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

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

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Evaluation of image quality and radiation dose in low tube voltage coronary computed tomography angiography

Seyedeh Shokoofeh Mousavi-Gazafroudi[(1)], Amirreza Sajjadieh-Khajouei[(2)], Maryam Moradi[(3)], Seyedeh Shabnam Mousavi-Gazafroudi[(4)], Ghasem Yadegarfar[(5)], Mohammad Bagher Tavakoli[(6)]

Original Article

Abstract

BACKGROUND: Coronary computed tomography angiography (CCTA) is an important modality in diagnosis of coronary artery disease (CAD). Owing to the fact that computed tomography (CT) examinations are performed using ionizing radiation; applying radiation dose-reduction strategies seems to be necessary. Lowering tube voltage (in kV) according to the patient's body mass index (BMI) or weight is an approach that is investigated by many researchers. The goal of this study was to evaluate the impact of low tube voltage CCTA on radiation dose and image quality in order to decrease radiation dose in selected patients who meet inclusion criteria of the introduced protocol.

METHODS: Patients with clinical indications of CCTA who met inclusion criteria were classified in two groups randomly. Imaging of two groups was performed using 120 kV and 100 kV, respectively. Subjective and objective parameters of image quality and radiation dose of two groups were measured. Afterward, data were analyzed by appropriate statistical tests using SPSS software.

RESULTS: While differences in image quality between two groups were not significant, radiation dose of patients who underwent 100 kV CCTA was significantly lower than the other group. Effective doses (EDs) of first and second groups were 22.30 ± 5.48 mSv and 13.82 ± 2.00 mSv, respectively ($P < 0.001$).

CONCLUSION: Lowering tube voltage in non-obese patients is an effective and practical approach to radiation dose reduction without missing image quality that should be considered especially for female patients.

Keywords: Coronary Angiography, Computed Tomography Angiography, Radiation Dosage, Contrast Agent, X-Rays, Image Enhancement

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Introduction

Coronary artery disease (CAD) is one of the main causes of death throughout the world.[1] Because of changing in lifestyles, CAD seems to be more common in developing countries.[2] Conventional coronary angiography (CCA) is the gold standard modality to evaluate cardiovascular system, but due to its major drawbacks[1] such as invasiveness and high costs,[3] coronary computed tomography angiography (CCTA) is applied as an alternative imaging modality.

Recent advances in multidetector computed tomography (MDCT) including high spatial and temporal resolution and post-processing features result in high-quality images; but the risk of radiation-induced cancer remains as a concern.[4-6] Therefore, there is an interest in low dose CCTA. Owing to this, different approaches such as high-pitch scanning, low tube kilo voltage (kV) technique, and tube current modulation were presented.[7-9]

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As known, radiation dose changes with square of tube voltage; therefore, lowering kV has a considerable effect on patient effective dose (EDs).[10-12] Moreover, low-energy photons underwent more attenuation through photoelectric phenomenon. So because of closing in to the iodine k-edge in contrast agent, vascular enhancement was improved.[11,13,14] The disadvantage of decreasing kV is increasing noise, particularly in obese patients.[15] Therefore, patient's body mass index (BMI) should be considered as an important factor in low kV scanning.

Various studies were done on impact of kV reduction in CTA. Leschka et al. reported that in dual source computed tomography (CT) system, lowering kV from 120 to 100 in normal-weight patients resulted in noise and contrast-to-noise ratio (CNR) increasing beside significant dose reduction.[16] Blankstein et al. stated that using 100 kV instead of 120 kV in dual source scanner with prospective electrocardiography (ECG)-gating method resulted in remarkable radiation dose reductions while image quality remained sufficient.[17] In contrast, Cody et al. recommended 100 kV instead of 80 kV in pediatrics, because of beam hardening artifact in low-energy photons.[18] Zhang et al. evaluated patients with BMI less than 25 kg/m^2 and reported negligible changes in image contrast and noise.[19]

The purpose of this study was to assess the effects of low kV CCTA on patient dose and image quality to achieve an optimum kV for cardiac CT in selected patients.

Materials and Methods

The present study was part of a larger study evaluating the impact of a double-low protocol (low kV and low concentration contrast media) on patient dose and image quality in patients with and without history of coronary artery bypass graft (CABG). 347 patients were referred to perform contrast enhanced CCTA between July 2015 to December 2015 in multislice CT (MSCT) department at Al-Zahra Hospital, Isfahan, Iran. Among them, data of 152 consecutive patients who had maximum BMI of 29 kg/m^2, maximum weight of 90 kg, and calcium score up to 300 Agatston units (AU) were collected prospectively. All the patients were evaluated in terms of heart rate (HR) and glomerular filtration rate (GFR), and if HR was more than 75 beats per minute (bpm), beta blockers were used orally. In this population, those who had history of CABG (n = 23), stent implanting (n = 43), renal failure (n = 14), and patients who could not hold their breath for about 15 seconds (n = 18) were excluded from the study. Then, 54 patients were classified in two groups randomly. First group underwent CCTA using 120 kV and second group scan was performed by 100 kV. Prior to scanning, patients filled informed consent form and a clinical checklist including history of some risk factors.

CCTA was performed on a 64-slice CT scanner (LightSpeed VCT, GE Healthcare, Waukesha, Wisconsin, USA). Whole heart was scanned from tracheal bifurcation to the end surface in craniocaudal direction. Retrospective ECG-gated scan was used with slice thickness of 0.625 mm and gantry rotation time of 350 ms. A window of 70% RR cardiac cycle and pitch factor of 0.22 were applied. Imaging was performed in 4 steps: 1. scout scan to determine field of view (FOV), 2. pre-contrast scans for calcium scoring, 3. timing bolus to schedule contrast media injection setting, and 4. main scan. Typically, 15 ml and 85 ml contrast agent with normal saline were injected during "timing bolus" and "main scan", respectively. Iopamidol 370 (Scanlux) was injected at a rate of 6 ml/s through 18 gauge needle.

ED was calculated through multiplying dose length product (DLP) by tissue weighting factor of region of interest. European working group for guidelines on quality criteria in CT suggested 0.017 mSv.mGy^{-1}.cm^{-1} as chest weighting factor.[20] DLP was measured through multiplying CT dose index (CTDI) by scan length. CTDI can be obtained from scanner console.

Subjective and objective indices of image quality were measured on off-line work station of GE healthcare. Evaluation of subjective image quality parameters was performed by two experienced physicians who were blinded to protocols. Four main coronary arteries including left main (LM), left anterior descending (LAD), right coronary artery (RCA), and circumflex (CX) were scored through a 5-point scale as follows: 1. unreadable: coronary arteries were not valuable, 2. poor: severe artifacts and intense arteries' blurring, 3. fair: medium artifact and moderate blurring, 4. good: slight artifact and negligible blurring, and 5. excellent: without artifact and with high sharpness view.

Objective parameters of image quality including signal-to-noise ratio (SNR), CNR, and noise were measured by drawing a region of interest (ROI) on axial images of arteries. SNR was defined as average attenuation values of RCA and LM divided by noise. CNR was derived from difference between mean attenuation value of proximal segment of LM and the fat tissue adjacent to arteries over noise.

Table 1. Patients characteristics

Patient information	120 kV	100 kV	P
Number of patients	27	27	-
Female gender	6 (22)	17 (63)	0.020
History of high cholesterol	3 (11)	4 (15)	0.680
History of diabetes	1 (4)	4 (15)	0.150
History of high blood pressure	3 (11)	5 (18)	0.440
Age (year)	51.88 ± 14.38	57.88 ± 13.36	0.140
BMI (kg/m²)	25.25 ± 2.47	25.24 ± 2.54	0.940
Calcium score (AU)	34.04 ± 55.25	27.63 ± 61.44	0.170
HR (bpm)	62.47 ± 6.98	60.22 ± 8.50	0.310
Tube current (mAs)	492.59 ± 67.51	492.59 ± 26.68	0.910

Note: Data for 54 patients are presented. Data are presented as n (%) or mean ± standard deviation (SD)
BMI: Body mass index; HR: Heart rate
Mann-Whitney U test and chi-square test were used for quantitative and qualitative parameters, respectively.

Standard deviation (SD) of CT numbers within a circular ROI in left ventricle was considered as noise.[21]

SPSS software (version 22, IBM Corporation, Armonk, NY, USA) was used to analyze data. Quantitative values were expressed as mean ± SD and qualitative parameters were presented as relative frequencies (%). In order to determine the association between qualitative variables of two groups, chi-square test was applied. To evaluate differences of quantitative demographic parameters, radiation dose parameters, and objective indices of image quality among groups, independent t-test was done and Mann-Whitney U test was used if data were not normally distributed. To account for multiple testing influences, Bonferroni correction was performed. P-values less than 0.05 were considered to indicate the statistical significance.

Results

Patients' demographic characteristics were demonstrated in table 1. In 120 kV group, 6 (22%) patients were female, while 17 (63%) patients of 100 kV group's population were female (P = 0.020). Age of patients in 120 kV group and 100 kV group was 51.81 ± 14.38 years (median = 55.00) and 57.88 ± 13.36 years (median = 58.00), respectively (P = 0.140). Distribution of age was normal, while the other variables were not distributed normally. Analyses of calcium score, HR, BMI, and related risk factors plus tube current revealed no significant differences between two groups of patients (Table 1).

Table 2 presents ED, CTDI, and DLP of two groups. Radiation dose of patients who were scanned by 100 kV (13.82 ± 2.00 mSv) were significantly lower compared with the radiation dose of the ones scanned by 120 kV protocol (22.30 ± 5.48 mSv) (P < 0.001). According to table 1, there was no significant difference in tube current between two groups (P = 0.910); therefore, changing radiation dose was directly related to the tube voltage. Lowering kV resulted in reduction of helical and total DLP and finally it decreased patient ED.

Objective parameters of image quality were displayed in table 3. As shown in this table, in 120 kV group noise was significantly lower than the other group (P = 0.003). Because of negligible difference in BMI, it seems that increasing of the noise is only because of kV decreasing. Difference of SNR was not significant, but it was slightly higher in 120 kV group. In contrast, CNR was slightly higher in 100 kV group.

Table 4 shows the number of each score for all segments in both groups. In each of two groups, each of four segments was assessed for 27 patients by 2 observers, so each segment was scored 54 times. Considering data analyzing, LM, LAD, and CX in all cases were found to be sufficient for diagnostic quality. In terms of RCA, two images of 120 kV group were unreadable.

Table 2. Radiation dose of two scanning protocols

X-ray energy	CTDIVOL (mGy)*	Helical DLP (mGy.cm)*	Total DLP (mGy.cm)*	ED (mSv)*
120 kV	58.72 ± 11.45	1218.77 ± 322.73	1311.92 ± 322.73	22.30 ± 5.48
100 kV	36.80 ± 5.06	721.68 ± 108.37	813.28 ± 118.11	13.82 ± 2.00
P**	0.002	< 0.001	< 0.001	< 0.001

CTDIVOL: Volume computed tomography dose index; DLP: Dose length product; ED: Effective dose
* Mean ± standard deviation (SD); ** Mann-Whitney U test was used

Table 3. Assessment of objective parameters of image quality

X-ray energy	SNR*	CNR*	Noise*
120 kV	14.71 ± 4.24	15.87 ± 4.64	29.00 ± 4.24
100 kV	13.62 ± 3.88	16.54 ± 3.95	61.00 ± 24.04
P**	0.194	0.473	0.003

SNR: Signal-to-noise ratio; CNR: Contrast-to-noise ratio
* Mean ± standard deviation (SD)
** Mann-Whitney U test was used; P < 0.050 was considered significant

94.1% of images in 120 kV group and 98.15% of images in 100 kV group had diagnostic value by gaining score of 3, 4, or 5. As shown in table 4, average score of all segments in 100 kV group was slightly better than that in 120 kV groups. In both groups, LM achieved maximum and RCA had minimum average score. Figure 1 demonstrates coronary artery scores for 100 kV and 120 kV; moreover, it shows total subjective image quality of two groups.

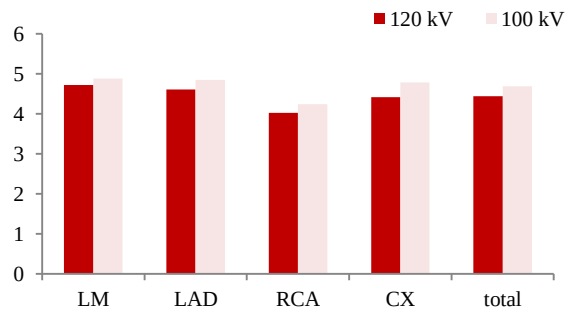

Figure 1. Comparison of subjective image quality between two groups
LM: Left main; LAD: Left anterior descending; RCA: Right coronary artery; CX: Circumflex

Discussion

Among different techniques of dose reduction in CCTA, lowering kV has a considerable effect on patient dose; because radiation dose is related to the square of kV. In the present study, lowering kV from 120 to 100 caused %38 radiation dose reduction. The same pitch factor, slice thickness, tube current (in mAs) and retrospective ECG-gating were used in both groups. Therefore, the amount of reduction in radiation dose is only due to decreasing kV. Basically, reduction in tube voltage is more advantageous than tube current reduction because of two major reasons. First, lowering mAs results in obvious reduction in SNR and beam intensity. Second, radiation dose has a linear relation with mAs and so mAs does not have an important role in decreasing patient dose.

In a number of studies, a comparison between 100 kV and 120 kV in terms of radiation dose and image quality was performed. Lee et al. evaluated 100 kV and 120 kV in patients with history of stent implanting and reported 28% reduction in radiation dose without missing image quality.[22] In another study by Zheng et al., 54% radiation dose reduction was reported in patients with normal BMI.[23] In a similar study by Yang et al., 50% reduction of ED was reported for patients with BMI less than 25 kg/m².[24] Khan et al., using 320 row detector to compare 100 kV and 120 kV CCTA, reported 30% reduction in radiation exposure and good image quality in patients with BMI up to 27 kg/m².[25] 26% radiation dose reduction and overestimating stenosis of coronary arteries were reported by Marwan et al. who studied use of 100 kV and 120 kV for calcium scan.[26] Acceptable image quality and 40% ED reduction were showed through a study by Ripsweden et al., in which CCTA was performed using 100 kV and 120 kV.[27] 26% increase in image noise and 53% decrease in radiation dose, using 100 kV instead of 120 kV, were reported by Bischoff et al. through a multi-center study.[28] Kidoh et al. showed non-significant differences in ED and image quality between 100 kV with increased mAs and 120 kV.[29] Feuchtner et al. studied patients with BMI < 28 kg/m² using 64-slice Siemens scanner and reported 47% reduction in radiation exposure with equal quantitative and qualitative parameters of image quality in 100 kV group.[30]

Table 4. Assessment of subjective parameters of image quality

Image scores		120 kV				100 kV			
		LM	LAD	RCA	CX	LM	LAD	RCA	CX
Number of scores	1	0	0	2	0	0	0	0	0
	2	0	1	6	2	0	0	4	0
	3	3	5	7	7	1	2	5	2
	4	9	8	10	11	4	4	19	7
	5	42	40	29	34	49	48	26	45
Average score		4.72	4.61	4.03	4.42	4.88	4.85	4.24	4.79

For each segment of coronary arteries in each group, 27 patients were studied twice (total number for each segment: 27 × 2 = 54).
LM: Left main; LAD: Left anterior descending; RCA: Right coronary artery; CX: Circumflex
Image quality scores: 1. unreadable; 2. poor; 3. fair; 4. good; 5. excellent

Because of tiny structure and high mobility of heart and its feeding arteries, high quality images of coronary arteries are required to diagnose their anomalies or diseases. Therefore, image quality of low dose protocol should be assessed. Evaluation of four main coronary arteries including LM, LAD, RCA, and CX indicates that subjective image quality of 100 kV is slightly better than 120 kV. For low-energy photons, photoelectric phenomenon is more likely to occur. So, kV reduction and then closing in to the k-edge absorption energy of iodine result in more attenuation and more coronary artery enhancement. Moreover, as a fact, LM gained maximum score among coronary arteries because of its large diameter. RCA achieved minimum score, probably because of its high mobility. Totally, all coronary arteries of both groups had diagnostic values. In terms of objective parameters of image quality, SNR in 120 kV group and CNR in 100 kV group were slightly better than the other group, but differences were not significant. As it was predicted, noise of 100 kV group was significantly higher than 120 kV group. Although this problem did not affect diagnostic value of CCTA images, it should be controlled by using some reconstruction methods such as adaptive iterative dose reduction (ADIR).

Generally, increasing noise due to decrease in photon flux especially in obese patients was considered as a kV reduction drawback. Since patients with cardiovascular disease (CVD) generally have high BMI, modulations of radiation parameters are not considered, whereas pediatrics as well as slim and normal patients should be taken into consideration. So, definition of a radiation protocol for such persons is deemed necessary. As an added disadvantage, beam hardening artifacts may happen because of tube voltage reduction and it limits this technique in patients with history of CABG or stenting and in patients with high calcium score, who were excluded from this study. Finally, 100 kV CCTA in selected patients is suggested as an effective strategy for patient dose reduction without missing image quality.

The present study needs to be assessed in light of some limitations. Our finding showed a significant difference in terms of gender which can make bias. Moreover, according to designed protocol, study was executable only in one imaging center in the province. Furthermore, owing to specific inclusion and exclusion criteria, many patients were not assessed. So, study population was small.

Conclusion

CCTA using 120 kV may impose patients to additional dose. Present study demonstrated that 100 kV CCTA resulted in significant reduction in patient dose without missing diagnostic quality. Thus, for selected patients in terms of BMI, weight, calcium score, stent implanting, and history of CABG, lowering kV is a practical approach to radiation dose reduction.

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Conflict of Interests

Authors have no conflict of interests.

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Household socioeconomic status in relation to childhood general and central obesity in Farrokhshahr, Iran

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Original Article

Abstract

BACKGROUND: Although the association between socioeconomic status (SES) and general/central obesity has extensively been examined, limited data are available in this regard among children. The aim of this study was to examine the association between household SES and obesity among children.

METHODS: This cross-sectional study was done in Farrokhshahr, Iran, among primary school children aged 6-12 years in 2009. SES was examined using participants' and their parents' oral responses to a pretested questionnaire. In the current study, participants were classified based on tertiles of SES score to low, medium, and high SES categories. General as well as central obesity was defined based on age- and sex-specific national cut-off points.

RESULTS: Comparing individuals in the highest versus lowest tertile of SES, there was no significant difference in mean waist circumference (WC), but those in the middle tertile of SES had greater means of body mass index (BMI) than those in the lowest tertile after controlling for potential confounders (16.19 ± 0.27 vs. 15.27 ± 0.27 kg/m^2, P = 0.002). We observed a greater chance of general obesity for those in the highest tertile of SES compared with those in the lowest tertile [odds ratio (OR): 4.00, 95% confidence interval (CI): 1.53-10.59, P_{trend} = 0.004]. No significant association was seen between SES and central obesity, either before or after controlling for potential confounders.

CONCLUSION: We found that children in the highest SES class had a greater chance of general obesity than those in the lowest SES class. There was no significant association between SES and central obesity.

Keywords: Obesity, Overweight, Socioeconomic Status, Children, Anthropometry

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Introduction

Obesity has been defined as excess body fat.[1] Childhood obesity is a major public health problem in both developed and developing countries.[2] It affects 16% of children in the United States (US).[3] Data from national studies among Iranian children

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have reported that 16% of girls and 13% of boys are overweight or obese.[4] Childhood obesity increases the risk of being obese in adulthood such that 80% of overweight adults were overweight in their adolescence period.[5] It has also been shown that overweight children are at increased risk of cardiovascular diseases (CVDs) and metabolic disorders.[6]

The exact etiology of childhood obesity remains unknown. Several factors including household socioeconomic status (SES) has been regarded as a probable cause of childhood obesity.[7] High prevalence of childhood obesity has been reported among household with poor SES.[8-10] In developed countries it has also been shown that individuals with high household SES were less likely to be affected by overweight compared with those with low household SES, whereas the opposite is true in developing countries.[11-13]

Some studies in developing countries like India[14] and Pakistan[15] have even shown a high prevalence of childhood obesity among families with high SES. However, some others have shown contradictory findings. Overall, data on the association of SES and childhood obesity are limited in Iran. As SES might influence body weight through its effects on dietary intakes, it seems that it is an important factor in obesity prevalence. The present study was conducted to determine the association between SES and childhood obesity in a group of Iranian children.

Materials and Methods

This study was financially supported by Isfahan University of Medical Sciences, Isfahan, Iran (project number: 288270). This cross-sectional study was done among primary school students of Farrokhshahr, Iran, aged 6-12 years in 2009. We recruited 380 students for the current study. Multi-stage cluster random sampling method was used to select participants from different socioeconomic districts of Farrokhshahr. At first, we randomly selected 3 schools (out of 8 in the whole city) in which boys were being trained. Within each school, we randomly chose one class from each grade, from which some students, proportionally to size, were randomly chosen to participate in the current study using simple random selection. The same process was also done for schools in which girls aged 6-12 years were being educated. All participants and their parents provided informed written consent. The study was ethically approved by the Research Council of Food Security Research Center, Isfahan University of Medical Sciences.

Measurement of height was done using a metal ruler in standing position without wearing shoes while shoulders were relaxed. Weight was measured in light clothing using a calibrated scale. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Subjects were defined as generally overweight and obese based on age- and sex-specific BMI cut-off points suggested by World Health Organization (WHO).[16] Individuals with a BMI between the 85th and < 95th percentile were defined as overweight and those with a BMI of ≥ 95th percentile were considered as obese. Central obesity was defined as waist circumference (WC) ≥ 75th percentile age- and sex-specific cut-off points of WC suggested for Iranians.[17]

SES was examined using parents' oral responses to a pretested questionnaire. The questionnaire contained some questions and the SES was defined based on scoring of the variables. The questions and the assigned scores were as follows: father and mother's education (lower than 12-year formal education = 5, higher than 12-year formal education = 8), father's occupation (engineer = 7, self-employed = 10, employee/lettered = 8, farmer/laborer = 5), mother's occupation (housewife = 1, employed = 8), income (lower than 3000000 Iranian Rials (IRRs) = 1, 3000000 to 5000000 IRRs = 5, more than 5000000 IRRs = 7), home ownership (rental = 1, owner = 5), car type (no car = 1, low price cars = 4, medium price cars = 6, high price cars = 8). Then, participants were classified based on tertiles of SES score to low, middle, and high SES. Physical activity was assessed using a validated physical activity questionnaire for Iranian children (PAQ-C) which was completed by the parents.[18] Participants' activity was categorized into three categories of light, moderate, and heavy based on tertiles of physical activity score.[18] Assessment of age and sex was also done using a questionnaire.

General characteristics of study participants across tertiles of SES were expressed as mean ± standard deviation (SD) for continuous variables and percentage for categorical variables. To examine the differences across categories, we used analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables. In case of non-normally distributed variables, we applied Kruskal-Wallis test. Participants were categorized based on household SES into three categories of low, middle, and high SES. Adjusted means for BMI and WC by tertiles of SES were compared using analysis of covariance (ANCOVA) and presented as mean ± standard error (SE). Binary

logistic regression analysis was used to assess SES in relation to general and abdominal obesity in crude and multiple-adjusted models. First, we controlled for age and gender. In the second model, further adjustments were done for physical activity. Additional potential confounders including breakfast consumption (consumer vs. non-consumer), number of meals per day, and number of family members were adjusted for in the final model. P for trends was determined by considering tertiles of SES as ordinal variables in the logistic regression analysis. All statistical analyses were done using the SPSS software (version 15, SPSS Inc., Chicago, IL, USA). P-values less than 0.050 were considered as statistically significant.

Results

General characteristics of study participants across different categories of SES are presented in table 1. Subjects in the lowest tertile of SES had lower BMI and were less likely to be educated, and more likely to have a father with low education and a mother with being employed. As expected, individuals with low SES had lower income and low percentage of them owned a house and car compared with those with a high SES. Distribution of participants in terms of gender and physical activity was not significantly different.

Table 1. Characteristics of study participants across tertiles of socioeconomic status (SES)*

Variables	Low SES 34 (25-36)†	Middle SES 40 (37-43)†	High SES 49 (44-58)†	P**
Number (%)	96 (35.0)	93 (33.9)	85 (31.1)	-
Male gender	46 (47.9)	49 (52.7)	44 (51.8)	0.785
Age (year)	9.47 ± 1.25	9.11 ± 1.56	9.11 ± 1.34	0.126
BMI (kg/m^2)	15.51 ± 2.97£	15.95 ± 2.42	16.64 ± 3.14	0.029
WC (cm)	58.80 ± 5.30	58.90 ± 5.50	59.60 ± 6.40	0.630
Maternal education				< 0.001
< 12-year formal education	86 (89.6)	71 (76.3)	36 (42.4)	
> 12-year formal education	10 (10.4)	22 (23.7)	49 (57.7)	
Father's education				< 0.001
< 12-year formal education	95 (99.0)	84 (90.3)	34 (40.0)	
> 12-year formal education	1 (1.0)	9 (9.7)	51 (60.0)	
Maternal occupation				< 0.001
Housewife	16 (16.7)	16 (17.2)	41 (48.2)	
Teacher/employee	80 (83.3)	77 (82.8)	44 (51.8)	
Father's occupation				< 0.001
Engineer	41 (42.7)	52 (55.9)	16 (18.8)	
Self-employed	1 (1.0)	19 (20.4)	64 (75.3)	
Employee/lettered	8 (8.3)	11 (11.8)	5 (5.9)	
Farmer/laborer	46 (47.9)	11 (11.8)	0 (0)	
Income (*1000 tomans)				< 0.001
< 300	74 (77.1)	26 (28.0)	2 (2.4)	
300-500	21 (21.9)	58 (62.4)	49 (57.6)	
> 500	1 (1.0)	9 (9.7)	34 (40.0)	
Home ownership (non-owner)	56 (58.3)	27 (29.0)	7 (8.2)	< 0.001
Having car	15 (15.6)	56 (60.2)	79 (92.9)	< 0.001
Physical activity				0.490
Light	35 (36.5)	32 (34.4)	22 (25.9)	
Moderate	27 (28.1)	32 (34.4)	29 (34.1)	
Heavy	34 (35.4)	29 (31.2)	34 (40.0)	
Breakfast consumption	71 (26.7)	68 (25.6)	61 (22.9)	0.700
Number of meals per day	3 (2-6)†	3 (2-6)	3 (2-5)	0.180‡
Family members (≥ 4)	83 (27.0)	80 (29.5)	78 (28.8)	0.420

* Data are expressed as mean ± standard deviation (SD) or n (%); ** Obtained from ANOVA or chi-square test, where appropriate; £ P < 0.050 compared with the high SES group; † Median (min-max); ‡ Obtained from Kruskal-Wallis test; SES: Socioeconomic status; BMI: Body mass index; WC: Waist circumference

Table 2. Crude and adjusted mean scores of body mass index (BMI) and waist circumference (WC) across tertiles of socioeconomic status (SES)

Variables	Low SES 34 (25-36)†	Middle SES 40 (37-43)†	High SES 49 (44-58)†	P
BMI (kg/m^2)				
Number (%)	96 (35.0)	93 (33.9)	85 (31.1)	-
Crude	15.51 ± 0.26	15.95 ± 0.21	16.64 ± 0.28	0.029
Model 1*	15.38 ± 0.27$^{\lambda}$	16.00 ± 0.27$^{\lambda}$	16.70 ± 0.29$^{\lambda}$	0.005
Model 2**	15.40 ± 0.27$^{\lambda}$	16.00 ± 0.27$^{\lambda}$	16.66 ± 0.29$^{\lambda}$	0.008
Model 3***	15.27 ± 0.27$^{\lambda}$	16.10 ± 0.27$^{\lambda}$	16.66 ± 0.28$^{\lambda}$	0.002
WC (cm)				
Number (%)	96 (35.0)	93 (33.9)	85 (31.1)	-
Crude	58.80 ± 0.51	58.90 ± 0.60	59.60 ± 0.62	0.620
Model 1*	58.40 ± 0.52	59.00 ± 0.53	59.80 ± 0.56	0.210
Model 2**	58.40 ± 0.52	59.10 ± 0.53	59.70 ± 0.56	0.240
Model 3***	58.30 ± 0.53	59.20 ± 0.53	59.80 ± 0.55	0.150

All analyses were conducted using analysis of covariance (ANCOVA) with Bonferroni post hoc test. Data are presented as mean ± SE; † Median (min-max); * Adjusted for age and gender; ** Adjusted for variables included in model one plus physical activity; *** Adjusted for all variables in model 2 plus breakfast consumption, number of meals a day, and numbers of family member; $^{\lambda}$ Values which do not share common superscripts are significantly different using Bonferroni post hoc test ($P < 0.050$). The BMI in those with low SES was significantly lower than children living in high SES families. Children with low and high SES families were not significantly different compared to those with middle SES in terms of their BMI.
SES: Socioeconomic status; BMI: Body mass index; WC: Waist circumference; SE: Standard error

Crude and adjusted means of BMI and WC across different categories of SES are shown in table 2. In crude model, comparing individuals in the highest versus lowest tertile of SES, there was no significant difference in mean WC; however, those in the highest tertile of SES had greater means of BMI than those in the lowest tertile after adjustment for potential confounders (16.66 ± 0.28 vs. 15.27 ± 0.27 kg/m^2, $P = 0.002$).

Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for general and central obesity across different categories of SES are provided in table 3. In the crude model, we observed a greater chance for general obesity in the highest tertile of SES compared with the lowest tertile (OR: 2.78, 95% CI: 1.18-6.54). When we adjusted for age and gender, the association between SES and general obesity became stronger (OR: 3.14, 95% CI: 1.31-7.55). Additional controlling for physical activity did not affect the findings (OR: 3.13, 95% CI: 1.30-7.52). Further adjustments for other potential confounders strengthened the association (OR: 4.00, 95% CI: 1.53-10.59). No significant association was seen between SES and central obesity, either before or after controlling for potential confounders.

Table 3. Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for general and central obesity across tertiles of socioeconomic status (SES)

Variables	Low SES 34 (25-36)†	Middle SES 40 (37-43)†	High SES 49 (44-58)†	P_{trend} £
General overweight/obesity				
Number (%)	96 (35.0)	93 (33.9)	85 (31.1)	-
Crude	1.00	1.29 (0.51-3.29)	2.78 (1.18-6.54)	0.016
Model 1*	1.00	1.39 (0.54-3.59)	3.14 (1.31-7.55)	0.008
Model 2**	1.00	1.40 (0.54-3.61)	3.13 (1.30-7.52)	0.009
Model 3***	1.00	1.85 (0.66-5.20)	4.00 (1.53-10.59)	0.004
Central obesity				
Number (%)	96 (35.0)	93 (33.9)	85 (31.1)	-
Crude	1.00	1.13 (0.50-2.55)	1.48 (0.66-3.29)	0.330
Model 1*	1.00	1.16 (0.51-2.65)	1.54 (0.68-3.45)	0.290
Model 2**	1.00	1.17 (0.51-2.67)	1.52 (0.67-3.42)	0.300
Model 3***	1.00	1.27 (0.54-2.95)	1.60 (0.69-3.67)	0.410

† Median (min-max); * Adjusted for age and gender; ** Adjusted for variables included in model one plus physical activity; *** Adjusted for all variables in model 2 plus breakfast consumption, number of meals a day, and numbers of family member; £ P-value for trends was determined by considering tertiles of SES as ordinal variables in the logistic regression analysis; SES: Socioeconomic status

Discussion

In this cross-sectional study, we examined the relationship between SES and general and central obesity among a sample of Iranian children. We found a positive association between SES, BMI, and overweight/obesity. Children in the high SES class had higher BMI and greater chance for overweight and obesity. To the best of our knowledge, this study is among the first studies that examined this association among Iranian children.

Childhood obesity is a public health concern.[2] The incidence of childhood obesity is increasing in both developed and developing countries.[6] Childhood obesity has important consequences for health during both childhood and adulthood life.[19] Therefore, prevention of childhood obesity is essential. We observed a positive association between SES and obesity. These observations were in line with the earlier results reported from Vietnam, Colombia, Sri Lanka, and Iran.[20-23] In a school-based cross-sectional study among Indian adolescent school children, a positive association between SES and BMI was observed.[24] An earlier study in Ukraine reported that higher social class was associated with elevated BMI.[25] In addition, in a cross-sectional study among 1860 children aged 5-12 years in Pakistan, rapid rise in overweight and obesity was observed, especially among affluent urban population.[15] Likewise, a population-based cross-sectional study among elementary school children in northeastern Romania showed that the prevalence of overweight and obesity was higher among children with high SES than those with low SES.[26] A systematic review of obesity and SES in developing countries also showed a positive association between SES and obesity among children.[27] In contrast to our findings, some studies did not confirm these findings. A study by Noh et al. among Korean children and adolescents indicated that low SES was significantly associated with overweight and obesity.[10] In a cross-sectional study in Korea, adolescent males in low SES class had a greater probability of either overweight or underweight.[28] It has been shown that low SES was indirectly associated with increased risk of overweight and obesity through low intake of fruit and vegetables among adolescent girls.[29]

We found no association between SES class and central obesity among children. In a cross-sectional study among adolescents aged 10-17 years in rural South Africa, those from the highest SES class had about twofold greater chance of being overweight/obese and centrally obese than those in the lowest category of SES class.[30] Furthermore, in a study among school-aged children and adolescents in Poland, abdominal obesity was positively associated with SES.[31] However, some studies have suggested that low SES may increase the risk of central obesity.[32] Different findings might be explained by the discrepancy in subjects' characteristics including age and gender, study sample size, lack of controlling for several confounders, the number of SES indicators as well as study location in terms of urban or rural areas.

Our study has some strengths as well as limitations. One of the strength points of this study is considering the role of potential confounders in data analysis. Unlike several prior studies, we considered several measures of the SES indicators, while earlier studies have mostly defined SES based on two or three variables and therefore, all aspects of SES have not been considered in these publications. Several limitations also need to be considered when interpreting the findings. First, due to cross-sectional nature of the present study, causality cannot be established. Second, the sample size in the current study was small. Further studies with larger sample size might be needed to confirm our findings. Third, dietary intakes can definitely influence the association between SES and overweight/obesity. We were unable to consider children's dietary patterns as a covariate in the current study. However, one might consider dietary intakes as a mediator between SES and obesity. Fourth, although we controlled for several potential confounders, residual confounding cannot be excluded. In addition, as the present study was performed among children only, the findings cannot be generalized to the adult population.

Conclusion

We found that children in the high SES class had a greater chance of being overweight/obese than those in the low SES class. Therefore, socioeconomic determinants should be considered when implementing preventive interventions in childhood overweight and obesity.

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Conflict of Interests

Authors have no conflict of interests.

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Production of antioxidant peptides through hydrolysis of medicinal pumpkin seed protein using pepsin enzyme and the evaluation of their functional and nutritional properties

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Original Article

Abstract

BACKGROUND: A hydrolyzed protein composition is a mixture of peptide and amino acids that have been achieved through hydrolysis by the enzyme from different sources, acid or caustic soda. These peptides show important health improving properties including anti-oxidation, antimicrobial, anti-cancer, anti-diabetic, anti-hypertensive activity.

METHODS: The aim of the present study was to hydrolyze the protein extracted from medicinal pumpkin seed (Cucurbita Pepo Con. Pepo Var Styriaca) seed meal by pepsin enzyme to obtain bioactive peptides with the highest antioxidant capacity. For this, response surface method (RSM) and central composite design were used at different enzyme concentrations (1%-2%), hydrolysis times (2-5 hours), and temperatures (30-40 °C) as independent variables. Then, the functional properties (emulsifying capacity, foaming capacity, water absorption capacity, and oil absorption capacity), heat and pH stability, and amino acid analysis were measured for the optimum treatment.

RESULTS: 2,2-diphenyl-1-picrylhydrazy (DPPH) radical scavenging capacity of peptides achieved in optimum conditions (82.07%) was highly similar to the results predicted by the software (80.31%) and their functional properties were significantly different from the initial protein ($P > 0.050$). Amino acid profile showed that the antioxidant capacity of the hydrolysates could be due to the total hydrophobic amino acid content that accounts for 39.85% of total amino acids in pumpkin seed meal.

CONCLUSION: According to the results, pumpkin seed meal hydrolysates, with outstanding functional properties, can be used in different food formulation to improve their physical and chemical properties and extend their shelf life, and as antihypertensive and antioxidant agents in the prevention of cardiovascular disease.

Keywords: Pumpkins, Hydrolysis, Antioxidants, Antihypertensives, Amino Acid Analysis

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Introduction

Proteins are vital components of health because they provide the nitrogen, amino acids, and energy needed by the body. However, applications of proteins are limited due to some of their properties such as solubility. Protein hydrolysis is a widespread strategy to improve their chemical, functional, and nutritional properties.[1] During the hydrolysis, proteins are broken into small peptides and amino acids. Because the enzymatic hydrolysis is performed in relatively mild conditions and no amino acid damage occurs, this kind of hydrolysis is preferred to acidic and alkaline hydrolysis.[2]

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Because of the potential applications of bioactive peptides in functional foods production, these compounds have great importance and application in human nutrition and health. Bioactive peptides from various food proteins can be used as natural substitutes for most expensive chemical medicines that are usually used for chronic diseases.[2] Hydrolysed proteins showed antioxidative activity and angiotensin-converting-enzyme (ACE) inhibiting effect which depended on the type of enzyme and was increased with increase in the hydrolysis time.[3] As synthesized anti-hypertensive drugs have been reported to exhibit several undesirable side effects or other health complications following long-term administration, food-derived ACE inhibitory peptides are considered to be safer in combating hypertension.[4] Therefore, many researchers have searched for natural sources of ACE inhibitors in the past decade. Recent studies on proteins and bioactive peptides with the aim to improve human health and prevent chronic diseases have led to further investigations about these bioactive peptides. Rayaprolu et al. purified and characterized bioactive peptides from soybean for cancer cell proliferation inhibition.[5] Lee et al. investigated the antioxidant and anticancer effects of functional peptides obtained from ovotransferrin hydrolysates.[6] Ghassem et al. identified two novel antioxidant peptides obtained from protein hydrolysates obtained from the Edible-nest Swiftlet (Aerodramus fuciphagus).[7]

Results of scientific literature show that bioactive peptides obtained from plant proteins through enzymatic hydrolysis have suitable functional properties such as emulsifying and foaming capacities (e.g., functional properties of soybean),[8] water and oil absorption, and outstanding health improving functions such as high antioxidant activity (peptides from soybean, black wheat, cotton seed, sunflower seed, peanut, and pumpkin),[9] cholesterol reduction (fish hydrolysates),[10] antimicrobial activity (peptides from cereals, legumes, and mushrooms),[11] antihypertensive activity (peptides from wheat, soybean, rice, and azufrado beans),[12] and metal chelating ability (peptides from collagen).[13] Takenaka et al. studied the antioxidant activity of soybean protein and its hydrolysats. They found that a diet containing 20% soybean protein and its hydrolysates has a preventive effect on thiobarbituric acid reactive substances (TBARS) in rats, and peptides obtained from soybean hydrolysis can decrease blood cholesterol more than non-hydrolyzed soybean proteins.[14] Lahart et al. investigated reasons for the prevention of oxidative processes in the presence of bioactive peptides and concluded that this preventive effect could be due to the metal chelating activity of peptides or some certain groups in their amino acid side chains that preferably bind with free radicals in fatty acids and prevent the oxidation process.[15] Klompong et al. studied the protein hydrolysates of yellowstripe scad (Selaroides leptolepis) obtained through hydrolysis using alcalase and flavourzyme, and suggested that these hydrolysates have proper functional properties.[16] During hydrolysis by both of the enzymes, protein solubility increased more than 85%, and interfacial activity (emulsifying, and foaming capacities and stabilities) of the hydrolysates was dependent upon the degree of hydrolysis and type of protease.

Pumpkin is of the Cucurbitaceae, and in this family, medicinal pumpkin seed (Cucurbita pepo) has the highest diversity. A large amount of oil products are obtained from plant resources each year. medicinal pumpkin seed with 23-35% protein and 20-55% oil is a rich source of protein and oil. Pumpkin seed oil contains high amounts of unsaturated fatty acids such as linoleic acid and oleic acid. Thus, pumpkin seed is an appropriate source for various industries.[17] The issue at hand is the amount of remaining wastes that mostly consist of pumpkin meal. Disposing of this amount of wastes is not cost-effective and causes environmental problems, and these wastes have nutritional and medicinal value; thus, they can be used in various processes to decrease waste and produce products with high nutritional values.

In the present study, enzymatic hydrolysis of proteins of pumpkin meal was carried out using protease enzyme pepsin, and therefore, the best treatment was selected using Design-Expert software (version 6.0.2, Stat-Ease Inc., Minneapolis, MI, USA) with response surface method (RSM) as optimum treatment for 2,2-diphenyl-1-picrylhydrazy (DPPH) radical scavenging activity. Subsequently, functional properties (emulsifying, foaming, water absorption, and oil absorption capacities), pH and heat stability, and amino acid profile for optimum treatment were investigated and compared to those of pumpkin seed protein isolate.

Materials and Methods

Medicinal pumpkin seed meal (Cucurbita pepo con. Pepo var. Styriaca), with 48.57% ± 3.51% protein, 10.32% ± 0.58% lipid, 4.24% ± 0.52% moisture,

and 6.045 ± 0.17 ash, was purchased from a soybean factory in Gorgan, Iran, and pepsin enzyme and DPPH were purchased from Merck KGaA, Darmstadt, Germany. All chemicals used were of analytical grade.

Pumpkin protein isolate production: Pumpkin protein was produced according to the process reported by Horax et al. Pumpkin meal flour was mixed with distilled water with 1:10 (w/v) ratio at room temperature and reached the highest solubility pH (pH = 10) with 1N NaOH. The sample was stirred for 1 hour at room temperature and centrifuged at 5000×g for 20 minutes (Combi514R, South Korea). The supernatant reached isoelectric point (pH = 3.49) with 1N HCL, and was left to settle at room temperature for 30 minutes. The resulting suspension was centrifuged at room temperature at 5000×g. The pellet was washed with 20 ml distilled water and dried using a freeze dryer (FD_4, Operon, South Korea).[18]

Optimization of the hydrolysis process by the response surface method: In the present study, in order to evaluate the effect of hydrolysis conditions on protein hydrolysate properties and to optimize this process, response surface design with three variables was used to find the relation between responses and variables. Effects of independent variables, enzyme to substrate ratio (X_1), time (X_2), and temperature (X_3) are presented in table 1.

Table 1. Independent variables and their levels used in the central composite design (CCD)

Independent Variables	Symbol	Coded Level		
		-1	0	+1
Enzyme/substrate Ratio (ml/g)	X_1	1	1.5	2
Time (minute)	X_2	2	3.5	5
Temperature (°C)	X_3	30	35	40

Enzymatic hydrolysis: According to the amounts calculated using the Design-Expert software, enzyme pepsin (from porcine stomach mucosa, 6907 U/g) was added in concentrations of 1, 1.5, and 2%, and hydrolysis time as independent factor was 2, 3.5, and 5 hours in a 200 rpm shaker incubator (8480-VS, South Korea). Hydrolysis temperatures were 30, 35, and 40 °C. After deactivating the enzyme at 85 °C for 15 minutes, the suspension was centrifuged at 4 °C for 30 minutes at 4000×g, and supernatant was collected as the protein hydrolysate.[19] The collected supernatants were lyophilized.[20]

Degree of hydrolysis: The degree of hydrolysis (DH) was estimated according to the method presented by Kaewka et al.; 10 ml protein hydrolysate was mixed with 10 ml trichloro acetic acid (TCA) 10% and centrifuged. Nitrogen content (N) of the supernatant and total nitrogen was measured through the Kjeldahl method and DH was measured using the following equation (1).[21]

Degree of Hydrolysis = N in TCA/N in whole hydrolysed sample (1)

DPPH radical scavenging activity: Hydrolysate at a concentration of 1000 µl was added to DPPH 0.1 M at a concentration of 1000 µl in ethanol (96%) and left to settle for 60 minutes at room temperature in a dark place. Absorbance was measured at 517 nm.[22] Ethanol was used as control. DPPH scavenging activity was calculated using equation (2).

DPPH Scavenging Activity (%) = Absorbance of Control – Absorbance of sample / Absorbance of Control × 100 (2)

Emulsifying capacity: Emulsifying capacity was investigated based on the method reported by Pearce and Kinsella.[23]; 10 ml corn oil was mixed with 30 ml protein hydrolysate 0.1%/protein solution through centrifugation at 14489 g for 1 minute. Then, 1 ml of emulsion was removed from the bottom and mixed with sodium dodecyl sulfate (SDS) 0.1% with the ratio of 1:100. The absorbance of the solution was measured at 500 nm immediately after emulsion formation at room temperature (A_0). Emulsifying activity (m^2/g) indicated the surface area that was stabilized by 1 g protein hydrolysate and was calculated using the following equation (3):

Emulsifying activity = 2 × 2.303 × A0 / F × (g) proteinweight × 100 (3)

Where F is the oil volume of the emulsion (0.25).

Foaming capacity: Foaming capacity was measured according to the method presented by Adebowale and Lawal[24] with slight modifications; 1 g protein/protein hydrolysate was mixed with 50 ml distilled water in a mixer (SBG-5725, Japan) with high speed for 5 minutes. Then, the solution was poured into a 250 ml scaled cylinder and foam volume was read after 30 seconds. Foaming activity was calculated using the following equation (4):[24]

FC (%) = (A0 – B) × 100 / B (4)

Where FC is foaming capacity (%), A_0 is sample volume after stirring, and B is sample volume before stirring.

Water absorption capacity: Water absorption capacity was measured according to the method reported by Kaur and Singh[25] with slight modifications; test tubes were weighted, and 10 ml distilled water was added to 1 g protein/ protein hydrolysate and they were mixed. After 30 minutes in room temperature, tubes were centrifuged for 30 minutes at 6000 ×g. After removing the supernatant, the tubes remained in 45 °C for 25 minutes in a 45-degree angle until surface water was removed. Then, the tubes were weighted again. Water absorption percentage is reported as g of absorbed water/ g of sample.[25]

Oil absorption capacity: Oil absorption capacity was measured according to the method presented by Kaur and Singh.[25] Test tubes were weighted and 0.5 g of protein/ protein hydrolysate was added to 6 ml sunflower oil and stirred with a metal spatula for 1 minute. After 30 minutes in room temperature, the tubes were centrifuged for 30 minutes at 6000 ×g. After removing the supernatant, the tubes were kept upside-down for 25 minutes to remove the excess oil, and then, weighted. Oil absorption percentage is reported as g of absorbed oil/ g of sample.[25]

pH and heat stability: To investigate pH stability, the protein hydrolysate sample was incubated at room temperature and exposed to pH 1-11 by 1M NaOH or HCl for 1 hour. Then, the pH of samples was set at 7 and DPPH radical scavenging activity was measured.

For heat stability investigation, 5 ml of each protein hydrolysate sample at a pH of 7 was poured into a test tube and heated at 100 °C in a water bath for 0, 30, 60, 90, 120, and 180 minutes, and cooled in cold water immediately after removal from the water bath. The control sample was kept at 25 °C. Then, DPPH radical scavenging activity was measured.[26]

Amino acid profile analysis: Amino acid profile analysis was carried out using reverse phase high performance liquid chromatography (RP-HPLC). pumpkin seed protein hydrolysate hydrolysate was used for this analysis; 30 mg of the hydrolysate sample was hydrolyzed with 6 N HCl at 110 °C for 24 hours. RP C-18 columns (15 × 0.46 cm) with 5 µ internal particle size were used for this analysis.

The treatments were optimized using RSM in the form of a central compound design in Design-Expert software. In the present study, in order to evaluate hydrolysis conditions on protein hydrolysates properties and to optimize this process, response surface design with three discrete variables [enzyme to substrate ratio (X_1), time (X_2), and temperature (X_3)] was used to find the relation between response (DPPH scavenging activity), that it is as continuous variables, and variables.

The data collected from experiments on the hydrolysate in optimized conditions was analyzed through a completely random design in SPSS software (version 21, IBM Corporation, Armonk, NY, USA). Each experiment was repeated three times. Duncan's test was used to compare the means of all evaluated parameters and the difference between different treatments were evaluated using t-test at probability level of 5% (≥ 5%). Microsoft Excel spreadsheet software (Microsoft Corporation, Redmond, WA, USA) was used to draw charts.

Results

DPPH radical scavenging activity: According to the experiment results, the hydrolysate sample with 1% enzyme concentration at 30 °C for 2 hours showed the highest DPPH scavenging activity (82.07%), with the R-squared and adjusted R-squared of 0.9092 and 0.9522 (P = 0.091), respectively, for optimization treatment. Therefore, it was suggested as the optimum treatment for free radical scavenging activity (degree of hydrolysis: 28%) by Design-Expert software. Table 2 shows the DPPH scavenging activity of hydrolysates obtained from pumpkin protein isolate.

Emulsifying capacity of pumpkin seed protein isolate and hydrolysate: Emulsifying capacity was significantly (P > 0.050) influenced by the degree of hydrolysis. As can be seen in figure 1, hydrolysis has a positive effect on emulsifying capacity. Changes in pH had a significant effect (P > 0.050) on emulsifying capacity, and the lowest and highest emulsifying capacities were observed at a pH of 4 and 10, respectively. As the pH range of most processed foods is 4-10, this range was used for evaluation of the functional properties of protein isolate and concentrate.

Foaming capacity of pumpkin seed protein isolate and hydrolyste: Changes in foaming capacities of pumpkin seed protein isolate and hydrolysates in different pH are shown in figure 1. Both hydrolysis process and pH variation showed significant effects (P > 0.050) on foaming capacity. As can be seen in figure 1, protein hydrolysates, within the whole pH range considered in this study, had higher foaming capacity than protein isolate. Changes in pH showed significant (P > 0.050) effects on the foaming capacity of pumpkin seed protein isolate and hydrolysates. The lowest and highest foaming capacities for protein isolate and hydrolysate were observed in a pH of 4 and 10, respectively.

Table 2. Antioxidant activities of different treatments used for enzymatic hydrolysis of pumpkin seed protein

Treatment	Enzyme concentration (%)	Temperature (°C)	Time (hour)	DPPH radical scavenging activity (%)	Average (%)	Standard deviation	P
1	2.0	30	2.0	68.11	67.41	0.61	0.169
2	1.0	30	2.0	82.07	81.39	0.53	0.091
3	2.0	30	5.0	72.00	71.17	0.62	0.032
4	1.0	30	5.0	70.31	69.56	0.61	0.967
5	1.5	30	3.5	50.18	49.27	0.65	0.101
6	1.5	35	3.5	65.90	64.77	0.81	0.040
7	1.5	35	2.0	70.34	69.53	0.61	0.228
8	1.5	35	3.5	65.13	64.53	0.64	0.398
9	1.5	35	3.5	68.00	67.35	0.62	0.409
10	1.0	35	3.5	79.24	78.34	0.64	0.064
11	1.5	35	3.5	68.44	67.54	0.64	0.255
12	1.5	35	3.5	62.39	61.77	0.63	0.155
13	1.5	35	3.5	67.84	67.11	0.61	0.321
14	1.5	35	5.0	68.93	68.45	0.72	0.048
15	2.0	35	3.5	79.00	78.46	0.68	0.065
16	1.0	40	5.0	62.67	61.90	0.61	0.155
17	1.5	40	3.5	43.52	42.70	0.61	0.015
18	2.0	40	2.0	68.72	68.33	0.79	0.271
19	1.0	40	2.0	76.83	75.95	0.63	0.197
20	2.0	40	5.0	65.31	65.51	1.47	0.041

DPPH: 2,2-diphenyl-1-picrylhydrazy

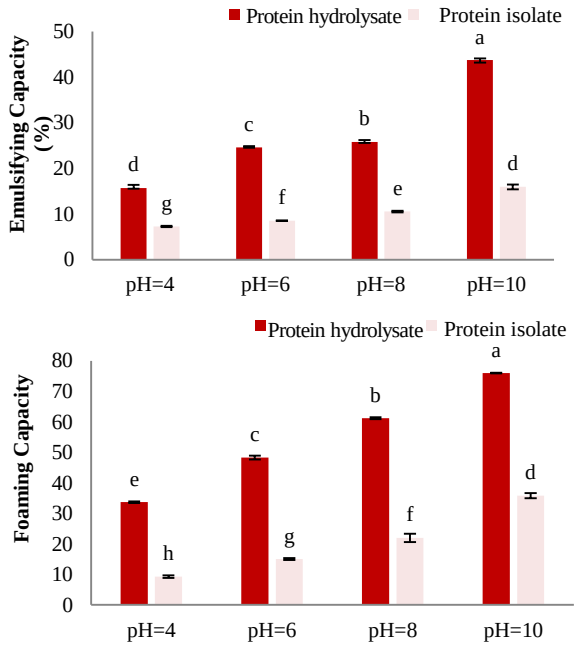

Figure 1. Emulsifying and foaming capacities of pumpkin seed protein isolate and hydrolysate

Data correspond to the mean ± standard division (SD) of the three independent experiments. ANOVA was performed in GraphPad Prism (version 6.0, GraphPad Software Inc., CA, USA). Values with different letters (a, b,…) indicate significant differences with emulsifying and foaming capacities of pumpkin seed protein isolate and hydrolysate ($P < 0.050$).

Duncan's test was used to compare the means of all evaluated parameters and the difference between different treatments were evaluated using t-test at probability level of 5 % (≥ 5%).

The lowest foaming capacity at a pH of 4 was related to the lower solubility and more compact structure of protein at pH near the isoelectric point.

Water absorption capacity of pumpkin seed protein isolate and hydrolysate: Water absorption capacity is defined as the ability of particles to absorb water molecules in a limited amount of water. Figure 2 shows the water absorption capacity of pumpkin seed protein isolate and hydrolysates. Enzymatic hydrolysis of pumpkin seed protein isolate had a significant ($P > 0.050$) direct effect on its water absorption capacity.

Changes in pH had significant ($P > 0.050$) effect on the water absorption of pumpkin seed protein isolate and hydrolysates. The lowest and highest water absorption capacity of both isolate and hydrolysates were at a pH of 4 and 10, respectively.

Oil absorption capacity of pumpkin seed protein isolate and hydrolysate: The oil absorption capacity increased in pumpkin seed protein hydrolysate compared to its isolate (Figure 2) which can be related to an increase in surface hydrophobicity after enzymatic hydrolysis that leads to an increase in physical entrapment of oil droplets.[27] Zhang et al. found similar results in their study on oil absorption capacity of rice bran protein hydrolysates compared to its isolate.[27]

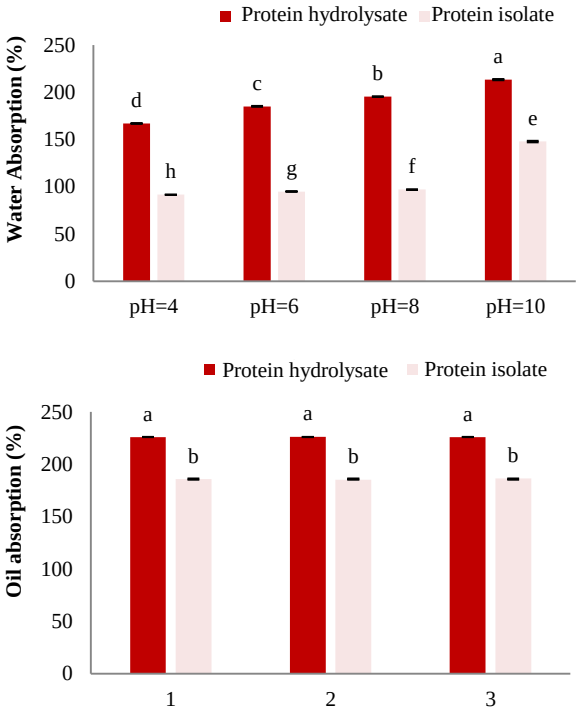

Figure 2. Water and oil absorption capacities of pumpkin seed protein isolate and hydrolysate

Data correspond to the mean ± standard division (SD) of the three independent experiments. ANOVA was performed in GraphPad Prism. Values with different letters (a, b,…) indicate significant differences with water and oil absorption capacities of pumpkin seed protein isolate and hydrolysate (P > 0.050). Duncan's test was used to compare the means of all evaluated parameters and the difference between different treatments were evaluated using t-test at probability level of 5 % (≥ 5%).

Heat stability: Figure 3 shows changes in the antioxidant activity of hydrolysates after incubation in 100 °C for 0, 15, 30, 60, 90, 120, and 180 minutes. There was no significant difference in the results (P > 0.0500). This shows that antioxidant activity in peptides after 180 minutes at 100 °C remains approximately unchanged.

pH stability: Changes in antioxidant activity of pumpkin seed protein hydrolysates with pH variation are shown in figure 3. There was no significant (P > 0.050) difference in antioxidant activity of samples in different pHs. As antioxidant activity of hydrolysates in most of the pHs had no significant difference with that in the pH of 7, pumpkin seed protein hydrolysates can be used as an antioxidant in food systems in the whole range of pH.

Amino acid analysis: Amino acid profile has a key role in the antioxidant activity of peptides.[28] This property has been evaluated to find a relation between antioxidant activity and amino acid content in pumpkin seed protein hydrolysate.

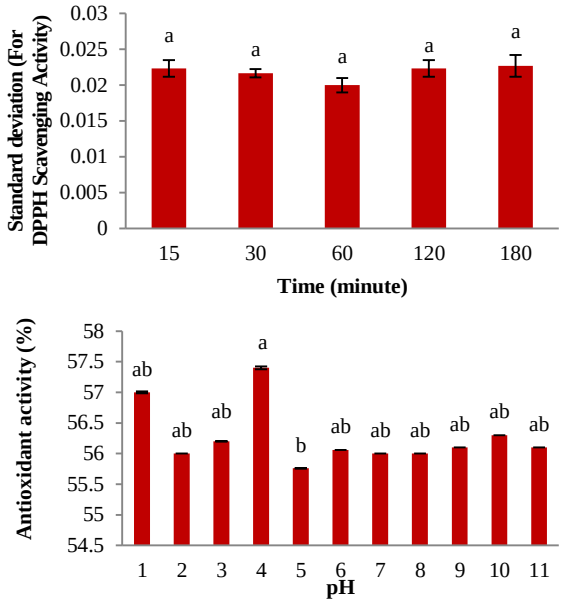

Figure 3. Heat (up) and pH (down) stabilities of pumpkin seed protein hydrolysate

Data correspond to the mean ± standard division (SD) of the three independent experiments. ANOVA was performed in GraphPad Prism. Values with different letters (a, b,…) indicate significant differences with heat (up) and pH (down) stabilities of pumpkin seed protein hydrolysate (P > 0.050). Duncan's test was used to compare the means of all evaluated parameters and the difference between different treatments were evaluated using t-test at probability level of 5 % (≥ 5%). DPPH: 2,2-diphenyl-1-picrylhydrazy

As can be seen in table 3, glutamic acid, leucine, and aspartic acid are the main amino acids in pumpkin seed protein hydrolysate.

Table 3. Amino acid composition of hydrolysed pumpkin seed proteins (mg/100 g)

Amino acid	Protein hydrolysate	FAO
Alanine	3046	
Serine	2889	
Aspartic acid	7049	
Glutamic acid	13643	
Histidine	1772	1900
Tyrosine	3383	6300
Arginine	2575	
Glycine	4029	
Threonine	4417	1400
Methionine	3143	2500
Valine	3344	3500
Leucine	7121	6600
Isoleucine	2722	2800
Lysine	2730	5800
Phenylalanine	4284	
Hydrophobic amino acids	25689	
Total	64449	

FAO: Food and Agriculture Organization

The estimated amount of aspartic and glutamic acid may be more than their real amount, because they may be produced by the deamination of glutamine and asparagine during the acidic treatment of samples.[29] According to table 3, although the amount of histidine is lower than other amino acids, it meets the human need (1.7 g/100 g body weight).

Discussion

DPPH radical scavenging activity: The pepsin ezyme can hydrolyze peptide bounds next to leucine and aromatic amino acids (phenylalanine, tryptophan, and tyrosine), and it has been acknowledged that the terminal phenyl group in the resultant peptide chain has free radical scavenging activity. Furthermore, it has been recognized that proteins' denaturation and loss of natural structure through hydrolysis leads to unfolding and exposure of active amino acids that can react with free radicals. There is a direct relation between free radical scavenging and hydrogen donating of amino acids. The change in peptide chain length during hydrolysis has an important effect on antioxidant activity, and peptides with smaller molecular weight have stronger antioxidant activities.[20]

Emulsifying capacity of pumpkin seed protein isolate and hydrolysate: The emulsifying mechanism of protein hydrolysate samples is defined as their adsorption of oil droplets, covering them, and prevention of their association after homogenization.[30] As emulsifying capacity is dependent upon the degree of hydrophobicity and molecular weight of hydrolysates, samples with hydrophobic amino acids and longer chain have higher emulsifying capacity.[30] During hydrolysis, the solubility of hydrolysates increases, and they migrate to the water-oil interface.[27,31]

As protein hydrolysates contain hydrophobic and hydrophilic sequences that are necessary for interfacial properties, these components are considered as surface active agents.[30] During hydrolysis, the balance between hydrophobic and hydrophilic sequences of hydrolysates leads to an increase in the emulsifying capacity of hydrolysates.[31] Emulsifying capacity at the pH of 4 can be related to the lower solubility of protein near the isoelectric point, while the increase in emulsifying capacity of the sample by increasing the pH could be related to negative charges association that not only causes electrostatic repulsion, but also increases the flexibility of protein and facilitates its propagation through the water-oil interface.[31]

Foaming capacity of pumpkin seed protein isolate and hydrolyste: Because of their high interfacial activity, proteins are responsible for foaming in flours. Soluble proteins can reduce the surface tension in the fluid-air interface and prevent the association of bubbles. Moreover, protein molecules can unfold, react with each other, and form a multilayer protein film that leads to higher flexibility in the water-air interface; consequently, breaking the bubbles becomes difficult and firm foam is formed.[24]

To show the foaming capacity, proteins have to easily disperse in water, readily migrate to the interface, and easily unfold to form a layer around the air/gas bubbles.[27] Protein flexibility, presence of hydrophobic amino acids, and reduced surface tension are factors that influence foaming properties.[16] The observed increase in foaming capacity of pumpkin seed hydrolysates compared to that of protein isolate might be related to the increase in solubility of hydrolysates due to enzymatic hydrolysis. Klompong et al. studied the enzymatic hydrolysis of yellowstripe scad by alcalase and flavourzyme in different degrees of hydrolysis (5%, 15%, and 25%).[16] They found that foaming capacity is influenced by type of enzyme and degree of hydrolysis, and increasing the degree of hydrolysis decreases the foaming capacity.[16] Increase in foaming capacity due to hydrolysis was also reported by Li et al.[31]

Water absorption capacity of pumpkin seed protein isolate and hydrolysate: Water absorption capacity has an important role in viscose systems such as soups and prevents water loss in bakery products like cakes.[27] Water holding capacity is related to the nitrogen solubility index, and higher nitrogen solubility index leads to higher water absorption capacity. As nitrogen solubility increases during hydrolysis,[27] hydrolysates have higher water absorption capacity compared to protein isolate.

Increase in water absorption capacity at a pH of 10 can be related to the increase in repulsion forces due to negative charge in basic pH, and decrease in this capacity can be related to a decrease in solubility around the isoelectric point.[24]

Oil absorption capacity of pumpkin seed protein isolate and hydrolysate: Generally, oil absorption is strongly affected by both solubility and surface hydrophobicity of protein[27] and because of the ability of protein to bridge between water and oil, oil absorption capacity has an important role in some food systems such as meat products, especially sausages.[32] Oil absorption is a key factor

in meat substitutes due to the role of this functional property in the enhancement of flavor and generation of a better mouthfeel.[32]

Heat stability: The slight change in antioxidant activity of some treatments can be due to the breakdown or aggregation of antioxidant peptides because of the heat. In general, proteins are sensitive to heat, so they aggregate. However, there are reports that smaller hydrolysed proteins are resistant to aggregation in higher temperatures. As this resistance is seen in our samples, these hydrolysates can be used in food processed under heating operations, without significant changes in antioxidant activity. The results of heat stability experiment are similar to those of Nalinanon et al. on fish (Nemipterus hexodon) hydrolysates.[26]

pH stability: Generally, pumpkin seed protein hedrolysates can exhibit 97-99% of their antioxidant activity in the whole pH range. Nalinanon et al. evaluated the pH stability of peptides from enzymatic hydrolysis of fish (Nemipterus hexodon) muscle by pepsin and reported that radical scavenging activity of peptides was stable at a pH of 1-10, while a slight decrease was observed at a pH of 11. They concluded that antioxidant peptides may be losing some of their activity in higher pHs.[26]

Amino acid analysis: Generally, pumpkin seed protein hydrolysates are a suitable source of essential amino acids, threonine, tyrosine, phenylalanine, leucine, cycteine, and methionine, and sufficient source of isoleucine, valine, and lysine that is the first limiting amino acid. In the non-hydrolyzed protein, glutamic acid, leucine, and aspartic acid were also the main amino acids and lysine was the first limiting amino acid. Similar results have been reported by Zhong et al.[28] for the amino acid composition of wheat germ protein and hydrolysate, and Khantaphant et al.[33] for stripe red snapper brown fish hydrolysate obtained by alcalase and flavourzyme. In the present study, tryptophan content was not estimated due to its sensitivity and decomposition during hydrolysis. According to Bougatef et al., sensitive amino acids such as methionine and tryptophan are rarely observed after protein hydrolysis.[22] Amino acid composition has an important role in antioxidant activity of protein hydrolysates. This factor, to a large extent, depends on the type of protease used for the hydrolysis.[34] Alcalase show high specificity for aromatic (alanine, tryptophan, and tyrosine), acidic (glutamic acid), sulfur containing (methionine), aliphatic (leucine, and isoleusine), hydroxylated (serine), and basic (lysine) amino acids.[35] It has been approved that aspartic and glutamic acid,[34] in addition to prolamin, arginine, methionine, histidine, leucine, isoleucine, alanine, tyrosine, and valine,[36] have strong antioxidant activities. According to the amino acid content of pumpkin seed's hydrolysates, it is clear that, in addition to the amount of aspartic acid and glutamic acid, there is also a correlation between antioxidant activities and amount of leucine, Phenylalanine, Threonine and Glycine. Furthermore, the hydrophobic amino acid content of hydrolysated pumpkin seed proteins, which positively correlates with its antioxidant activity, was estimated as 25689 mg/100 g that accounts for 39.85% of total amino acid content of pumpkin seed hydrolysates. According to the amino acid scoring pattern for adults provided by the Food and Agriculture Organization (FAO) of the United Nations, although the tyrosine, histidine, and lysine content of hydrolysated pumpkin seed proteins is less than the suggested amount, it can be a balanced source of essential amino acids (threonine, methionine, valine, leucine, isoleucine, and phenylalanine); therefore, it can provide the major amino acids requirement for better health performance, and can be used as dietary supplement in diets contain food protein's deficient in essential amino acids.

Conclusion

Application of antioxidants is a way of extending the shelf life of high fat foods. Presently, the application of synthetic antioxidants is decreasing due to their chemical nature and risk of being carcinogenic. Bioactive protein hydrolysates obtained from enzymatic hydrolysis are components that can be a good substitution for synthetic antioxidants in foods, and can be used as effective antioxidants and antihypertensive agents in preventing cardiovascular disease. Pumpkin seed protein hydrolysates contain a large amount of hydrophobic amino acids and the high antioxidant activity of these hydrolysates can be related to their hydrophobic sequences. Furthermore, the results showed that enzymatic hydrolysis can improve functional properties such as emulsifying and foaming capacities and water and oil absorption in food formulations like meat and bakery products and some protein food supplements, and thus, improve their physical and chemical properties and extend their shelf life. Pumpkin seed hydrolysates contain essential amino acids (except lysine), so they can be a suitable source of such amino acids according to FAO's amino acid scoring pattern for adults.

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Conflict of Interests

Authors have no conflict of interests.

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Design and methodology of heart failure registry: Results of the Persian registry of cardiovascular disease

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Original Article

Abstract

BACKGROUND: Heart failure (HF) resulted from ultimate pathway of many cardiovascular diseases (CVDs) or as a separate entity poses a considerable increasing prevalence and economic burden, but its registry for better management is less frequently done. In this study, we aimed to design and implement HF registry.

METHODS: Persian Registry Of cardioVascular diseasE (PROVE) was initiated from March 2015 and continuously collected information of patients suffering from HF, ST-elevation myocardial infarction (STEMI), atrial fibrillation (AF), percutaneous coronary intervention (PCI), stroke, familial hypercholesterolemia (FH), congenital heart disease (CHD), chronic ischemic cardiovascular disease (CICD), and acute coronary syndrome (ACS) from 18 different cardiac centers. Data of patients with HF were collected from their medical forms and recorded in a registry system of PROVE/HF plus telephone follow-up survey of 1, 6, and 12 months after the date of HF attack.

RESULTS: Assessment of all related questions led to definition of a final questionnaire including 27 items regarding demographic information, underlying disorders and their complications, patients' symptoms and signs, and laboratory and relevant para-clinic data at admission time, during hospitalization, and post discharge. Follow-up information was mostly based on patients' general status and medication usage.

CONCLUSION: PROVE execution was a successful and hopeful project providing data of major CVDs in order to design appropriate preventive actions and better management and treatment strategies plus a valuable data center being utilized in multiple future comprehensive projects.

Keywords: Heart Failure, Methodology, Registries, Iran

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Introduction

Heart failure (HF) syndrome is the ultimate pathway of many cardiovascular diseases (CVDs)[1] and is considered as one of the major public health problem.[2] HF prevalence has increased in recent decades because of population aging as well as therapeutic advances in the management of patients in the earlier stages of heart disease allowing them to survive until they finally develop HF.[3]

Although about 80% of CVDs occur in low-income as well as developing countries,[4-7] most studies done in developed and European nations and few published articles reported high prevalence of these disorders among Asian countries.[8]

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While most HF survival rates data all over the world are based on their national registry systems, there are few available reliable epidemiologic statistical information in order to estimate the incidence or prevalence of CVDs or even long-term survival rates in Iran.[9,10] Moreover, these Iranian studies have mostly evaluated short-term results or were performed with small study population. The first registry program of CVDs in Iran was launched in Isfahan City (as a pilot study) in 2015, named the Persian Registry Of cardioVascular diseasE (PROVE) because of necessity for implementing a national data registry of individuals suffering from CVDs and further data analysis and follow-up assessments. This ongoing project registers information of patients with HF, ST-elevation myocardial infarction (STEMI), atrial fibrillation (AF), percutaneous coronary intervention (PCI), stroke, familial hypercholesterolemia (FH), congenital heart disease (CHD), chronic ischemic cardiovascular disease (CICD), and acute coronary syndrome (ACS).[11] To the best of our knowledge, PROVE is the first national comprehensive CVDs database registry done in Iran with the least similarity in the Eastern Mediterranean region.

The purpose of this registry is to improve and develop the care of patients with diagnosis of HF by providing continuous information about care and therapy. Moreover, establishing this national HF registry enables an assessment of how thoroughly participating units are following recommended guidelines on diagnosis and treatment of patients with HF in addition to the creation of a platform for an open discussion of these important issues. Current study describes the design and implementation of PROVE/HF registry methodology in Isfahan.

Materials and Methods

PROVE/HF is a registry of HF patients' data from certain hospitals in Isfahan. This city is the capital of the third widest province located in central part of Iran. This registry project was started in late 2014 and launched in March 2015. Ethics Committee affiliated to Isfahan University of Medical Sciences approved this study. A checklist was designed according to the outcomes of the Swedish Heart Failure Registry (SHFR)[12] and Thai Acute Decompensated Heart Failure Registry (Thai ADHERE)[13] for data registration of individuals with HF. After completion of the first draft of the checklist, 10 faculty members including cardiologists and other experts unaware of the project were invited to evaluate the content of the checklist in a way that they were asked to determine whether the questions would appropriately measure the desired outcome and contain the entire content of what was needed, and after that all relevant questions were considered in the checklist, the protocol and the related dictionary were written in addition to full description of the procedure plus explanation of all pre-defined questions, options, and codes.[14] Finally, questionnaire, protocol, and dictionary were approved by Quality Control (QC) of PROVE Committee.

Afterwards, based on the prepared checklist and protocol as well as dictionary, data entry method was taught to the personnel. The training began with three two-hour sessions on how to extract data from medical records, complete data sheets, and read diagnostic tests as needed as well as explanation of the objectives and the protocol. Moreover, managers and principal investigators who were allowed to visit the archives of the hospital and correct probable mistakes had monthly sessions. The registry information was gathered from 18 distinct cardiac centers with appropriate equipment and trained personnel in terms of both diagnosing and management of HF including ten, five, and three teaching, private, and governmental hospitals, respectively. List of patients diagnosed with HF by International Classification of Diseases, 10th Revision (ICD-10) such as those with preserved and low ejection fraction (EF) or with acute or exacerbated and decompensated status hospitalized in all cardiac hospitals having medical history in that health care center were given to data collectors.

Diagnosis of HF had been confirmed by cardiologists' opinion written in patients' medical records. Consent form was signed by each participant before admission to the hospital. For data confidentiality and not disclosing patient personal information, a unique code with Huffman phonetic codes using combination of last name, first name, and date of birth was utilized for each participant.[15,16] At the initiation of the study, it was defined to obtain data with two distinct methods of prospective and retrospective manner simultaneously. However, due to occurrence of some problems and probable biases in terms of data gathering in retrospective method, we decided to continue the project with only prospective way. Furthermore, we just collected data with hospital-based method in a way that eligible patients admitted with diagnosis of HF could be enrolled in our registry. Data collectors recorded data in

questionnaires using the data in the medical records of hospitals' archives. Then, they delivered the completed questionnaire to the Registry Unit at the Isfahan Institute of Cardiology on a weekly basis. The questionnaires were reviewed by the data management team and any observed missed or mistaken cases was returned back. Data were entered into the relevant software after being approved by the data management team.

Patients were followed 1, 6, and 12 months after the date of HF occurrence by telephone. In absence of answer for three times within a period of 24 hours, the subject follow-up data would be discarded form the project. In cases of doubting about HF diagnosis or unavailability of basic information in their records, they were invited to a face to face meeting provided by a specialist. If death occurred, the date and etiology (cardiac or non-cardiac) as well as decease place (home or hospital) data would be assessed from the relatives.

In addition to internal QC of PROVE/HF, this project was controlled by the team's supervisor and externally evaluated by the committee which consisted of experienced and trained members who were not one of the PROVE executive members and were unaware of it and performed an external and continuous control over the entire registry components from the beginning to the end.

Results

After confirmation of the QC committee, a questionnaire consisting of 27 items was finally designed. The questionnaire included data on demographic variables, underlying diseases and comorbidities leading to HF plus past medical history, pre-admission medications usage and treatments, implementation of any procedures during admission, diagnostic and laboratory test results, patients' symptoms and signs, and results of para-clinic examinations including electrocardiography (ECG), echocardiography, and chest X-ray. We collected data both at admission time and during hospitalization as well as discharge date. During follow-up periods after 1, 6, and 12 months, information on current patients' status and medications usage was collected and in cases of death, the cause and place were also recorded.

Discussion

Questionnaires of HF registries in the world often contain comprehensive information and items including demographic factors, underlying diseases and complications, drug usage and treatment methods, diagnostic and laboratory test results, symptoms and signs, and results of relevant examinations.[12,17-22] The important difference in PROVE/HF questionnaire was that most of the questions were filled in three periods including at admission and discharge time plus during hospitalization period. This manner enabled us to monitor the patient status in the treatment process from admission to discharge. As mentioned above, some of the disease registrations were performed through prospective and some through retrospective method with their own advantages and disadvantages. For example, prospective way needs more personnel and would be consequently more costly, also it is highly associated with data missing especially during holidays or the time personnel would not be at work. However, since information could be registered simultaneously with the incidence of the cardiovascular events, it leads to a more complete access to relevant information and more accurate registration outcome. On the other hand, retrospective registration can be performed months or years after the CVDs incidence and needs fewer personnel, but could be associated with incompleteness or inaccuracy of data due to usage of past records.[23]

Because of extensive PROVE/HF questions and limited personnel for data gathering, registration began retrospectively; however, due to tendency for joining EURObservational Research Programme (EORP)[22] and collaboration with them and considering this point that most HF registry data are gathered prospectively and through web-based method and also due to high prevalence of data incompleteness via retrospective model, hospitals affiliated to Isfahan University of Medical Sciences have switched to prospective registration way.[12,17,18]

In literature, data registry of patients with HF is divided to two distinct methods including outpatient or hospital-based ones.[17,19,22] Due to limited staff, numerous number of patients, and lack of specialized clinics, PROVE/HF was performed through hospital-based method. It should be considered that in some registers, the follow-up questionnaires may have more information about the patient's condition, medications, and treatments.[22] The collection of long-term follow-up data is often the pivotal step in the registry's objectives[24] and is an important component of the disease registries usually performed for one year,[19,22] providing mortality during the desired follow-up.[24] Participants in PROVE/HF study were followed for longer duration after hospital discharge

with multiple intervals. Because of prospective method of data collection and periodical follow-up assessment in a short interval period to minimize patients' loss, information and data on current patients' status and medication usage were available with acceptable accurateness.

We presented the way of development and implementation of our feasibility study of the national comprehensive CVDs registry. Also, we discussed the patients' recruitment methods, follow-up duration, data collection, and QC measurements. Disease registry databases are used for evaluating that whether a therapeutic option is done appropriately for the disease or not. Moreover, these critical databases would help understand how to improve care quality and consider probable outcomes that might be achieved using these databases. Also, these registries could be useful in terms of health-related issues for policy makers for implementing proper strategies for disease control and even prevention.

CVDs are the leading cause of mortality worldwide, specifically in Iran. A registration system for patients with CVDs, especially HF, stroke, AF, and ACS could be useful for better assessment of diseases courses, proper diagnosis and treatment, acute phases and chronic conditions, medications, in and out-of-hospital complications plus clinical outcomes. Coronary angiography and intervention made improvements in the field of cardiology and the safety and efficacy of these treatment methods were challenged through these database registries based on the patients' information.[11]

Although PROVE/HF was the first registration for patients with HF in Iran and provided information on appropriate admission to collect data from patients, it was not free from limitations that identification of them might help for better generalization of the results.

Due to retrospective design of data gathering in PROVE/HF registry at first which might be associated with missing data and confounding variables, generalization of our findings related to the medical documents and patients' records must be done cautiously; however, we tried to complete the missing information and questionnaires as much as possible in follow-up sessions from patients and their families. Moreover, one year after initiation, registration of this disease changed to EORP/HF based on related protocol as prospective method.

Less accurate data gathering method on follow-ups by telephone on drug usage and awareness of participants about follow-up checklists might affect our outcomes. Another limit would be hospital-based design of data collection which provided less comprehensive information compared to population-based method.

Conclusion

PROVE development and implementation as a feasibility study seemed to be a successful project. Although this project was initiated in Isfahan, scale-up pilot study in other parts of the country has been started. This registry can be used in several sections including improving the current CVDs management in participating centers and at a national level, filling the gaps in preventative care, establishing effective treatment and disease control guidelines, and as a useful source for local and international studies.

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Conflict of Interests

Authors have no conflict of interests.

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Interleukin 10, lipid profile, vitamin D, selenium, metabolic syndrome, and serum antioxidant capacity in elderly people with and without cardiovascular disease: Amirkola health and ageing project cohort-based study

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Original Article

Abstract

BACKGROUND: The age-related autoinflammation-mediated atherosclerosis is associated with some immunological, nutritional, and metabolic parameters and redox status. Here, we evaluated the association of circulatory interleukin 10 (IL-10) levels with lipid profile, some nutrients, and total anti-oxidant capacity in elderly people who presented cardiovascular disease (CVD) with or without metabolic syndrome (MetS) and in healthy subjects.

METHODS: In this cross-sectional case-control study, 258 sera prepared from elderly people (144 healthy and 114 patient subjects) who participated in a community-based study, the Amirkola Health and Ageing Project (AHAP), were analyzed for IL-10, lipid profile, vitamin D, selenium (Se), antioxidant capacity, and MetS.

RESULTS: Compared to patients, the healthy subjects exhibited higher levels of circulatory IL-10 among individuals with detectable serum IL-10 ($P = 0.036$). However, this difference was not observed when total subjects from both groups were compared, since more than 90% of those people were IL-10-negative. Se, vitamin D, and antioxidant levels were similar in both groups. There was a negative association between IL-10 and body mass index (BMI) ($P < 0.050$) and an equivocal association with vitamin D levels, whereas the association between IL-10 and other indicated variables was not significant. Significant association was observed between MetS and CVD prevalence ($P < 0.001$). There was a positive correlation between Se and total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) ($P < 0.010$) in healthy subjects and with TC in patients ($P < 0.050$).

CONCLUSION: A major proportion of elderly people were serum IL-10-negative, whereas independently to IL-10, MetS was most common in patients with CVD. Weight loss may have the potential to increase IL-10 levels in the elderly.

Keywords: Interleukin 10, Lipids, Cardiovascular Diseases, Antioxidants, Metabolic Syndrome, Elderly

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Introduction

The age-related ischemic heart disease (IHD) is still the leading cause of death worldwide.[1] Aging could be defined as a period of human life, in which the effects of modifiable risk factors for atherosclerosis, such as dyslipidemia and metabolic syndrome (MetS), are maximally piled in the body.

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Thus, the exploration of those modifiable risk factors in elder people is worth to be performed, to access to some new predisposing or preventing factors for premature cardiovascular diseases (CVDs). Indeed, CVD is common in younger people (< 65 years). In men, 25% and 50% of total new-onset CVD events occur before age of 55 and 65 years, respectively.[2]

Atherosclerosis is a prevalent cause of coronary heart diseases (CHDs).[3] It is also recognized as an inflammatory disease.[4,5] Even the radiation-mediated atherosclerosis is attributed to the deoxyribonucleic acid (DNA) damage-induced chronic inflammation.[6] Thus, targeting the inflammation was recently noticed as an attractive strategy to reduce the CVD risk factors.[7] Moreover, the oxidized low-density lipoprotein (oxLDL)-derived substances such as oxidized cholesterol esters as the damage-associated molecular pattern (DAMP)-related molecules are well-known culprit in induction of inflammation in context of atherosclerosis, through activation of pattern recognition receptors (PRRs) such as toll-like receptor 4 (TLR4).[8] Due to the inflammatory nature of atherosclerosis, it is reasonable to assume that the anti-inflammatory cytokines such as interleukin 10 (IL-10) can play some beneficial roles in amelioration of this process. For instance, in macrophages, IL-10 induces the down-regulation of the receptor for oxLDL cholesterol (OxLDL-C), i.e., CD36 and scavenger receptor A, and thereby inhibits the influx of this well-known atherogenic lipid, and subsequently precludes one of the key steps in atherosclerosis, namely foam cells formation, which is defined as a hallmark of atherosclerosis.[9] Also, IL-10 prevents the apoptosis-mediated foam cells death[10] and protects against ageing-induced dysfunction of endothelial cells.[11] We have previously reported that healthy adult people have higher circulating IL-10 when compared to adult subjects with unstable angina.[12] We also found a significant positive correlation between the serum levels of high-density lipoprotein cholesterol (HDL-C) with two major anti-inflammatory cytokines, IL-10 and IL-4.[12] However, to our knowledge, scanty study reported the serum levels of IL-10 in elderly people. There is a report indicating that serum IL-10 is positively associated with risk of CVD in the elderly.[10]

Furthermore, since the oxidative stress is considered as one of the best-known inflammation-inducing factors in CVD,[13] the anti-oxidant defense can also be considered as a proper partner for IL-10 to diminish the hazardous effects of inflammatory process which is involved in atherosclerosis. Probably the antioxidant capacity increase in elderly people[14] is a contra-reactive mechanism to such insult. There are different types of anti-oxidant systems in our body, such as superoxide dismutase (SOD), catalase, and especially glutathione peroxidase (GPx).[14] For the latter enzyme, selenium (Se) acts as a main cofactor which is necessary for proper functioning of this enzyme.[15] Se also plays a pivotal role in different aspects of immune system including cytokine production as well as in regulation of inflammatory reactions.[16] High dietary intake of Se leads to an increase in pro-inflammatory cytokine production, i.e., interferon-gamma (IFN-γ) through skewing of naive T-helper cells differentiation to IFN-γ producer Th1 cells, while low dietary intake of Se causes increased levels of anti-inflammatory cytokine, i.e., IL-4.[16]

Vitamin D3 (cholecalciferol) is another nutrient which in recent years has been appeared as a main player in glucose homeostasis and cardiovascular functions in elderly individuals[17] as well as in regulation of immune responses.[18] One billion of people especially elderly people suffer from vitamin D3 deficiency worldwide.[18] Contrary to Se, this steroidal hormone is believed to contribute to the differentiation of naive T-cells to an anti-inflammatory type of T-helper, i.e., Th2.[19] Thus, this vitamin can be considered as an anti atherogenesis factor acting probably through enhancing of IL-10 production.

MetS is a multicomponent modifiable risk factor for CVD which is considered as a manifestation of host inflammatory response.[20] This worldwide prevalent syndrome has been associated to reduced IL-10 production especially in elderly people.[21]

Thus, the knowledge about the IL-10 levels and the determining factors in biogenesis of this anti-inflammatory cytokine in elderly people may provide some reliable evidence to take an effective immune modulation strategy to delay the premature atherosclerotic plaque formation and plaque rupture. To examine this strategy, in this population-based study, we determined for the first time the serum levels of IL-10, Se, and vitamin D as well as the lipid profile and total antioxidant capacity, and investigated the presence of MetS in elderly subjects with CVD and healthy controls, to evaluate the potential association of these immunological, nutritional, and biochemical parameters with CVD. This study showed that most elderly people had no significant levels of serum

IL-10. However, in subjects with detectable levels of serum IL-10, there was a negative association between IL-10 and body mass index (BMI), and an equivocal association with vitamin D levels. Moreover, patients with CVD suffered from MetS much more than normal subjects, independently to serum IL-10. Thus, weight loss may have the potential to compensate this IL-10 deficiency in elderly.

Materials and Methods

Patients and healthy control subjects: Subjects were selected among 1616 individuals who participated in Amirkola Health and Ageing Project (AHAP) during April 2011-July 2012.[22] In this project, the health status of elderly people who lived in Amirkola, a city located in the northern part of Iran, near the Caspian Sea, was evaluated. AHAP proposal was approved by the Ethics Committee of Babol University of Medical Sciences, Babol, Iran, and informed consent was obtained from all participants or their relatives. In the current cross-sectional case-control study, at first step, 375 patients with a history of angina, heart failure (HF), high blood pressure, and myocardial infarction (MI) were selected based on their medical records and medications that they had used for heart diseases. Among these subjects, 175 patients presenting rheumatoid arthritis (RA), 42 with fractures and trauma, 31 with diabetes, 12 with stroke history, and one person suffering from cancer were excluded from the study. Finally, 114 subjects were included in patient group. Among the remained old people (1241 of 1616 subjects), to select healthy control subjects, we excluded those who had diseases that could change the level of IL-10 in blood circulation. Thus, 152 subjects were selected as healthy control group, which were age- and sex-matched with subjects of patient group. Then, we measured the C-reactive protein (CRP) levels in sera of these subjects to exclude those with a significant common and uncommon inflammatory condition based on previous report.[18] As mentioned, the CVDs are considered as inflammatory diseases with increased levels of CRP, so this marker was not used as a criterion in patients selection. Consequently, eight CRP-positive subjects were excluded from the study, and finally 144 subjects were selected as healthy control group. The necessary volumes of serum specimens of all selected subjects were thawed from -80 ^{o}C for further experiments.

The number of subjects with or without MetS was extracted from AHAP data bank in which those subjects have been already classified according to the Iranian National Committee on Obesity (INCO) criteria.[23]

Serum IL-10 detection by enzyme-linked immunosorbent assay (ELISA): The quantitative detection of circulating IL-10 level was performed by using the Orgenium's kit (Orgenium Laboratories, Vantaa, Finland) which was based on sandwich ELISA with sensitivity of 2 pg/ml. Some serum specimens with undetectable levels of IL-10 analyzed by this kit were rechecked with another ELISA kit (R&D systems, USA) which exhibited a higher level of sensitivity (0.17 pg/ml). The optical density (OD) for each well was obtained by microplate reader (Stat Fax 4200 Awereness Technology, USA).

Measurement of lipid profile: Demographical data as well as serum levels of triglyceride (TG), LDL-C, and HDL-C were extracted from AHAP data bank. The indicated analytes were measured by Pars Azmoon kit (Iran) and Hitachi Auto Analyzer (Japan).

Se assessment: Serum Se concentration was measured by atomic absorption spectrophotometry (AAS) technique using Atomic Absorption Spectrophotometer (PG990, China).

Vitamin D assessment: The related values for 25-hydroxy vitamin D concentrations in sera of patients and control subjects were extracted from AHAP study data bank. These data have been provided by assessing of sera 25-hydroxy vitamin D with an ELISA-based kit (IDS, UK).

CRP detection: A qualitative CRP latex kit (Bionik/Iran) was used to detect CRP in serum of the control subjects.

Antioxidant capacity assessment: For measuring the total plasma antioxidant activity, we used the ferric reducing ability of plasma (FRAP) test. This method is based on the ability of plasma to reduce ferric ion (Fe^{3+}) to ferrous ion (Fe^{2+}) at low pH.[24]

Statistical analyses: The continuous data were expressed as mean ± standard deviation (SD), and discontinuous data were expressed as frequency and percentage. Kolmogorov-Smirnov test (K-S test) was used to examine the data normality. Mean values were compared by independent samples t-test for data with normal distribution; otherwise, Mann-Whitney U test was used. Pearson and Spearman correlation coefficient values were determined for indicated normally- and non-normally-distributed data, respectively. The discontinuous data were evaluated by chi-square test. Data were analyzed by SPSS software (version 18, SPSS Inc., Chicago, IL, USA). $P < 0.050$ was considered as a significant level in all statistical tests.

Table 1. The demographic data and mean values of serum lipid profile in patients and controls

Variables	Groups		P
	Patients (n = 114)	Controls (n = 144)	
Sex (female/male) [n (%)]	51 (44.7)/63 (55.3)	49 (34.0)/95 (66.0)	0.080
Age (year)**	70.1 ± 8.1	68.5 ± 7.1	0.093
BMI (kg/m^2)**	27.4 ± 4.3	27.8 ± 4.9	0.361
TG (mg/dl)**	157.0 ± 81.0	135.0 ± 60.0	0.016*
HDL-C (mg/dl)**	38.0 ± 4.0	39.0 ± 4.0	0.354
LDL-C (mg/dl)**	124.0 ± 52.0	137.0 ± 39.0	0.035*
TC (mg/dl)**	190.0 ± 47.0	207.0 ± 41.0	0.018*

* Considered as significant (P < 0.050) in t-test and chi-square test; ** Mean ± standard deviation (SD)
BMI: Body mass index; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TC: Total cholesterol

Results

As a major risk factor for coronary atherosclerosis, the lipid profile was evaluated in patients and control groups. In table 1, it can be seen that the apparently healthy elderly people had significantly higher levels of total cholesterol (TC) and LDL-C when compared to the subjects with heart diseases (P = 0.018 and P = 0.035, respectively), while surprisingly the mean of HDL-C level was almost equal. The serum levels of TG was higher in patients group in comparison with healthy controls (P = 0.016).

As a main anti-inflammatory and anti-atherogenic cytokine, we determined the serum levels of IL-10 in all studied subjects. As shown in figure 1, the mean ± SD IL-10 concentration was 0.26 ± 1.10 (pg/ml) and 0.92 ± 3.69 (pg/ml) in subjects with heart disease and healthy controls, respectively. This difference was not statistically significant due to a large variation between variables in the two studied groups (P > 0.050). Indeed, most samples (more than 90 %) had no detectable levels of serum IL-10. However, this difference appeared at a significant level when only the subjects with detectable levels of serum IL-10 in each group were statistically compared (P = 0.036) (Figure 1).

FRAP test was used to evaluate the levels of antioxidant defense systems between the two groups. The mean ± SD of total serum antioxidant levels was 893 ± 120 µmol/l and 966 ± 243 µmol/l in healthy controls and patients group, respectively. This difference was not statistically significant (P > 0.050).

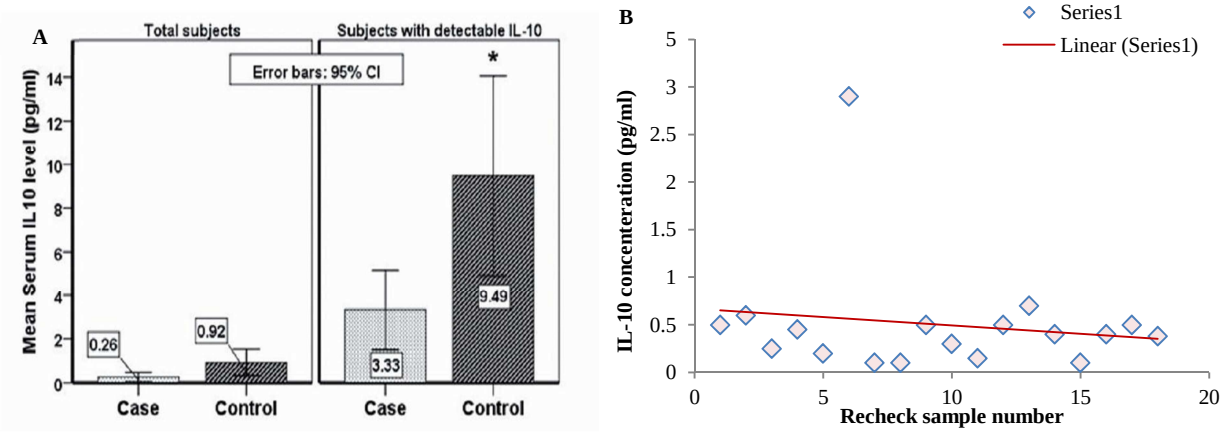


Figure 1. (A) Means of serum interleukin 10 (IL-10) concentration in total subjects with heart disease (n = 114) and total apparently healthy controls (n = 144) (left panel). Right panel shows the means of serum IL-10 concentration in subjects with detectable levels of this cytokine from each group. For subjects with heart disease (n = 9) and for apparently healthy control subjects (n = 14)

* P < 0.050 is considered significant. (B) Scatter plot of rechecked serum samples for IL-10 concentrations. We rechecked the IL-10 levels in 18 sera which had undetectable levels of this cytokine in our previous experiment with enzyme-linked immunosorbent assay (ELISA) kit with analytical sensitivity of 2 pg/ml. As it can be seen, the IL-10 concentration was ≤ 0.5 pg/ml in 15 out of 18 (83%) of sera. This value for remaining three serum samples was 0.6 and 0.7 for two samples and only one sample exhibited a result that was higher than 2 pg/ml (2.9 pg/ml). The median value for rechecked serum IL-10 concentration was calculated as 0.44 pg/ml and the 95% confidence interval (CI) was obtained as 0.20-0.85 pg/ml for mean.

To evaluate the possible protective role of IL-10 in MetS development, we compared the number of all subjects suffering from MetS (n = 97) or without MetS (n = 161) in all serum IL-10-positive (n = 23) and negative (n = 235) individuals. No significant association between serum IL-10 and MetS prevalence was observed when the data were analyzed by chi-square test (P > 0.050). Moreover, MetS was much more common in patient subjects versus control ones (P < 0.001).

The association between serum IL-10 levels with BMI, one of the well-known criteria of obesity, was also investigated. As shown in figure 2, the subjects with detectable levels of IL-10 exhibited a significantly lower value of BMI when compared to subjects with undetectable IL-10 levels (P = 0.045). Among subjects with detectable IL-10 serum levels, there was a person with outlier of BMI; if we ignore this case, the observed difference will become more significant (P = 0.016).

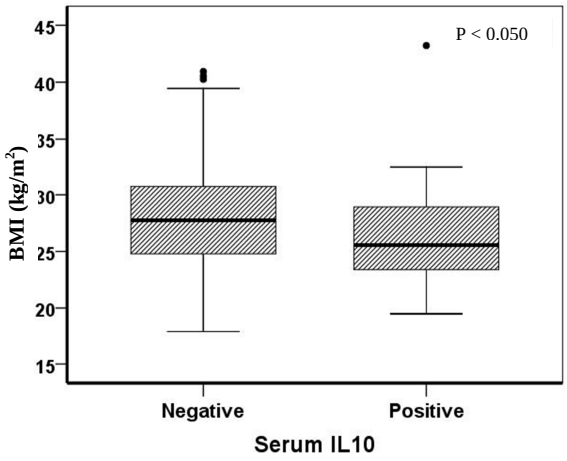
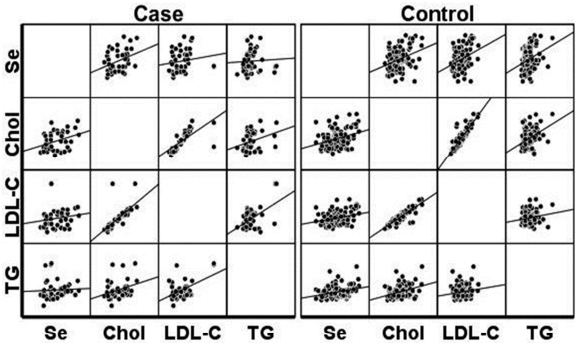


Figure 2. Body mass index (BMI) in subjects with (n = 23) and without detectable serum interleukin 10 (IL-10) (n = 235). Horizontal lines represent the median values. Boxes represent 25th-75th percentiles and vertical bars represent the minimum and maximum values. Spots show outlier values.
* P < 0.050=0 is considered significant.

Due to the well-known beneficial effects of Se on immune system as well as its important role as a cofactor for the GPx, this trace element was determined in the serum of studied subjects. Then by Pearson test, the correlations between serum Se and serum IL-10 as well as serum Se with lipid profile were determined.

The mean ± SD of serum Se levels were 79.8 ± 17.0 µg/l (n = 114) and 82.4 ± 16.8 µg/l (n = 144) in patients and healthy controls, respectively. This difference was not statistically significant (P > 0.050). Moreover, there was no significant correlation between serum IL-10 levels and Se concentrations (P > 0.050). A positive correlation was found between serum Se and TC (r = 0.33, P < 0.050 in patients and r = 0.32, P < 0.010 in control group), LDL-C (r = 0.29, P < 0.010), and TG (r = 0.30, P < 0.010) only in control group. There was no significant correlation between Se and HDL-C in both groups (P > 0.050) (Figure 3).



	Chol	LDL-C	TG
Case	r = 0.33, P < 0.050	NSC	NSC
Control	r = 0.32, P < 0.010	r = 0.29, P < 0.010	r = 0.30, P < 0.010

NSC: No significant correlation

Figure 3. Correlation between serum selenium (Se) levels and lipid profile in subjects with heart disease (above left panel). Right panel shows these correlations in control subjects. In patient group, there was a positive correlation between Se and total cholesterol (Chol) but not with low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG). In control group, there was a positive correlation between Se and all study components of lipid profile (table below)
* P < 0.050 is considered significant.

To examine the hypothesis that 25-hydroxy vitamin D exerts its beneficial effects on cardiovascular system through modification of IL-10 production, we compared the mean ± SD of this vitamin in subjects with and without detectable levels of IL-10 in serum, (40.48 ± 59.30 ng/ml and 24.23 ± 23.00 ng/ml, respectively).

As it can be seen in figure 4, subjects with detectable IL-10 exhibited higher levels of this vitamin in their serum compared to subject without IL-10, although this difference was not significant (P > 0.050) due to the existence of great variation between the two groups. If the variation was equal between groups, then this difference would become significant (P = 0.009).

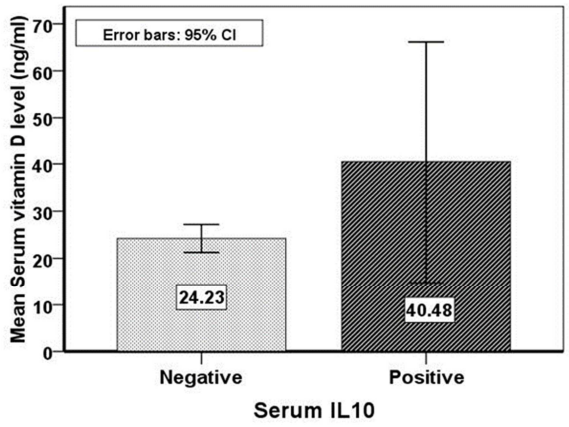


Figure 4. Means of vitamin D concentration in subjects with (n = 23) and without detectable serum interleukin 10 (IL-10) (n = 235).
P < 0.050 is considered significant.
CI: Confidence interval

Discussion

In consistence with our previous study,[12] we found a significant higher level of serum IL-10 in apparently healthy elderly subjects in comparison with those with CVD who had detectable amounts of this cytokine in their sera. However, we were not able to find any significant difference in serum IL-10 levels between the two groups in total subjects. This may be due to our another interesting finding indicating that the serum samples prepared from more than 90% of elderly subjects in both groups had undetectable levels of IL-10. In this study, healthy subjects had significant higher levels of serum LDL-C and TG, and same levels of HDL-C when compared to patients group. To interpret these findings, we assumed that patients used the cholesterol-lowering drugs including atorvastatin which could decrease the serum LDL-C levels, whereas it has a less effect on plasma concentrations of HDL-C and TG.[25]

As a macrophage deactivating factor and consequently as a blocker of anion superoxide production, a potent inflammatory and oxidative agent, we determined the correlation between serum IL-10 levels and serum total antioxidant activity. We were not able to find any significant correlation between these two variables. However, in an ex-vivo model, Huet et al. recently reported the IL-10 as an anti-inflammatory cytokine that exhibits also an anti-oxidant activity.[26] Probably this variation originated from different techniques used in these studies.

We investigated the existence of a well-known inflammatory state, i.e., MetS, in subjects with detectable levels of serum IL-10. We were not able to find any association between serum IL-10 concentrations and the existence of MetS, whereas the prevalence of this syndrome was significantly higher in patient subjects. We did not find any correlation between serum IL-10 concentrations and each single component of serum lipid profile in patient and control groups. van Exel et al. reported a correlation between low production capacity of IL-10 and MetS in old inhabitants of Leiden City, Netherlands.[20] Contrary to our study, they measured the cytokine levels in lipopolysaccharide (LPS)-activated whole blood culture supernatants and not the circulating levels of IL-10. However, we found that old subjects with detectable levels of serum IL-10 were thinner than those without IL-10.

To explore natural modifiers of IL-10 concentrations, we also studied the effects of two nutrients on CVD as well as on the serum levels of IL-10. In this study, we found that the elderly people with heart disease had a lower concentration of serum Se (79.8 ± 17.0 µg/l) compared to apparently healthy control subjects (82.4 ± 16.8 µg/l). Although this difference was not statistically significant, it can be concluded that in both groups the dietary intake of Se was sufficient to protect their heart against CHDs, if we suppose that the required serum Se concentration is 45 µg/l according to an existing report.[27] However, Flores-Mateo et al.[28] and Sabino et al.[29] in their recently-published reviews criticized about the protective role of Se against heart diseases. Indeed, in the present study, we found a positive correlation between serum Se concentrations and serum TG, LDL-C, and TC levels but not with HDL-C concentrations. To our knowledge, there is no direct evidence to interpret the correlation between Se and hyperlipidemia, but there are some indirect evidence supporting this hypothesis.[30-33]

25-hydroxy vitamin D was another nutrient that we investigated its relationship to serum IL-10 levels. We found that subjects with detectable levels of serum IL-10 had also higher levels of vitamin D in their sera (almost two folds) when compared to subjects with undetectable levels of serum IL-10. This difference was statistically significant (amended) if we assume that the vitamin D concentration variation is similar in both groups. However, this difference disappeared due to the existence of significant difference in vitamin D distribution patterns between the two groups. Indeed this study provided an equivocal evidence for correlation between serum IL-10 and vitamin D levels in elderly individuals.

The most important limitation of this study was the high variation in serum vitamin D levels in our population. However, this variation can disappear if the elderly people receive the same regimen to compensate their vitamin D deficiency. Such strategy may cause much more IL-10 production in these individuals and subsequently result in CVD prevention. There are some studies that support this idea. Recently, Dimeloe et al. reported that the active form of vitamin D [1,25 (OH) D3] can induce IL-10 production in $CD4^+$ T-cells through up-regulation of α-1-antitrypsin synthesis in these lymphocytes.[34] Kiani et al. also reported that vitamin D significantly reduced the risk of CVD events in people without MetS syndrome.[35]

Collectively, the data generated by this study indicate that independently of Se and lipid profile but equivocally associated with serum vitamin D, the old people with CVD had significant lower levels of serum IL-10 compared to old apparently healthy subjects who had detectable levels of serum IL-10. Moreover, there was no significant association between serum IL-10 and prevalence of MetS totally, whereas this cytokine was inversely associated with obesity in old people.

Conclusion

Independent to IL-10, the prevalence of MetS was higher in patients with CVD versus control group. There was no significant difference between elderly people with and without CVD in serum Se, vitamin D, and redox state, while most of those people had no detectable level of IL-10 in their blood circulation. Thus, applying some strategies such as weight loss and probably vitamin D supplementation to improve the production of this anti-atherosclerogenic cytokine may have some beneficial outcomes for those people.

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Conflict of Interests

Authors have no conflict of interests.

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Development and evaluation of the psychometric properties of a hypertension self-care questionnaire

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Original Article

Abstract

BACKGROUND: There are a number of tools to assess self-care in hypertension (HTN), but they do not cover all the dimensions of self-care and do not have a good reliability and validity. This study was conducted to develop and evaluate the psychometric properties of a tool for self-care assessment in HTN.

METHODS: This cross-sectional, methodological study was conducted in Isfahan, Iran. An expert panel was held to assess the qualitative face validity of the tool. The content validity ratio (CVR) and content validity index (CVI) were measured. The questionnaire was distributed among 20 patients to measure its internal reliability. After 14 days, it was re-distributed among the same patients, as a measure of external reliability. The questionnaire was completed by 203 patients with HTN and an exploratory factor analysis was performed in order to assess the construct validity of the tool.

RESULTS: The items of the self-care tool were confirmed with a CVR ≥ 0.5, Kappa ≥ 0.71, I-CVI = 0.69, and intraclass correlation coefficient (ICC) = 0.952. The factor analysis showed that the 16-item questionnaire has 5 dimensions, including follow-up [3 items; factor loadings (FL) = 0.619 to 0.869, and Cronbach's alpha (α) = 0.737], healthy lifestyle (5 items; FL = 0.709 to 0.846, α = 0.703), promoting qualifications (4 items; FL = 0.610 to 0.791, α = 0.594), medication therapy (2 items; FL = 0.699 and 0.740, α = 0.717), and following recommendations (2 items, FL = 0.577 and 0.744, α = 0.701). These 5 dimensions explained 62.686% of the variance. The Cronbach's alpha coefficient of the final self-care assessment questionnaire was 0.833.

CONCLUSION: The developed questionnaire proved to have appropriate psychometric properties for measuring self-care in patients with HTN.

Keywords: Blood Pressure, Chronic Disease, Hypertension, Self-Care

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Introduction

The prevalence of hypertension (HTN) is high in developed and developing countries. Globally, 40% of people over the age of 25 years have high blood pressure, and the number of people with elevated blood pressure has increased from 600 million in 1980 to a billion in 2008.[1] HTN is a controllable risk factor for cardiac diseases, cerebrovascular diseases, kidney failure, and peripheral vascular diseases. The failure to manage this condition results in serious damage to the vital organs and premature death,[2] and is a cause of about 16.5% of all deaths.[3]

This disease is poorly managed around the world, particularly in low-income and middle-income countries.[4]

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Blood pressure control is possible and can lead to a significant reduction in the costs related to advanced medical care.[5]

The failure to prevent and control HTN is still a medical and social problem in most countries.[6] In Iran, 23% of those aged 30 to 55 years and 50% of those over 55 years of age have HTN.[7] In addition, according to some studies, suitable HTN control is missing in this area, and only about 16% of the cases have their blood pressure under control.[8]

Self-care is an essential step in the management of chronic illnesses such as HTN and is performed in both healthy and ill states. The results of clinical trials suggest that self-care is crucial to the management of blood pressure.[9]

Self-care is defined as "the ability of individuals, families and communities to promote health, prevent diseases and maintain health for fighting disease and disability with or without the support of a physician".[10] The theory of self-care emphasizes activities performed or initiated by each individual to sustain life, health, and well-being. Orem's self-care model is one of the most complete models of self-care; it recommends the offering of clinical guidance for planning and administrating self-care among patients.[11]

The patients' adherence to treatment is a key factor in blood pressure control; however, 50% of patients with HTN do not reach their goals for the control and management of this disease. Offering encouragement and helping patients change their lifestyle toward a healthier one can be effective in this regard.[12,13] Moreover, non-compliance with a healthy lifestyle, lack of regular consumption of the prescribed medications, and non-compliance with self-care behaviors contribute to stroke and premature death due to HTN.[11]

As the incidence of HTN, as a chronic disease, is increasing, greater emphasis is being placed on the role of self-care in its management in order to reduce the global burden of the disease. In addition, self-care may improve personal performances and promote independence and the quality of disease management.[9] Self-care reduces physician visits and emergency referrals.[14] For this reason, self-care should be adequately supported to transform the passive role of patients in their care process into a more aware and active role; therefore, it is important to plan for the active participation of patients in their process of disease control, accountability, and motivation.[15]

A number of tools are available for assessing self-care in hypertensive patients, but they do not cover all the areas of self-care, have poor reliability and validity, and have often been developed without a clear theoretical framework. Most tools used in HTN self-care research, such as the Morisky Medication Adherence Scale (MMAS) and Hill-Bone Compliance to High Blood Pressure Therapy Scale (HB-HBP), are not comprehensive, and are often related exclusively to medication adherence or have inappropriate theoretical frameworks and insufficient psychometric quality.[16] Relevant comprehensive tools are therefore necessary to assess all the aspects of self-care in these patients. Due to the above reasons and the lack of a tool to cover all the mentioned areas with valid psychometric properties to assess self-care in hypertensive patients, the present study was conducted to develop a hypertension self-care questionnaire and determine its psychometric properties.

Materials and Methods

This cross-sectional, methodological study was implemented in over 13 months from 2014 to 2015 in Isfahan, Iran, through the following steps.

1. The process of designing and developing the questionnaire and its items

First, the researcher developed 25 items on self-care with the help of experts on HTN and through the available clinical guidelines, a review of literature, the existing validated HTN self-care instruments [such as the HB-HBP, MMAS, and European Heart Failure Self-care Behavior Scale (EHFScBS)], and qualitative studies on hypertensive patients. The qualitative face validity of the tool and its quantitative validity were assessed using the content validity ratio (CVR) and content validity index (CVI).

- *Face Validity:* Specialist meetings were held with 11 experts (3 cardiologists, 1 psychiatrist, 2 nutritionists with a master's degree, 2 nurses with a master's degree, and 3 statisticians with a master's degree and PhD). Their views on the compatibility between the content of the questionnaire and the research objectives were used in order to determine whether the content of the questionnaire was fit for measuring the research objectives and whether the tool could measure the properties that it was initially designed to examine, and to evaluate the tool's validity.

During these sessions, the questionnaire was presented to the experts and they were asked to give their suggestions for enhancing the face validity of the items, which resulted in simpler, and more comprehensible and relevant items. In addition, items with duplicate or common concepts were

discarded or merged (3 items). The final version of the questionnaire consisted of 22 items. The dimensions of this questionnaire included nutrition and weight control (3 items), physical activity, sleep, and rest (3 items), lack of smoking and alcohol consumption (1 item), stress (3 items), medication therapy (2 items), improved knowledge (2 items), use of sources of support (2 items), seeking care and follow-up (4 items), and blood pressure measurement and satisfaction with blood pressure control (2 items). The questionnaire was ultimately approved by all the experts.

- *Content validity ratio:* The CVR of the tool was calculated to determine its ability to measure all the aspects of self-care. For this purpose, 25 experts and specialists gave their opinions and were asked to comment on each item based on a 3-point scale of 'essential', 'important but not essential', and 'not essential'. Given that the panel consisted of 25 members, the content validity of each item was confirmed if the calculated CVR exceeded 0.44.[17]

- *Content validity index:* To calculate the CVI, the self-care questionnaire was given to 17 specialists and experts (4 cardiologists, 4 general practitioners, 6 nursing PhDs, 2 nurses with master's degree, and 1 nurse with bachelor's degree), and they were asked to rate the relevance, simplicity, and clarity of the questionnaire items with a score of 1 to 4. The number of people who gave an item a score of 3 or 4 was divided by the total number of people, and the mean of all the items was defined as the CVI of the tool. Cohen's Kappa coefficient has been recommended as a measure of content validity. Cohen's Kappa is a consensus index of inter-rater agreement that adjusts for chance agreement. A Kappa value of over 0.74, 0.60-0.74, and 0.40-0.59 is considered as "excellent", "good", and "fair", respectively.[18,19] The present study used Kappa values of above 0.71. Any item with an item-level content validity index (I-CVI) of greater than 0.78 is considered as "excellent", and items with an I-CVI between 0.69 and 0.77 are candidates for revision. Those with very low I-CVI values are candidates for elimination.[18]

2. The initial reliability of the questionnaire

- *Internal reliability:* To evaluate the internal reliability of the questionnaire, it was distributed among 20 patients with HTN (who were part of the statistical population) to complete with responses based on a 5-point Likert scale (from 'strongly agree' to 'strongly disagree'). A Cronbach's alpha of > 0.9, > 0.8, > 0.7, > 0.6, > 0.5, and < 0.5 was considered as excellent, good, acceptable, questionable, poor, and unacceptable.[20]

- *External reliability:* To evaluate the external reliability of the questionnaire, it was distributed among the same people after 14 days for a re-test and the intraclass correlation coefficient (ICC) of the tool was calculated. An ICC ≥ 0.75, $0.4 \leq$ ICC < 0.75, and ICC < 0.4 was taken to indicate excellent reliability, fair to good reliability, and poor reliability, respectively.[21] One-way random effect model and average measurement were used to determine ICC and its significance for determining absolute agreement.

- *The pre-final version of the questionnaire:* After performing these steps, 9 items were excluded from the initial questionnaire and 16 items remained for the next steps (final validity and reliability assessment).

3. Validity assessment

A cross-sectional study was designed and implemented to assess the validity of the questionnaire. Studies have revealed that adequate sampling is partly determined by the nature of the data. A larger sample can help determine whether the factor structure and individual items are valid or not.[22] To evaluate the construct validity, exploratory factor analysis was conducted to extract the possible dimensions of the developed instrument. In this regard, 203 patients with HTN were recruited based on the following criteria. The inclusion criteria consisted of age of over 18 years, residing in urban areas of Isfahan, and history of HTN for at least 1 year based on the patient's self-report. The exclusion criterion was unwillingness to complete the questionnaire. Ethical considerations were observed by obtaining consent from subjects for participation in the study and assuring them of the confidentiality of their data and their anonymity (i.e., no names and addresses were requested).

The orthogonal equamax rotation was used to facilitate the interpretability of the factors and the Kaiser-Meyer-Olkin (KMO) test was used to evaluate the sample adequacy. A KMO value of greater than 0.5 was considered as illustrative of an adequate sample size. Bartlett's test of sphericity was used to ensure that the correlation between the questionnaire items was not 0, and its significant value was a confirmation for feasibility of factor analysis.[23] The amount of variance of each dimension and the cumulative variance of the dimensions was also determined.

4. The reliability of the final questionnaire

The Cronbach's alpha coefficient was calculated for each dimension and for the entire 16-item questionnaire in order to assess the final reliability

of the questionnaire. The corrected item-total correlation (CITC) was also measured for each item, and CITC values larger than 0.3 were considered as acceptable.[24] Items with a CITC of higher than 0.4, between 0.21 and 0.4, and less than 0.2 were considered as highly discriminative, somewhat discriminative, and poorly discriminative, respectively.[25] Data were analyzed in SPSS software (version 19, SPSS Inc., Chicago, IL, USA).

Results

The questionnaire was evaluated by 25 experts and specialists [7 cardiologists (28%), 8 nurses with a PhD (32%), 3 general practitioners (12%), 2 nutritionists with a master's degree (8%), 2 statisticians with a master's degree (8%), 1 statistician with a PhD (4%), 1 pharmacist with a PhD (4%), and 1 MBA-holder (4%)].

According to Lawshe's table and the study done by Ayre and Scally,[17] items with a CVR ≥ 0.5 were selected and a total of 3 items were eliminated from the questionnaire. In calculating the CVI based on the Cohen's Kappa coefficient, questionnaire items with a K ≥ 0.71 and an I-CVI ≥ 0.69 were selected and only 1 item was removed from the questionnaire. Table 1 presents the CVR and I-CVI of the items. Minor revisions were made to the items as per the CVI results at the researchers' discretion.

Table 1. Assessing the content validity of the self-care questionnaire using the content validity ratio and content validity index

Number of Items	N	CVR	Lawshe's Result	Colin Ayre Result	I-CVI	Kappa	Modified Kappa	I-CVI Main Group
1	22	0.76	1	1	0.88	0.88	Excellent; very relevant	appropriate
2	20	0.60	1	1	0.76	0.76	Excellent; very relevant	needs some revision
3	19	0.52	1	1	0.69	0.71	Good; relevant, but needs minor revision	needs some revision
4	20	0.60	1	1	0.82	0.82	Excellent; very relevant	appropriate
5	23	0.84	1	1	1.00	1.00	Excellent; very relevant	appropriate
6	19	0.52	1	1	0.69	0.71	Good; relevant, but needs minor revision	needs some revision
7	18	0.50	1	1	0.69	0.71	Good; relevant, but needs minor revision	needs some revision
8	21	0.68	1	1	0.88	0.88	Excellent; very relevant	appropriate
9	20	0.60	1	1	0.82	0.82	Excellent; very relevant	appropriate
10	21	0.68	1	1	0.69	0.71	Good; relevant, but needs minor revision	needs some revision
11	19	0.52	1	1	0.69	0.71	Good; relevant, but need minor revision	needs some revision
12	21	0.75	1	1	0.82	0.82	Excellent; very relevant	appropriate
13	21	0.68	1	1	0.82	0.82	Excellent; very relevant	appropriate
14	23	0.84	1	1	1.00	1.00	Excellent; very relevant	appropriate
15	19	0.52	1	1	0.74	0.75	Excellent; very relevant	needs some revision
16	21	0.68	1	1	0.88	0.88	Excellent; very relevant	appropriate

CVR: content validity ratio; I-CVI: Item-level content validity index

In calculating the internal reliability of the questionnaire with Cronbach's alpha using the SPSS software (version 18, SPSS Inc., Chicago, IL, USA), 2 items were removed from the questionnaire. The Cronbach's alpha coefficient of the initial self-care questionnaire was calculated as 0.703. The ICC of the questionnaire was 0.952 (range: 0.880-0.981).

After assessing the face validity, content validity, and internal and external reliability of the questionnaire, this 16-item tool was presented for a construct validity assessment using exploratory factor analysis.

In the cross-sectional study implemented for the exploratory factor analysis, 203 patients with HTN completed the questionnaire of whom 101 (49.8%) were women with a mean age of 62.72 ± 10.48 years and 102 were men with a mean age of 64 ± 8.98 years. The patients had a minimum age of 37 years and a maximum of 82 years. The KMO value of 0.829 and Bartlett's test of sphericity value ($P < 0.001$) for the questionnaire showed that factor analysis could be used for the data. The results of the factor analysis of the 16-item self-care questionnaire using orthogonal equamax rotation[25] revealed 5 dimensions for the questionnaire, which included follow-up (3 items), healthy lifestyle (5 items), promoting qualifications (4 items), medication therapy (2 items), and following recommendations (2 items).

The factor loadings of the items ranged from 0.577 to 0.869 and all of them were statistically significant.

Table 2. Dimensions, factor loadings, Cronbach's alpha, and variance and cumulative variance of the self-care questionnaire

Dimension	Item	Factor Loading	Cronbach's Alpha	Variance (%)	Cumulative variance (%)
Follow-up	I visit the physician and medical team on time to continue the treatment.	0. 869	0.737	8.704	62.686
	I visit the physician or the medical team every one to two months to have my blood pressure measured.	0.868			
	I take the necessary blood pressure tests on time as per the medical team's recommendations.	0.619			
Healthy lifestyle	I follow a low-salt diet.	0.846	0.703	32.492	
	I follow the medical team's recommendations for a healthy diet.	0.812			
	I have reached my optimal weight as per the medical team's recommendations.	0.712			
	I avoid stress and psychological tension.	0.804			
	I follow the medical team's recommendations for keeping active and performing physical exercise.	0.709			
Promoting qualifications	I have enough knowledge on hypertension and its treatment, and have sought to promote it further.	0.691	0.594	6.439	
	I rely on the support from my family and the medical team and I benefit from them.	0.669			
	I am familiar with referral and support centers for hypertensive patients in the city.	0.610			
	I ask my questions from the health personnel (physicians, nurses, etc.) to better understand the disease and the medical recommendations.	0.791			
Medication therapy	I follow the physician's and medical team's recommendations about the time, dose, and appropriate storage of my prescribed medications.	0.699	0.717	8.912	
	I buy my medicines on time.	0.740			
Following recommendations	I follow the medical team's recommendations about quitting/not smoking and drinking and avoiding second-hand smoke.	0.744	0.701	6.139	
	I actively try to maintain my blood pressure below 140/90 (as recommended by the physician).	0.577			

Table 3. The Corrected Item–Total Correlations for the items of the self-care questionnaire

Number	Item	CITC
1	I follow the physician's and medical team's recommendations about the time, dose, and appropriate storage of my prescribed medications.	0.528
2	I buy my medicines on time.	0.371
3	I have enough information about hypertension and its treatment and have sought to promote it.	0.419
4	I visit the physician and medical team on time to continue the treatment.	0.661
5	I take the necessary blood pressure tests on time as per the medical team's recommendations.	0.557
6	I visit the physician or the medical team every one to two months to have my blood pressure measured.	0.439
7	I rely on the support from my family and the medical team, and I benefit from them.	0.431
8	I follow a low-salt diet.	0.608
9	I follow the medical team's recommendations for a healthy diet.	0.666
10	I actively try to maintain my blood pressure below 140/90 (as recommended by the physician).	0.593
11	I am familiar with referral and support centers for hypertensive patients in the city.	0.433
12	I have reached my optimal weight as per the medical team's recommendations.	0.384
13	I follow the medical team's recommendations about quitting/not smoking and drinking, and avoiding second-hand smoke.	0.125
14	I ask my questions from the health personnel (physicians, nurses, etc.) to better understand the disease and the medical recommendations.	0.365
15	I avoid stress and psychological tension.	0.383
16	I follow the medical team's recommendations for keeping active and performing physical exercise.	0.452

CITC: Corrected item-total correlation

The 5 dimensions of the questionnaire explained 62.686% of the total variance. The Cronbach's alpha coefficient of the final version of the questionnaire was 0.833. The dimensions, factor loadings of each item, Cronbach's alpha of each dimension, variance of each dimension, and cumulative variance of the dimensions are presented in table 2. The CITC of each item ranged from 0.365 to 0.666, except for 1 item that had a CITC of 0.125. Table 3 presents the CITC of the items of the self-care questionnaire.

Confirmatory factor analysis: In order to assess the factor structure and determine the construct validity of the questionnaire using confirmatory factor analysis, 400 patients with HTN were randomly selected to complete the questionnaire. Chi-square ratio of was lower than 3 (2.85) which shows suitable structure. The normed fit index (NFI), incremental fit index (IFI), comparative fit index (CFI), tucker-lewis index (TLI), and root mean square error of approximation (RMSE) were, respectively, 0.85, 0.89, 0.89, 0.86, and 0.068, and thus, confirmed the model (Figure 1).

Discussion

Self-care is a set of voluntary and acquired health behaviors and the selection of a suitable lifestyle that prevents disease, or in the case of a disease, helps the individual seek effective treatment with knowledge and awareness.

In the present study, a valid and reliable questionnaire was developed for examining self-care in patients with HTN. The Cronbach's alpha of this questionnaire exceeded 0.8, which shows the high reliability of the tool. The self-care questionnaire developed by Han et al. with an alpha of 0.7 was also acceptable.[16] The ICC of the self-care questionnaire developed in the present study was 0.952, suggesting the excellent reliability of the tool.

The CITC of each item in this self-care questionnaire ranged from 0.365 to 0.666, except for 1 item. In the HTN self-care questionnaire developed by Han et al., the CITC of each item ranged from 0.2 to 0.63 .[16] In the self-care assessment tool developed by Sidani and Doran, a CITC exceeding 0.3 was deemed acceptable for all the items.[24] In another study examining an acceptance of HTN questionnaire, the CITC of all the items ranged from 0.32 to 0.67.[25] In a study by Erkoc et al., the CITC of the questionnaire items ranged from 0.27 to 0.5.[26]

Factor analysis showed that the 16-item self-care questionnaire developed in this study has 5 dimensions.

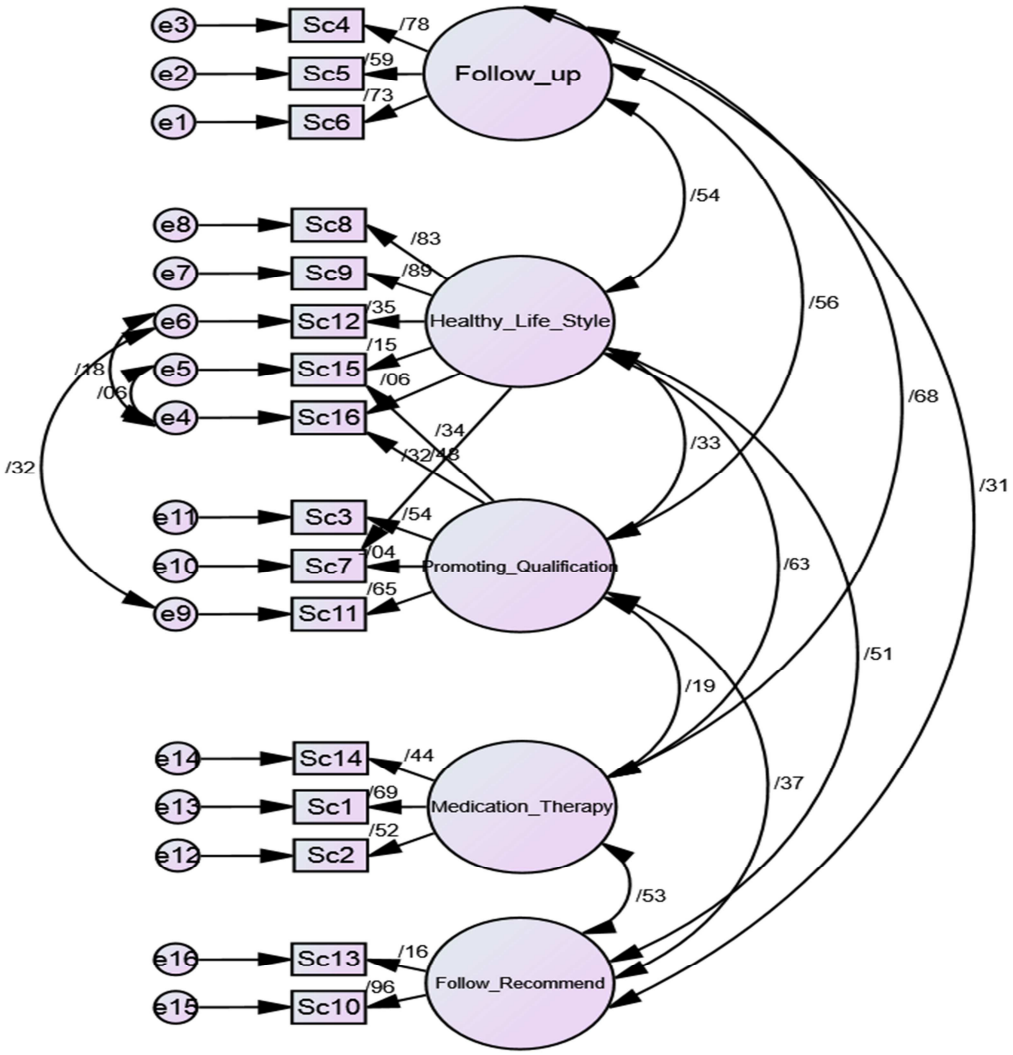

Figure 1. Standardized coefficients for the five-factor model for self-care based on confirmatory factor analysis with AMOS 21.0. (NFI = 0.85, CFI = 0.90, RMSEA = 0.068)
AMOS: Analysis of moment structures; NFI: Normed fit index; CFI: Comparative fit index; RMSEA: Root mean square error of approximation

The dimension of follow-up consisted of regular visits to the physician, undergoing the recommended tests, and having one's blood pressure regularly measured. The dimension of healthy lifestyle consisted of following a healthy low-salt diet, weight control, physical exercise, and avoiding stress. The dimension of promoting qualifications consisted of improving one's knowledge about HTN and its treatment, asking questions to better understand the disease and the medical recommendations, benefiting from the support of the family and the medical team, and familiarity with referral and support centers for hypertensive patients. The dimension of medication therapy consisted of the timely procurement of one's medicines, and adherence to the recommendations of the physician and medical team about the time, dose, and appropriate storage of the medications. The last dimension consisted of following the medical team's recommendations regarding quitting/not smoking and drinking, avoiding second-hand smoke, and maintaining one's blood pressure below 140/90 as recommended by the physician.

This questionnaire can thus be said to cover the most important areas of self-care, including medication administration and adherence, blood pressure self-monitoring, regular physician visits, stress reduction, adaptation to a new lifestyle of weight management, low-sodium and low-fat diet, physical activity, non-smoking, and moderation in alcohol consumption. Moreover, the subscales of

the Hypertension Self-Care Activity Level Effects (H-SCALE) questionnaire include medication, weight management, physical activity, tobacco exposure, alcohol intake, and healthy diet.[27] In their development and validation of the Hypertension Self-Care Profile with 20 items, Han et al.[16] examined HTN medication therapy (2 items), lifestyle factors such as physical exercise and a low-salt and low-fat diet (10 items), weight control, reduction of alcohol consumption, avoiding/quitting smoking, blood-pressure self-measurement, regular visits to the physician (1 item for each), and stress reduction (2 items).

The strength of this study is that several steps were taken for the development and psychometric assessment of the self-care questionnaire and that all the dimensions of self-care were taken into account in its design.

One limitation of this study is that the study subjects examined for the development and validation of the tool all resided in cities; however, it is necessary to examine patients with HTN living in rural areas. Due to the high prevalence of HTN in the community and the importance of self-care, it is recommended that future studies investigate the validity and reliability of this tool in larger samples, in urban and rural areas, and in hypertensive patients with different age ranges, genders, and cultural and ethnic backgrounds so as to achieve a valid and simple HTN self-care assessment tool for patients.

Additional studies for the comparison of this scale with other validated self-care questionnaires is necessary.

Conclusion

The developed questionnaire proved to have suitable psychometric properties for measuring self-care in patients with HTN. The administration of this questionnaire to patients with HTN by researchers and clinical staff can provide a more accurate assessment of their self-care and additional insight into the patients' self-care. The patients' adherence to treatment, which is a key factor in the management of blood pressure, can thus be improved and a reduction in physician visits and emergency referrals may be accomplished.

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Conflict of Interests

Authors have no conflict of interests.

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A rare case of patent ductus arteriosus diagnosed during coronary artery bypass grafting operation in a 73-year-old man

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Case Report

Abstract

BACKGROUND: Although patent ductus arteriosus (PDA) is more prevalent among infants and children, it might be seen among adults as well. It is not usually seen among adults, since it is often diagnosed and treated in childhood.

CASE REPORT: In the present case, a 73-year-old man referred to the hospital with symptoms including dyspnea, cold sweating, and chest pain with a burning nature which was lasting for 30 minutes. Angiography revealed coronary artery obstruction, so he became a coronary artery bypass grafting (CABG) candidate. Except for dilatation of the left atrium, no specific findings were reported in the patient's echocardiography report. When the pump was turned off by the surgeon, the patient's heart filled up and he was not able to get off the pump. Simultaneously, the patient started to have bloody respiratory secretions. With all that in mind, the surgeon suspected that he might suffer from a PDA, then he found an 8-mm PDA and closed it. Then, the patient was taken off the cardiorespiratory pump.

CONCLUSION: Although PDA is more common among children and infants, it can be found among adults according to previous cases and our case as well. Since patients with PDA refer to physicians for other clinical issues, it is recommended to apply more precision in diagnostic methods such as taking a good history, echocardiography, and electrocardiogram (ECG). Moreover, it is recommended that if a patient has conditions similar to our patient, the surgeon must be sure of a possible PDA.

Keywords: Patent Ductus Arteriosus, Adult, Coronary Artery Bypass Grafting

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Introduction

Patent ductus arteriosus (PDA) is a vascular structure that connects the proximal segment of descending aorta to the roof of the pulmonary trunk near the left pulmonary artery (LPA).[1] PDA is closed spontaneously in 24-48 hours after the birth of a full-term infant.[2] The reported incidence of PDA in term neonates is only 1 in 2000 births accounting for 5%-10% of all congenital heart diseases (CHDs).[1] PDA is two times more prevalent among women than in men.[3] Although PDA is the third common congenital heart anomaly after atrial septal defect (ASD) and ventricular septal defect (VSD),[4] it is not usually seen among adults, since it is often diagnosed and treated in childhood. Nonetheless, a mortality rate of 1.8% per year is reported for untreated PDA in adults. Based on the previous studies, a 92-year-old woman and a 90-year-old man were the oldest reported cases with PDA.[5] The case in this study was a 73-year-old man presented with myocardial infarction (MI), in whom PDA was diagnosed during coronary artery bypass grafting (CABG) operation.

Case Report

The patient was an old 73-year-old man (72 kg weight and 159 cm height) with a blood pressure of 110/100 mmHg with a history of high blood pressure in the last 10 years, cerebrovascular accident (CVA) in the last 4 years, and prostate surgery 5 years ago.

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He was referred to the hospital with symptoms of dyspnea, cold sweating, and chest pain with a burning nature which was lasting for 30 minutes. The patient was clinically improved following the administration of trinitroglycerin (TNG). He was diagnosed as a candidate for angiography based on the electrocardiogram (ECG) and according to clinical signs and a troponin of more than 30 ng/l. Angiography revealed coronary artery obstruction, indicating that he was a CABG candidate. The triple-vessel disease was reported with a 80% stenosis of left anterior descending (LAD), and on the other hand, except for dilatation of the left atrium, no specific findings were reported in the patient's echocardiography report (Figure 1) and chest X-ray (Figure 2). Consequently, the patient underwent an on pump CABG. When the pump was turned off by the surgeon, the patient's heart filled up and he was not able to get off the pump. Simultaneously, the patient started to have bloody respiratory secretions. With all that in mind, the surgeon suspected that the case might suffer from a PDA; after which, an 8-mm PDA was found and closed by the surgeon. Then, the patient was taken off the cardiorespiratory pump and was sent to the cardiac intensive care unit (CICU) for further monitoring and the treatment continued with the administration of aspirin tablet 80 mg daily, pentazole 20 mg daily, Plavix 75 mg daily, atorvastatin 40 mg daily, triamterene-hydrochlorothiazide daily, and losartan 25 (half) twice a day; finally, he was discharged with good general condition after 6 days.

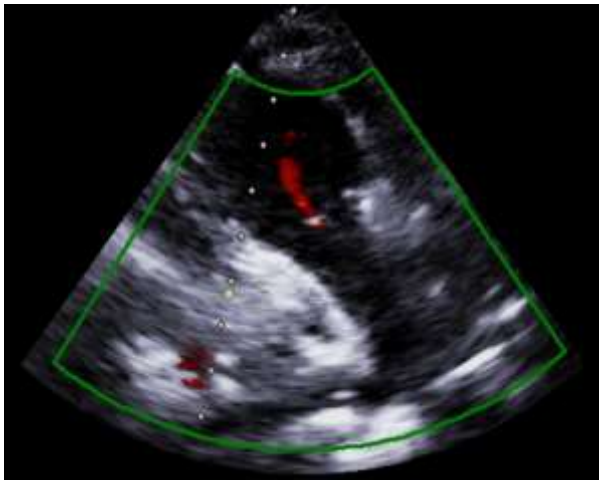

Figure 1. Echocardiography shows no patent ductus arteriosus (PDA)

Discussion

PDA prevalence in infants has increased in the two recent decades due to improved survival of preterm infants. PDA is still a rare finding in adults, since it is diagnosed and treated in childhood.[6]

Figure 2. Chest X-ray shows no cardiomegaly

Diagnosis of PDA is difficult in adults, since cardiac and pulmonary diseases are related to each other. On the other hand, PDA is commonly "quiet" with no clinical symptoms, or is asymptomatic, discovered incidentally during routine physical examinations or echocardiography for other purposes[7] or like our case during an operation. It is obvious that heart failure (HF), pulmonary hypertension (PHTN), endocarditis, and Eisenmenger's syndrome are among PDA complications. Moreover, rubella virus infection in the first trimester can lead to PDA, VSD, and pulmonary stenosis.[8] PDA has clinical manifestations, though, small PDAs may not show significant symptoms. PDA sizes vary from small (< 2 mm), moderate (2-4 mm), and large (> 4 mm);[9] hence, the PDA in this case (8 mm) belongs to the large size.

PDA mortality rate in adults is generally 1.8% (0.42% in the second decade, 1.0%-1.5% in the third decade, and 2.0%-2.5% in the fourth decade). Consequently, one-third of patients die before 40 and 60% before 60 years of age.[10] In this case, however, the patient was 73 years old. PDA is usually diagnosed using three methods of physical examination, ECG, and echocardiography.[1] In the present case, physical examination revealed dyspnea (the most common presentation of PDA in adults) and palpitation. In spite of the fact that ECG usually suggests dilatation of the left atrium in PDA cases, ECG did not show any significant change in the present case. Finally, echocardiography indicated dilatation of the light atrium.

Ejection fraction (EF), cardiomyopathy, and left

ventricular hypertrophy (LVH) should be discussed. According to Wiyono et al., EF is an independent factor that does not improve after PDA closure. It is, therefore, recommended that PDA be closed before EF reduction.[1]

PDA can be treated by surgery or subcutaneous closure using a coil, of which the latter is suggested in adults unless PDA is very prominent.[1] In this case, PDA was diagnosed during CABG; thus, it was closed by the first method.

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None.

Conflict of Interests

Authors have no conflict of interests.

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