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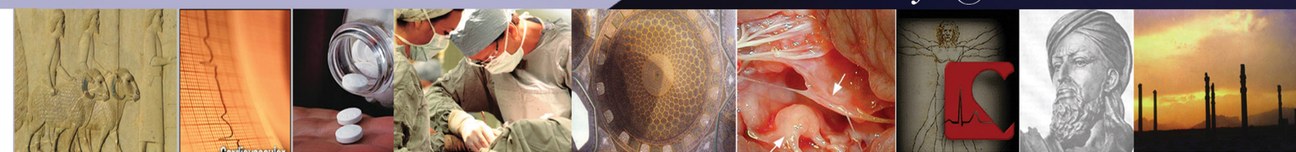

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2. Bonow RO, Mann DL, Zipes DP, Libby P. Braunwald's Heart Disease E-Book: A Textbook of Cardiovascular Medicine. 7th ed. Philadelphia, PA: Elsevier Health Sciences; 2007. p. 1976, 1981, 1982.

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

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The benefits of cardiac rehabilitation for patients with sleep apnea

Saeid Komasi[(1)]

Editorial

Date of submission: 23 Mar. 2018, *Date of acceptance:* 12 May 2018

Sleep apnea (SA) is the most common type of breathing-related sleep disorders, defined as a frequent stop and start breathing.[1] SA is characterized by symptoms such as frequent snoring, silent pauses in breathing, choking and breathing symptoms, sleepiness or daily fatigue, insomnia and frequent waking up during the night, morning headaches, not refresh and uneasy feeling after awakening, and irritability and mood changes.[2] In this disorder, breathing stops occur more than 30 times during sleep, and continue a few seconds to minutes.[1]

SA, which is an independent risk factor for cardiovascular disease, affects 38,000 heart deaths each year.[3,4] SA is common among 50-66 percent of patients with heart diseases, and generally leads to numerous health outcomes.[5,6] Increased blood pressure due to SA, decreased left ventricular function and central blood flow, myocardial damage, heart rate fluctuations, systemic infection, endothelial dysfunction, increased sympathetic activity, and metabolic abnormalities are among the most important outcome of SA in patients with cardiovascular diseases.[4,5]

Appropriate treatments for SA include automatic positive airway pressure (APAP) and continuous positive airway pressure (CPAP). Advantages of the APAP method include fluctuation between low and high level pressure during the whole night, and automatically adjust the pressure level, automatic elevation of pressure, and uniform maintenance of pressure level set by patient itself. The limitations of this therapeutic approach are APAP algorithm varies from one person to another; sometimes slowing the pressure change during apnea events, and expensive.[1] The CPAP method, as a non-invasive treatment, quickly relieves symptoms, and alleviates heart problems. An increase in expiratory effort, sense of forced air through the nostrils of the patient, and uniform maintenance of pressure level set by the physician are among the CPAP constraints.[1] This treatment is generally associated with positive outcomes such as decreased blood pressure caused by SA, and improving the function of the left ventricle and oxygenation.[5] Despite the usefulness of the APAP and CPAP, SA screening in Iranian patients with cardiovascular diseases is not a routine. For this reason, in most cases, this problem remains underdiagnosed, and without a proper treatment.

Although the aforementioned treatments have been used relatively successful for many years, recent studies have shown that cardiac rehabilitation (CR) can be considered as a new treatment for SA.[5] CR reduces the severity of SA by 55% through improving VO_2peak by 20-27 percent.[7-10] Physical exercise and regular exercise in CR can regulate the autonomic nervous system, and reduce the severity of SA.[10]

In spite of sufficient evidence regarding the usefulness of CR in significantly reducing morbidity and mortality,[11] Iranian patients tend to have very little to participate in these programs. In Iran, less than 20% of patients [mostly those with coronary artery bypass graft (CABG)] refer to CR, and almost half do not complete the sessions.[12-14] Not surprisingly, patients with heart failure, valve heart surgery, percutaneous coronary intervention, or myocardial infarction are also not generally encouraged by experts to enroll in CR. Therefore, the number of patients with cardiovascular diseases enrolled in the CR is limited to a number of patients with CABG. Based on these considerations, the numbers of patients with cardiovascular diseases with underdiagnoses/diagnosed SA, who benefits from CR, are very small.

Obviously, SA is a treatable and modifiable disorder.[4] The above-mentioned literature refers to the benefits of exercise and CR in controlling and reducing the severity of this disorder. CR is effective in controlling and improving SA, though weight loss and body mass index (BMI), modifying the diet, increasing cardiorespiratory fitness,

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enhancing VO_2peak, decreasing leg fluid accumulation, and preventing the nocturnal rostral fluid shift implicated in upper airway collapse.[15] Moreover, other reports refer to the combination of exercise training with ventilation therapy to achieve more positive outcomes.[16] In sum, CR seems to be a potential replacement therapy or complement for existing treatments. However, further studies are needed to confirm this claim.

Acknowledgments

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Conflict of Interests

Authors have no conflict of interests.

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The relation between mortality from cardiovascular diseases and temperature in Shiraz, Iran, 2006-2012

Manizheh Dadbakhsh[1], Narges Khanjani[2], Abbas Bahrampour[3]

Original Article

Abstract

BACKGROUND: Several studies have suggested that temperature may have an effect on the number of cardiovascular deaths in societies. Global warming is a concern, and cardiovascular diseases are the top cause of death worldwide. This study investigated the relation between temperature and cardiovascular mortality in Shiraz City, Iran.

METHODS: In this ecological study, data about temperature and cardiovascular deaths (in age and gender groups) in Shiraz City were inquired from 2006 to 2012. The simultaneous and delayed relation between monthly temperature and cardiovascular deaths was examined using Spearman and Pearson correlation tests, and crude and adjusted negative binomial regression analysis with adjustment for confounding factors such as humidity, rainfall, wind direction, wind speed, and air pollutants. Analysis was done using MINITAB and STATA software.

RESULTS: During this period 17,167 deaths were reported in Shiraz. The lowest number of cardiovascular deaths was reported in 20 °C. No significant relation was observed between mean monthly temperature and cardiovascular deaths in the same month after adjusting for confounding factors. Although, cardiovascular death in 18- to 60-year-old people showed an inverse significant relation with minimum [Incidence rate ratio (IRR) = 0.98989, P = 0.020], maximum (IRR = 0.99046, P = 0.011), and mean temperature (IRR = 0.98913, P = 0.006) of the same month in the crude model, it was not significant in the adjusted model (IRR = 0.99848, P = 0.848, IRR = 0.99587, P = 0.584, and IRR = 0.99512, P = 0.506, respectively).

CONCLUSION: It seems that there is no significant relation between temperature and cardiovascular deaths in Shiraz, which is probably due to its moderate climate, and the fact that no major heat or cold wave occurred during this time.

Keywords: Temperature, Global Warming, Cardiovascular Diseases, Mortality, Iran

Date of submission: 26 Jan. 2016, ***Date of acceptance:*** 18 May 2018

Introduction

Dissemination of greenhouse gases and compounds such as chlorofluorocarbons (CFCs), can damage the ozone layer in the stratosphere, and has led to global warming and concerns over its effects on human health.[1] Global warming causes melting of glaciers, sea level rise, flooding, and destruction of valuable environmental areas, destruction of cities, and loss of humans, animals, and plants.[2] Generally, as temperature rises or drops from the human comfort zone, distress and mortality increases.[3] Deaths that are directly related to temperature, such as increase in body temperature, can result from cardiovascular disorders, respiratory disorders, or poorly functioning blood vessels.[4] Some evidences show the relation between respiratory mortality and temperature, and a great increase in the number of respiratory deaths in cold temperatures.[5]

Some studies have suggested that low temperature increases the incidence of heart attacks and possibly cardiovascular deaths.[6] Moghadamnia et al. conducted a systematic review based on studies that were mainly conducted in south east Asia, and concluded that both increase and decrease in ambient temperature related to cardiovascular mortality; but suggested that more studies from different geographical regions and climates should be conducted.[7] Jahanbakhsh et al. in Ahar, Iran,

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found a negative significant correlation (r = -0.34, P = 0.01) between temperature and number of deaths due to myocardial infarction.[6] Studies from England show that low temperatures increase the risk of ischemic heart disease mortality,[8] and cold weather is associated with higher death rates in all ages, and especially in older people.[9]

A study conducted in 12 cities in the United States showed that both cold and hot temperatures affect mortality from myocardial infarction (MI) and all cardiovascular diseases (CVDs); but the effects of these extreme temperatures are different. Cold temperature had a more homogeneous and continuous effect on both outcomes. Warm temperature had a more important effect on death due to MI compared to all CVDs, and death due to MI was higher in these temperatures. In hot cities, cold weather did not show any effect on cardiovascular mortality.[10]

A significant inverse relation was observed between cardiovascular deaths and temperature in a study in Iran, Kerman City, which has a desert climate.[11] Most epidemiologic studies on temperature and death were conducted in North America and Europe, most of which had temperature increase over the two last decades. Europe has been warming 0.3 °C per decade since 1970.[12] Death rates increased by 70 percent in Britain in some winters compared to summers. The increased death rate in winter was associated with the difference between low temperature and high temperature in winter and summer.[13]

Further studies are needed for better understanding the relation between temperature and human death rates. Although these deaths are probably also affected by ambient air pollutants and pre-existing health backgrounds, further research is required in regions with various climate conditions and different cultures to further clarify the effect of temperature on human death rates. This study investigated the relation between temperature and cardiovascular death in different age and gender groups in a city in the south west of Iran, Shiraz.

Materials and Methods

The current study was an ecological population-based study conducted in Shiraz. Shiraz is the fifth most populous city of Iran, and the capital of the Fars Province. In the 2011 census, the population of this city was 1,700,665. Shiraz is located in the southwest of Iran, on the Dry River which is seasonal river. It has a moderate climate, and is one of the oldest cities of ancient Persia.[14]

Initially, the number of deaths per day and their causes were inquired from 2006 until 2012 from the Health Deputy of Shiraz University of Medical Sciences, Shiraz, Iran. This information was anonymous. Only deaths due to cardiovascular diseases were selected, and other causes were excluded. Cardiovascular deaths were classified into the following groups: age at death below 18 years, 18-60 years, and above 60 years, and men and women deaths.

Cardiovascular deaths consisted of recorded deaths resulting from myocardial infarction, stroke, high blood pressure, pulmonary embolism, arterial embolism, thrombosis, aortic aneurysm, dissecting aneurysm, other vascular diseases, other heart diseases, other cardiovascular diseases, non-rheumatic mitral and aortic valve disorders, acute and subacute endocarditis, acute pericarditis, acute myocarditis, cardiomyopathy, heart failure, and cardiovascular congenital malformations.

The daily mean values of temperature (mean, minimum, and maximum), rainfall, relative humidity, and wind direction and speed were inquired from the meteorology department of Shiraz, and the recorded air pollutant levels were inquired from the Shiraz Environmental Protection Agency, and included carbon monoxide (CO), nitric oxide (NO), nitrogen dioxide (NO_2), nitrogen oxides (NO_x), sulfur dioxide (SO_2), ozone (O_3), particulate matter with aerodynamic diameter ≤ 10 μm (PM_{10}), methane (CH_4), total hydrocarbons (THC), and non-methane hydrocarbons (NMHC) for the same time period.

Later in this study, as the number of cardiovascular death counts per day was zero on many days; and also air pollution data was not available for every day of each month due to device malfunction, the overall monthly mortality, and the monthly average of meteorological variables (including temperature, humidity, rainfall, wind direction, and wind speed), and air pollution data were used.

In this study, the relation between mean monthly temperature and cardiovascular mortality, and the percent of change in cardiovascular mortality per degree Celsius change in temperature was computed. The best statistical model to predict the changes was selected by using the highest coefficient of determination (R^2). The minimum death temperature, which meant the temperature that the least number of death occurred, was calculated by taking the derivative of the equation and setting it equal to zero, and solving the equation for x.

Table 1. The number of cardiovascular mortality per month in Shiraz City, Iran, from March 2006 to March 2012

Month	Number of cardiovascular mortality*					
	Total	Sex		Age (year)		
		Men	Women	Under 18	18 to 60	Over 60
January	1696	910	786	14	309	1370
February	1193	658	535	12	263	918
March	1246	712	534	9	268	968
April	1487	835	655	13	224	1239
May	1374	774	600	8	232	1129
June	1365	732	633	18	256	1085
July	1423	780	643	13	214	1196
August	1398	781	617	10	240	1134
September	1267	706	561	9	222	1046
October	1405	767	638	15	242	1156
November	1504	828	676	12	276	1228
December	1809	994	812	21	285	1513
Total	17167	9477	7690	154	3031	13982

* Based on the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)

In order to determine the relation between the minimum, maximum, and mean temperatures and cardiovascular mortality the negative binomial regression was used and incidence rate ratio (IRR) was computed in univariate and multivariate models. Of course, various analyzes can be used.[15] Beforehand the fitting of Poisson regression analysis on cardiovascular mortality data was tested, and due to over-dispersion (variance greater than mean), negative binomial regression was used instead. The multivariable model included independent variables (minimum, maximum, or mean monthly temperature) and confounding variables (monthly relative humidity, monthly rainfall, wind speed and direction, and air pollutants including CO, NO_x, PM_{10}, SO_2, O_3, and THC). Some studies have shown a relation between air pollutants and cardiac deaths.[16] In this study, the base population size for each study group was acquired from the Statistical Center of Iran.

The correlations between temperature and cardiovascular mortality in the next month were calculated using the Pearson correlation coefficient or Spearman correlation coefficient. If the distribution of the data was normal, Pearson correlation coefficient was used, and if data distribution was not normal, Spearman correlation coefficient was used. All analyses were done on 6 groups of under 18 year old, 18-60 year old, above 60 year old, and men and women deaths. Data were analyzed using MINITAB (version 16, Minitab Inc., State College, PA, USA) and STATA (version 11, StataCorp LLC., College Station, TX, USA).

Results

Descriptive analyses of cardiovascular deaths during March 2006 to March 2012 are shown in table 1. The total number of cardiovascular deaths in Shiraz during March 2006 to March 2012 was 17167. The maximum number of cardiovascular deaths in the general population, and in other sub-categories, occurred in December and January with an average temperature of 11.90 and 6.1 °C, respectively, during these 6 years. The averages of meteorological variables from March 2006 to March 2012 in Shiraz are shown in table 2.

Table 2. The mean temperature, relative humidity, rainfall, and wind speed and direction per month and pollutants in Shiraz City, Iran, from March 2006 to March 2012

Month	Temperature (Celsius degree)			Rainfall (mm)	Relative humidity (%)	Wind direction (Degree)	Wind speed (m/s)
	Minimum	Maximum	Mean				
January	4.03	19.76	11.90	31.55		12.50	220
Febuary	0.96	14.33	7.65	34.95	26.25	10.66	250
March	8.73	23.11	15.92	33.84	45.73	11.16	250
April	13.50	30.28	21.89	31.15	2.28	12.83	255
May	17.65	35.98	26.81	27.69	0.11	11.33	257
June	20.56	38.88	29.72	29.99	0.00	10.50	245
July	20.43	37.93	29.18	29.55	1.66	9.16	248
August	16.76	35.28	26.02	30.20	0.43	12.33	253
September	11.58	30.71	21.15	28.86	0.01	9.16	268
October	6.51	23.35	14.93	32.02	11.63	9.33	248
November	0.43	15.73	8.08	33.03	50.40	7.83	218
December	-1.00	13.30	6.15	32.37	39.61	9.33	220

Table 3. The level of pollutants in Shiraz City, Iran, during the years 2006 to 2012

Pollutant	Mean	Median	Minimum	Maximum	SD
CO (ppb)	3034.758	2866.150	1205.630	5864.000	1290.237
PM_{10} (µg/m³ air)	86.143	80.372	28.341	212.007	35.751
NO (ppb)	57.598	48.105	22.790	181.430	30.336
NO_2 (ppb)	30.996	28.722	22.110	55.080	7.133
NO_x (ppb)	88.235	82.078	44.850	223.530	34.433
O_3 (ppb)	17.490	16.289	4.480	40.180	8.368
SO_2 (ppb)	101.531	82.734	3.100	292.740	94.238
CH_4 (ppmc)	2.416	2.506	0.832	4.449	0.753
NMHC (ppmc)	1.535	1.374	0.538	4.098	0.635
THC (ppmc)	3.989	3.950	1.663	7.887	1.149

SD: Standard deviation, ppb: Parts per billion; PM_{10}: Particulate matter with aerodynamic diameter ≤ 10 µm; ppmc: Parts per million carbon; CO: Carbon monoxide; NO: Nitric oxide; NO_2: Nitrogen dioxide; NO_x: Nitrogen oxides; SO_2: Sulfur dioxide; CH_4: Methane; O3: Ozone; NMHC: Non-methane hydrocarbons; THC: Total hydrocarbons

The level of pollutants is shown in table 3 as well.

Results of negative binomial regression between mean monthly temperature and cardiovascular mortality are shown in table 4. The multivariate analysis has been adjusted for humidity, rainfall, wind speed, wind direction, and air pollutants including CO, NOx, PM_{10}, SO_2, O_3, and THC.

The relation between temperature and cardiovascular death in total people, men, women, and people with age of fewer than 18 years and above 60 years was inverse and non-significant. An inverse significant relation was observed between cardiovascular deaths in 18- to 60-year- old people and minimum (P = 0.020), maximum (P = 0.011), and mean temperature (P = 0.006); but after adjusting for confounders, this relation disappeared (P = 0.848, P = 0.584, and P = 0.506, respectively).

To investigate the relation between cardiovascular mortalities and the temperature of the previous month, depending on normal or abnormal distribution of variables, Pearson or Spearman correlation tests were performed which are shown in table 5.

Correlation tests indicated that there was an inverse significant relation only between the number of cardiovascular deaths in 18- to 60-year-old and minimum (r = -0.268, P = 0.020), maximum (r = -0.238, P = 0.046), and mean temperature (r = -0.253, P = 0.034) in the previous month. This means as the minimum, maximum, and mean temperature decreased, the number of cardiovascular mortality that happened in the 18- to 60-year-old age group, in the next month, increased.

Table 4. The results of crude and adjusted negative binomial regression analysis

Group		Temperature	Crude IRR (95% CI)	P	Crude IRR (95% CI)	P
Total deaths		Minimum	0.99555 (0.98906-1.00209)	0.182	0.99645 (0.98445-1.00860)	0.566
		Maximum	0.99598 (0.99062-1.00137)	0.144	0.99410 (0.98441-1.00388)	0.236
		Mean	0.99534 (0.98966-1.00105)	0.110	0.99376 (0.98388-1.00375)	0.221
Sex	Men	Minimum	0.99574 (0.98938-1.00215)	0.193	0.99833 (0.98684-1.00995)	0.778
		Maximum	0.99626 (0.99098-1.00156)	0.167	0.99626 (0.98692-1.00569)	0.436
		Mean	0.99566 (0.99007-1.00128)	0.130	0.99634 (0.99606-1.00330)	0.870
	Women	Minimum	0.99535 (0.98779-1.00298)	0.332	0.99428 (0.97988-1.00890)	0.441
		Maximum	0.99567 (0.98943-1.00195)	0.176	0.99139 (0.97983-1.00309)	0.149
		Mean	0.99498 (0.98837-1.00164)	0.139	0.99060 (0.97805-1.00253)	0.123
Age (year)	Under 18	Minimum	0.98817 (0.96279-1.01422)	0.370	0.97078 (0.92391-1.02003)	0.240
		Maximum	0.99280 (0.97144-1.01463)	0.515	0.99116 (0.93829-1.04699)	0.751
		Mean	0.99276 (0.96989-1.01616)	0.541	0.98949 (0.94887-1.03184)	0.621
	18-60	Minimum	0.98989 (0.99895-0.98091)	0.020†	0.99848 (0.98309-1.01410)	0.848
		Maximum	0.99046 (0.98317-0.99780)	0.011†	0.99587 (0.98124-1.01072)	0.584
		Mean	0.98913 (0.98144-0.99688)	0.006†	0.99512 (0.98090-1.00955)	0.506
	Over 60	Minimum	0.99530 (0.97517-1.01585)	0.652	0.98354 (0.94756-1.02089)	0.383
		Maximum	0.99645 (0.97959-1.01361)	0.164	0.99280 (0.96135-1.02527)	0.660
		Mean	0.99480 (0.97711-1.01281)	0.569	0.99236 (0.96029-1.02550)	0.648

IRR: Incidence rate ratio; The calculated IRR was adjusted for humidity, rainfall, wind speed, wind direction, and air pollutants including CO, NO_x, particulate matter with aerodynamic diameter ≤ 10 µm (PM_{10}), SO_2, O_3, and total hydrocarbons (THC)
† Statistically significant; 95% CI: 95% Confidence interval; NO_x: Nitrogen oxides; CO: Carbon monoxide; SO_2: Sulfur dioxide; O_3: Ozone
The ratio shows increase in death in month per unit of increase in minimum, maximum, or mean temperature in the same month in different subgroups.

Table 5. The correlation between mean temperature and cardiovascular deaths happening one month later, in different population subgroups

Group		Temperature	Pearson correlation coefficient (r)	P
Total people		Minimum	-0.104	0.388
		Maximum	-0.048	0.694
		Mean	-0.073	0.543
Sex	Women	Minimum	-0.085	0.483
		Maximum	-0.034	0.777
		Mean	-0.057	0.635
	Men	Minimum	-0.106	0.377
		Maximum	-0.054	0.656
		Mean	-0.078	0.518
Age (year)	Under 18	Minimum	-0.073	0.547
		Maximum	-0.065	0.589
		Mean	-0.062	0.605
	18-60	Minimum	-0.268	0.024†
		Maximum	-0.238	0.046†
		Mean	- 0.253	0.034†
	Over 60	Minimum	-0.044	0.714
		Maximum	0.008	0.944
		Mean	-0.015	0.898

† Statistically significant

A second degree equation was a better fit for the data than a first degree equation. This equation showed that the lowest number of cardiovascular death (222 cases) was in the average temperature of 20 °C (Figure 1).

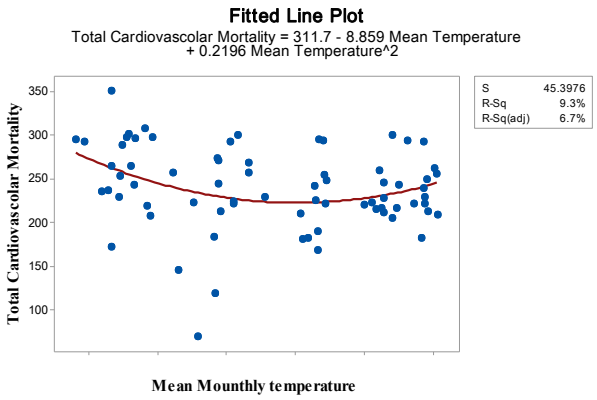

Figure 1. The scatter plot of deaths linked to cardiovascular and average temperature in Shiraz City, Iran, during the years 2006-2012

Discussion

Our study did not show a significant effect of temperature on cardiovascular deaths in Shiraz. This finding maybe due to the moderate climate of Shiraz. However, Studies have shown that temperature can affect human health.[17] There are various mechanisms for temperature to affect human death. Cold weather may have direct effects on the cardiovascular system due to changes in blood pressure, vasoconstriction, increased blood viscosity and increased levels of red blood cells, plasma cholesterol, and plasma fibrinogen.[18] The effect of environmental temperature on atherogenesis is not clear. Studies about ambient temperature and fat metabolism have led to controversial results. However, cold temperatures can probably harmfully change plasma lipid concentrations, and lead to abnormal thrombosis and chronic atherogenesis.[13]

Low temperatures can lead to thrombosis due to increased red blood cells.[19] In cold conditions, the concentration of some clotting factors and platelets, as well as platelet aggregation increase. The greater number of coronary events in cold weather may be related to blood clots. Plasma fibrinogen concentration is inversely related to environmental temperature; however, part of the increase in fibrinogen concentration during winter may be the result of seasonal respiratory infections.[20] Ambient temperature is inversely related to blood pressure and hypertension in a cold environment, has several side effects, and causes changes in the myocardial oxygen supply, particularly in patients with fixed stenosis. In this situation, the ventricular wall work load and oxygen demand increase. This additional load causes reduced mechanical efficiency of the heart; blood flow to coronary arteries might impair, and thus, cold weather can accelerate myocardial ischemia. Cold-induced peripheral vasoconstriction may cause acute pulmonary edema, which imposes an overload on the left ventricle, even in patients

without coronary artery disease, and especially in those prone to high blood pressure. In patients with left ventricular dysfunction, the long-term effects of this high load induced by cold environments, may have adverse effects on survival.[13]

The effects of cold weather and air pollution following the inversion phenomenon in the cold seasons are very important in causing heart attacks. The inversion phenomenon happens in the cold season. In this phenomenon cold weather and air pollutants are trapped in layers close to earth, which can directly cause increased cardiovascular deaths. Moreover, activities such as snow plowing, installing tyre chains, and pushing cars stuck in snow increase in cold temperatures. Heavy activity on cold days imposes extra-pressure on the heart and the risk of heart attack increases. Reduced temperature also leads to a compensatory mechanism that increases body metabolism to produce heat. It also increases heart activity which increases the risk of heart attack.[6]

Results of a study from Ahar, Iran, showed an inverse, significant, and average correlation between temperature and death due to myocardial infarction. In that study, the number of deaths due to myocardial infarction increased with the start of cold weather (autumn season), and continued until the start of the warm season (around May).[6] The study by Khanjani and Bahrampour in Kerman, Iran, showed that cardiac death increased by 0.6 percent with every 1° C reduction in temperature. In that study, the relation between cardiac deaths and temperature was almost linear, and with temperature increase, the number of cardiac deaths decreased, which may be due to people getting accustom to desert climate over the years in this region.[11]

However, time series analysis in 12 United States (US) cities showed that the probability of death from MI is twice on warm days compared to cold days, while death due to cardiovascular diseases is five times less on warm days compared to cold days.[10] A study from the Netherlands showed that cardiovascular death increased 1.86 percent per 1 °C temperature increase over optimal temperature in the previous month.[21] In Ishigami et al. study in three cities from European countries, the strongest heat effect on death increase was seen in cardiovascular deaths; and death due to cardiac disease happened more on warm days than other causes of death in all cities except one.[12] Although the above-mentioned studies showed the effects of temperature on cardiac deaths, in the present study, this effect was not observed.

Seasonal and geographical data indicate that low ambient temperature has a significant impact on increased cardiovascular death.[13] Some researchers think mean blood pressure in cold climates is higher than warmer regions. Temperature difference between winter and summer in Britain has led to 5 ml mercury differences in blood pressure, and it is expected that such differences in blood pressure is the reason for at least 21 percent difference in the incidence of coronary events, and at least 34 percent difference in the incidence of stroke.[13] In a study in Tehran, Iran, the highest number of deaths due to myocardial infarction and stroke occurred in cold months, and the increase in total deaths that happened in low temperatures was due to increases in this type of death. They cocluded that the effect of temperature decrease on death increase is different depending on the type of disease (heart attacks and strokes), but its effect on heart attacks is more tangible.[22]

It was shown in another study in Oslo, Norway, that in temperatures lower than 10 °C, every 1 degree decrease in average temperature in the last seven days was associated with 1.7 percent increase in cardiovascular diseases, but no significant increase was observed in cardiac deaths in temperatures above 10 °C.[23] In Huynen et al. study in the Netherlands, cardiovascular death increased by 1.69 percent per one °C decrease below optimal temperature in the last month. Excessive mortality in cold weather is mostly related to increased cardiovascular deaths and mortality in old people.[21] These studies are consistent with the current study, since the highest cardiac death number in Shiraz in the total population and in all sub-groups was in cold months, and months with low temperature averages.

Results obtained from crude analysis indicated that there was an inverse significant relation between cardiovascular death in 18- to 60-year-old people and minimum, maximum, and mean temperature variables, and this group was more sensitive to temperature reduction. However, adjusted multivariate analysis in all sub-groups showed that there was no significant relation between temperature and cardiac death, and probably this finding was due to the fact that Shiraz has a moderate climate with an average annual temperature of 18 °C,[24] and without any heat or cold waves during this study period.

Temperature of minimum mortality (TMM) is the temperature in which the lowest mortality occurs, and if temperature goes higher or lower

than this temperature, mortality increases. This temperature is obtained from studying the relation between number of deaths and average temperature, and varies by different cities.[22] The number of heart attacks increased in Ahar when temperature decreased beyond 15° C.[6] TMM was 19 °C in London, United Kingdom,[25] and in Huynen et al. study in the Netherlands, the TMM was 16.5 °C.[21] In the current study, the lowest number of cardiovascular deaths happened in the average temperature of 20 °C, and the relation was J shaped. In other studies, the temperature of 20 °C has been considered the optimal temperature in open space.[26] It seems that the adverse consequences of temperature are observed less in this temperature (TMM).[27] It has been shown that the dominant geographical climate may determine the optimal temperature of the region.[18] Generally in studies, most observed deaths occur in high or low temperatures, and the number of deaths is lower in average temperatures.[28]

The relation between cardiovascular deaths one-month later and temperature was also investigated in the current study. In the study by Braga et al. in 12 US cities, it was shown that moderate temperatures had no significant effect on death resulting from cardiovascular causes in warm cities. However, delayed effects of warm temperatures (after 4-6 days) were observed for MI deaths. But in cold cities, high and low temperatures were associated with increased mortality rate due to CVD. Generally the effect of cold temperature on these deaths lasted for several days, while the effect of higher temperatures was confined to the same day or a few days later.[10] In another study in the US, it was shown that heat is related to death on the same day or previous day, while cold temperature was related to deaths with longer delays and even up to 25 days after temperature drops.[29] In this current study, correlation results indicated that there was an inverse significant relation between cardiac death in 18- to 60-year-old people and minimum, maximum, and mean temperatures in the previous month.

One limitation of this study was that aggregated data were used, and therefore the results cannot directly be generalised to the individual-level. Moreover, we were not able to adjust for population dynamics or migration.[30] Meanwhile, we were not able to do calculations for joint age-gender groups, because the mortality data were inquired as de-identified information in separate age and gender groups. However, because the number of mortality cases would be low in these joint groups, due to low power, it is very unlikely that results would become significant.

Conclusion

Although cardiovascular deaths in 18- to 60-year-old people in Shiraz showed an inverse significant relation with minimum, maximum, and mean temperature of the same month, but the relation was not significant after adjusting. The lack of relation between cardiac deaths and temperature is probably due to the relatively moderate climate in Shiraz. Low and high temperatures may influence the number of cardiovascular deaths, but temperature-related cardiovascular deaths are lower in moderate temperatures.

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Conflict of Interests

Authors have no conflict of interests.

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The effect of resveratrol on expression of matrix metalloproteinase 9 and its tissue inhibitors in vascular smooth muscle cells

Effat Farrokhi[1], Keihan Ghatreh-Samani[2], Najmeh Salehi-Vanani[3], Amin Mahmoodi[3]

Original Article

Abstract

BACKGROUND: Matrix metalloproteinase 9 (MMP-9) is involved in extracellular matrix degradation and remodeling. An increase in MMP-9 expression by vascular component cells plays an important role in atherosclerotic plaque formation and rupture. Resveratrol, a polyphenolic substance, was suggested to play a role in preventing the progress of atherosclerotic disease. The aim of this study was to investigate the effect of resveratrol on MMP-9 and tissue inhibitors of metalloproteinases (TIMPs) in vascular smooth muscle cells (VSMCs) after treatment with H_2O_2.

METHODS: Cultured VSMCs were pre-treated with 0.2 mM of H_2O_2 before stimulation with different concentration of resveratrol. Expression of MMP-9, TIMP-1, and TIMP-3 genes were measured using real-time polymerase chain reaction (PCR) method, and MMP-9 protein level was detected using western blot analysis.

RESULTS: Resveratrol at 120 µmol/l concentration reduced the elevated level of MMP-9 induced by H_2O_2 in VSMCs as 1.85 ± 0.35 folds ($P < 0.050$) and 8.70 ± 1.20 folds ($P < 0.050$) after 24 and 48 hours, respectively. Resveratrol increased the diminished level of TIMP-1 induced by H_2O_2 as 2.5 ± 0.48 folds following the treatment with 120 µmol/l after 48 hours ($P < 0.050$).

CONCLUSION: Resveratrol as an antioxidant can decrease MMP-9 production, not only by suppressing MMP-9 expression, but also by augmenting TIMP-1 production. Altogether, resveratrol as an antioxidant can regulate the MMP-9/TIMP-1 balance, and may be considered as a preservative agent in the treatment and prevention of atherosclerosis.

Keywords: Matrix Metalloproteinase 9, TIMPS, Resveratrol, Vascular Smooth Muscle

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Introduction

Atherosclerosis is the most common cause of death in the world, and oxidative stress has a critical role in the pathogenesis and development of atherosclerosis. Matrix metalloproteinase 9 (MMP-9) is a member of the family of endopeptidases, that is involved in extracellular matrix degradation and remodeling. Increased expression of MMP-9 by vascular component cells during vascular injury and inflammation plays an important role in atherosclerotic plaque formation and rupture.[1]

MMPs activity is regulated by tissue inhibitors of metalloproteinases (TIMPs).[2] Changes in TIMP levels are considered to be important due to their direct effect on MMP activity. Resveratrol is a natural polyphenolic antioxidant, and several studies have confirmed its protective effects on the cardiovascular system in patients with coronary artery disease (CAD).[3,4]

Resveratrol has a cardioprotective activity via various mechanisms such as anti-inflammatory and antioxidant activity.[5,6]

Resveratrol reduces neural damage after cerebral ischemia. The elevated levels of MMP-9 were notably diminished in the resveratrol-treated mice as compared to the vehicle MCAO mice; suggesting that resveratrol can protect neural tissue against acute ischemic stroke, which could be attributed to its activity against MMP-9 by inhibiting JNK and PKC signal transduction.[7,8]

It seems that inhibition of MMPs activation or prevention of their upregulation could inhibit the

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effects of oxidative stress on atherosclerotic plaque formation. The aim of this study was to investigate the effect of resveratrol on MMP-9 and TIMPs in vascular smooth muscle cells (VSMCs) after treatment with H_2O_2.

Materials and Methods

In this experimental study, human aorta-vascular smooth muscle cells (HA-VSMC) were purchased from cell bank of Pasteur Institute of Iran in Tehran, Iran. The cells were cultured in F12K growth medium. F12K media contained 10% fetal bovine serum (FBS), 0.05 mg/ml ascorbic acid, 0.01 mg/ml insulin, 0.05 mg/ml transferrin, 10 ng/ml sodium selenite, 0.03 mg/ml human epidermal growth factor (EGFs), 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) to a final concentration of 10 mM, penicillin (100 U/ml), and streptomycin (100 U/ml).

Cells were cultured in a humidified incubator containing 5% CO_2 at 37 °C. Daily control of cell growth and cell division in culture condition were done. Cells used for the experiments were 3 to 7 passages.

3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was used to determine resveratrol concentration causing 50% cell death (the half maximal inhibitory concentration or IC50). Briefly, the cells were seeded at a density of 15 × 10^3 in 96-well plates. After achieving approximately 80% confluence, cells were treated with increasing concentration of resveratrol (40 to 200 µmol/l) for 48 hours. Thereafter, 20 µl MTT (5 mg/ml, Sigma-Aldrich, Germany) solution was added to each well. The formazan crystal was dissolved by adding 150 µl dimethyl sulfoxide (DMSO) to each well after 4 hours, and the optical density of each well was measured at 490 nm on an enzyme-linked immunosorbent assay (ELISA) plate reader (Awareness, USA) following 4 hours of incubation at 37 °C.

The cells were seeded in a 12-well plate at a density of 1 × 10^4 cells per well. When the cells achieved approximately 80% confluence, they were pretreated with physiologic concentration (0.2 mM) of H_2O_2 for inducing oxidative stress.[9] Then, the cells co-cultured with 80, 100, and 120 µmol/l resveratrol (Sigma, USA) for 24 and 48 hours.

RNA isolation and cDNA synthesis: Total RNA was extracted from the cells using Trizol (Invitrogen, USA) according to the manufacturer instructions. RNA was quantified using a Nanodrop 2000C spectrophotometer (Thermo Scientific, USA) and treated with DNase. Then, cDNA was synthesized from 0.5 mg total RNA using random primer and the cDNA Synthesis kit (Thermo Fisher Scientific, USA).

Real-time polymerase chain reaction (Real-time PCR): The expression of MMP-9, TIMP-1, and TIMP-3 genes was measured using quantitative real-time PCR. The experiments were performed using Rotor-Gene 3000 real-time DNA amplification system (Corbett Research, Australia) and SYBR green method. Primers used for real-time PCR are listed in table 1. Experiments were performed in triplicate,[6] using 5 µl SYBR green PCR Master Mix, 0.2 µl primer sets, 2 µl cDNA (40 ng), and 3.6 µl nuclease-free H_2O to yield a 10 µl reaction. The amplification conditions were as follow: initial denaturing at 94 °C for 5 minutes, then 40 cycles of 95 °C for 15 seconds, 59 °C for 20 seconds, and 72 °C for 30 seconds. The comparative cycle threshold (CT) (ΔΔCT) method was used for data quantitation, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene expression was used as an endogenous reference.

Table 1. Primer sequences and product length

Genes	Genes Primer sequences (5'-3')	Amplicon length (bp)	Gene bank reference
MMP-9	Forward: GCTCACCTTCACTCGCGTGTA Reverse: TCCGTGCTCCGCGACA	70	NM_004994.2
TIMP-1	Forward: CCTGGCTTCTGGCATCCTG Reverse: CCACGAACTTGGCCCTGATG	125	NM_003254.2
TIMP-3	Forward: GTCGCGTCTATGATGGCAAG Reverse: AAGCAAGGCAGGTAGTAGCA	151	NM_000362.4
GAPDH	Forward: ACACCCACTCCTCCACCTTTG Reverse: TCCACCACCCTGTTGCTGTAG	112	NM-002046.5

MMP-9: Matrix metalloproteinase 9;TIMP: Tissue inhibitors of metalloproteinases; GAPDH: Glyceraldehyde-3-phosphate dehydrogenase

Western blot analysis: Western blot analysis was used for detecting MMP-9 protein expression. VSMCs were lysed in ice-cold radioimmune precipitation assay buffer (6 ×) containing protease inhibitor cocktail. Samples were electrophoresed on 12% sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE). The separated proteins were transferred to nitrocellulose membranes, and incubated overnight at 4 °C with blocking solution [5% nonfat dried milk in phosphate-buffered saline (PBS) containing 0.1% Tween 20]. Membranes were incubated with MMP-9 antibody (1:3000) at room temperature for 2 hours. After washing, the membrane was incubated with goat anti-rabbit IgG horseradish peroxidase conjugate (1:10,000) at room temperature for 90 minutes. Finally, the color was developed with the addition of 3,3',5,5'-tetramethyl-benzidine membrane peroxidase substrate. Beta-actin was detected as a sample loading control.

All experiments were done in triplicate. Results are expressed as the mean ± standard error of mean (SEM). Statistical analysis was done using nonparametric Kruskal-Wallis test. The nonparametric Mann-Whitney U test was used to compare differences between control and test groups. P value of less than 0.050 was considered as the level of significance.

Results

The IC50 of resveratrol estimated by MTT assay was about 120 µmol/l. This concentration of resveratrol was chosen for further experiments.

In this study, the resveratrol effects on expression of MMP-9 and its inhibitors (TIMP-1 and -3) were investigated in VSMCs after inducing with H_2O_2. H_2O_2 used at the non-toxic concentration of 0.2 mM. MMP-9 expression increased 1.43 ± 0.29 and 1.98 ± 0.54 folds after 24 and 48 hours, respectively ($P < 0.050$ for both) after treatment of the cells with H_2O_2 without resveratrol. In contrast, resveratrol at different concentrations decreased MMP-9 expression, when given simultaneously with H_2O_2.

After 24 hours, MMP-9 expression was decreased 1.60 ± 0.21, 1.57 ± 0.30, and 1.85 ± 0.35 folds following the treatment with 80, 100, and 120 µmol/l resveratrol when compared with the H_2O_2-treated group ($P < 0.050$ for all) (Figure 1).

After 48 hours, resveratrol at 80, 100, and 120 µmol/l concentrations reduced the elevated level of MMP-9 induced by H_2O_2 as 6.20 ± 1.28, 5.50 ± 1.96, and 8.70 ± 1.20 folds, respectively, when compared with the H_2O_2-treated group ($P < 0.050$ for all) (Figure 1).

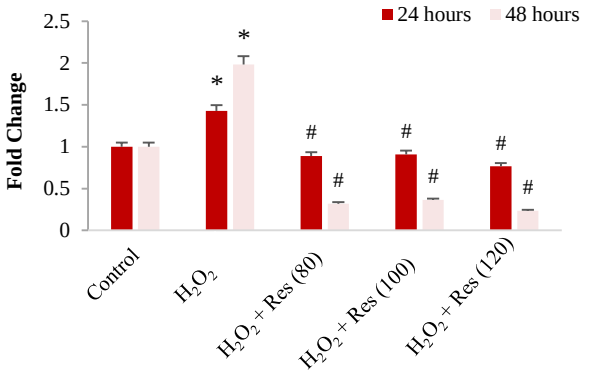

Figure 1. H_2O_2 upregulated the expression of matrix metalloproteinase 9 (MMP-9) in vascular smooth muscle cells (VSMCs). Resveratrol at 80, 100, and 120 µmol/l concentrations reduced the elevated level of MMP-9 induced by H_2O_2.
* $P < 0.050$ compared with control group
# $P < 0.050$ compared with H_2O_2-treated group

Western blot analysis confirmed the changes observed at MMP-9 mRNA level (Figure 2). In western blot analysis, beta-actin (42 kDa) was used as internal control.

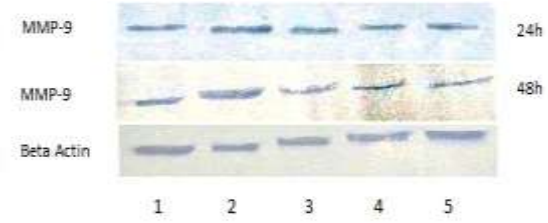

Figure 2. The expression of matrix metalloproteinase protein 9 (MMP-9) determined by western blot analysis after treatment with 80, 100, 120 µmol/l resveratrol in vascular smooth muscle cells (VSMCs). Beta-actin (42 kDa) was used as an internal control to standardize the protein loading in western blotting.
Lane 1: control; Lane 2: treated with H_2O_2; Lane 3-5: treated with H_2O_2 and various concentration of resveratrol (80, 100, and 120 µmol/l, respectively).

After treating the cells with H_2O_2 without resveratrol, TIMP-1 expression decreased 1.73 ± 0.26 folds after 48 hours ($P < 0.050$). In contrast, resveratrol at different concentrations increased TIMP-1 expression when given simultaneously with H_2O_2.

After 48 hours, resveratrol at 80, 100, and 120 µmol/l concentrations increased the diminished level of TIMP-1 induced by H_2O_2 about 1.74 ± 0.51,

1.93 ± 0.37, and 2.50 ± 0.48 folds, respectively, compared with the H_2O_2-treated group ($P < 0.050$ for all) (Figure 3). There was no significant change in the expression of TIMP-1 after 24 hours.

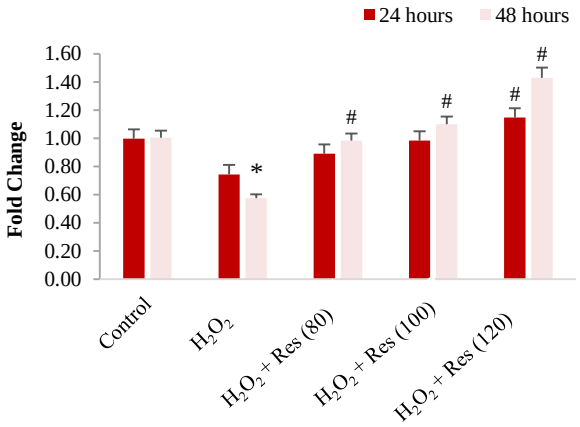

Figure 3. H_2O_2 downregulated the expression of tissue inhibitors of metalloproteinase 1 (TIMP-1) in vascular smooth muscle cells (VSMCs). Resveratrol in 80, 100, and 120 µmol/l concentrations increased the diminished level of TIMP-1 induced by H_2O_2 after 48 hours.
* $P < 0.050$ compared with control group
# $P < 0.050$ compared with H_2O_2-treated group

We found no significant effect by resveratrol on TIMP-3 expression by real time PCR (not shown).

Discussion

In this study, we investigated the resveratrol effect on MMP-9 expression in H_2O_2-induced VSMCs. Resveratrol decreased MMP-9 expression in H_2O_2-induced VSMCs.

Matrix metalloproteinases play important roles in cardiovascular diseases, and oxidative stress has destructive effect on vascular biology through the activation of MMPs.[10]

MMP-9 is involved in the breakdown of extracellular matrix proteins in various physiological and pathological conditions, such as angiogenesis, bone development, and atherosclerosis plaque rupture.[1]

Enhanced expression and activities of MMP-9 have been observed in vascular injury. TIMP-1 is endogenous inhibitor of MMP-9, and it is suggested that TIMP-1 plays an important role in cardiovascular disease.

Regarding the effects of oxidative stress in vascular remodeling, antioxidant approaches are used to reduce the upregulation of MMPs, and attenuate the tissue dysfunction and remodeling during vascular diseases.[11-13]

In this study, H_2O_2 increased MMP-9 expression in VSMCs. Upregulation of MMP-9 is not unexpected in conditions that free radicals were increased by H_2O_2 or other oxidants. Elevated levels of MMP-9 due to oxidant stress in VSMCs has been demonstrated in many studies.[10,14]

Resveratrol decreased MMP-9 expression in H_2O_2-induced VSMCs. Resveratrol displays potent antioxidant activity, thereby can scavenge free radicals produced by H_2O_2, and so reduce the oxidative effects of H_2O_2 in the environment.

Previous studies have demonstrated that polyphenols interfere with MMP-9 expression, and reduce inflammatory angiogenesis through MMP-9 inhibition.[15,16] The results of this study and other studies[17,18] support a potential protective role for dietary polyphenols in cardiovascular diseases.

Resveratrol inhibits the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signal transduction pathway that mediates the expression of MMPs and many other genes involved in inflammatory and pro-oxidant processes associated with vascular disease development.[19] The capability of resveratrol in reducing of NF-κB activity may be considered indicative to change MMP-9 expression in this study.

The MMPs are tightly regulated, not only at the transcriptional level, but also by their specific inhibitors.[20,21] The effect of antioxidant on MMP or TIMP expression in different cells has been previously reported.[22-24]

Epigallocatechin-3-gallate, as an antioxidant agent, reduces the activity and expression of MMP-9, and enhances the expression of TIMP-1 in cancer cell line MDA-MB-231.[22]

In a recent study, resveratrol attenuated blood-brain barrier dysfunction via regulation of MMP-9 and TIMP-1.[23]

According to a study, use of polyphenol extract from olive pomace oil down-regulated the levels of matrix MMP-2 and MMP-9, and increased TIMP-1 expression in human endothelial cells,[24] which could represent a powerful tool for the prevention and treatment of endothelial dysfunction-associated vascular disease.

Matrix metalloproteinases contribute to plaque rupture, atherothrombosis, and myocardial infarction.[25] For this reason, using MMP inhibitors can be considered as a preservative agent for the prevention and treatment of cardiovascular diseases.[26]

The results of this study showed that resveratrol, as an antioxidant, can decrease MMP-9 expression,

not only by suppressing MMP-9 production, but also by augmenting TIMP-1 production.

It seems that due to the dual role of resveratrol with regard to regulation of the MMP-9/TIMP-1 balance, it could be a good choice for preventing and treating cardiovascular diseases.

Conclusion

Altogether, the results of this study showed that resveratrol, as an antioxidant, can regulate the MMP-9/TIMP-1 balance, and may be considered as a preservative agent in the prevention and treatment of atherosclerosis. To better understand the atherosclerosis prevention and treatment with resveratrol, further studies with animal models are necessary.

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Conflict of Interests

Authors have no conflict of interests.

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Cardiovascular disease risk prediction among Iranian patients with diabetes mellitus in Isfahan Province, Iran, in 2014, by using Framingham risk score, atherosclerotic cardiovascular disease risk score, and high-sensitive C-reactive protein

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Original Article

Abstract

BACKGROUND: Risk assessment in clinical practice plays an important role in classifying population for appropriate preventive medicine for each category. Several multivariable risk predictor algorithms and inflammatory biomarkers are developed for assessing risk for cardiovascular diseases (CVDs). We aimed to depict a picture of the cardiovascular risk profiles in the Iranian population with diabetes mellitus (DM) through three risk predictors for the first time, as the patients with DM have an increased risk for CVDs.

METHODS: In this cross-sectional study, the sample size consisted of 418 patients with DM from Diabetes Clinic of Shariati hospital, Isfahan, Iran, in February to July, 2014. We collected the latest information, and then calculated the 10-year CVD risk using Framingham risk score (FRS) and atherosclerotic cardiovascular disease (ASCVD) risk score; while high-sensitivity C-reactive protein (hs-CRP) was measured for them based on their physicians' prescription. Finally, all data were analyzed using SPSS software.

RESULTS: The mean 10-year risk prediction of CVDs in the 30- to 74-year-old Iranian patients with DM was high in all three predictors based on their cut-off points, 16.31%, 12.39%, and 3.46 mg/l for FRS, ASCVD risk score, and hs-CRP level, respectively. Although the mean FRS and ASCVD risk scores were significantly higher among men than women ($P < 0.0500$), the mean hs-CRP level was slightly lower in men than women ($P > 0.0500$).

CONCLUSION: Mean FRS and ASCVD risk scores and hs-CRP in patients were high, and a considerable proportion of patients with DM in our study were at intermediate and high risk for CVDs in the next 10 years. Future cohort studies would investigate the accuracy of different predictors in upcoming years, and also help to derive a specific model or recalibrate existing predictors with characteristic of Iranian populations and specific target groups.

Keywords: Cardiovascular Diseases, Risk Assessments, Diabetes Mellitus, C-Reactive Protein, Risk Factor

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Introduction

Cardiovascular diseases (CVDs) are the single leading causes of death globally.[1] Data show that 17.3 million people died from CVDs in 2008, and almost 23.6 million people will die by the year 2030.[2] Multiple risk factors have been proved to play a role in the pathogenesis of CVDs in which diabetes mellitus (DM) is an important one. The total number of people with DM is going to be raised from 171 million in 2000 to 366 million in 2030.[2,3] patients with DM have a 2-4 times greater chance of CVDs and death in comparison with those without DM.[4] Therefore, multivariate cardiovascular risk scores have been used in many countries to identify Individuals who are at high risk of getting CVDs.[5] In addition, among inflammatory biomarkers, high-sensitivity C-reactive protein (hs-CRP) has been accepted as an independent

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predictor of CVDs.[6] The aim of risk assessment is to categorize population into those at low, moderate, and high CVD risk for performing appropriate preventive approaches in each one.[7]

Framingham Heart Study, which was conducted as a large project in 1948, could made algorithm to estimate CVD in general population, and widely was used for assessing major CVDs in future. Result of less than 10%, 10% to 20%, and more than 20% are defined as low, intermediate and high risk, respectively.[8-10] In 2013, National Heart, Lung and Blood Institute (NHLBI) in support of CVD prevention guidelines via Risk Assessment Work Group (RAWG) assessed CVDs risk factors and developed atherosclerotic cardiovascular disease (ASCVD) risk estimator for more practical risk assessment. In this measurement, result of less than 5%, 5% to 7.5%, and more than 7.5% were defined as low, intermediate, and high risk, respectively.[11] Moreover, In the early 1990s, an inflammatory biomarker named hs-CRP had been shown to have relationship with CVDs. hs-CRP of less than 1, 1-3, and more than 3 mg/l are defined as low, intermediate, and high risk, respectively.[12,13]

Some studies, done using different CVD risk calculators and biomarkers on different populations or certain target groups, showed controversial results. For instance, Framingham risk score (FRS) overestimates the risk of coronary heart disease in German, Chinese, and Mexican populations. While, Tehran Lipid and Glucose prospective study (TLGS) in Middle East showed the FRS function was good in normal population.[14-17] Furthermore, ASCVD risk score is predicted to overestimate in some populations such as Chinese and Hispanic Americans.[18] Moreover, there are few studies focus on suitable cut-off points of measuring hs-CRP in different groups or populations.[13]

As there was no study evaluate these three risk predictors in patients suffering DM in Iranian population before this study, we aimed to assess the 10-year ASCVD risk, FRS, and hs-CRP levels in 30- to 74-year-old Iranian patients with DM through a cross-sectional study for the first time. Knowing 10-year risk of CVD is helpful in strengthen preventive medicine.

Materials and Methods

This cross-sectional study that was conducted from February 2014 to July 2014, and in patients with DM aged between 30-74 years that were visited two days per week during that period in Diabetes Clinic of Shariati hospital, Isfahan, Iran. Based on 2 different calculators, we collected required parameters to calculate 10-year CVD risk for patients with DM. Anyone who had one or more than one DM criteria was included in the study [glucose tolerance test ≥ 200 mg/dl, or random glucose ≥ 200 mg/dl, or hemoglobin A1c (HbA1c) ≥ 6.5%, or fasting blood sugar ≥ 126 mg/dl].

In 2153 patients, the demographic information such as sex, age, race, and smoking status, as well as presence/absence of hypertension treatment and blood pressure level that was taken with a standard method by their physicians, and other routine check-up measurements such as total cholesterol, high-density lipoprotein (HDL) cholesterol, and hs-CRP level that were recorded in patients' files, were gathered through a checklist. If patient showed any manifestation of atherosclerotic disease such as cerebrovascular accident (CVA) or transient ischemic attack (TIA), coronary artery disease, carotid artery disease, peripheral vascular disease, positive exercise tolerance test, typical angina history, congestive heart failure (CHF), or electrocardiography (ECG) with evidence of myocardial infarction (MI) or ischemic heart disease (IHD), he/she was excluded from study.

After applying these criteria, 418 patients were eligible for entering to our study. Research protocol was approved by the Research Review Board of School of Medicine, Najafabad Branch, Islamic Azad University, Najafabad, Iran. Patients' names were not used in the study for confidentiality reasons, and instead of their names, codes were used. In addition, for all participants, written informed consent was provided. This research was conducted by personal funds.

In our study, age, sex, and race were demographic variables. DM, hypertension, smoking, total cholesterol, HDL cholesterol, and hs-CRP were independent variables. CVDs were dependent variables.

After excluding duplicate or missing data, CVD risk assessment was performed all 418 patients using FRS and ASCVD risk calculators for. Finally, for quantitative variables, results were presented as mean ± standard deviation (SD); and categorical variables were demonstrated as frequencies and percent. Analysis was applied based on gender and age categories (less than 56, 56-65, and more than 65 years). For categorical variables, chi-square test was used. 95% of confidence interval (CI) was considered, too. For FRS, we used 10-year CVD risk calculator that required sex, age, systolic blood pressure, existence of hypertension treatment, DM, smoking status, HDL level, and total cholesterol level.

Table 1. The mean and intensity of Framingham risk score (FRS) in the 30-74-year-old Iranian patients with diabetes mellitus (DM)

Characteristics		Mean (95% CI)	Intensity [n (%)]		
			Low (< 10%)	Intermediate (10%-20%)	High (> 20%)
Total (n = 418)		16.31 (15.31-17.30)	127 (30.40)	171 (40.90)	120 (28.70)
Gender	Men (n = 166)	22.90 (21.12-24.68)	16 (9.60)	60 (36.10)	90 (54.20)
	Women (n = 252)	11.97 (11.17-12.77)	111 (44.0)	111 (44.00)	30 (11.90)
P		< 0.0001		< 0.0001	
Age group (year)	≤ 55 (n = 132)	9.30 (8.47-10.13)	84 (63.60)	41 (31.10)	7 (5.30)
	56-65 (n = 161)	16.16 (14.90-17.43)	32 (19.90)	90 (55.90)	39 (24.20)
	≥ 66 (n = 125)	23.90 (21.81-25.99)	11 (8.80)	40 (32.00)	74 (59.20)
P		< 0.0001		< 0.0001	

CI: Confidence interval

In FRS, result of less than 10%, 10% to 20%, and more than 20% were defined as low, intermediate, and high risk, respectively. ASCVD risk calculator required gender, age, race, HDL cholesterol, total cholesterol, systolic blood pressure, existence of hypertension treatment, DM, and smoking status. In ASCVD risk score, result of less than 5%, 5% to 7.5%, and more than 7.5% were defined as low, intermediate, and high risk, respectively. In addition, hs-CRP of less than 1, 1-3, and more than 3 mg/l were defined as low, intermediate, and high risk, respectively. P-values of less than 0.05 were considered statistically significant. T test was used for quantitative variables. All statistical analysis was performed using SPSS software (version 20, IBM corporation, Armonk, NY, USA).

Results

From the total of 418 participants, 166 (39.7%) were men and 252 (60.3%) were women. The mean age was 59.84 years with the SD of 8.77. Sex-specific age distribution showed the mean age of 60.5 ± 9.5 and 59.5 ± 8.3 years for men and women, respectively, but the difference was not statistically significant (P = 0.21). Of the patients, 132 had 55 years or less, 161 were between 56 and 65 years, and 125 patients had 66 years or more.

FRS percentages were between 1.30% and 57.90%, and the mean 10-year risk of CVD based on FRS was 16.31% (95% CI: 15.31-17.30). The frequency of low-, intermediate-, and high risk patients based on FRS was 30.40%, 40.90%, and 28.70%, respectively. The mean FRS were significantly higher in men than women (P < 0.0001). The mean FRS increased significantly by increasing age to reach 23.90% in age group over 66 years, compared with 9.30% in age group of below 55 years (P < 0.0001). Moreover, the frequency of high-risk patients was significantly higher in higher groups in FRS (P < 0.0001); and the frequency of high-risk patients in men was significantly higher than women (P < 0.0001) (Table 1).

ASCVD risk scores were between 0.50% to 54.30%, and the mean 10-year risk of ASCVD risk score on target group was 12.39% (95% CI: 11.32-13.47). The frequency of low-, intermediate- and high-risk patients based on ASCVD risk was 28.90%, 12.10%, and 59.00% respectively. The mean ASCVD risk were significantly higher in men than women (P < 0.0001). The mean ASCVD risk increased significantly by increasing age to reach 23.83% in age group of over 66 years, compared with 3.82% in age group of below 55 years (P < 0.0001). In addition, the frequency of high risk patients in ASCVD risk score was significantly higher in age group over 66 years than lower age groups (P < 0.0001). The frequency of high-risk patients in men was significantly higher than women (P < 0.0001) (Table 2).

Table 2. The mean and intensity of atherosclerotic cardiovascular disease (ASCVD) risk score in the 30-74-year-old Iranian patients with diabetes mellitus (DM)

Characteristics		Mean (95% CI)	Intensity [n (%)]		
			Low (< 5%)	Intermediate (5%-7.5%)	High (> 7.5%)
Total (n = 339)		12.39 (11.32-13.47)	98 (28.90)	41 (12.10)	200 (59.00)
Gender	Men (n = 126)	18.30 (16.29-20.31)	15 (11.90)	9 (7.10)	102 (81.00)
	Women (n = 213)	8.89 (7.92-9.87)	83 (39.00)	32 (15.00)	98 (46.00)
P		< 0.0001		< 0.0001	
Age group (year)	≤ 55 (n = 106)	3.82 (3.32-4.32)	83 (79.00)	11 (10.50)	11 (10.50)
	56-65 (n = 136)	10.77 (9.77-11.76)	14 (10.30)	30 (22.10)	92 (67.60)
	≥ 66 (n = 98)	23.83 (22.01-25.65)	1 (1.00)	0 (0.00)	97 (99.00)
P		< 0.0001		< 0.0001	

CI: Confidence interval

Table 3. The mean and intensity of high-sensitivity C-reactive protein (hs-CRP) level in the 30-74-year-old Iranian patients with diabetes mellitus (DM)

Characteristics		Mean (95% CI)	Intensity [n (%)]		
			Low (< 1 mg/l)	Intermediate (1-3 mg/l)	High (> 3 mg/l)
Total (n = 418)		3.46 (3.08-3.84)	65 (15.60)	192 (45.90)	161 (38.50)
Gender	Men (n = 166)	3.24 (2.65-3.84)	33 (19.90)	72 (43.40)	61 (36.70)
	Women (n = 252)	3.60 (3.10-4.10)	32 (12.70)	120 (47.60)	100 (39.70)
P		0.3600		0.1400	
Age group (year)	≤ 55 (n = 132)	3.53 (2.88-4.18)	22 (16.70)	54 (40.90)	56 (42.40)
	56-65 (n = 161)	3.19 (2.61-3.78)	21 (13.00)	87 (54.00)	53 (32.90)
	≥ 66 (n = 125)	3.73 (2.96-4.50)	22 (17.60)	51 (40.80)	52 (41.60)
P		0.5100		0.1400	

CI: Confidence interval

hs-CRP values were between 0.00 to 33.01 mg/l, with a mean level of 3.46 (95% CI: 3.08-3.84). The frequency of low-, intermediate- and high-risk patients based on hs-CRP level was 15.60%, 45.90%, and 33.00%, respectively. The mean level of hs-CRP was slightly lower in men than women (P > 0.0500). The mean hs-CRP level increased insignificantly by increasing age (P > 0.0500). The frequency of high-risk patients in men was slightly lower than women (P > 0.0500) (Table 3).

Discussion

The aim of this research was assessment of cardiovascular risk prediction in the Iranian population with DM through FRS and ASCVD risk scores, and hs-CRP predictors in the 30-74-year-old patients. According to our findings, the mean FRS was considerably high (16.31%) in Iranian population with DM, and FRS was higher in men compared with women. While some studies suggested the FRS varies between populations,[19] FRS have been shown good efficacy in Iranian normal population in TLGS, previously.[20,21] The difference between this study and TLGS is that while both focused on same age range and same race, but they targeted different groups, those with DM vs. normal population.

Moreover, we found out that the mean ASCVD risk score is significantly high (12.39%) in Iranian population with DM. Similar to FRS, the mean ASCVD was higher in men compared with women. In one retrospective cohort study done by Chia et al., 922 individuals were selected, and FRS and ASCVD risk scores were calculated for each one. The result showed that ASCVD overestimated CVD risks rather than FRS. Due to their research design, recall bias would be a great limitation in that article. In addition, they focused on different age group (40-79 years) and normal population.[22]

The mean hs-CRP level was considerably high (3.46 mg/l) in this study, same as for FRS and ASCVD risk scores; but hs-CRP level was very slightly lower in men compared with women. Seo et al. showed that hs-CRP had significant correlation with CVD risk in 1561 patients with established DM or CHD over 18 years of age in Korean population.[23] Besides, Ballantyne et al. showed that hs-CRP in middle-aged men and women was related to CHD risk.[24]

In this study, FRS and ASCVD risk scores were higher in men, and in older age groups; while hs-CRP was not age-related. Ford et al.[25] and Motamed et al.[26] studies declared the same concept for FRS and ASCVD risk scores. Moreover, Khera et al. found out that race and gender could affect the distribution of CRP in different populations.[27]

One possible theory about the difference between the results of FRS and ASCVD calculators with hs-CRP level could be due to the role of hs-CRP as an acute phase reactant, that is increased in presence of insulin-resistance situation as well as other chronic conditions; and the other one is the fact for calibration of different risk calculators based on certain parameters, such as race and baseline diseases, in target groups.

Like other researches, our study was not free of limitations. Participants for contributing in this study were chosen from one DM clinic and with small sample size. In addition, as this study was cross-sectional, we cannot comment about correlation of future CVD events based on risk predictors. So, other studies should be done on larger DM population, and in different cities, with cohort design.

Conclusion

In conclusion, this study showed that mean FRS and ASCVD risk scores in the 30- to 74-year-old Iranian

patients with DM are significantly high. These results demonstrated that in the upcoming years, the Iranian population is going to be in great risk for cardiovascular events, and as this study was the first done in literature evaluating the cardiovascular risk through three CVD risk estimators in Iranian patients with DM, it would be useful for initiating cohort researches to find out which one can predict CVD most accurate in 10 years. Moreover, those studies will help to derive a model with characteristic of Iranian populations and specific target groups, or recalibration of existing predictors.

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Conflict of Interests

Authors have no conflict of interests.

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The comparison of waist circumference, waist-to-hip ratio, and waist-to-height ratio among rural women adults in the North of Iran, between the years 2004 and 2013

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Original Article

Abstract

BACKGROUND: Central obesity is a common health disorder, and the main objective of this study was to compare its changings among rural women in the north of Iran, between the years 2004 and 2013.

METHODS: Two cross-sectional studies were established on the 2839 and 2478 subjects in 2004 (first stage) and 2013 (second stage), respectively. Among 118 villages, 20 were selected using random sampling; they were the same in two studies. Central obesity was defined as waist circumference (WC) > 88 cm, waist-to-hip ratio (WHR) > 0.8, and waist-to-height ratio (WHtR) > 0.5.

RESULTS: The prevalence of central obesity in 2013 based on WC, WHR, and WHtR were 37.4%, 73.5%, and 67.8%, respectively. Compared with 2004, the prevalence of central obesity based on WHR increased as 5.4% (68.1% vs. 73.5%) (P = 0.001), whereas morbid obesity (WHtR > 0.6) based on WHtR decreased as 3.7% in 2013 (28.8% vs. 25.1%) (P = 0.004). Central obesity based on WHR significantly decreased in less or equal 24-year-old group (76.6% vs. 70.1%) (P = 0.003), while it increased in 25-34- (65.1% vs. 74.0%) and in equal or more than 35-year-old group (54.1% vs. 78.9%) (P = 0.001 for all). Moreover, morbid obesity decreased in all age, economic, and education groups (except uneducated one) (P < 0.050 for all).

CONCLUSION: Despite the decrease in central obesity based on WC and WHR indices in 2004-2013 duration, we found the evidence of a decline in sever obesity based on WHtR in that period. These trends have an alarm for health policy makers, not only in this area but also in same communities. Comprehensive studies are recommended to determine the best obesity indicator related to health in future.

Keywords: Central Obesity, Trends, Women, Socioeconomic Status, Iran

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Introduction

Non-communicable diseases will account for approximately three quarters of all deaths in the developing countries by the year 2020.[1] Among them, obesity is a main risk factor for chronic diseases, and plays a central role in the "metabolic syndrome" or "insulin resistance", which includes hyperinsulinemia, hypertension, hyperlipidemia, and type 2 diabetes mellitus.[2]

Obesity has been increased in recent years in the world,[3] and is well-known as a health problem in Iran.[4,5] Besides, central obesity has been recognized as a major health problem in the north of Iran,[6] and its prevalence is 9.7-12.9 and 54.5-63.7 percent in Iranian men and women, respectively.[7,8]

Several indices such as body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR) are used to classify general and central obesity in clinical practice. Even though, WHtR and WC are better measures of visceral and abdominal fat distribution.[9,10] On the other hand, some studies reported that WC is a better indicator of cardiovascular disease (CVD) risk than BMI and WHR;[11-13] however, a high WHR has been identified as an increasing risk factor of dyslipidemia, hypertension, CVD, and diabetes mellitus compared with BMI.[14]

Golestan province is located in the north of Iran (south east of Caspian Sea), and among its 1.7 million people, 25.6% live in rural areas. Agriculture is the main job in rural areas, and different ethnic groups such as Fars-native, Turkmen, and Sistani are living in this region.[15]

Some studies have identified that life style,

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education, economic status, and ethnicity are the major obesity associated factors.[11,16,17] On the other hand, rapid socio-economic development and industrialization over the last decades have undoubtedly changed the life style in Iran. However, as far as the researchers concerned, there has been no discussion about the changing of obesity trend based on WC, WHR, and WHtR in rural women in Golestan province. In this regard, this study aimed to compare the central obesity based on WC, WHR, and WHtR, and some related socio-demographic factors between the years 2004 (first stage) and 2013 (second stage) in rural women in the north of Iran.

Materials and Methods

Two cross-sectional studies in 2004 with 2839 cases (first stage),[18] and in 2013 with 2478 cases (second stage) were conducted among women living in rural areas in the north of Iran. 20 of 118 villages in Gorgan and Aq-Qala districts (two capital cities in the north of Iran), were selected by random sampling. Villages and questioners were the same in two studies. A trained 20-member reviewer team completed a questionnaire including socio-demographic questions as age, economic status, and educational levels, and measured the anthropometric indices. The recorded data were combined and statistically analyzed. Sampling methods were similar to previous study.[18]

Based on age distribution among client women to primary health care, age was classified in three groups as ≤ 24, 25-34, and ≥ 35 years. Economic status was categorized based on possession of 10 facility items necessary for modern-day life, such as telephone, running water, gas pipeline, personal house, color television, computer, microwave oven, private car, freezer, and cooler.[18] According to this list, the economic status of sample population in these studies was categorized as low: ≥ 3, moderate: 4-6, and good: 7-10. According to the education classification in Iran, the education was categorized as uneducated (those women who could not write and read), 1-12 years of schooling, and college educated (who were educated at university).

Weight measurement without shoes and clothing was carried out using the health system scale (Seca, UK), and recorded as the nearest 0.5 kg. Height, waist, and hip measured using a tape measuring as the nearest 0.5 cm, while the participants were standing on their feet. WC was measured over the iliac and lower border of the ribs. Hip circumference was measured at the widest point over the buttocks.[19]

WHR was obtained by dividing the WC by hip circumference, and WHtR was obtained by dividing WC by mean of height. Abdominal obesity defined by WC > 88 cm and WHR > 0.8 cm.[19] WHtR was classified as normal: < 0.4, overweight: 0.4-0.5, obese: 0.5-0.6, and morbidly obese: > 0.6.[20,21] All women who were coming to primary health centers participated in two studies. Pregnant women and the subjects who did not like to participate were excluded from the studies.

The WC, WHR, and WHtR values were reported based on mean and standard deviation (SD), and categorized by obesity indices. To control the confounding effects of age, economic status, and education level, we compared the obesity indices by their subgroups in two stage studies. Categorical data has been presented by frequencies and percent.

After establishing the normality using the Kolmogorov-Smirnov test, data were analyzed using SPSS software (version 18.0, SPSS Inc., Chicago, IL, USA). Statistical analyses included independent sample t test, and analysis of variance (ANOVA) for continues variables. In addition, two-way ANOVA was used for assessing of interaction between economic status and education levels based on obesity indices, and Tukey's test was used for group comparisons. For categorical variables, chi-square test was used. P-value of less than 0.050 was considered as significant.

The studies were approved by Ethical Research Committee of Golestan University of Medical Sciences, Gorgan, Iran (G-P-35-1112), and verbal informed consents were received from all cases.

Results

Table 1 illustrates the main characteristics of two studies. As indicated, there was a little change in age, and hip and WC values. However, significantly increasing changes were seen in height and weight. WHR and WHtR values decreased significantly during two studies (P < 0.050 for all). Moreover, the improving of economic condition and education levels were seen during the two studies.

The mean and SD of WC, and the prevalence of central obesity based on it are compared between the two studies in table 2. The prevalence of central obesity by WC > 88 cm was 37.4% in 2013; however, this value unchanged during two studies. The change of central obesity during two studies was not significant by age groups and education levels (P > 0.050 for all); however, central obesity significantly decreased (5.7%) in moderate economic group during the two studies (P = 0.003).

Table 1. The comparison of anthropometric indices and socio-demographic factors status between the years 2004 and 2013

Variable		Year 2004 (2753 cases) Mean ± SD	2013 (2386 cases) Mean ± SD	P
Age (year)		28.290 ± 6.140	28.010 ± 5.670	0.093
Hip (cm)		97.950 ± 10.990	98.100 ± 12.320	0.645
Height (cm)		157.710 ± 5.970	158.790 ± 5.800	< 0.001
Weight (kg)		62.420 ± 12.940	65.470 ± 13.410	< 0.001
Waist circumference (WC) (cm)		84.400 ± 12.770	83.890 ± 13.260	0.161
Waist to hip ratio (WHR)		0.861 ± 0.082	0.856 ± 0.092	0.040
Waist to height ratio (WHtR)		0.536 ± 0.018	0.529 ± 0.083	< 0.001
Variable		**n (%)**	**n (%)**	**P**
Economy*	Poor	1067 (38.8)	554 (23.2)	< 0.001
	Moderate	1521 (55.2)	1250 (52.4)	
	Good	165 (6.0)	582 (24.4)	
Education	Uneducated	658 (23.9)	188 (7.9)	< 0.001
	1-12 years schooling	1917 (69.6)	2145 (89.9)	
	College	178 (6.5)	53 (2.2)	
Age group (year)	≤ 24	1043 (37.9)	706 (29.6)	< 0.001
	25-34	1357 (49.3)	1344 (56.3)	
	≥ 35	353 (12.8)	336 (14.1)	

SD: Standard deviation

* According to 10 facilities, the economic status categorized as low: ≥ 3, moderate: 4-6, and good: 7-10.

Chi-square and t tests were used for qualities and quantities values, respectively.

Table 3 shows the comparison of mean and SD of WHR, and the prevalence of central obesity based on it between the two studies. The prevalence of obesity by WHR > 0.8 was 73.5% in 2013, and increased (5.4%) during the two studies (P = 0.001).

The increasing trends of WHR were seen in 25-34 and ≥ 35 years age groups (P = 0.001 for all), while it decreased (6.5%) in ≤ 24 years age group (P = 0.003). In addition, central obesity significantly increased during two studies in moderate and good economic groups, besides in 1-12 years schooling and in uneducated groups (P < 0.050 for all).

The mean and SD of WHtR and central obesity are presented in table 4. The prevalence of overweight, obesity, and morbid obesity in 2013 were 24.1%, 18.6%, and 25.1%, respectively. Despite morbid obesity tend to decrease in total and in all groups but, obesity increased in these groups.

Tukey's post hoc test revealed statistical significant differences by three central obesity indices between age groups with together in two studies (P < 0.050 for all).

Table 2. The comparison of waist circumference (WC) of adult women in the north of Iran between the years 2004 and 2013

Variable	Year	2004 n	WC (cm) Mean±SD	Normal weight [n(%)]	Central obesity [n(%)]	2013 n	WC (cm) Mean±SD	Normal weight [n(%)]	Central obesity [n(%)]	P**
Age (year)	≤24[a]	1043	81.52 ± 12.28	754 (72.3)	289 (27.7)	706	80.95 ± 12.12	506 (71.7)	200 (28.3)	0.819
	25-34[b]	1357	85.77 ± 12.58	767 (56.5)	590 (43.5)	1344	84.36 ± 13.33	810 (60.3)	534 (39.7)	0.053
	≥35[c]	353	87.68 ± 13.25	181 (51.3)	172 (48.7)	336	88.21 ± 13.84	177 (52.7)	159 (47.3)	0.770
				P=0.001*				P=0.001*		
Economy#	Poor[d]	1067	81.99 ± 2.31	746 (69.9)	321 (30.1)	554	81.03 ± 13.34	399 (72.0)	155 (28.0)	0.409
	Moderate[e]	1521	85.70 ± 12.74	881 (57.9)	640 (42.1)	1250	83.80 ± 12.92	795 (63.6)	455 (36.4)	0.003
	Good[f]	165	88.04 ± 13.38	75 (45.5)	90 (54.5)	582	86.82 ± 13.30	299 (51.4)	283 (48.6)	0.209
				P=0.001*				P=0.001*		
Education	Uneducated[g]	658	83.88 ± 12.87	425 (64.6)	233 (35.4)	188	85.32 ± 13.83	112 (59.6)	76 (40.4)	0.241
	1-12 years of schooling[h]	1917	84.49 ± 12.73	1169 (61.0)	748 (39.0)	2145	83.75 ± 13.26	1347 (62.8)	798 (37.2)	0.247
	College[i]	178	85.55 ± 12.78	108 (60.7)	70 (39.3)	53	84.75 ± 10.56	34 (64.2)	19 (35.8)	0.767
				P=0.221*				P=0.266*		
Total		2753	84.40 ± 12.77	1702 (61.8)	1051 (38.2)	2386	83.89 ± 13.26	1493 (62.6)	893 (37.4)	0.600

WC: Waist circumference; SD: Standard deviation

* One-way ANOVA was used for quantitative values for more than two groups; ** Chi-square test was used for qualitative values;

According to 10 facilities, the economic status categorized as low: ≥ 3, moderate: 4-6, and good: 7-10.

Tukey's post hoc revealed statistical significant differences between quantitative values of a and b, a and c, b and c, d and e, and d and f (P < 0.050 for all) in 2004, and of a and b, a and c, b and c, d and e, d and f, and e and f in 2013 (P < 0.050 for all).

Table 3. The comparison of waist to hip ratio (WHR) of adult women in the north of Iran between the years 2004 and 2013

Variable	Year	2004 n	2004 WHR Mean ± SD	2004 Normal weight [n (%)]	2004 Central obesity [n (%)]	2013 n	2013 WHR Mean ± SD	2013 Normal weight [n (%)]	2013 Central obesity [n (%)]	P**
Age (year)	≤24[a]	1043	0.84 ± 0.08	244 (23.4)	799 (76.6)	706	0.85 ± 0.09	211 (29.9)	495 (70.1)	0.003
	25-34[b]	1357	0.87 ± 0.08	472 (34.9)	882 (65.1)	1344	0.86 ± 0.09	350 (26.0)	994 (74.0)	0.001
	≥35[c]	353	0.89 ± 0.07	162 (45.9)	191 (54.1)	336	0.87 ± 0.09	71 (21.1)	265 (78.9)	0.001
				P = 0.001*				P = 0.001*		
Economy#	Poor[d]	1067	0.85 ± 0.08	287 (26.9)	780 (73.1)	554	0.85 ± 0.09	163 (29.4)	391 (70.6)	0.309
	Moderate[e]	1521	0.87 ± 0.08	519 (34.2)	1000 (65.8)	1250	0.85 ± 0.09	337 (27.0)	913 (73.0)	0.001
	Good[f]	165	0.87 ± 0.08	72 (43.9)	92 (56.1)	582	0.86 ± 0.09	132 (22.7)	450 (77.3)	0.001
				P = 0.001*				P = 0.080*		
Education	Uneducated[j]	658	0.87 ± 0.08	229 (34.6)	429 (65.2)	188	0.87 ± 0.09	43 (22.9)	145 (77.1)	0.003
	1-12 years of Schooling[h]	1917	0.86 ± 0.08	599 (31.3)	1315 (68.7)	2145	0.86 ± 0.09	575 (26.8)	1570 (73.2)	0.002
	College[p]	178	0.86 ± 0.08	50 (28.1)	128 (71.9)	53	0.85 ± 0.08	14 (26.4)	39 (73.6)	0.949
				P = 0.005*				P = 0.061*		
Total		2750	0.86 ± 0.08	878 (31.9)	1872 (68.1)	2386	0.86 ± 0.09	632 (26.5)	1754 (73.5)	0.001

WHR: Waist to hip ratio; SD: Standard deviation

* One-way ANOVA was used for quantitative values for more than two groups; ** Chi-square test was used for qualitative values; # According to 10 facilities, the economic status categorized as low: ≥ 3, moderate: 4-6, and good: 7-10.

Tukey's post hoc revealed statistical significant differences between quantitative values of a and b, a and c, b and c, d and e, d and f, and h and j (P < 0.050 for all) in 2004, and of a and b, a and c, and b and c in 2013 (P < 0.050 for all).

In education groups, this differences were seen based on WHR index between 1-12 years schooling and uneducated groups in two studies (P < 0.050 for all).In addition, the results of this test were significant between different economic groups by all central obesity indices (P < 0.050 for all), except between moderate and good economic groups by WHR and WHtR in 2004 and by WHR in 2013 (Tables 2-4).

The results of two-way ANOVA between economic status and education levels by three indices are presented in table 5. In the first study, the main effects were statistically significant with economic status in WC [F = 13.852 at 2 degrees of freedom (df), P < 0.001], WHR (F = 6.889 at 2 df, P = 0.001), and WHtR (F = 9.485 at 2 df, P < 0.001). In addition, there was no interaction between economic status and education levels in those indices. In the second study, the main effects were statistically significant with economic status in WC (F = 4.454 at 2 df, P = 0.012) and in WHtR (F = 3.632 at 2df, P = 0.027). The interaction between economic status and educational levels was not seen in none of three central obesity indices.

Discussion

We discuss the variation of central obesity during 2004 to 2013 and its association with age, economic status, and educational levels in this section. The interesting finding is that WHR increased while WHtR decreased during two studies. Besides, the risk of obesity in older people was more than the other age groups. The associations of education and economy with the kinds of central obesity are not alike. In case, low educated groups were more than other groups at risk of morbid obesity. Moreover, the positive association was seen between economic status and WHR, but it was opposite to WHtR.

One of the important findings of this study was that WC did not change, but while WHtR decreased, WHR increased during two studies. In a trend study in the north of Iran, central obesity elevated as 14.1% over 5 years.[22] In Tehran, Iran, it increased as 23.2% from 1999 to 2011.[23] In this respect, in Colombian adults,[24] central obesity increased from 13.9% to 16.4% during 2005 to 2010. Moreover, in Australia, obesity based on WHtR was prevalent as 8.6%, 13.6%, and 18.3% in 1985, 1995, and 2007, respectively.[25] The decline observed in WHtR in our study could be attributed the increase of height and in the same way, this situation has been approved in other studies in this area.[26,27] Using of WHtR should be re-evaluated in the areas under height failure.

Determining the central obesity rate based on WC, WHR, and WHtR is another finding of the present study. In that respect, it was seen in 37.4%, 73.5%, and 43.7% of women. The prevalence of central obesity based on WC in the north of Iran and in the whole Iran was 56.7% and 43.4%, respectively.[28]

Table 4. The comparison of waist to height ratio (WHtR) of adult women in the north of Iran between the years 2004 and 2013

Variable	Year	2004 n	2004 WHtR Mean ± SD	2004 Normal [n (%)]	2004 Overweight [n (%)]	2004 Obese [n (%)]	2004 Morbidly obese [n (%)]	2013 n	2013 WHtR Mean ± SD	2013 Normal weight [n (%)]	2013 Overweight [n (%)]	2013 Obese [n (%)]	2013 Morbidly obese [n (%)]	P**
Age group (year)	≤ 24[a]	1043	0.52 ± 0.08	409 (39.2)	282 (27.1)	135 (12.9)	217 (20.8)	706	0.51 ± 0.08	275 (39.0)	189 (26.7)	124 (17.6)	118 (16.7)	0.021
	25-34[b]	1357	0.54 ± 0.08	377 (27.8)	310 (22.9)	227 (16.7)	443 (32.6)	1344	0.53 ± 0.08	423 (31.5)	308 (22.9)	245 (18.2)	368 (27.4)	0.001
	≥ 35[c]	353	0.56 ± 0.09	76 (20.1)	86 (24.4) P = 0.001*	63 (17.8)	133 (37.7)	336	0.56 ± 0.09	69 (20.6)	78 (23.2) P = 0.001*	75 (22.3)	114 (33.9)	0.047
Economy#	Poor[d]	1067	0.52 ± 0.08	396 (37.1)	273 (25.6)	141 (13.2)	257 (24.1)	554	0.51 ± 0.08	216 (38.5)	148 (26.6)	89 (16.1)	104 (18.8)	0.024
	Moderate[e]	1521	0.54 ± 0.08	419 (27.6)	373 (24.5)	256 (16.8)	473 (31.1)	1250	0.53 ± 0.08	408 (32.6)	303 (24.2)	226 (18.1)	313 (25.1)	0.002
	Good[f]	165	0.55 ± 0.08	42 (25.4)	32 (19.4) P = 0.001*	28 (17.0)	63 (38.2)	582	0.55 ± 0.08	146 (25.1)	124 (21.3) P = 0.001*	129 (22.2)	183 (31.4)	0.301
Education	Uneducated[j]	658	0.53 ± 0.08	205 (31.2)	165 (25.1)	117 (17.7)	171 (26.0)	188	0.53 ± 0.09	62 (33.0)	35 (18.6)	29 (15.4)	62 (33.0)	0.122
	1-12 years of schooling[h]	1917	0.54 ± 0.09	599 (31.2)	469 (24.5)	279 (14.6)	570 (29.7)	2145	0.53 ± 0.08	690 (32.2)	522 (24.3)	406 (18.9)	527 (24.6)	0.001
	College[p]	178	0.54 ± 0.08	53 (29.8)	44 (24.7) P = 0.511*	29 (16.3)	52 (29.2)	53	0.53 ± 0.07	15 (28.3)	18 (34.0) P = 0.068*	9 (17.0)	11 (20.7)	0.491
Total		2753	0.54 ± 0.08	857 (31.1)	678 (24.7)	425 (15.4)	793 (28.8)	2386	0.53 ± 0.08	767(32.2)	575 (24.1)	444 (18.6)	600 (25.1)	0.002

WHtR: Waist-to-height ratio; SD: Standard deviation; WHtR scaling: Normal: < 0.4, Overweight: 0.4-0.5, Obese: 0.5-0.6, Morbidly obese: > 0.6

* One-way ANOVA was used for quantitative values for more than two groups; ** Chi-square test was used for qualitative values; # According to 10 facilities, the economic status categorized as low: ≥ 3, moderate: 4-6, and good: 7-10.

Tukey's post hoc revealed statistical significant differences between quantitative values of a and b, a and c, b and c, d and e, and d and f (P < 0.050 for all) in 2004, and of a and b, a and c, b and c, d and e, d and f, e and f in 2013 (P < 0.050 for all).

Table 5. The results of two-way ANOVA analysis between economic status and education levels based on waist circumference (WC), waist-to-hip ratio (WHR), and waist to height ratio (WHtR) indicies

Criteria	Year / Variable	2004 Mean square	2004 F Statistic	2004 P	2013 Mean square	2013 F Statistic	2013 P
WC	A: Economic	2204.826	13.852	0.001	764.386	4.454	0.012
	B: Education	35.210	0.221	0.802	255.157	1.487	0.226
	A*B	25.203	0.158	0.959	163.925	0.955	0.431
WHR	A: Economic	0.045	6.889	0.001	0.016	1.971	0.140
	B: Education	0.010	1.572	0.208	0.018	2.164	0.115
	A*B	0.003	0.525	0.718	0.005	0.636	0.637
WHtR	A: Economic	0.063	9.485	0.001	0.025	3.632	0.027
	B: Education	0.001	0.220	0.802	0.016	2.349	0.096
	A*B	0.003	0.517	0.724	0.009	1.305	0.266

WC: Waist circumference; WHR: Waist-to-hip ratio, WHtR: Waist-to-height ratio

In other countries, as Ghana,[29] Malaysian women,[30] South Brazil,[16] Sri Lankan adults,[31] and Bangladesh,[32] the prevalence was 29.8%, 39%, 38.9%, 26.2%, and 39.8%, respectively. In addition, the prevalence of obesity based on WHR in women in north of Iran[18] and in the whole Iran[33] was 68.1% and 72.2%, respectively. In other regions, the prevalence was 71.6% in Bangladesh,[32] and 64.6% in Oman.[34] Data on WHtR obesity is rare; however, in high school students in Iran[35] it was 18.2%, in Portuguese adults[36] 18.3%, and in Bangladesh[32] 42.1%. Compared with other studies, an alarming rate of central obesity was seen in northern women in Iran, and it was outstanding for WHtR index. It is necessary to establish a preventive program in the north of Iran.

Variation of central obesity among different age groups is another result of present study. In spite of the fact that WHR among ≤ 24 years age group decreased, an upward trend was seen in the older ones. A direct association was seen between central obesity and age in the north of Iran[6] and in the other countries.[29,36] The most prevalence of central obesity was seen in 50-59 years age group in Brazil.[16]

The decline trend of central obesity in young women is interesting in our study. We did not study all contributing factors on the age and central obesity but, height significantly increased in 2013 compared with 2004, and it was concordant with data from previous study in this area.[26] On the other hand, marriage is well-known as an obesity risk factor in women.[6] Though, the trend studies by age differences are rare in literature, the improvement of height and rising marriage age of women may explain the decline trend of central obesity in young women in this area.

Moreover, heterogenic trend of central obesity among age groups verifies the nutrition transition idea[37] in Iran, and the shape of central obesity is predictable in Iranian northern people in future.

Another finding of present study is determining the role of education on the trend of central obesity, hence it has been salient in uneducated group. In spite of constant trend in educated groups, WHR and WHtR increased (especially in morbid group) in second study. Published studies identified heterogenic association between education and obesity. Central obesity in Ghana,[29] for instance, was seen more in high-educated people but, in Bangladesh,[32] Malaysia,[38] Oman,[34] and Portugal,[36] it was contrary. Besides, low education was considered as an obesity risk factor in a review study.[39] Like above studies in developing countries, illiteracy is an important factor in the central obesity distribution in the north of Iran, and it is necessary to have a preventive program for it, as a CVD risk factor, with emphasis on uneducated people.

The inverse relationship between high economic group and central obesity indices is another finding of present study. In this regard, WHR trend increased; however, WHtR declined in high economic group in second study. Some studies[16,17,29,30] showed the influence of socio-demographic factors on the central obesity; however, it was fixed in economic groups. Furthermore, short stature was identified as a health problem in Iranian northern children, and it is more in low income families.[26,40]

As a result, inverse association between economic status and WHtR may be related to short stature in low income groups. This study revealed that classification of obesity by WC, WHR, and WHtR indices should be re-evaluated on the basis of socio-demographic conditions.

In the present study, all of the nutrition-related factors such as food intake, physical activities, ethnicity, and body composition were not assessed. Besides, a proper statistical test was not used in considering the design effect caused by cluster sampling, and maybe economic values has been changed since recent decade in Iran. Therefore, it can be formed a bias in comparison phase at two studies. Those are our limiting study factors.

Conclusion

Obesity remained as a health problem among rural women in the north of Iran. Despite, central obesity decreased based on WC and WHR indices in 2004-2013 period, we found the evidence of a decline in sever obesity based on WHtR index in that period. These trends are an alarm for health policy makers in this area and in the same communities. Downward trend of WHtR obesity is related to height values improvement in last years. Comprehensive studies are recommended to determine the best obesity indicator related to health in future.

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Conflict of Interests

Authors have no conflict of interests.

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The effect of tadalafil on functional capacity and echocardiographic parameters in patients with repaired Tetralogy of Fallot

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Original Article

Abstract

BACKGROUND: Tetralogy of Fallot (TOF) is one of the most common cyanotic congenital heart diseases (CHD) in children. Various surgical procedures including palliative shunts and TOF total correction (TFTC) were done with some complications, of which, the most common is pulmonary valve regurgitation (PR). Tadalafil is a phosphodiesterase 5 inhibitor which reduces pulmonary vascular resistance, and improves right ventricular function and vascular endothelium, and may have some beneficial effects after TFTC.

METHODS: We studied 18 patients with TOF and PR, with some impaired right ventricular function after TFTC. Tadalafil tablets at a dose of 1 mg per kg (maximum 40 mg) per day as a single dose was administered orally for 8 weeks. In all patients, before and after taking tadalafil, functional class assessment, electrocardiography (ECG) changes, some echocardiographic and endothelial function parameters [flow-mediated dilation (FMD) and intima-media thickness (IMT) of carotid artery], and exercise test were determined.

RESULTS: The patient's mean age was 10.11 ± 4.03 years, and the mean age of operation was 2.52 ± 1.12 years. The effect of tadalafil on different echocardiographic parameters and also on tricuspid valve regurgitation (TR) and PR severity and gradient was not significant. Moreover, it had no effects on QRS duration. Tadalafil had a significant effect on improving FMD and exercise test (P = 0.01). The effect of tadalafil on echocardiographic parameters, carotid artery IMT, and ECG parameters was not significant (P > 0.05). Tadalafil was tolerated well, and the most common side effects were headache and myalgia.

CONCLUSION: This study showed that tadalafil is a safe and well-tolerated drug. It might improve exercise performance, endothelial function, and functional class, and possibly could allow patients a longer period of well-being and could possibly delay the need for pulmonary valve replacement (PVR).

Keywords: Tetralogy of Fallot, Cardiac Surgery, Tadalafil

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Introduction

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease (CHD) in children.[1,2] Various surgical procedures are popular at different ages to treat episodes of cyanosis in these patients, and includes the creation of a palliative shunt and TOF total correction (TFTC).[2] One of the most common problems after TFTC surgery is pulmonary valve regurgitation (PR).[1,2] Therefore, continuous follow-up of patients after TFTC via electrocardiography (ECG), chest radiography, echocardiography, exercise test (ET), magnetic resonance imaging (MRI), and sometimes angiography should be performed as needed.[1,3] There are some paraclinical parameters which are correlated with long-term prognosis in these patients, and include QRS prolongation in ECG, degree of right ventricular (RV) dilatation and systolic function, degree of PR and tricuspid valve regurgitation (TR), and arrhythmia such as premature ventricular contraction (PVC). These patients may need pulmonary valve replacement (PVR) procedure either by surgical or percutaneous approaches. Drugs which improves ventricular

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function, and reduce long-term PR in these patients, may have a positive effect in improving the above-mentioned complications, and delay the PVR.[4-6]

In recent years, studies had shown the positive effect of sildenafil in the treatment of adults with heart failure.[6] Over the past few years, several studies about the effects of sildenafil on myocardial performance index (MPI) were conducted, but no study has been done on the effects of tadalafil on MPI.[4] Tadalafil is a selective inhibitor of phosphodiesterase 5 that is used once a day.[7,8] It is used for treatment of pulmonary arterial hypertension (PAH) in both children and adults.[4,9] Moreover, endothelial dysfunction can play an important role in deterioration of the clinical condition in patients with CHD, especially in patients with cyanosis.[6,10] With the best of our knowledge, there are no studies about the effect of tadalafil after TFTC, and so we decided to study the effect of tadalafil on symptoms and physical activity, and also the degree of PR and right ventricular function in these patients.

Materials and Methods

The study was conducted in the Imam Hussein Children's Hospital of Isfahan University of Medical Sciences, Isfahan, Iran, from April 2015 to September 2016. This study in terms of ethics in research involving human subjects was approved by Isfahan University of Medical Sciences, and ethical approval of Regional Ethics Committee of Isfahan University of Medical Sciences was received with the code number 395032. All the performed procedures in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The study population included 18 patients who had TFTC and PR, and some impaired RV functions. All patients were initially informed about the side effects and benefits of the project and the informed consent form was signed by their parents or the patients. Two of these patients deny continuing the study due to side effects of the drug (headache and myalgia) in first day, and excluded.

Inclusion criteria's were as patients with TOF after TFTC, aged 6 to 35 years, did not use any drugs which could affect endothelial function (diuretics, lipid-lowering agents, nitrates, etc.), lack of systemic diseases, and did not use vitamins or fruits which has effect on flow-mediated dilation (FMD) (vitamin C, Kiwi, strawberry, etc.) at least during 5 days before the paraclinical evaluation.

Exclusion criteria were as patients with residual defects remaining after TFTC surgery, such as atrial or ventricular septal defect, severe renal or hepatic dysfunction, patients with dysrhythmia or has pacemaker, the use of tadalafil in the past three months, and hypersensitivity to tadalafil.

After reviewing the patients' files, history taking, and physical exam, baseline assessment which included lab workup for renal and hepatic function and complete blood count, echocardiogram, sonographic evaluation of endothelial function (FMD), and intima-media thickness (IMT) of carotid artery, and ET was done for all patients. Tadalafil tablets at dose of 1 mg per kg (maximum 40 mg) per day in single dose were administered orally for 8 weeks. Patient's functional class was evaluated using New York Heart Association (NYHA) classification. In all patients, before and after taking the tadalafil, an ECG, brachial artery diameter at rest, the diameter of the brachial artery at the time of hyperemia, carotid artery IMT at rest, and evaluation of echocardiographic parameters such as left ventricular ejection fraction (LVEF) and fractional shortening (FS), LV myocardial performance index (LV MPI), RV size and MPI, tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC), PR, and TR were determined. ET was done according to modified Bruce protocol before and after taking tadalafil in five steps (four running and one recovery step), each step lasted 3 minutes.[3] During the follow-up and medical visits, patients were asked about the side effects of tadalafil (headache, nasal congestion, flushing, myalgia, allergic reactions, and priapism).

Echocardiogram was performed with an ultrasound system (EKO 7, Samsung Medison Company, South Korea) before and after tadalafil administration by a certified pediatric cardiologist.[10] Echocardiographic parameters were obtained according to the standards of the American Society of Echocardiography.[11] Each Doppler variable was measured several times, and the mean value was used for analysis. FS and EF were obtained using M-mode images from a parasternal long-axis view. Early diastolic inflow velocity (E-wave) and late diastolic inflow velocity (A-wave) were obtained by using pulse wave Doppler at the tips of the atrioventricular valves (AVV) leaflets in an apical 4 chamber view. MPI was calculated as (a-b)/b, where a is the distance between cessation and onset of mitral or tricuspid valve inflow, and b is the ejection fraction of the ventricular outflow.[11]

TAPSE, PR, and TR were measured according to the pediatric echocardiography references.[11]

TOF after repair needs careful evaluation of the RV size and function. Currently, cardiac MRI (CMR) is the gold standard for RV function evaluation. Echocardiogram is the most non-invasive method for RV assessment.[3] Promphan et al.[3] showed significant correlations between RV end-diastolic volume index (RVEDVI) and RVED area ($R = 0.768$, $P < 0.01$), RVEF with FAC ($R = 0.759$, $P < 0.01$), and RVEF with TAPSE ($R = 0.688$, $P < 0.01$). They found 100% correlation in moderate to severe PR assessment by echocardiography and CMR (Kappa = 0.912).[3] According to their results and because of feasibility of echocardiography, we assessed our patients with echocardiogram carefully.

Endothelial function (IMT, FMD) was assessed after 6 hours fast in the morning with ultrasound images using 7-MHz linear array transducer.[11] In the longitudinal plane, at 2-5 cm above the antecubital fossa, the artery was evaluated, and from anterior to posterior at end-diastole incident with the R wave on the ECG, the measurements were taken. Arterial flow velocity was evaluated using a pulsed Doppler signal at 70 angles to the vessel. A baseline scan after 15 minutes initial rest period was taken in the supine position.[9,10,12] A proper pneumatic tourniquet was used and inflated to 50 mm Hg above the systolic blood pressure of the patient for 5 minutes, then released. Reactive hyperemia was measured 60 seconds after cuff deflation by another scan. FMD was measured as percentage of increase in arterial diameter during hyperemia compared to the corresponding value at rest as FMD = (D2 - D1)/100, where D1 is the vessel diameter at rest, and D2 is the vessel diameter during reactive hyperemia as described.[13] A 7-MHz high-frequency vascular linear transducer was used to image the right carotid artery for IMT. At supine position and while head turned 45 degree away from the scanner, IMT was taken. Three segments of the common carotid artery 1 cm distal to its bifurcation were measured at a distance between the lumen-intima and the media-adventitia interface on a B-mode image, and the average value was used.[9,10,12] A single pediatric cardiologist performed these evaluations.

Data were analyzed using SPSS software (version 18.0, SPSS Inc., Chicago, IL, USA). Normality of data was checked using Kolmogorov-Smirnov test; continuous and discrete variables were represented as mean ± standard deviation (SD) and number (percent), respectively. Quantitative and qualitative data of the parameters before and after tadalafil were compared using paired t test. For all analyses, statistical significance was assessed at a level equal or less than 0.05.

Results

Of the 18 studied patients, 7 (31.9%) were boys and 11 (61.1) were girls. The mean age of the patients was 10.11 ± 4.03 years. Patient demographics data are shown in table 1.

Associated CHD and details of the surgical procedures are shown in table 2. Fourteen patients had only TOF and 3 had associated patent ductus arteriosus (PDA) and one had pentalogy of Fallot [TOF with atrial septal defect (ASD)]. All of them were corrected by transannular patch. Two patients had a previous Blalock-Taussig (BT) shunt operation. The mean ± SD age of operation was 2.52 ± 1.12 years.

The frequencies of each echocardiographic parameter in this study as well as mean ± SD values of before and after tadalafil administration are shown in table 3. The effect of tadalafil was not significant on TR, and PR severity and gradient.

Mean ± SD of ET parameters, NYHA functional class, and ECG findings before and after tadalafil usage is shown in table 4. The results showed that tadalafil had a significant effect on improving FMD and ET, as well as improvement in NYHA functional class of patients ($P = 0.01$). Tadalafil had no significant effect on echocardiographic parameters (LVEF and LVFS, LV MPI, RV MPI, TAPSE, FAC, PR, and TR), IMT, and ECG parameters ($P > 0.05$ for all).

The most common side effects of tadalafil were headache in 7 patients (38.9%), and myalgia in 3 patients (16.7%). These side effects were transient and lasted for 3-7 days. 8 patients (44.4%) had no side effects after tadalafil use.

Table 1. Patients' demographics data (n = 18)

Demographics	Minimum	Maximum	Mean ± SD
Age (year)	6.00	19.00	10.11 ± 4.03
Age at TFTC (year)	1.50	6.00	2.47 ± 1.11
Weight (kg)	13.50	60.00	31.25 ± 14.91
Height (cm)	110.00	170.00	132.94 ± 17.82

TFTC: Tetralogy of Fallot total correction; SD: Standard deviation

Table 2. The history of congenital heart disease (CHD), cardiac malformations, and surgical procedures in study population

Patient number	Cardiac malformation	Surgical procedures	Age of TFTC (years)	History of palliation surgery
1	TOF	TFTC (with transannular patch)	2.5	No
2	TOF, PDA, PFO	TFTC (with transannular patch and PDA ligation)	3.0	No
3	TOF	TFTC (with transannular patch)	4.0	No
4	TOF	TFTC (with transannular patch)	1.5	No
5	TOF	TFTC (with transannular patch)	2.0	No
6	TOF	TFTC (with transannular patch)	2.0	No
7	TOF	TFTC (with transannular patch)	3.0	No
8	TOF	TFTC (with transannular patch)	6.0	No
9	TOF, PDA	TFTC (with transannular patch and PDA ligation)	3.0	No
10	PFO	TFTC (with transannular patch and ASD closure)	2.0	BT shunt
11	TOF	TFTC (with transannular patch)	1.5	No
12	TOF	TFTC (with transannular patch)	2.0	No
13	TOF	TFTC (with transannular patch)	3.0	No
14	TOF	TFTC (with transannular patch)	1.5	No
15	TOF, PDA	TFTC (with transannular patch and PDA ligation)	2.0	No
16	TOF	TFTC (with transannular patch)	2.0	BT shunt
17	TOF	TFTC (with transannular patch)	3.0	No
18	TOF	TFTC (with transannular patch)	1.5	No

TOF: Tetralogy of Fallot; TFTC: Tetralogy of Fallot total correction; PDA: Patent ductus arteriosus; PFO: Pentalogy of Fallot; ASD: Atrial septal defect

Discussion

Drugs that reduce pulmonary vascular resistance and improve RV function and vascular endothelium might have positive effect on patients with cyanosis. This study appears to be the first one according to the best of our knowledge on the effectiveness of tadalafil among patients with TOF that suffered PR and RV dysfunction after TFTC. The results showed that the use of tadalafil after TFTC surgery had a positive effect on exercise performance, NYHA functional class, and improvement in endothelial function (FMD). Improvement in well-being was observed in most patients, and they have a tendency to continue the tadalafil use. A previous study by Sabri and Beheshtian[9] performed in children with PAH showed that tadalafil had a better effect than sildenafil on this group of children.

Table 3. Echocardiogram parameters before and after tadalafil administration following Tetralogy of Fallot total correction (TFTC)

Variable		Before tadalafil Mean ± SD	After tadalafil Mean ± SD	P
FMD		12.88 ± 2.16	11.88 ± 1.64	0.04
IMT		0.19 ± 0.01	0.18 ± 0.01	0.96
LVEF		66.38 ± 1.37	66.33 ± 1.02	0.93
LV FS		35.44 ± 0.51	35.38 ± 0.50	0.70
LV MPI		0.36 ± 0.01	0.36 ± 0.01	0.33
RV MPI		0.33 ± 0.01	0.32 ± 0.01	0.28
TAPSE		13.03 ± 1.30	13.22 ± 1.11	0.52
FAC		28.61 ± 5.33	28.11 ± 4.94	0.08
PR gradient		25.66 ± 4.05	23.27 ± 4.83	0.10
TR gradient		35.88 ± 8.53	35.33 ± 7.27	0.90
		Frequency (%)	Frequency (%)	P
PR severity	Mild	5 (27.8)	9 (50.0)	0.10
	Moderate	13 (72.2)	9 (50.0)	
TR severity	Mild	11 (61.1)	10 (55.6)	0.65
	Moderate	7(38.9)	8(44.4)	

SD: Standard deviation; FMD: Flow-mediated dilation; IMT: Intima-media thickness; LV: Left ventricular; LVEF: Left ventricular ejection fraction; FS: Fractional shortening; MPI: Myocardial performance index; RV: Right ventricular; TAPSE: Tricuspid annular plane systolic excursion; FAC: Fractional area change

Table 4. Performance parameters before and after tadalafil administration following Tetralogy of Fallot total correction (TFTC)*

Variable		Before tadalafil Frequency (%)	After tadalafil Frequency (%)	P
Exercise test	Stage 2	1 (5.6)	0 (0.0)	0.02
	Stage 3	11 (61.1)	8 (44.4)	
	Stage 4	6 (33.3)	10 (55.6)	
Functional class	Class 1	0 (0.0)	5 (27.8)	0.01
	Class 2	16 (88.9)	12 (66.7)	
	Class 3	2 (11.1)	1 (5.6)	
		Mean ± SD	Mean ± SD	P
QRS widening (ms)		0.106 ± 0.012	0.103 ± 0.011	0.16

SD: Standard deviation

* Exercise test protocol: Modified Bruce, functional class in New York Heart Association (NYHA)

In another study that performed by Sabri et al.[10] as the first report on the effectiveness of tadalafil among patients undergoing modified Fontan operation, the use of tadalafil after modified Fontan operation had a positive effect on myocardial function and performance, exercise performance, and improvement in NYHA functional class. The most common side effects in their patients were transient priapism, leg pain, headache, and back pain that lasted 2-7 days.[10]

In Rosano et al report,[7] by long-term therapy with tadalafil in patients with high-risk cardiovascular disease, the endothelial function improved (improving FMD). Other researches on the effect of tadalafil and sildenafil on exercise capacity had different results.[4,13] Some of them showed no significant improvement, and others indicated a significant effect. The long-term effect of tadalafil should be investigated with a higher number of cases for better evaluation. The most common side effects reported for tadalafil are headache, myalgia, nausea, nasal congestion, flushing, and allergic reactions.[8,14-16]

The limitations of present study include its small sample size, lack of control or placebo group (because of limit TOF cases with this situation in this center), unavailability of CMR in most patients, and relatively short observational period. We hope these findings introduce a basic and primary data for future large-scale clinical studies in this field.

Conclusion

This study showed that tadalafil is a safe drug, well-tolerated and its side effects were disappeared after a few days and could be used after TFTC. It might improve exercise performance, endothelial function and functional class and possibly could allow patients a longer period of well-being and could possibly delay the need for PVR.

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Conflict of Interests

Authors have no conflict of interests.

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The role of human T-lymphotropic virus (HTLV) in cardiovascular diseases: A review of literature

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Review Article

Abstract

Cardiovascular diseases are a major cause of morbidity and mortality. Chronic inflammation is an important risk factor for atherosclerosis, and viral infections can cause cardiovascular disease by developing inflammation. Infection with human T-lymphotropic virus (HTLV) is endemic in some parts of the world such as Japan, Africa, Caribbean islands, South America, and Iran. HTLV-1 is an oncogenic retrovirus, and can cause adult T-cell leukemia/lymphoma (ATL or ATLL). It also causes HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP). A number of inflammatory diseases such as uveitis, arthritis, and Sjogren's syndrome are also associated with the virus. A few case reports have shown the direct involvement of the heart in HTLV-1-positive patients who develop ATLL. The purpose of this study was to review the literature relevant with the role of HTLV in cardiovascular diseases.

Keywords: Cardiovascular Disease, HTLV Infection, Atherosclerosis

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Introduction

Atherosclerosis which is the main cause of cardiovascular diseases, is a condition of chronic inflammation.[1] Infection with viral and bacterial agents are today recognized as a possible risk factor for atherosclerosis alongside other risk factors such as hypertension, smoking, hypercholesterolemia, hyperglycemia, and genetic factors.[1,2] Examples of viral pathogens found in atherosclerotic plaque are: cytomegalovirus (CMV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), herpes simplex viruses (HSV), and Epstein-Barr virus (EBV).[2,3] Therefore, other viruses could be potential risk factors for cardiovascular diseases, too.

Human T-lymphotropic virus type 1 (HTLV-1) is a member of Deltaretrovirus genus of the subfamily Orthoretrovirinae, Retroviridae family which mainly infects T-lymphocytes.[4]

HTLV-1 is an oncogenic retrovirus, and can cause adult T-cell leukemia/lymphoma (ATL or ATLL).[5] It is also the causative agent for a neurologic disease named HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP).[6] Fortunately, these conditions occur in a small percent of the infected individuals, and more than 95% of them remain as asymptomatic carriers throughout their lives.[5]

We intend to review the available literature concerning the cardiovascular effects of HTLV infection. To obtain a comprehensive overview of the available information, we searched the PubMed and Scopus databases with the terms “HTLV”, "ATLL", “cardiovascular", "cardiac", and "heart".

Virus structure

The structure of HTLV-1 is similar to other retroviruses. Its capsid contains two simple RNA strands together with the reverse transcriptase and integrase enzymes.[7] Its genome contains structural and enzymatic genes: gag, pro/pol, and env, which are flanked by two long terminal repeats (LTRs). The pX region which is located between the env gene and the 3́-LTR codes for the Tax (p40), Rex (p27), p12, p13, p21, and p30 regulatory proteins. Among these, Tax has an especially important role in viral persistence and pathogenesis.[8] Another important gene is HTLV-1 b-ZIP factor (HBZ)

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which is encoded from the 3́-LTR in the complementary strand of the genome. HBZ functions in two different forms, its mRNA form promotes cell proliferation, and its protein form downregulates Tax expression.[7]

P12 functions to promote viral escape from the immune system by different mechanisms, one of which is interaction with the interleukin-2 (IL-2) receptor.[8] The p30 protein acts as a negative post transcriptional regulator through the nuclear retention of Tax/Rex RNA, and promotes viral latency.[9] As with all retroviruses, HTLV-1 infects cells permanently.[8]

Epidemiology

HTLV infection is reported from all over the world. Certain parts of the world in which the prevalence rate of HTLV infection is more than 1% are assumed as endemic areas,[10] such as Japan, Africa, Caribbean islands, South America,[11] and northeastern of Iran.[12,13] The prevalence ranges between 1% to 10% in the general population of the mentioned areas; southern Japan have the highest prevalence.[13-15] It is estimated that 10 to 20 million individuals are infected with the virus throughout the world.[15]

There are three main cities in northeastern of Iran in which HTLV infection is prevalent, Mashhad,[16] Neyshabour,[13] and Sabzevar[17] with the prevalence rate of 2.12%, 7.2%, and 1.66%, respectively.

The transmission of this virus occurs through infected cells. Cell-free virions are said to be poorly infectious. Therefore, the virus is transmitted via four main routs: mother to child transmission which is mainly through breastfeeding, sexual transmission with a higher transmission rate from men to women, through contaminated blood products, and transmission between intravenous drug users.[14,15]

HTLV-1-associated diseases

ATL and HAM/TSP are the two important diseases caused by HTLV which develop only in a small percentage of patients infected with the virus.

ATL is the malignancy of cluster of differentiation 4 ($CD4^+$) T-lymphocytes and as mentioned earlier, the Tax protein is responsible for the abnormal growth of cells infected with HTLV-1. This poor prognosis malignancy usually presents with lymphadenopathy, hepatosplenomegaly, and skin lesions.[15]

HAM/TSP is a debilitating neurodegenerative disease on which current treatments have had poor effect.[18] Studies on the pathogenesis of central nervous system (CNS) involvement by HTLV-I have shown that the indirect involvement of the nervous system by lymphocytes is more probable than the direct attack of the virus to the neurons.[6] Paraparesis of the lower limbs, which appears gradually, is the most common clinical feature.[15]

Other inflammatory diseases

HTLV-1 may cause many other inflammation-based diseases including uveitis and keratoconjunctivitis sicca in the eye,[19] Sjogren's syndrome,[20] arthritis,[21] polymyositis,[22] and systemic lupus erythematosus (SLE).[23]

Autoimmunity

HTLV-1-infection induces both the cellular and humoral immune responses. The immune dysregulation caused by the virus may play an important role in the development and pathogenesis of the associated diseases.[24]

Changes in the systemic immune response has been seen in HTLV-1-infected patients, even in those who are asymptomatic. The virus induces changes in the activity of regulatory CD4 T-cell molecules which affect the homeostasis of cytokines, including interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), transforming growth factor beta (TGF-β), and IL-10. This disrupts the balance between inflammatory and anti-inflammatory responses, and leads to the loss of tolerance and the development of autoimmunity.[7]

Co-infection with other viruses

It has been shown that HTLV-1/HCV co-infection can increase liver disease and liver cancer mortality, and thus leads to the hypothesis that an immune modulation and inflammatory cytokine dysregulation is caused by HTLV-1, and causes progression to liver disease.[25,26] It has also been discussed that T-cells infected with HTLV-1 can trigger a virus-specific immune response, and can increase cytokine production.[24]

Chronic inflammation

Two mechanisms are proposed for the role of inflammation caused by microorganisms in atherosclerosis, the direct mechanism which is related to the infection in the vessel wall, and the indirect mechanism which is related to the increased secretion of cytokines.[27] HTLV-1, like many other viruses, activates the immune system's response.

Eradication of the pathogen is the main goal of this response, and it is done through an inflammation mechanism which involves the release of several cytokines and chemokines.[28]

A number of studies have revealed evidence related to the presence of chronic inflammation in HTLV-1 affected individuals. For example, it has been shown that patients infected with HTLV-1 have a greater carotid intima-media thickness (IMT) than healthy subjects.[29]

In a retrospective study in Iran, the sero-prevalence of HTLV-1 was assessed in patients with cardiac symptoms, and was compared with the general population. It showed that patients with cardiac symptoms were nearly 3 times more infected with HTLV-1.[30]

It is confirmed that HTLV-1 infects regulatory $CD4^{+}FOXP3^{+}$ T-cells which facilitates persistent infection. This pattern could contribute to the pathogenesis of the virus-associated diseases.[28]

The concurrency of HTLV-1 and the inflammatory diseases mentioned earlier supports the inflammatory role of the virus in causing cardiovascular disease.[19-23]

HTLV-1 and cardiovascular diseases

In general, cardiovascular diseases refer to the diseases of the heart, vascular diseases of the brain, and diseases of blood vessels. Among these, a subgroup of the diseases of the heart -called ischemic heart diseases which include angina and myocardial infarctions- and also the cerebrovascular disease and hypertension are related to atherosclerosis, and impose a great burden on health services.[31]

It has been demonstrated that the presence of antibodies against specific infectious agents increases the risk of cardiovascular disease. Among them, many viruses have been studied widely but due to the epidemiology of HTLV-1 and its regional distribution, its relation with atherosclerosis and cardiovascular disease has only been explained in few studies.[30]

Regarding the relationship between HTLV-1 and non-atherosclerotic heart diseases such as heart failure, myocarditis, and cardiomyopathies, the scientific literature is limited to a few case reports which are discussed later in this article.

As the main cause of myocarditis is viral infections, it would be wise to consider HTLV-1 as a possible etiology for the disease, and test patients suffering from myocarditis for this virus infection.

Cardiovascular autonomic dysfunction

Ohishi et al. showed that the mean systolic and diastolic blood pressures were lower in patients with HTLV-associated myelopathy (HAM) than in healthy subjects; while the mean heart rate was higher in patients than controls. They thus suggested that subclinical cardiovascular autonomic dysfunction can be found in patients with HAM.[32]

Case reports

A number of cases are reported regarding the involvement of the heart in patients diagnosed with ATLL due to HTLV-1 infection.

In 1993, Gabarre et al. found T-cell non-Hodgkin's lymphoma in the aortic and mitral valves in a 60-year-old Iranian woman whose serum was positive for HTLV-1 antibodies.[33]

Daisley and Charles described a case of metastatic calcification of the heart, lungs, and kidneys in a man who had an HTLV-1-associated lymphoma.[34]

In 1997, the same authors reported three autopsy cases of HTLV-infected subjects who had lymphoma/leukemia affecting the heart; although none of the three patients had ante-mortem manifestation of cardiac involvement. Their cardiac involvement varied from microscopic foci to macroscopic infiltration mimicking myocardial infarction.[35]

Furukawa et al. reported metastatic calcification in the myocardium of a 52-year-old man with ATLL which caused heart failure and death; but the ATLL cells did not infiltrate in the myocardium.[36]

Toyama et al. reported a case of lymphoma-type ATL with initial massive cardiac involvement presenting as tumors in the right atrium.[37]

Shepherd et al. discussed a case of fatal cardiovascular instability due to hypercalcemia in a patient with ATLL. Their patient who was diagnosed with HTLV-1 infection and ATLL only after death, had extensive intra- and extracellular calcium deposition in her myocardium and other organs due to ATLL.[38]

A summary of the related studies is shown in table 1.

Conclusion

The literature relevant with the cardiovascular effects of HTLV-1 are scant, and are limited to a number of case reports and a few retrospective studies.

Table 1. The summary of the studies regarding the effect of human T-lymphotropic virus type 1 (HTLV-1) infection on the heart

Study type	Year	Author	Key finding
Case control	2014	Layegh et al.[29]	Greater carotid intima-media thickness in patients infected with HTLV-1
Case control	2013	Farid et al.[30]	Patients with cardiac symptoms are 3 times more infected with HTLV-1 than healthy controls
Case control	1993	Ohishi et al.[32]	Cardiovascular autonomic dysfunction in patients with HTLV associated myelopathy
Case report	1993	Gabarre et al.[33]	T-cell lymphoma in cardiac valves
Case report	1993	Daisley and Charles[34]	Calcification in the heart in a patient with lymphoma
Case report	1997	Daisley and Charles[35]	3 cases of lymphoma affecting the heart
Case report	1991	Furukawa et al.[36]	Calcification in the myocardium in a patient with lymphoma
Case report	2002	Toyama et al.[37]	Cardiac involvement in a patient with lymphoma
Case report	2016	Shepherd et al.[38]	Calcium deposition in the myocardium in a patient with lymphoma

HTLV-1: Human T-lymphotropic virus type 1

Aside from the direct involvement of the heart itself in HTLV-1-positive patients who develop ATLL, evidences indicate that HTLV-1 could cause atherosclerosis and cardiovascular disease.

It is therefore necessary to examine HTLV-1-infected patients' cardiovascular system on a routine basis, even in asymptomatic carriers.

The calcification seen in the myocardium of a number of patients affected with HTLV-1 makes necessary the study of this biochemical change, and its relying cause in those patients.

More practical studies are to be done to confirm the concept of the role of HTLV-1 in atherosclerosis which lead to cardiovascular disease.

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Conflict of Interests

Authors have no conflict of interests.

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