary heart disease, stroke, and heart failure.[33] It also significantly decreased all-cause mortality by 13%.[33]

Furthermore, the results of this study showed that although there was no significant difference between the two groups before the intervention in terms of the MA score, there was a significant difference between the two groups after the study. The MA score of the intervention group had increased, while the MA score of the control group had decreased. In fact, this multifaceted intervention has been able to notably enhance this substantial element in controlling and treating HTN.

According to the results of this study, the average score of MA before the study in the intervention and control group was about 4, which is indicative of a poor MA in all subjects. This outcome was in line with the cross-sectional study by Al-Ramahi in which over 54% of the participants had poor adherence.[34]

Based on the findings, the mean changes in MA score in the intervention and control group were

2.91 ± 1.64 and -0.36 ± 1.15, respectively, and the two groups had a significant difference meaning a greater increase in the score of the intervention group than the control group. Fakhri et al. performed a study with the purpose of determining the effect of a theory-based education on improving the compliance with the drug regimen with 3 sessions of training for 1 month. Before the intervention, 8.6% of the participants in the intervention group and 7.1% in the control group had a good MA that reached 50% in the intervention group after the intervention, while the control group had an unchanged percentage.[30]

Conclusion

The results of this study indicated that family support of the patient along with healthcare team phone call follow-ups have complemented the effects of training and the use of a drug reminder box. It has also contributed to the stabilization of trained behaviors, thus positively affecting the management of systolic and diastolic BP and MA.

According to the findings of the research, it can be concluded that a multifaceted intervention focusing on healthy lifestyle education, strengthening patient support for drug use by its most important supporter, the family, and using a drug reminder box to eliminate untimely medication intake can significantly affect the reduction of BP and its control, and therefore, reduce systolic and diastolic BP by more than 25 and 6 mmHg, respectively. Research findings also suggested that this multifaceted intervention not only reduces BP, but also improves patient MA, which is one of the most important challenges the healthcare team are faced with. Therefore, it can decline the concern for disease control and improper use of drugs for patients, their families, and the healthcare team in the society.

It can be concluded that the increase of the 3 MA scores in the intervention group in comparison with the control group shows that this type of intervention has had an undeniable contribution to medication use and adherence to HTN medication in hypertensive patients.

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Conflict of Interests

Authors have no conflict of interests.

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Water hardness zoning of Isfahan Province, Iran, and its relationship with cardiovascular mortality, 2013-2015

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Original Article

Abstract

BACKGROUND: Cardiovascular disease (CVD) is one of the common diseases and today, it is considered as not only an important cause of mortality but also a significant aspect of health geography. The evidence presented in the literature indicates that hard water may reduce the cases of sudden death caused by CVDs because drinking water contains significant amounts of calcium and magnesium, which play a crucial role in the electrical activity of heart. Hence, the present study aimed at investigating the relationship between water hardness and CVD mortality rate in Isfahan, Iran.

METHODS: In this ecological study, the available data regarding the cardiovascular mortality rate and water hardness have been used. Preparation of zoning map has been conducted using the Geographic Information System (GIS) software considering Inverse Distance Weighting (IDW) interpolation models. Moreover, statistical analysis has been conducted using SPSS software.

RESULTS: A reverse relationship was observed between cardiovascular mortality rate and water hardness. However, the observed relationship was not statistically significant (2013: r = -0.066, 2014: r = -0.155, 2015: r = -0.051, P > 0.050).

CONCLUSION: The results of mapping with GIS and statistical analysis with SPSS both indicated a non-significant inverse relationship between the water hardness and CVDs. However, lack of a significant relationship highlights the necessity of conducting similar studies involving larger sample sizes and wider areas of investigation to present a definitive and generalizable result.

Keywords: Water, Hardness, Cardiovascular Diseases, Iran

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Introduction

Cardiovascular disease (CVD) is the leading cause of mortality and disability worldwide.[1,2] Today, in most countries of the world including developing countries, it is recognized as one of the most significant threats to human health.[3] In this regard, the World Health Organization (WHO) has estimated that if no measure is taken to improve cardiovascular health, by 2020, 25% of health years will have been lost due to CVD.[4,5]

Although CVDs are recognized as the leading cause of death in most countries of the world, over the past few decades, the rate of mortality resulted from these diseases has considerably declined in European, American countries, etc. The trend is unfortunately increasing in other countries such as China, India, Pakistan, and Iran.[4-6]

Accordingly, the occurrence of CVDs is different in different geographic regions. In this respect, a bulk of epidemiologic studies has identified the factors that could explain it and identified the underlying causes of this disease including diets, genetics, and environmental factors.[7,8] According to the previous studies, one of the environmental factors which plays a large and important role in CVD is water type, water quality, and its hardness.[9-12] Water hardness is related to magnesium, calcium, strontium, iron, and other ions, which are soluble in water with bicarbonate anions, carbonate, sulfate, and chlorine.[13]

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Total water hardness is defined as the temporary or carbonate hardness plus permanent or non-carbonate hardness. A good number of studies have been devoted to not only evaluating water hardness by separating dissolved salts from hard water but also examining its relationship with various diseases such as blood pressure disorders, gastric cancer, esophagus disorders, CVDs, etc.[9-15] Studies have shown that magnesium changes can be of great importance in hypertension (HTN),[16] electrical disorders of the heart and arrhythmias,[17] and cardiovascular system.[18] Moreover, dietary calcium intake can reduce the risk of cardiovascular events associated with high blood pressure, so that the higher the calcium, the stronger the muscle contractions of the heart will be.[17] Hence, as hard water can provide up to 9% of the daily calcium intake, mineral-rich water can significantly contribute to supplementing dietary intake of calcium and magnesium.[19]

Despite the existence of studies confirming the association between water hardness and CVD or its mortality rate, many other studies have found no significant relationship between the disease and water hardness or even the direct relationship between water hardness and mortality rate.[20,21] Therefore, it seems that the existence and the relationship between hardness and mortality due to CVD is still uncertain and further studies in this regard is essential, especially in Iran, as one of the developing countries with a high rate of mortality due to this disease and in areas with specific geological climates.

Nowadays one of those software programs which is wildly used to inform health management systems in research in addressing the zoning of various disease is Geographic Information System (GIS).[22]

The selection of Isfahan Province, Iran, as the target area of the study was due to its limestone and chalky land structure, which has led to variation of water hardness level in various areas of this province. This problem has been exacerbated due to the low level of rainfall and occurrence of drought in this region. Hence, the present study provided the mortality zoning of CVDs and water hardness by GIS and statistical relationships between the mentioned variables during the years 2013-2015 in Isfahan.

Materials and Methods

This ecological study was conducted on the rate of cardiovascular mortality in the years of 2013-2015 in 25 cities of Isfahan Province.

The data required in this study were collected in two parts. In the first stage, information on water hardness was studied over a period of three years from the Urban and Rural Water and Wastewater Department of Isfahan Province. To ensure the accuracy of the recorded data, the samples of drinking water were randomly selected and analyzed in three cities and the degree of hardness of water and salts (calcium, magnesium) was extracted. As the test results did not contradict the information recorded in this organization, the water hardness assessed in the organization was assured.

In the second stage, mortality data from CVDs were extracted and recorded from the Registration Department and Provincial Health Center of Isfahan during 2013-2015. In addition, the population of these cities was taken over the past three years by the Bureau of Statistics and Information of Isfahan Province.

Given the following formula for calculating the mortality rate, the mortality rate due to CVD was calculated in each of the three years in each of the 25 cities of Isfahan Province.

$$\text{The mortality rate due to CVD} = \frac{\text{Number of deaths due to CVD in the desired year}}{\text{Total population of the province within the same year}} \times 1000$$

The zoning of the mortality frequency of CVDs as well as water hardness was prepared in GIS software (version 9.9, ESRI, USA) using Inverse Distance Weighting (IDW) models.

According to previous studies, the ideal water hardness was 170 mg/l, so that levels above 170 mg/l had definite relevance for reducing CVD.[12] Also in this study, water hardness went under the rubric of soft, moderate, and hard: soft (161-175 mg/l), moderate (175-300 mg/l), and hard (> 300 mg/l), which is used for zoning water hardness in GIS.[23] Furthermore, to prepare the zoning map of the cardiovascular mortality rate, the total average of mortality rate in the three-year survey (2013-2015), which was 5.8 per 1000, was used.

Collected data were entered into SPSS software (version 20, IBM Corporation, Armonk, NY, USA) and data were represented as mean ± standard deviation (SD). At the level of inferential statistics, due to the use of mortality rate and its normal distribution, Kolmogorov-Smirnov test (K-S test), one-way analysis of variance (ANOVA), and Pearson correlation coefficient were used. Finally, the results extracted from this software were matched with the results of the GIS zoning map.

Results

Mortality rate and water hardness in each of the three years in each of the 25 cities of Isfahan Province are shown in table 1.

Table 1. Mortality rate of cardiovascular diseases (CVDs) in the years 2013-2015

City	Mortality rate 2013	Mortality rate 2014	Mortality rate 2015
Aran and Bidgol	2.4	2.6	2.8
Ardestan	3.2	3.2	2.8
Isfahan	1.7	1.6	1.7
Borkhar	2.8	3.2	3.2
Boin and Miandasht	2.8	3.6	3.7
Tiran and Karvan	1.7	1.5	1.9
Chadegan	2.1	1.5	2.1
Khomeini Shahr	1.8	1.8	2.4
Khansar	4.8	4.0	3.4
Khor and Biabanak	3.0	3.8	4.2
Dehaqan	3.0	3.0	2.7
Semirom	3.0	1.8	2.2
Shahin Shahr	3.6	3.4	3.2
Shahreza	2.1	2.2	2.0
Fereidan	1.6	1.6	1.5
Fereydun Shahr	2.0	1.5	1.7
Falavarjan	2.4	1.4	1.3
Kashan	2.2	2.0	1.9
Golpayegan	2.8	2.6	3.2
Lanjan	1.5	1.4	1.9
Meimeh	2.4	3.0	4.4
Mobarakeh	2.0	1.7	2.1
Naeen	4.0	2.6	2.6
Najaf Abad	2.4	1.8	2.0
Natanz	3.0	3.0	2.5

The results of the evaluation of cardiovascular mortality rates in 25 cities of Isfahan Province during 2013-2015 indicated that the mean cardiovascular mortality rate in 2013, 2014, and 2015 was 2.57 ± 0.79, 2.39 ± 0.84, and 2.54 ± 0.82, respectively, which had no significant difference in the three years of study ($P > 0.050$) (Table 2).

In addition, comparison of this rate among the 25 cities of Isfahan Province in a total of three years showed that the cities of Lanjan and Fereidan with the mean of 1.60 ± 0.26 and 1.57 ± 0.06, respectively, had the lowest rate and Khansar and Khor and Biabanak with the mean of 4.07 ± 0.70 and 3.67 ± 0.61, respectively, had the highest mortality rates due to CVDs. Statistically, the mortality rates were significantly different among the cities under study ($P < 0.001$) (Figure 1).

In the same vein, in figure 2, the zoning map of mortality rate of CVDs in Isfahan Province is presented using the IDW model.

On the other hand, the range of water hardness during the years 2013-2015 in total of 25 studied cities was 161 mg/l to 800 mg/l and the mean value was 280.24 ± 134.73 mg/l, so that 3 cities (12%) (Meyme, Borkhar, Shahin Shahr) were in the range of water hardness of 161-175 mg/l, 16 cities (64%) were in the range of water hardness of 175-300 mg/l, and 6 cities (24%) (Aran and Bidgol, Natanz, Shahreza, Dehaghan, Lanjan, and Falavarjan) were in the range of over 300 mg/l (Figures 3a, 3b).

Moreover, the relationship between cardiovascular mortality rate in three years with water hardness was reversed and poor, equal to -0.062, which was not statistically significant ($P = 0.769$); in addition, in evaluating this relationship in each of the three years, it was found that the relationship was reversed and negligible ($P > 0.050$). In fact, it can be said that water hardness has a reverse relationship with cardiovascular mortality that in this study due to the evaluation in a limited area and sample size, this relationship is not significant (Table 3).

Discussion

The present study investigated the water hardness zoning and cardiovascular death. According to surveys, the cities with higher water hardness have lower rate of cardiovascular death.

However, there was no significant relationship between water hardness and cardiovascular death in this study. Matching of the two zoning maps (water hardness and cardiovascular death) illustrated that Aran and Bidgol, Natanz, Falavarjan, Lanjan, Dehaghan, and Shahreza had high water hardness (more than 300 mg/l) and cardiovascular mortality rates were lower in these areas than in areas where water hardness was lower (Meimeh, Borkhar, Khomeini Shahr, Khansar). The CVD deaths were even low in the cities with medium range of water hardness.

Table 2. Determining and comparing the rate of cardiovascular mortality in the years 2013-2015

Mortality rate	Minimum	Maximum	Mean ± SD	P
2013	1.50*	4.80**	2.57 ± 0.79	0.713
2014	1.40*†	4.00**	2.39 ± 0.84	
2015	1.30†	4.40††	2.54 ± 0.82	

* Lanjan; ** Khansar; † Falavarjan; †† Meimeh
SD: Standard deviation

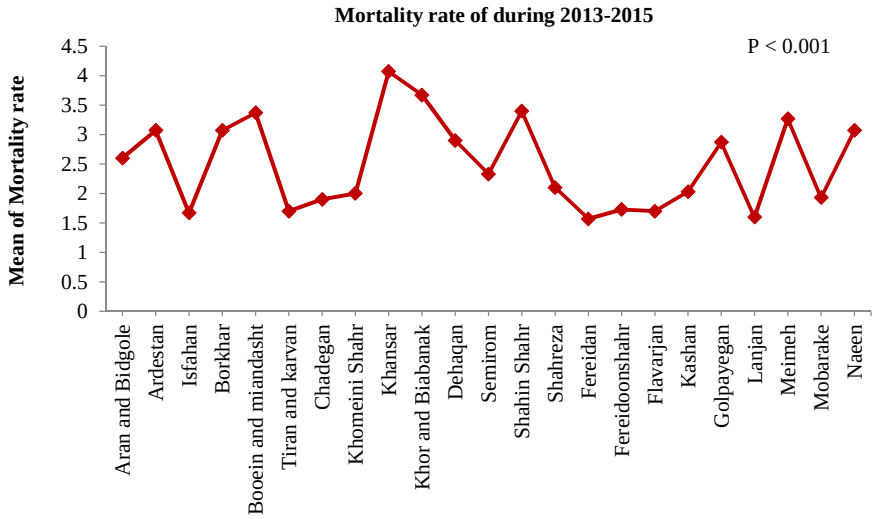

Figure 1. Mean mortality rate of cardiovascular disease (CVD) for a total of 3 years in 25 cities of Isfahan Province, Iran

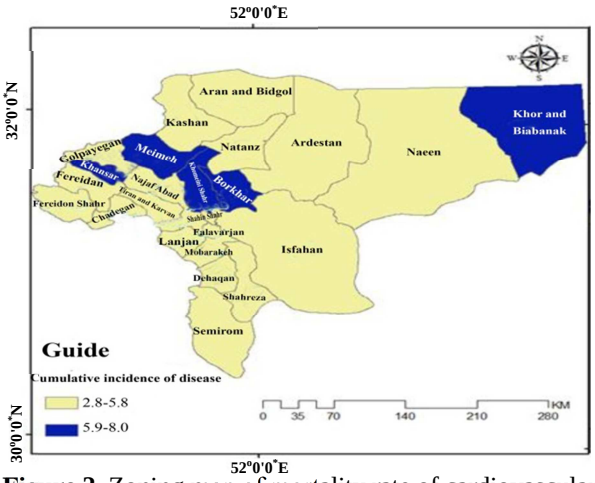

Figure 2. Zoning map of mortality rate of cardiovascular diseases (CVDs) in Isfahan Province, Iran, using the Inverse Distance Weighting (IDW) model

The conducted zoning demonstrated that most of the regions of the province had hard or very hard water. Investigation of the geographical structure effects on water hardness showed that geomorphological factors such as slope, height, and channel directions affected the geographical structure of the studied region and resulted in a situation in which the water hardness was not high in regions with lime soil, because the dissolved lime was transferred to underground water of downstream regions due to high slope and height of the region. That is why in Semirom and Fereydun Shahr, the water hardness was lower than the downstream regions.

A study was conducted in Japan which showed a significant relationship between the quality of drinking water and CVD deaths.[24]

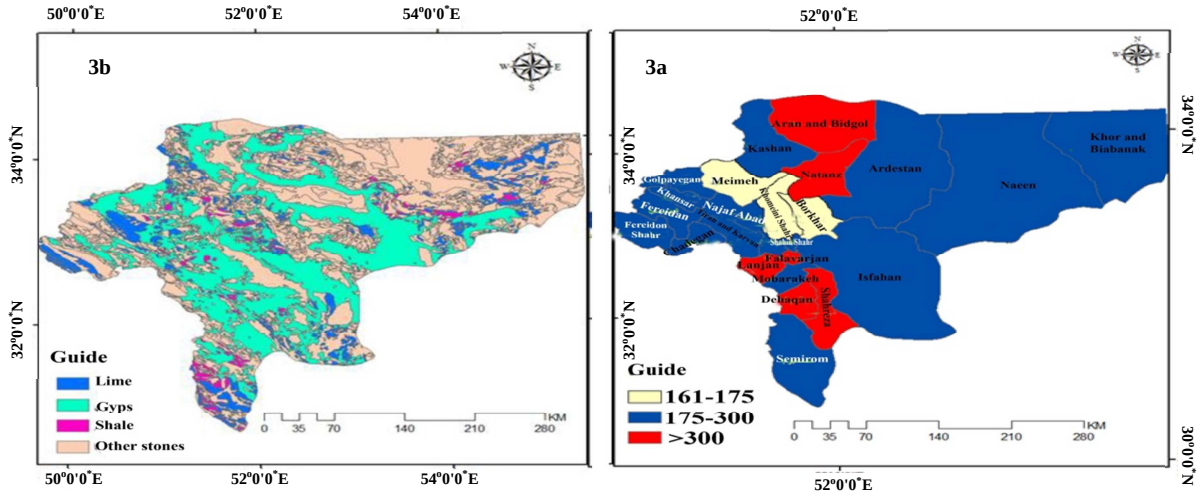

Figure 3. Zoning map of water hardness in various cities of Isfahan Province, Iran; a) According to water hardness, b) According to minerals present in water

Table 3. The relationship between mortality rate of cardiovascular disease (CVD) and water hardness in 2013-2015

Mortality	Water hardness	
	Correlation	P
2013	-0.066	0.755
2014	-0.155	0.459
2015	-0.051	0.807
Total (in three years)	-0.062	0.769

After that, several other studies in different countries revealed negative relationship between cardiovascular death and water hardness.[20] Several papers have been published about drinking of hard water and its impact on health but none of them showed correlation. Most of the studies showed a negative and significant relationship between magnesium-containing water and CVD death. Water hardness may be also associated with CVD risk factors; for instance, positive correlations of water magnesium and calcium with blood pressure is documented.[25] In 2003, a study in Sweden revealed a significant relationship between calcium level and CVDs.[26] Another study in the same year showed a significant relationship between calcium level and CVD, when calcium level was more than 94 mg/l and the protective effect of magnesium was between 4 and 11 mg/l.[13]

In Valencia, Spain, it was said that there was a relation between the mortality rate of CVD and the hardness of drinking water, and this is more related to the concentration of magnesium.[27] In 2010, it was revealed that there was no significant relationship between CVD and water hardness; however, there existed a reverse relationship between consumption of magnesium-containing water and death due to cerebral stroke.[20]

A study was conducted in Khansar, Iran, and the data on water hardness was collected from urban and rural centers, and a comparison was made in 2010 and 2011. It was concluded that the protective effects of water hardness with magnesium were related to CVDs.[19] The results of another showed that water hardness might have a protective role against the early stages of atherosclerosis in children and adolescents.[28]

In 2014, a study was conducted in Bosnia and Herzegovina (Mostar City) on soft and hard water consumers. It was shown that those who used soft water had CVD prevalence rate of 21.3%, while this rate was 13.7% in hard water consumers.[12] In the same year, a study in Sweden showed a strong relationship between water hardness and CVD and expressed that for having preventive effects, magnesium and calcium should be considered together.[11]

Other study has shown that the relationship between magnesium of drinking water and the risk of mortality rate of CVD was considerable in Scandinavia.[29]

Conclusion

Acording to the results of this study, there was a non-significant inverse relationship between water hardness and mortality, but it seems that due to the geographical conditions and water hardness in this area and the results of the other study, more advanced studies can produce more accurate results in this regard.

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Conflict of Interests

Authors have no conflict of interests.

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The effectiveness of dialectical behavior therapy on adherence to treatment and self-caring behavior in patients with coronary heart disease

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Original Article

Abstract

BACKGROUND: The aim of this study was to investigate the effectiveness of dialectical behavior therapy (DBT) on adherence to treatment and self-caring behavior in patients with coronary heart disease (CHD).

METHODS: This was an experimental study based on control and experimental groups with pre-test and post-test. 32 male and female patients with CHD having at least high school diploma, referring to Isfahan cardiovascular research institute, Isfahan, Iran, were selected and placed randomly in two groups of control and experimental. Pre-test stage was done for both two groups by 8-item Morisky Medication Adherence Scale (MMAS-8) and Self-Care of Coronary Heart Disease Inventory (SC-CHDI). The experimental group was placed under the intervention of DBT for 8 sessions of 2 hours (once a week). Afterwards, the post-test was done for both groups.

RESULTS: It was shown by analyzing results from t-test that adherence to treatment and self-care behavior significantly increased in experimental group comparing to control group [(1.81 ± 0.75 vs. 5.19 ± 1.22, P < 0.001) and (72.50 ± 4.38 vs. 55.50 ± 7.42, P < 0.001), respectively]. Also results showed that self-caring and adherence to treatment significantly increased after being adjusted for baseline measurement (P < 0.001). The findings showed that DBT had effect on adherence to treatment and self-caring behavior of patients with CHD.

CONCLUSION: On the basis of results, it could be said that DBT intervention can have positive impact on adherence to treatment and self-caring behavior of patients with CHD.

Keywords: Coronary Disease, Dialectical Behavior Therapy, Treatment Adherence, Self-Care

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Introduction

Today, cardiovascular diseases (CVDs) are the most common causes of death in most countries of the world such as Iran and are the most important causes of disability. Despite quick diagnostic and treatment progresses, one third of patients who suffer from a heart attack are still dying; also, two thirds of those who survive will never fully recover and return to normal life.[1]

Cardiovascular specialists have linked well-known physical factors such as high blood pressure, high level of bad cholesterol, diabetes, lack of physical activities, obesity, and heredity to vascular disease. However, evidence suggests that these factors predict a maximum of 50% of the disease and the above-mentioned physical factors cannot singly explain the incidence and persistence of coronary heart disease (CHD). Health psychologists have been attracted to the key role of non-biological factors in CHD by new medical-behavioral progresses and it has been a while that researches about this disease have been directed to psychological and mental-social factors.[2] One of the most important factors that can have a significant impact on mental illness is "adherence to treatment".

Studies have shown that at least 50% of patients do not follow their therapeutic recommendations and this leads to their re-hospitalization.[3]

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It has been especially considered to review effective factors on adherence to treatment in these patients due to the high prevalence of CHD.[4] According to this, 30%-70% of all patients do not completely follow treatment advises. Adherence is a multiple concept which consists of all behaviors conformed to recommendations of health experts and indicates the extent to which the patient responds to the acts or treatments which were advised by physician.[5]

Nowadays, CHD has become a social problem in Iran; therefore, self-care behaviors are important for people with chronic illnesses. And patients can affect their comfort, functional abilities, and disease progress by gaining self-care skills.[6] The key principle in self-care is participating in and accepting responsibility by patients who can control many complications of the disease by proper managing of self-care behaviors.[7]

Effective self-care is an important factor in promoting positive health outcomes and preventing repetitive hospitalization of patients with CHD.[8] It causes re-hospitalization and making patients worse the self-care non-observance; therefore, it has been more focused on accepting treatment and self-care during last year.[9]

According to the relationship between life quality and mental health and also high spread of psychological issues in patients with CHD, it seems urgent to effectively involve improving mental health conditions and life quality of patients. In this research, dialectical behavior therapy (DBT) is used to adhere to treatment and self-care and consequently reduce CHD. By considering the role of non-adherence to treatment and self-care behaviors in arising and sustaining heart disease, therapies which emphasize to improve conflicts and emotions for removing conflicts and gaining social supports could play an important role in treatment and prevention of recurrence of heart disease. One of the inventions in psychological treatments is DBT, which emphasizes on both gaining skills and adjusting emotions.

DBT is a cognitive-behavioral approach, which emphasizes on the psychosocial-social aspects of treatment. This approach mixed interventions related to cognitive-behavioral treatments which are based on principle of change with oriental philosophy of mind tests and techniques based on principle of acceptance; accordingly it suggests four interventional components in its treatment method: fundamental consciousness and distress tolerance as components of acceptance and emotional adjustment and interpersonal efficiency as change components.[10] This method trains patient the required skills to deal with unsafe behaviors and change them.[11]

The main issue of this study comes from this point that in spite of beneficial effects of DBT that is a special type of cognitive-behavioral psychological treatment, the lack of such studies is so obvious in chronic diseases such as CHD by reviewing conducted researches in Iran. It is clear that DBT is an effective treatment in this field. Therefore, in this research, the main issue is to review effectiveness of DBT on adherence to treatment and self-care behavior of patients with CHD. According to what mentioned before, the question is whether DBT can affect the adherence to treatment and self-care behavior of patients with CHD?

Materials and Methods

This experimental study with control group was conducted in late 2017 on patients with CHD who referred to Isfahan Cardiovascular Research Center, Isfahan, Iran. The criteria for entry included the education level of at least high school diploma, age over 20 years, and the failure to receive any other educational program before and during the conduct of DBT; and the criteria for exclusion were: severe psychiatric illness simultaneously with CHD and other chronic diseases including diabetes. The sample size was selected based on the quasi-experimental researches, which is considered to be at least 15 in each quasi-experimental study.[12] So, after coordinating with the management and authorities of the Isfahan Cardiovascular Institute, 800 files of patients that referred to this center were submitted and evaluated, and by preliminary examination of the cases, about 80 people were eligible to participate in the research based on the criteria for inclusion and exclusion. Among them, 40 patients with CHD were selected through available sampling method and then randomly divided into two experimental and control groups (each included 20 people). Since some of the patients lived far from the hospital, number of participants in all groups was reduced to 16.

In the pre-test phase, for the two groups, the 8-item Morisky Medication Adherence Scale (MMAS-8)[13] and the Self-Care of Coronary Heart Disease Inventory (SC-CHDI)[14] were used. Then, DBT interventions (a brief description of DBT intervention in table 1) were performed for the experimental group for 8 sessions (2 months of a 2-hour session a week). In the post-test, again, the mentioned questionnaires were performed for both experimental and control groups and the data were analyzed.

Table 1. A brief description of dialectical behavior therapy (DBT) intervention sessions based on Marsha Linehan instructions[15-17]

Sessions	Brief description
Session 1 (mindfulness 1)	Familiarity with the concept of mindfulness and three mental states (reasonable mind, emotional mind, and wise mind)
Session 2 (mindfulness 2)	Teaching two types of skills to attain mindfulness; "What" skills (including viewing, description, and participation) and "How" skills (including non-judgmental stance, inclusive self-consciousness)
Session 3 (distress tolerance 1)	Learning distraction strategies with ACCEPTS skills (activities, contributing, comparisons, emotions, pushing away, thoughts, and sensation)
Session 4 (distress tolerance 2)	Learning self-soothing with five senses
Session 5 (emotion regulation 1)	Teaching a pattern of identifying emotions and tagging them, which leads to increased emotional control
Session 6 (emotion regulation 2)	Teaching positive emotional experiences by creating short-term positive emotional experiences
Session 7 (interpersonal effectiveness 1)	Opportunities for interpersonal effectiveness (the proportionality between your demands and the demands of others; the proportion of demands and musts)
Session 8 (interpersonal effectiveness 2)	The goals of interpersonal effectiveness (obtaining goals in a situation and confronting with resistance and conflict)

MMAS-8 was used to measure patient adherence to the drug regimen. The scale consists of eight questions, first seven items having a dichotomous answer (yes/no) that indicates adherent or non-adherent behavior. For item 8, a patient can choose an answer on a 5-point Likert scale, expressing how often happens that a patient does not take his medications. MMAS-8 scores can range from 0 to 8 points.[13] The scores of all the items in the questionnaire are added together to calculate the total score of the questionnaire. The overall score ranges from zero to eight. For a score of more than two, poorer drug adherence, score one and two, moderate adherence, and zero score, high adherence is considered.

Regarding validity and reliability of this questionnaire (MMAS-8), in the research of Kooshyar et al., the formal and content validity of the tool was confirmed by specialists, and also its internal reliability was reported by Cronbach's alpha of 0.68.[14]

SC-CHDI for CHD was developed by Vaughan et al.[18] The questionnaire consisted of 22 items and 3 sub-scales (self-care maintenance, management, and confidence). Self-care maintenance scale items were ranked on four grades from 1 (never) to 4 (always), self-care management scale items, on the grading of 5 from zero (never) to 4 (very sure/always), and items of self-confidence scale were ranked on four grades of 1 (not sure) to 4 (very sure). To compute the total score of the questionnaire, the scores of all the items were summed up. The questionnaire score was between 16 and 88, which means that the higher score obtained from the questionnaire indicates a more favorable level of self-care behavior, and vice versa.

Content validity of the SC-CHDI was verified by several cardiologists, neurologists, and clinical psychologists as well as their applied comments and suggestions. To examine the face validity of the questionnaire, a pilot study was carried out before sampling and a questionnaire was provided to 80 subjects with CHD who were eligible to participate in the study. The questionnaire was given to the same 80 people within 10 days to determine the reliability of the questionnaire. The correlation between the results of the two stages was 0.85. The internal consistency of the questionnaire was confirmed with Cronbach's alpha of 0.91.

To observe research ethics, DBT was also applied for the control group in 4-5 sessions after the post-test stage.

Data were analyzed using SPSS software (version 15, SPSS Inc., Chicago, IL, USA). For all analyses, statistical significance was assessed at a level of 0.05 (two-tailed). Discrete variables were presented as frequency (percentage), whereas continuous variables were expressed as mean ± standard deviation (SD).

To compare average age in experimental and control groups, we used independent t-test. Chi-square test was used for comparing sex, marital, employment, and economic status between two groups.

For comparison of means of adherence to treatment and self-care score in experimental and control groups, paired sample t-test and independent t-test were used for evaluating within and between

Table 2. Demographic data in the study groups

Demographic variables	Experimental (n = 16)	Control (n = 16)	P
Sex (male) [n (%)]	10 (62.5)	9 (56.3)	0.710*
Marital status (married) [n (%)]	12 (75.0)	11 (68.8)	0.690*
Employment status (employer) [n (%)]	12 (75.0)	11 (68.8)	0.690*
Economic situation (low & moderate) [n (%)]	12 (75.0)	11 (68.7)	0.700*
Age (year) (mean ± SD)	49.56 ± 11.52	49.06 ± 12.45	0.900**

* Obtained from chi-square test; ** Obtained from independent samples t-test
SD: Standard deviation

groups effects, respectively. Analysis of covariance (ANCOVA) was used to compare means of dependent variables after intervention, when adjusted for the value of baseline measurement.

Results

The results of comparison of demographic variables are presented in table 2. According to the P-values reported in table, there was not a significant difference between variables in control and experimental groups.

According to table 3, there were not any significant differences between variables before intervention ($P > 0.050$). On the other hand, significant differences were seen after intervention in experimental group and not in control one. Results of ANCOVA test showed the significant differences between experimental and control groups after intervention ($P < 0.001$).

Therefore according to the results, DBT had an effect on the adherence to treatment and self-care behavior.

Discussion

By considering the results of this study, the intervention of DBT in patients with CHD in the post-test phase affected the adherence to treatment and self-care behavior of patients with CHD. Given this effect, it seems that intervention of DBT has significantly increased the utility of adhering to the treatment of CHD. Our results are in line with those of Shikany et al.,[19] Iakovleva,[20] Mosleh and Almalik,[21] Rosenzweig et al.,[22] and Merkes.[23]

It seems that the intervention of DBT has been able to lead to favorable follow-up in patients, although its main purpose is not adherence to treatment by patients. It can be concluded that the coronary heart problem in patients with this condition makes the patients feel that they have no control over their conditions. Moreover, the effect of CHD on their academic, family, occupational, and social performance made by illness, creates this feeling in the person that he/she is vulnerable and there is no longer hope to reach a relative or complete recovery. It is natural that such conditions in the patient cause distress and despair, followed by adverse treatment. By having information about DBT intervention and psychological comprehension, people identify stress and distress patterns of mental-physical therapy and search about coping with the challenges of life.

Therefore, in this intervention, patients are trained to practically learn about the tolerance and control of disturbances associated with the management of their daily life challenges and full conscious control of the excitement created by distress. And then they will appropriately behave through the training of interpersonal effectiveness skills. It seems that the intervention of DBT has led to adoption of adverse conditions by the patients with CHD and thereby has increased the amount of distress tolerance and control of excitement; consequently, they found desirable performance in terms of adherence.

Table 3. Mean and standard deviation (SD) of pre-test and post-test scores of variables

Variable	Group	Pre-test (mean ± SD)	Post-test (mean ± SD)	P*
Adherence to treatment	Experimental	5.19 ± 1.04	1.81 ± 0.75	< 0.001
	Control	5.00 ± 1.21	5.19 ± 1.22	0.670
		0.640	< 0.001***	< 0.001**
Self-care	Experimental	52.94 ± 7.93	72.50 ± 4.38	< 0.001
	Control	52.56 ± 8.60	55.50 ± 7.42	0.210
		0.900	< 0.001***	< 0.001**

*Obtained from paired sample t-test; **Obtained from analysis of covariance (ANCOVA) when baseline measurements were adjusted; ***Obtained from independent t-test
SD: Standard deviation

Also, since DBT intervention is focused on mindfulness, problem solving, and coping strategies, individuals are encouraged to more comply with treatment regimens and attribute their recovery to their adhering not to environmental factors.

It seems that the patients' life style greatly and significantly benefited from adding techniques which are associated with physical activities even by mind-boggling techniques such as correct breathing (diaphragm) and body meditation. One of those benefits is more favorable and accurate adherence to their drug treatment.

In these techniques, alternating ventricular expansion and contraction and increased abdominal pressure cause blood flow increasing and better heart working as well as other internal organs. Thesetechniques causes adjustment of organic factors such as blood pressure in patients with CHD and reaching the appropriate level close to the normal one. As a result, it is necessary to significantly reduce the doze of certain medications, which largely reduces the risk and mortal-disabling effects of CHD.

It seems that based on the present study, should make people to attend and care of themselves by DBT exercises such as mind-boggling which emphasized on contemplating, being present in the moment, and not judging, as well as DBT exercises which made people be aware of themselves and respect and love themselves. It could also causes things like adherence to treatment and drug compliance.

Further, according to the pre-test of the experimental group, it seems that the intervention of DBT has increased the level of patients' self-caring. Our results are in line with those of Rosenzweig et al.,[22] Merkes,[23] Sherwood et al.,[24] and Lukkarinen and Hentinen.[25]

In explaining the above result, it could be said that more than ability to develop, implement, and maintain planned behavior, self-care also requires high flexibility; and this acceptability and flexibility certainly requires having a high acceptance. Most patients with CHD have low self-control and excitement due to their mental health problems. Adoption, through the experience of being in the moment, makes people be receiver and flexible towards the subject, instead of being silent and distant from it.

The high self-care, flexibility, and consequently awareness of different aspects of the condition of a disease helps people make a conscious decision and have a thoughtful awareness of themselves and their illness.

It seems that in this research, all of the DBT techniques have been able together to get favorable results in patients with CHD. However, it could be said that among DBT skills, mental skills such as the "wise mind" technique and the "what" and "how" techniques have been able to influence the self-care of patients; because they lead to vigilant living and self-consciousness, wise decision making, non-judgmental attitude, and efficient operation in patients. Patients in these techniques find out how they can pay attention to anything purposefully and focally (through observation, description, and participation) and how careful attention can reveal things that they have not seen in the past and can even change this experience.

It also seems that effective communication skills have also had a positive effect on patient's self-care among other DBT skills; because they help achieve goals in a situation and cope with internal and external resistances and conflicts in patients. Also they bring balance between the needs and the wants by their symmetry, followed by a rise in self-esteem and self-respect.

Through DBT skills, patients could see how their complex mental states and being controlled by their excitement can easily control them and reduce their self-care up to an undesirable level. They can also understand how they can achieve desirable self-esteem by controlling their excitements (rather than being controlled by excitements).

Following this study and taking into account the results of the analysis of collected data, DBT intervention can be used to improve mental health and address the psychological problems of patients with CHD; cardiovascular experts can help patients reduce their side effects by reducing their drug intake in collaboration with clinical psychologists. It should be noted that this research has been done in Isfahan Cardiovascular Research Center in 2017, so it is better to be cautious in generalizing its results to other similar clinics and research centers. Also the reaction of people against some DBT techniques differs not only in different communities but also between different groups of one society.

Conclusion

On the basis of results, it could be said that DBT intervention can have positive impact on adherence to treatment and self-caring behavior of patients with CHD.

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Conflict of Interests

Authors have no conflict of interests.

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Youngest documented rheumatic mitral stenosis with regurgitation in a 28-month-old girl

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Case Report

Abstract

BACKGROUND: Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) are the leading causes of acquired diseases in children and young adults in developing countries carrying considerable morbidity and mortality. Rheumatic fever (RF) commonly affects children between 5-15 years old and is rarely seen in < 5 years old. Mitral stenosis (MS) is the most common sequela, as it bears maximum onslaught. In India, few patients follow an unusually rapid course in developing severe MS because of its fulminant nature following attack of ARF.

CASE REPORT: Our patient was a 28-month-old girl who had developed severe MS, mitral regurgitation (MR), and pulmonary hypertension (PH) as the sequelae of ARF which she had suffered at the age of 18 months old.

CONCLUSION: To the best of our knowledge, this is the youngest reported case of rheumatic MS following ARF after extensive search in the literature. This case highlights the fact that very young population is not immune to ARF contrary to prior belief and therefore, more stringent preventive measures need to be implemented for it and possibility of ARF should be kept in mind while evaluating carditis in a child.

Keywords: Acute Rheumatic Fever, Mitral Stenosis, Mitral Regurgitation, Pulmonary Hypertension

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Introduction

Rheumatic fever (RF) is an autoimmune disorder, being a hypersensitivity reaction of immune system to group A beta-hemolytic streptococci (GABHS) strain. With the passage of time, it is on a declining path which began prior to introduction of modern antibiotic and accelerated with introduction of penicillin. Decline in preantibiotic era was due to improvement in environmental factors, decrease in rheumatogenicity of streptococcal strain, and improved specificity in diagnosis. Rheumatic heart disease (RHD), a sequela of RF, continues to be the major health hazard in most developing countries. Recent resurgence of RF in developing countries may be due to change in virulence of the existing strain, emergence of new strain, increased overcrowding and poor sanitation due to population explosion, and improper implementation of preventive measures. As a result, cases have been reported in much younger population (< 5 years old) with its devastating consequences. Rheumatic mitral stenosis (MS) may rarely occur in children < 5 years of age, wherein rapid hemodynamic progression and cardiac morbidity and mortality may occur.

Case Report

An 18-month girl weighing 10 kg was admitted to our hospital with complaints of respiratory distress, poor feeding, and irritability for past 2 weeks. Her past history included low-grade fever and sore throat which subsided by itself. There was no exanthem accompanying fever. After an interval of few weeks, arthralgia of knee and ankle joints was noted.

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Figure 1. Electrocardiogram (ECG) at initial presentation in a 18-month-old girl

It was so painful as she refused to crawl. It was not accompanied by swelling and redness and was non-migratory. Her arthralgia got dramatic relief after treatment with analgesics containing salicylates as advised by her paediatrician. The parents denied any history of vomiting, involuntary movements, urinary problem, redness of tongue, swelling in neck, and desquamative lesions. Birth, family, and past histories were insignificant except that she had been fed with formula milk till 9 months of age. She was referred to unit of paediatric cardiology. On examination, blood pressure (BP) and pulse rate were 82/54 mmHg and 140 beats per minute (bpm), respectively. On cardiovascular system examination, apex beat was situated in 6th intercostal space, 1 cm lateral to midclavicular line which was hyperdynamic in character. There was grade I parasternal heave. On auscultation, the first heart sound (S1) was soft, second heart sound (S2) was wide with variable split with loud pulmonic component (P2), and the third heart sound (S3) was audible. There was a soft, blowing grade 3/6 pansystolic murmur which was best audible at apex although it was also radiating to axilla. Bilateral fine basal crepitations were also present. There was tender hepatomegaly, palpable 2 cm below the right subcostal margin. Electrocardiogram (ECG) indicated sinus tachycardia (Figure 1). Chest X-ray revealed cardiomegaly with evidence of pulmonary venous hypertension (PVH) (Figure 2). Routine haemogram revealed normal leukocyte and platelet count and mild anaemia. Antistreptolysin O (ASO) titer, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were 653 IU/ml (normal limit: 240 IU/ml), 98 mg/l, and 88 mm in 1 hour, respectively, whereas antinuclear antibody (ANA) and troponin level were negative. Echocardiogram revealed dilated left atrium and left ventricle. Color Doppler interrogation showed severe mitral regurgitation (MR) as confirmed by presence of jet in ≥ 2 views, jet length ≥ 2 cm in at least 1 view, peak velocity > 3 m/s, and pansystolic jet in at least 1 envelope along with tricuspid regurgitation (TR) with V_{max}/PG_{max} of 4.36 m.sec/76 mmHg. Left ventricular function was within normal limit (Figures 3A, 3B).

Figure 2. Chest X-ray showing cardiomegaly with pulmonary venous hypertension (PVH) during the first episode of rheumatic carditis

Juvenile rheumatoid arthritis (JRA) was ruled out; patient had only arthralgia which got relieved with salicylates and had severe carditis which is not seen in JRA. Collagen vascular disorders were ruled out by negative ANA and presence of severe carditis.

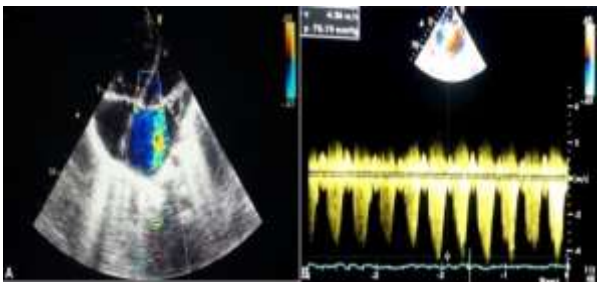

Figure 3. Severe mitral regurgitation (MR) (A) with tricuspid regurgitation (TR) (B) during the first episode of rheumatic carditis

Fever without exanthem and severe carditis

ruled out viral disorders like rubella, herpes virus, and parvovirus. Viral myocarditis was ruled out with characteristic arthralgia, negative troponin level, lack of any left ventricular dysfunction, and characteristic jet of MR on echocardiogram. Kawasaki disease was ruled out as fever was not accompanied by rash, lymphadenopathy, and desquamative lesions, and platelet count and diameter of proximal coronary arteries were normal (Figure 4).

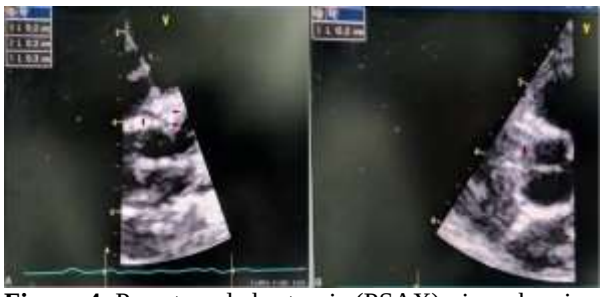

Figure 4. Parasternal short-axis (PSAX) view showing proximal diameter of coronary arteries (left main coronary artery, left anterior descending artery, circumflex artery) (A); right coronary artery (B)

The baby was managed with supportive therapy including benzathine penicillin 0.6 million units intramuscularly, intravenous furosemide 1mg/kg twice daily, and prednisolone 2 mg/kg in four divided doses daily. She was stabilized after 5 weeks when ESR and CRP level came to normal. Aspirin 90 mg/kg in four divided doses daily was started after 5 weeks, tapered to 60 mg/kg after two weeks, and continued for 3 months while prednisolone was continued for 6 weeks. She was discharged in stable condition with haematinic for anaemia correction and benzathine penicillin 0.6 million units intramuscularly every 3 weeks. With treatment, the patient improved symptomatically. MR was persisting at the time of discharge though her congestive symptoms resolved. On the follow-up after 8 months, S1 was loud, S2 was loud with wide variable split, and a long mid diastolic rumble with presystolic accentuation was heard along with pansystolic murmur of mitral leak on auscultation. Her echocardiogram revealed severe MS as mitral valve area (MVA) was 0.9 cm^2 (1.1 cm^2/m^2 body surface area), thickened mitral leaflets (5 mm), fixed posterior mitral leaflet (PML), and doming of anterior mitral leaflet (AML) imparting characteristic hockey stick appearance, commissural fusion, and enlarged left atrium (Figure 5) with severe MR (Figure 6). She was referred to cardiovascular surgery department for possible repair or replacement.

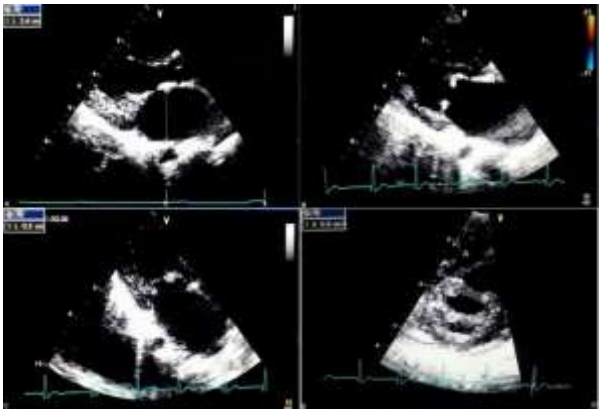

Figure 5. Severe mitral stenosis (MS) on follow-up after 8 months interval: enlarged left atrium (A); characteristic hockey stick appearance of anterior mitral leaflet (AML) and fixed posterior mitral leaflet (PML) (B); thickened mitral leaflet (C); fish mouth appearance with mitral valve area (MVA) of 0.9 cm^2 by planimetry (D)

Discussion

Although acute rheumatic fever (ARF) has declined in developed nations in the past 5 decades, it still remains one of the most important causes of cardiovascular morbidity and mortality among socioeconomically-challenged populations in the developing countries where its incidence reaches epidemic levels.[1-3]

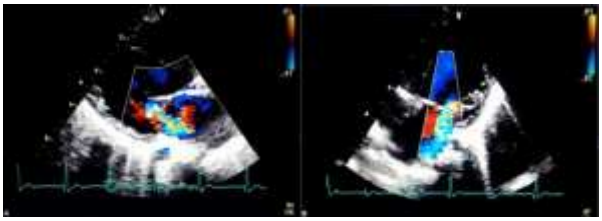

Figure 6. Severe chronic mitral regurgitation (MR) on follow-up after 8 months interval; A: Parasternal long axis view, B: Apical 4 chamber view

ARF is a host's immunological response to infection by GABHS. It is rare below six months of age as babies are protected from maternal antibodies transferred transplacentally and later on as they are breastfed which gives similar degree of protection. In our case, she was fed on formula milk which might have been one of the reasons that first episode of ARF occurred at 18 months of age. MS is rarely seen in children and adolescents except in developing countries where RF is still very common.[4-6] MS may rarely be congenital. Congenital MS occurs due to the presence of supravalvular ring of the left atrium, accessory mitral valve tissue (AMVT), congenital commissural

fusion, shortened chordae tendineae, anomalous mitral arcade, anomalous position of the papillary muscles, and parachute mitral valve (PMV). Firstly, these features were not seen in our case. Secondly, the temporal development of MS in the background of mitral leak is seen only as a sequela of ARF. Furthermore, echocardiographic findings were pathognomonic of rheumatic MS in our case (Figure 5). Latent period for rheumatic MS to manifest is 10-30 years in developing countries, whereas it may be as long as 50 years in developed countries after the initial episode of ARF. In developing countries like India, early evidence of MS may develop as early as the teenage years, presumably because of a more aggressive initial attack and/or recurrent bouts of RF which has been coined as juvenile MS (JMS).[4] RF causes more often moderate to severe carditis with milder form of arthritis or sometimes only arthralgia when presents in age less than 5 years compared to older individuals.[1] Among the few case reports of RHD in children aged < 5 years, the youngest patient documented till now was a 2 year and 6 months old.[7] Our case was just 20 months old at the time of rheumatic carditis and 28 months old at the time of RHD, the youngest of JMS with severe MR ever reported. This is also unique and surprising that the patient developed stenosis within a span of just 8 months which shows complex interplay of host genetic susceptibility, immune response, environmental influence, and virulence of GABHS. As the younger age is associated with more severe valvulitis, prompt recognition and treatment of sore throat because of GABHS should be done. Therefore, ARF may occur in babies in their second year of life when severe carditis may accompany mild arthralgia. Furthermore, ARF may present with only arthralgia as the earliest manifestation and therefore opportunity to diagnose it may be missed as it appears minor to the family. Severe MS may occur as early as 10 months following onset of acute rheumatic carditis as a result of virulent strain and infidel genetic susceptibility, and exuberant immune response may be the responsible factor behind such a malignant course and outcome of RF.

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None.

Conflict of Interests

Authors have no conflict of interests.

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Nebivolol for improving endothelial dysfunction in cardiac syndrome-x; Is it ready for clinical use?

Alireza Fatahian[(1)]

Letter to Editor

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Dear Editor

It is assumed that endothelial dysfunction (ED) of coronary arteries is one of the important underlying mechanisms for cardiac syndrome-X (CSX). ED reduces coronary vasodilatation capability, causes abnormal arterial contraction, and impairs endothelium dilatation. These events of ED along with reduced bioavailability of endogenous nitric oxide (NO) reduce blood flow in microvasculature of myocardium.[1] For this reason, this syndrome is also called microvascular angina. Accordingly, the principal component of treatment in patients with CSX is improving ED. However, the optimal treatment for this pathological mechanism has not yet been determined.[1]

In the not-too-distant past, the promising results of several individual studies showed that nebivolol has beneficial effects on improving endothelial function in patients with CSX, by increasing NO release in endothelial cells.[2] However, after that, the researchers did not show much interest in repeating that research. The reason for discontinuing research in this area is unclear; but the findings of pharmacological studies imply that nebivolol, as a highly potent selective β-adrenoceptor antagonist, can affect L-arginine/NO pathway, and therefore, can lead to endothelial vasodilatation.[2,3]

Regarding the effect of nebivolol on endothelial dysfunction in patients with CSX, clinical research began in 2009 and then disappeared in 2010. In 2009, nebivolol (5 mg daily) was compared with metoprolol (50 mg daily) in a randomized clinical trial with 34 patients with CSX.[4] Patients received these interventions for 12 weeks. Researchers found that nebivolol therapy could increase exercise duration, reduce exercise-induced myocardial ischemia, lower the number of angina attacks, and increase plasma L-arginine/NO levels. As a result, coronary microvascular function and exercise-induced myocardial ischemia were improved in patients with CSX.

In another study in 2010, Kayaalti et al. compared 5 mg nebivolol with control group (the authors did not specify what drug or placebo was prescribed for control group) to investigate the effect of nebivolol on endothelial function on 38 patients with CSX.[5] Patients received these interventions for 4 weeks. In this study, instead of a cardiac function, patients were evaluated for their brachial artery response (lumen diameter) as well as biochemical and inflammatory markers. They found that nebivolol therapy was associated with increased brachial artery lumen diameters and decreased inflammatory markers by improving endothelial function.[5]

The effect of nebivolol (5 mg/day) on oxidative stress also was compared with metoprolol (50 mg/day) in patients with CSX. They found that nebivolol could increase plasma level of NO, and therefore improve exercise stress test results.[6]

Based on the current evidence, it seems that nebivolol, as a highly selective beta-adrenergic blocker, can increase plasma levels of NO. This increase indirectly indicates the effects of this drug on improvement of endothelial cells function. Although pharmacological studies have confirmed these effects,[2,3] limited clinical studies have examined the efficacy of this drug in improving endothelial function of coronary arteries in patients with CSX. Only one study[4] directly evaluated the efficacy of nebivolol on endothelial function, and there is a need to further well-designed clinical trial studies to investigate whether nebivolol can improve endothelial function in patients with CSX.

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Conflict of Interests

Authors have no conflict of interests.

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