Isfahan Cardiovascular Research Institute

ARYA Atherosclerosis

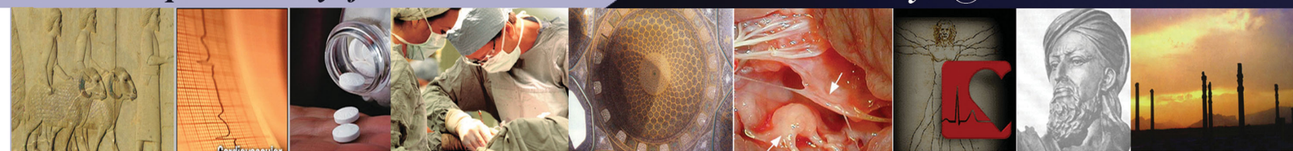
ARYA Atherosclerosis has been Licensed as a scientific & research journal by the iranian commission for medical publications, ministry of health and medical education

Indexed by:
- PubMed
- PubMed Central
- Scopus
- Islamic World Science Citation (ISC)
- WHO/EMRO/Index Medicus
- NLM Catalog
- Directory of Open Access Journals (DOAJ)
- Index Copernicus
- Academic Search Complete EBSCO Publishing databases
- Scientific Information Database
- Open J Gate
- Google Scholar
- Iranmedex
- Magiran

Serial Issue: 46 *Volume 11, Issue 2, March 2015* *Print ISSN: 1735-3955*
Online ISSN: 2251-6638

http://www.aryajournal.ir

Email: arya@crc.mui.ac.ir



ARYA Atherosclerosis

Official Journal of the Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences

Publisher: Isfahan University of Medical Sciences,
Email: publications@mui.ac.ir

Copy Edit, Layout Edit, Design and Print: Farzanegan Radandish Co.
Tel: +98-311-2241953
+98-311-2241876
Email: f.radandish@gmail.com

Circulation: 500
Distribution: International
Language: English
Interval: Bimonthly
Print ISSN: 1735-3955, **Online ISSN:** 2251-6638

Address: ARYA Journal Office, Isfahan Cardiovascular Research Institute, Seddigheh Tahereh Research Complex, Khorram Ave. Isfahan, Iran
PO. Box: 81465-1148 Tel: +98-311-3377883 Fax: +98-311-3373435
Email: arya@crc.mui.ac.ir Web: www.aryajournal.ir

Address: ARYA Journal Office, Isfahan Cardiovascular Research Institute, Seddigheh Tahereh Research Complex, Khorram Ave. Isfahan, Isfahan, Iran
PO. Box: 81465-1148 Tel: +98-311-3377883 Fax: +98-311-3373435 E-mail: arya@crc.mui.ac.ir Web: www.aryajournal.ir

ARYA Atherosclerosis

INSTRUCTIONS FOR AUTHORS

MANUSCRIPTS

Manuscripts containing original material are accepted for consideration if neither the article nor any part of its essential substance, tables, or figures has been or will be published or submitted elsewhere before appearing in the *Journal*. This restriction does not apply to abstracts or press reports published in connection with scientific meetings. Copies of any closely related manuscripts must be submitted along with the manuscript that is to be considered by the *Journal*. Authors of all types of articles should follow the general instructions given below. Please see Types of Articles for specific word counts and instructions.

SUBMISSION

- Only online submission is acceptable. Please submit online at: http://www.aryajournal.ir
- Manuscripts should be divided into the following sections: (1) Title page, (2) Abstract and Keywords, (3) Introduction, (4) Methods, (5) Results, (6) Discussion, (7) Acknowledgements, (8) Authors contribution, (9) References, (10) Figures' legend, (11), Tables and (12) Appendices. Figures should be submitted in separate files using JPEG or TIF format.
- Prepare your manuscript text using a Word processing package (save in .doc or .rtf format NOT .docx). Submissions of text in the form of PDF files are not permitted.

COVER LETTER

A covering letter signed by corresponding author should provide full contact details (include the address, telephone number, fax number, and Email address). Please make clear that the final manuscript has been seen and approved by all authors, and that the authors accept full responsibility for the design and conduct of the study, had access to the data, and controlled the decision to publish. There should also be a statement that the manuscript is not under submission elsewhere and has not been published before in any form.

AUTHORSHIP

As stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, credit for authorship requires substantial contributions to: (a) conception and design, or analysis and interpretation of data; (b) the drafting of the article or critical revision for important intellectual content and (c) final approval of the version to be published. Authors should meet conditions a, b and c. All authors must sign authorship form attesting that they fulfill the authorship criteria. Your submitted manuscript will not be processed unless this form is sent. There should be a statement in manuscript explaining contribution of each author to the work. Those contributors who did not fulfill authorship criteria should be listed in acknowledgments.

Any change in authorship after submission must be approved in writing by all authors.

ASSURANCES

In appropriate places in the manuscript please provide the following items:

- If applicable, a statement that the research protocol was approved by the relevant institutional review boards or ethics committees and that all human participants gave written informed consent
- The source of funding for the study
- The identity of those who analyzed the data
- Financial disclosure or a statement indicating "None" is necessary.

TITLE PAGE

With the manuscript, provide a page giving the title of the paper; titles should be concise and descriptive (not declarative). Title page should include an abbreviated running title of 40 characters, the names of the authors, including the complete first names and no more than two graduate degrees, the name of the department and institution in which the work was done, the institutional affiliation of each author. The name, post address, telephone number, fax number, and Email address of the corresponding author should be separately addressed. Any grant support that requires acknowledgment should be mentioned on this page. Word count of abstract and main text as well as number of tables and figures and references should be mentioned on title page. If the work was derived from a project or dissertation, its code should also be stated. For clinical trials, a registry number like Iranian Registry of Clinical Trials (IRCT) should also be provided.

Affiliation model: Academic Degree, Department, Institute, City, Country

Example: Associate Professor, Department of Cardiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

ABSTRACT

Provide on a separate page an abstract of not more than 300 words. This abstract should consist of four paragraphs, labeled **Background, Methods, Results, and Conclusion**. They should briefly describe the problem being addressed in the study, how the study was performed, the salient results, and what the authors conclude from the results, respectively. Three to 10 keywords may be included. Keywords are preferred to be in accordance with MeSH terms. Find MeSH terms: http://www.ncbi.nlm.nih.gov/mesh

CONFLICT OF INTEREST

Authors of research articles should disclose at the time of submission any financial arrangement they may have with a company whose product is pertinent to the submitted manuscript or with a company making a competing product. Such information will be held in confidence while the paper is under review and will not influence the editorial decision, but if the article is accepted for publication, a disclosure will appear with the article.

Because the essence of reviews and editorials is selection and interpretation of the literature, the *Journal* expects that authors of such articles will not have any significant financial interest in a company (or its competitor) that makes a product discussed in the article.

REVIEW AND ACTION

Submitted papers will be examined for the evidence of plagiarism using some automated plagiarism detection service. Manuscripts are examined by members of the editorial staff, and two thirds are sent to external reviewers. We encourage authors to suggest the names of possible reviewers, but we reserve the right of final selection. Communications about manuscripts will be sent after the review and editorial decision-making process is complete. After acceptance, editorial system makes a final language and scientific edition. No substantial change is permitted by authors after acceptance. It is the responsibility of corresponding author to answer probable questions and approve final version.

COPYRIGHT

JOURNAL STYLE

Use normal page margins (2.5 cm), and double-space throughout.

Tables

Double-space tables and provide a title for each.

Figures

Figures should be no larger than 125 (height) x 180 (width) mm (5 x 7 inches) and should be submitted in a separate file from that of the manuscript. The name of images or figures files should be the same as the order that was used in manuscript (fig1, fig2, etc.). Only JPEG, tif, gif and eps image formats are acceptable with CMYK model for colored image at a resolution of at least 300 dpi. Graphs must have the minimum quality: clear text, proportionate, not 3 dimensional and without disharmonic language. Electron photomicrographs should have internal scale markers.

If photographs of patients are used, either the subjects should not be identifiable or the photographs should be accompanied by written permission to use them. Permission forms are available from the Editorial Office.

Medical and scientific illustrations will be created or recreated in-house. If an outside illustrator creates the figure, the *Journal* reserves the right to modify or redraw it to meet our specifications for publication. The author must explicitly acquire all rights to the illustration from the artist in order for us to publish the illustration. Legends for figures should be an editable text as caption and should not appear on the figures.

References

The Vancouver style of referencing should be used. References must be double-spaced and numbered as superscripts consecutively as they are cited. References first cited in a table or figure legend should be numbered so that they will be in sequence with references cited in the text at the point where the table or figure is first mentioned. List all authors when there are six or fewer; when there are seven or more, list the first six, then "et al." In the following some examples are listed:

1. McLaughlin TJ, Aupont O, Bambauer KZ, Stone P, Mullan MG, Colagiovanni J, et al. Improving psychologic adjustment to chronic illness in cardiac patients. The role of depression and anxiety. J Gen Intern Med 2005; 20(12): 1084-90.
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/

Units of Measurement

Authors should express all measurements in conventional units, with Système International (SI) units given in parentheses throughout the text. Figures and tables should use conventional units, with conversion factors given in legends or footnotes. In accordance with the Uniform Requirements, however, manuscripts containing only SI units will not be returned for that reason.

Abbreviations

Except for units of measurement, abbreviations are discouraged. Consult Scientific Style and Format: The CBE Manual for Authors, Editors, and Publishers (Sixth edition. New York: Cambridge University Press, 1994) for lists of standard abbreviations. Except for units of measurement, the first time an abbreviation appears, it should be preceded by the words for which it stands.

Drug Names

Generic names should generally be used except for studies on comparative effects of different brands. When proprietary brands are used in research, include the brand name and the name of the manufacturer in parentheses in the Methods section.

For any more detail about the writing style for your manuscripts refer to:

http://www.icmje.org

Try to prepare your manuscript in accord with the scientific writing checklists available in EQUATOR Network:

http://www.equator-network.org

AFTER YOUR SUBMISSION

When a manuscript arrives to ARYA office, a staff member checks it to make sure that all materials required for submission are included. If everything is present, the article is registered in office and referred to the managing editor.

The first step the manuscript makes on its editorial journey is on the desk of the editor-in-chief, who reviews each submission (in his absence this is done by the managing editor) and decides on the basis of its general content whether it is appropriate even for consideration for publication. Each of the remaining scientific manuscripts is assigned to an associate editor with expertise in the subject area covered by the study, who makes an independent assessment of the value and validity of the paper. If the associate editor believes that even with favorable reviews the paper would not be published because it lacks novelty or importance, or if he/she spots a major flaw in experimental design, performance or statistical analysis the manuscript is returned to the authors.

If, on the other hand, the associate editor believes that the paper may merit publication, it is sent to two of our outside **reviewers**. They are asked to provide a frank evaluation of the *scientific validity of the manuscript, insight into its freshness, clinical impact, and timeliness, and an overall opinion* of its worthiness for publication. This is the key step in manuscript evaluation. As editors, we are grateful to all our reviewers for their continued contribution to the rating process. We are careful not to refer to them as "referees," which would suggest that the decision to publish a paper rests entirely with them. It does not. The reviewers provide critiques and advice that the editorial staff uses in making decisions. But we, **ARYA editorial board**, make the decisions.

When both outside reviews are returned, the associate editor then assesses the manuscript again, along with the comments of the reviewers. She may seek additional opinions from other reviewers, or may discuss the manuscript at a meeting of the entire editorial staff. At this meeting a decision is made either to reject the paper or to proceed further editorial consideration, including, if appropriate, a formal review of the statistical or experimental methods. In some cases, the editorial staff may recommend additional review by outside reviewers. On completion of this process, the manuscript is usually returned to its authors along with a letter inviting them to revise it and to respond to certain questions. When all the requested information has been received, the manuscript is reconsidered by an associate editor, and it may be discussed again with other members of the editorial staff. We then make our final decision to *accept* or *reject* the paper.

We recognize that the peer-review process is not perfect, but we earnestly believe that it is the best way to select and publish the most important medical research. Peer review is labor-intensive and sometimes *time-consuming*, but without it physicians themselves would have to assess the validity of new medical research and decide when to introduce new treatments into practice.

We do all our efforts to finalize this process in a *3 to 4 months* period for each manuscript.

We understand the importance of a submitted manuscript to its authors. **We invite you to submit your best research to us; we will treat it with respect, and you can follow it on its journey**.

Type of Articles Considered to be Published in *ARYA Atherosclerosis Journal*

ARYA Atherosclerosis is a quarterly peer-reviewed scientific Journal providing academically sound, clinically practical information for physicians, medical scientists and health care providers. ARYA Atherosclerosis is published by Isfahan Cardiovascular Research Institute. Journal editors review articles in fields of atherosclerosis, its risk factors and related diseases.

ORIGINAL RESEARCH

- **Original Articles** are scientific reports of the results of original clinical research. The text is limited to 3000 words (excluding abstracts and references), with a structured abstract, a maximum of 5 tables and figures (total), and up to 40 references.
- **Special Articles** include data and generally focus on areas such as economic policy, ethics, law, or health care delivery. The text is limited to 3000 words, with an abstract, a maximum of 5 tables and figures (total), and up to 40 references.
- **Short communication articles** are short scientific entities often dealing with methodological problems or with byproducts of larger research projects and are suitable for the presentation of research that extends previously published research. A short communication is for a concise, but independent report representing a significant contribution to cardiology. Short communication is not intended to publish preliminary results. It should be no more than 1500 words, and could include two figures or tables. It should have at least 8 references. Short communications are also sent to peer review.

CLINICAL CASES

- **Brief Reports** usually describe one to three patients or a single family. The text is limited to 2000 words, a maximum of 3 tables and figures (total), and up to 25 references. They do not include an abstract.

- **Clinical Problem-Solving** manuscripts consider the step-by-step process of clinical decision making. Information about a patient is presented to an expert clinician or clinicians in stages (in the manuscript this is indicated in **boldface** type) to simulate the way such information emerges in clinical practice. The clinician responds (regular type) as new information is presented, sharing his or her reasoning with the reader. The text should not exceed 2500 words, and there should be no more than 20 references. The use of clinical illustrative materials, such as x-ray films, is encouraged.

REVIEW ARTICLES

All review articles undergo the same peer-review and editorial process as original research reports.

Conflicts of Interest: Because the essence of review articles is selection and interpretation of the literature, the ***ARYA Atherosclerosis Journal*** expects that the authors of such articles will not have a significant financial association with a company (or its competitor) that makes a product discussed in the article.

- **Clinical Practice** articles are evidence-based reviews of topics relevant to practicing physicians, both primary care providers and specialists. Articles in this series should include the following sections: clinical context, strategies and evidence, areas of uncertainty, guidelines from professional societies, and recommendations from the authors. The text is limited to 2500 words, and a small number of figures and tables. They do not include an abstract.
- **Current Concepts** articles focus on clinical topics, including those in specialty areas but of wide interest. The text is limited to 2400 words, with a maximum of four figures and tables (total), and up to 50 references. They do not include an abstract.
- **Drug Therapy** articles detail the pharmacology and use of specific drugs or classes of drugs, or the various drugs used to treat particular diseases. The text is limited to 4000 words, with a maximum of six figures and tables (total), and up to 120 references. They do not include an abstract.
- **Mechanisms of Disease** articles discuss the cellular and molecular mechanisms of diseases or

categories of diseases. The text is limited to 3500 words, with a maximum of six figures and tables (total), and up to 100 references. They do not include an abstract.

• **Medical Progress** articles provide comprehensive, scholarly overviews of important clinical subjects, with the principal (but not exclusive) focus on developments during the past five years. Each article details how the perception of a disease, disease category, diagnostic approach, or therapeutic intervention has evolved in recent years. The text is limited to 3500 words, with a maximum of six tables and figures (total), and up to 100 references. They do not include an abstract.

OTHER SUBMISSIONS

• **Editorials** usually provide commentary and analysis concerning an article in the issue of the *Journal* in which they appear. They may include an illustration or table. They are nearly always solicited, although occasionally, unsolicited editorials may be considered. Editorials are limited to 1200 words, with up to 15 references.

• **Perspectives** are also nearly always solicited, but we are willing to consider unsolicited proposals. Perspectives provide background and context for an article in the issue in which they appear. Perspectives are limited to 800 words and usually include an illustration. There are no reference citations.

• **Sounding Board** articles are opinion essays. They are similar to editorials but not tied to a particular article. They often present opinions on health policy issues and are normally unsolicited. The text is limited to 2000 words.

• **Clinical Implications of Basic Research** articles discuss single papers from preclinical journals. The purpose is to explain the findings and comment on their possible clinical applications in fewer than 1000 words. There may be one figure and up to four references. We do not consider unsolicited manuscripts in this category.

• **Images in Clinical Medicine** are classic images of common medical conditions. Visual images are an important part of much of what we do and learn in medicine. This feature is intended to capture the sense of visual discovery and variety that physicians experience. Images in Clinical Medicine are not intended as a vehicle for case reports.

• **Special Reports** are miscellaneous articles of special interest to the medical community. They are limited to 2700 words.

• **Legal Issues in Medicine** are nearly always solicited, but *Journal* is willing to consider unsolicited manuscripts or proposals for manuscripts.

• **Health Policy Reports** are nearly always solicited, but *Journal* is willing to consider unsolicited manuscripts or proposals for manuscripts.

• **Occasional Notes** are accounts of personal experiences or descriptions of material from outside the usual areas of medical research and analysis.

• **Book Reviews** are generally solicited.

• **Letters to the Editor:** Letters to the Editor are considered for publication (subject to editing and abridgment) provided they do not contain material that has been submitted or published elsewhere. The text, not including references, must not exceed 175 words if it is in reference to a recent *Journal* article, or 400 words in all other cases. A letter must have no more than five references and one figure or table. It must not be signed by more than three authors. Letters referring to a recent *Journal* article must be received within three weeks of its publication.

Table of Contents

Randomized controlled trial on the effects of legumes on cardiovascular risk factors in women with abdominal obesity

Abdolrasoul Safaeiyan[(1)], Bahram Pourghassem-Gargari[(2)], Rasoul Zarrin[(3)], Javid Fereidooni[(4)], Mohammad Alizadeh[(3)]

Original Article

Abstract

BACKGROUND: The effect of legume-based hypocaloric diet on cardiovascular disease (CVD) risk factors in women is unclear. This study provides an opportunity to find effects of high-legume diet on CVD risk factors in women who consumed high legumes at baseline.

METHODS: This randomized controlled trial was undertaken in 34 premenopausal women with central obesity. After 2 weeks of a run-in period on an isocaloric diet, subjects were randomly assigned into two groups: (1) hypocaloric diet enriched with legumes (HDEL) (n = 17) (two servings per day) and (2) hypocaloric diet without legumes (HDWL) (n = 17) for 6 weeks. The following variables were assessed before intervention, 3, and 6 weeks after it: Waist to hip ratio (WHR), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-sensitive-C-reactive protein (hs-CRP), total antioxidant capacity (TAC), nitric oxides (NO_x), and Malondialdehyde (MDA).

RESULTS: Both hypocaloric diets reduced hs-CRP in 3 weeks and returned it to basal values after 6 weeks (P = 0.004). HDWL significantly reduced WHR [P = 0.010 (3.2%)] and increased TC [P < 0.001 (6.3%)]. Despite the significant effect of HDEL on increasing TAC in 3 weeks [P = 0.050 (4%)], the level of TAC remained the same in 6 weeks. None of the diets had any significant effects on NO_x and MDA.

CONCLUSION: The study indicated that beneficial effects of legumes on TC, LDL-C, and hs-CRP were achieved by three servings per week, and consuming more amounts of these products had no more advantages.

Keywords: Legume, Cardiovascular Disease, Caloric Restriction, Central Obesity, Premenopause

Date of submission: 8 Oct 2013, ***Date of acceptance:*** 30 Dec 2014

Introduction

Cardiovascular disease (CVD) is number one killer in the world.[1] Although many factors can increase the risk of CVDs, central obesity is usually considered underlying risk factor for CVD, which can disrupt lipid profile and endothelial function and enhance inflammatory and oxidative markers.[2] Central obesity is more prevalent among men around the globe; however, some studies shows that it is more common across women in Middle East countries.[3]

Although CVDs are one of the major causes of morbidity and mortality, some aspects of the relationship between nutrition and CVD are still unknown. Legumes are one of the main important fractions of healthy dietary patterns and they are also relatively inexpensive sources of protein, fiber, phytochemicals, vitamins and minerals.[4] That is the reason why studies related to legumes and their beneficial effects on cardiovascular risk factors is the focus of a body of recent nutrition research.[5-7] The beneficial effects of soybeans on lipids profile are well known.[8] Soy beans can protect the body from oxidative stress because it has isoflavones, saponins, and other components with anti-oxidant capacity.[8] Low amounts of soy beans are consumed in Iran,

1- Department of Vital Statistics and Epidemiology, School of Health, Tabriz University of Medical Sciences, Tabriz, Iran
2- Professor, Nutrition Research Center AND Department of Biochemistry and Dietetics, School of Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran
3- Assistant Professor, Food and Beverages Safety Research Center AND Department of Nutrition, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran
4- Assistant Professor, Department of English Language, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran
Correspondence to: Mohammad Alizadeh, Email: alizade85@yahoo.com

while non-soy legumes such as red, white and wax beans, cowpea, chickpeas, split peas, and lentils are conventional foods, and thinking to cook without non-soy legumes is a hard task. Non-soy legumes and soy beans have a similar composition. Nutritionists are increasingly concerned about the beneficial effects of non-soy legumes on CVD risks.[5,9-11] Several studies showed different aspects of the beneficial effects of legumes on CVD. Kabagambe et al. concluded the risk of myocardial infarction was reduced by 38% in the subjects who consumed one serve of beans per day in a case–control study[9] and similar results were reported in a cohort study conducted by Bazzano et al.[10] Two RCTs showed that an isocaloric diet with high legumes could reduce total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) more than an isocaloric diet containing no legumes in men. Other RCTs which prescribed hypocaloric diets with high legumes showed more reduction in weight, TC, LDL, systolic blood pressure, Malondialdehyde (MDA), CRP, complement C3 and urinary 8-Isoprostane F_{2a} in both genders compared to a legume-less hypocaloric diet.[6,11,12] Our present study takes advantages of higher consumption of legumes among subjects at baseline in comparison with other similar studies.[13-15] The baseline amount of legume consumption in participants is effective in outputs of studies prescribing legume enriched diets. In Middle East countries, the consumption of legumes is more common than western countries. The mean intake of legumes among Iranians is almost three servings per week compared to two servings per week in US and Spain.[13-15] To our knowledge, this is the first study that investigates the role of legume-based hypocaloric diet with the exclusion of soy bean on CVD risk factors among women with abdominal obesity.

Materials and Methods

The study was a voluntary based randomized control trial with an 8 weeks follow-up period. To select the participants, we published advertisements in local newspapers. A total of 257 pre-menopausal women were found eligible to enter the study.

Inclusion criteria were age (pre-menopausal women aged 20-50 years), waist circumference (WC) >88 cm, no participation in weight-reduction programs, and maintenance of a stable weight (± 2 kg) during the previous 6 months.

Exclusion criteria were: any secondary cause of hyperglycemia (as trauma) or hypertension (as renal disease); treatment with oral hypoglycemic agents or insulin, consumption of anti-lipemic drugs or anti-hypertensive drugs; consumption of vitamin or mineral supplements or antacids containing magnesium or calcium; psychiatric disorders; untreated hypothyroidism; cancer; hepatic, systemic, pulmonary, renal or CVDs; inflammatory or infectious diseases; smoking; alcoholism; and legume intolerance.

Finally, 42 pre-menopausal women were enrolled. Of these, 8 subjects did not complete the study: 4 patients in hypocaloric diet enriched with legumes (HDEL) group, and 2 patients in hypocaloric diet without legumes (HDWL) group because of poor compliance, and 2 patients in the HDWL group to homogenize the groups. Thirty-four women remained for the study analysis. Figure 1 shows the flowchart of the participants of the study.

The study was registered at www.irct.ir (irct ID: irct138712101720N1) and approved by the Ethics Committee of Tabriz University of Medical Sciences, Iran. Written informed consent was obtained from all selected subjects.

The caloric needs for each subject were determined separately using the equation from the Food and Nutrition Board of the Institute of Medicine.[16] In the run-in period, the participants consumed an isocaloric diet for 2 weeks. In the intervention period, members of first group ate HDEL (which comprised two servings or 1 cup per day of cooked non-soy legumes including red, white and wax beans; cowpea, chickpeas, split peas; and lentil instead of meat), and second group ate HDWL. The composition of each diet was 55% carbohydrate, 30% fat, and 15% protein. All participants in two groups were given a diet of 500-kcal less than their caloric needs in the intervention period. Participants were being visited every week; each session for each participant lasted 20-30 min. Behavioral counseling was instigated for all participants. The nutritionist described the advantages of diets for the participants, explaining that the central obesity could be controlled by continuing the diets. Diets were prescribed individually using a calorie count system. An "exchange list" was also given to each participant for calorie counting and exchanging food items. A nutritionist taught participants how to write "food diaries". Each participant had to write her 3 days diet and physical-activity records before the run-in period as well as before, in the middle, and at the end of the intervention. The diaries were evaluated by the investigators. A validated menu of 7 days with 42 meals and snacks at 17 calorie levels (1,200-2800) was developed for each diet. Participant compliance was evaluated by reviewing the 3 days food records and weekly visits. Each week, the number of reported food-group exchanges from 3 days food records was compared with prescribed exchanges. Participants

who completed ≥ 80% of the planned diets were encouraged to follow it diligently for the subsequent weeks. Volunteers who did not complete ≥ 80% of the prescribed diets for 2 successive weeks were excluded from the study (n = 6).

We made weekly contacts with the subjects during the 8 weeks period of the study. The true isocaloric needs of some of the subjects were different from the amount determined in the equation from the Food and Nutrition Board at the Institute of Medicine. In such cases, an isocaloric diet would cause the reduction or gain of weight rather than weight maintenance. Such individuals could cause biases in the study. Hence, among individuals eligible to enter the study, only those who maintained their weight at the end of the run-in period using an isocaloric diet calculated according to the equation were selected (n = 42). Moreover, the dietary pattern of each participant was different and could affect the results of interventions. Therefore, a run-in period was planned to standardize macronutrient consumption and to get detailed information about the study population. After 2 weeks of the run-in period on an isocaloric diet, subjects were randomly assigned into two groups: (1) HDEL and (2) HDWL for 6 weeks. To get randomized and matched groups, all participants were divided into four groups using factor analysis method. Participants in each group were similar in general characteristics and CVD risk factors. Participants in each group were then randomly allocated to two study groups. We repeated random allocation several times and selected the most homogenous groups. For the allocation of the participants, a computer-generated list of random numbers was used.

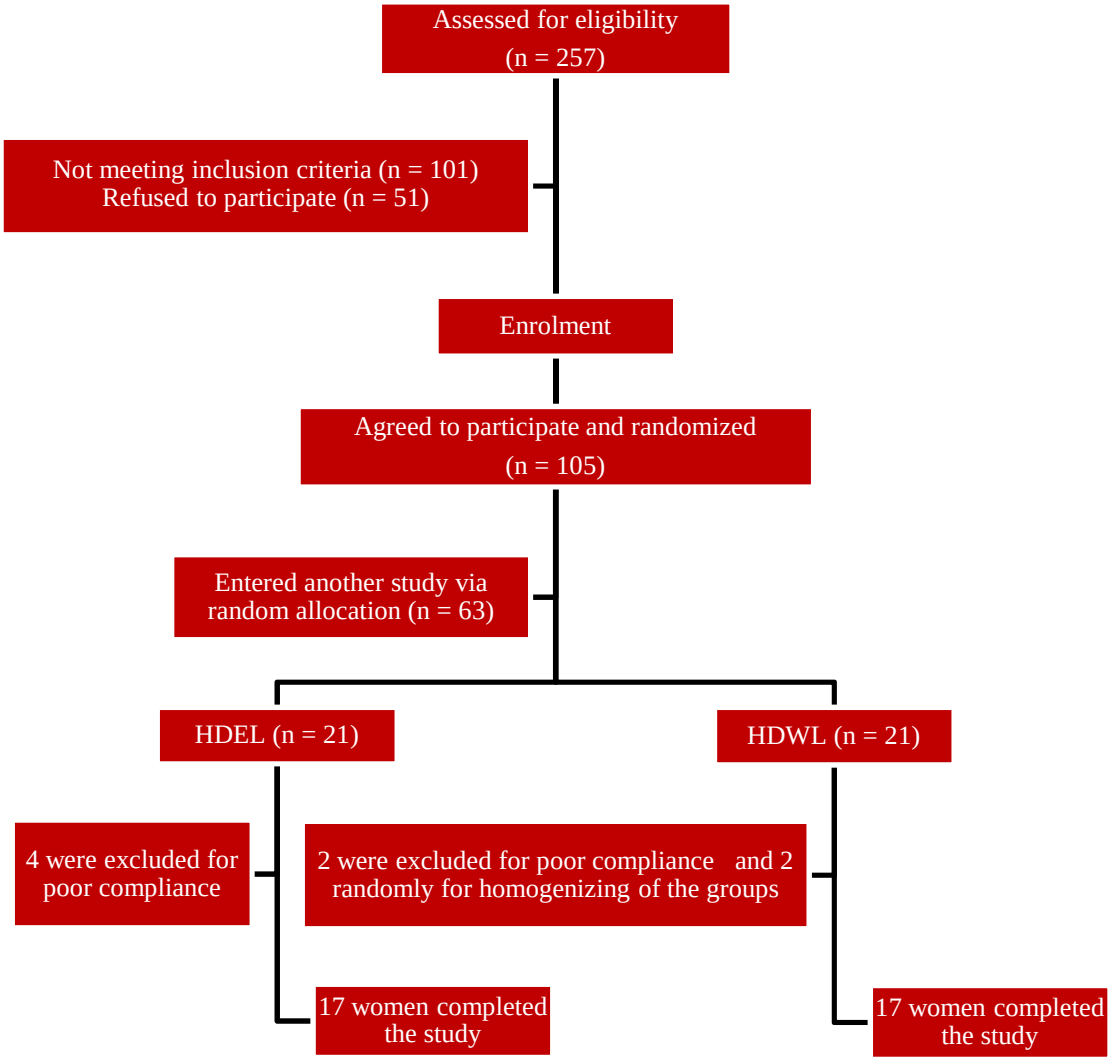


Figure 1. Flowchart for enrolment of participants
HDEL: Hypocaloric diet enriched in legumes; HDWL: Hypocaloric diet without legumes

The measurements were obtained before, in the middle, and at the end of the intervention. Participants were told not to vary their usual physical activity during the study.

All measurements were conducted by the same researcher using the same instrument at the baseline and follow-up assessments. Laboratory staff was blinded about grouping of the participants. WC was measured (to the nearest 0.1 cm) at the narrowest point and the hip circumference at the largest circumference without pressure to the body surface by the light clothing using a standard tape measure.

After 12 h fasting, blood samples were taken, centrifuged (500 g, 10 min, 4 °C), and serums were separated. All parameters except MDA, total antioxidant capacity (TAC) and nitric oxides (NO_x) were measured on the day of blood collection. Serums were frozen at –80 °C until they were analyzed for the assessment of other parameters.

Levels of TC were measured by enzymatic means (ParsAzmoun, Tehran, Iran). Levels of LDL-C were calculated using the Friedewald formula. Plasma concentrations of high-sensitive-C-reactive protein (hs-CRP) were measured using an immunoturbidimetric assay with an enzymatic kit (ParsAzmoun).[17]

Levels of nitrites/nitrates were measured concurrently using the Griess reaction.[18] Briefly, nitrates were reduced to nitrites by vanadium (III), and then the level of total nitrites measured. MDA was measured using a modified version of the Yagi et al. protocol based on the thiobarbituric acid reaction.[19] We used the ferric reducing ability of plasma assay for measuring TAC based on the protocol devised by Benzie and Starin.[20]

Inter- and intra-assay coefficients of variation were 1.22 and 0.61% for TC and 1.7 and 1% for hs-CRP, respectively.

Additional covariate information was obtained by the validated questionnaires. "Chronic dieters" were distributed into the groups as they were likely to lose less weight with hypocaloric diet. Subjects were stratified into three levels considering the following parameters: (a) education level (not completed high school, diploma, and university graduates); (b) subject income level (no income (housewife), < $350 (USA) per month, and > $350 (USA) per month); (c) family income level [< $350 (USA) per month, ≥ $350 (USA) < $700 (USA), ≥ $700 (USA)]; (d) overweight subjects and the metabolic syndrome in the family (any relative, first-degree relative, and second-degree relative diagnosed overweight or with metabolic syndrome). A participant was characterized as overweight if the body mass index was > 25 kg/m^2. Definition of the metabolic syndrome was based on the criteria set by the Adult Treatment Panel III.[21]

The sample size for each group was estimated based on the studies conducted on obese women.[22,23] With a 1-β = 95% and 1-α = 95%, the maximum sample size was achieved from WC indicators and were evaluated to be 16 persons. Values are means ± standard deviation at each time interval.

We used nested M-ANOVA repeated measurements of a multifactor model by a Minitab (version 13, Minitab, State College, PA, USA). to recognize the effect of interventions on variables. In this method, we also used another model for controlling the effect of the reduction in WC. Mauchly's sphericity test was used to validate repeated measure analysis. If the condition of sphericity was met, univariate model of repeated measurement was used. Multivariate test statistics (MANOVA) was used in instances that sphericity was violated. ANOVA repeated measurements with Bonferroni post hoc analysis was used for evaluating the within group effect of interventions in each group.

We used independent t test and χ^2 test to assess significant differences in baseline values among two groups. For appropriate variables, we merged subclasses of variables and then used the χ^2 test. $P < 0.050$ (two-tailed) was considered significant.

Results

The general characteristics of the subjects are shown in table 1. The mean age of obesity onset in all participants was 16.4 years. Thirty percent of participants did not complete high school, and 65% of participants were housewives. Family income per month for 50% of the participants was ≥ $350 (USA) < $700 (USA). Only 6% of the participants did not have overweight member, and 47% did not have a history of the metabolic syndrome among first- and second-degree relatives. Mean values for the number of diets completed and weight losses were 1 and 6 kg, respectively, but only 3% of participants maintained their weight loss. There were no significant differences in the general characteristics of the two groups.

Table 2 represents food intake of the groups, calorie intake, and calories expended in activities before the run-in period. The mean intake of milk and fruit in both groups was low. There were no differences before the run-in period with respect to food intake between the groups.

The effect of interventions on CVD risk factors

are outlined in table 3. No significant difference was found in basal (before intervention) measurements between two groups (not shown in table 3).

After 6 weeks HDEL and HDWL administration, the following results were obtained (Table 3): (1) Time effect: Both HDEL and HDWL significantly reduced the hs-CRP level in the first 3 weeks and returned it to basal levels in the subsequent 3 weeks (P = 0.004) but this significant effect disappeared after controlling of WC and/or weight reduction. (2) Treatment effect: No significant effect of legumes on parameters was found. (3) Interaction of time and treatment: No significant effect because of the interaction of time and treatment was found.

By within group analysis, the following results were obtained (Table 4): (1) HDWL significantly increased TC in 6 weeks as much as 6.3% (P = 0.000); (2) HDWL marginally increased LDL-C in the first 3 weeks (8.4%, P = 0.060); (3) both HDEL and HDWL significantly reduced the hs-CRP level in the first 3 weeks and HDEL returned it to basal levels in the subsequent 3 weeks; (4) and HDEL increased TAC in 3 weeks (4%, P = 0.050).

Table 1. Baseline characteristics of the groups

Baseline characteristics	Treatments		Total	P
	HDEL	HDWL		
n	17	17	34	-
Age (year) (mean ± SE)	35.5 ± 8.6	36.8 ± 7.8	36.1 ± 8.2	0.340*
Height (cm) (mean ± SE)	158.6 ± 7.0	157.0 ± 5.5	157.8 ± 6.0	0.510*
Age of obesity onset (year) (mean ± SE)	17.2 ± 8.7	15.6 ± 11.3	16.4 ± 9.8	0.330*
Education [n (%)]				
Not obtained a high-school diploma	8 (47)	2 (12)	10 (30)	0.160**
High school diploma	4 (23)	8 (47.1)	12 (35)	
University graduates	5 (29)	7 (41)	12 (35)	
Income status [n (%)]				
Without income (housewife)	12 (70)	10 (59)	22 (65)	0.250**
< $350 (USA) per month	2 (12)	1 (6)	3 (9)	
≥ $350 (USA) per month	3 (18)	6 (35)	9 (26)	
Overweight subjects in family [n (%)]				
Any relative	1 (6)	1 (6)	2 (6)	0.120**
First-degree relatives	13 (76)	15 (88)	28 (82)	
Second-degree relatives	3 (18)	1 (6)	4 (12)	
The metabolic syndrome in family [n (%)]				
Any relative	9 (53)	7 (41)	16 (47)	0.190**
First-degree relatives	7 (41)	9 (53)	16 (47)	
Second-degree relatives	1 (6)	1 (6)	2 (6)	
Family economic status [n, (%)]				
< $350 (USA) per month	4 (23)	3 (17)	7 (20)	0.150**
≥ $350 (USA)> $700 (USA) per month	7 (41)	10 (59)	17 (50)	
≥ $700 (USA) per month	6 (35)	4 (24)	10 (30)	
Dieting history [n (%)]				
Yes	9 (53)	14 (82)	23 (68)	0.270**
No	8 (47)	3 (18)	11 (32)	
Number of diets completed (n) (mean ± SE)	1.1 ± 1.6	0.9 ± 0.5	1.0 ± 1.2	0.910*
Dieting duration (day) (mean ± SE)	253.0 ± 877.0	81.0 ± 97.0	167.0 ± 620.0	0.400*
Weight loss in dieting periods (kg) (mean ± SE)	4.2 ± 8.3	7.8 ± 9.2	6.0 ± 7.8	0.180*
Time of dieting [n (%)]				
Any time	8 (46)	3 (18)	11 (32)	
6 months until 1 year ago	3 (18)	5 (29)	8 (23)	0.220**
1-5 years ago	3 (18)	7 (41)	10 (30)	
5 years ago	3 (18)	2 (12)	5 (15)	
Weight maintenance in past diets [n (%)]				
No dieting	9 (53)	3 (17)	12 (35)	
Maintenance of redaction	0 (0)	1 (6)	1 (3)	0.120**
Some maintenance	0 (0)	2 (12)	2 (6)	
No maintenance	8 (47)	11 (65)	19 (56)	

HDEL: Hypocaloric diet enriched in legumes; HDWL: Hypocaloric diet without legumes; SE: Standard error
* Independent t test was used; ** χ^2 test was used

Table 2. Intake of food, calorie intake and calories expended in activity before the run-in period

Variables	HDEL	HDWL	P
Milk (serving/day)	0.6 ± 0.6	0.6 ± 0.5	0.940
Vegetable (serving/day)	2.6 ± 0.2	2.0 ± 1.1	0.500
Fruit (serving/day)	1.6 ± 1.2	1.9 ± 1.3	0.450
Meat (serving/day)	2.9 ± 1.6	3.4 ± 1.0	0.330
Cereal (serving/day)	9.0 ± 3.8	8.5 ± 3.8	0.780
Legumes (serving/day)	0.5 ± 0.5	0.4 ± 0.3	0.620
Sugar (serving/day)	2.4 ± 1.1	2.4 ± 1.2	0.900
Fat (serving/day)	11.1 ± 7.6	12.5 ± 5.5	0.770
Activity calories (kcal/day)	324.0 ± 186.0	295.0 ± 205.0	0.120
Calories intake (kcal/day)	1883.0 ± 725.0	1929.0 ± 520.0	0.240

Values are means ± SE; HDEL: Hypocaloric diet enriched in legumes; HDWL: Hypocaloric diet without legumes; SE: Standard error

Table 3. Effect of interventions on cardiovascular risk factors by nested M-ANOVA for repeated measurements of a multi-factor model

Variables	Treatment						$P_{(hypocaloric\ diet)}$	$P_{(legumes)}$	$P_{(hypocaloric\ diet\ and\ legume)}$
	HDEL			HDWL					
	T_1 (mean ± SE)	T_2 (mean ± SE)	T_3 (mean ± SE)	T_1 (mean ± SE)	T_2 (mean ± SE)	T_3 (mean ± SE)			
WHR	0.8 ± 0.05	0.8 ± 0.05	0.8 ± 0.05	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.23	0.97	0.95
TC (mg/dl)	188.4 ± 31.5	197.9 ± 34.8	191.0 ± 42.2	188.0 ± 19.9	193.8 ± 28.3	199.6 ± 25.2	0.41	0.78	0.12
LDL-C (mg/dl)	111.6 ± 30.0	120.9 ± 32.0	117.5 ± 40.0	110.4 ± 17.8	124.1 ± 20.2	123.4 ± 15.6	0.19	0.69	0.35
hs-CRP (mg/l)	2.5 ± 1.7	1.2 ± 1.1	2.2 ± 1.6	2.4 ± 1.9	1.3 ± 1.5	1.8 ± 1.5	0.004	0.87	0.28
TAC (µmol/l)	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.1	0.8 ± 0.2	0.8 ± 0.1	0.8 ± 0.1	0.88	0.88	0.14
NO_x (µmol/l)	29.3 ± 33.9	37.2 ± 38.8	33.0 ± 30.4	29.0 ± 62.2	31.0 ± 65.9	49.8 ± 76.8	0.53	0.74	0.43
MDA (nmol/ml)	2.2 ± 0.7	2.4 ± 1.0	2.3 ± 0.9	2.2 ± 0.2	2.3 ± 1.0	2.4 ± 1.0	0.74	0.92	0.73

Values are means ± SE; HDEL: Hypocaloric diet enriched in legumes; HDWL: Hypocaloric diet without legumes; T_1: Before intervention; T_2: Three weeks after intervention; T_3: Six weeks after intervention; WHR: Waist to hip ratio; TC: Total cholesterol; LDL-C: Low-density lipoprotein-cholesterol; hs-CRP: High-sensitivity C-reactive protein; TAC: Total antioxidant capacity; NO_x: Nitrite/nitrate; MDA: Malondialdehyde; SE: Standard error

Table 4. Within group effect of interventions on risk factors for cardiovascular disease (CVD) by ANOVA repeated measurements with Bonferroni post-hoc analysis

Variables	Intervention					
	HDEL			HDWL		
	$P_{T2.T1}$ (change percent)	$P_{T3.T2}$ (change percent)	$P_{T3.T1}$ (change percent)	$P_{T2.T1}$ (change percent)	$P_{T3.T2}$ (change percent)	$P_{T3.T1}$ (change percent)
WHR			0.07↓ (2 ± 3.3)	0.09↓ (2.1 ± 3.8)	0.01↓ (1.1 ± 1.4)	0.01↓ (3.2 ± 4.2)
TC (mg/dl)						0.00↑ (6.3 ± 6.6)
LDL-C (mg/dl)				0.06↑ (8.4 ± 11.9)		
hs-CRP (mg/l)	0.04↓ (19.2 ± 73.3)	0.00↑ (59.1 ± 104.7)		0.03↓ (49.8 ± 40.7)		
TAC (µmol/l)	0.05↑ (4 ± 5.8)					

Values are means ± SE; HDEL: Hypocaloric diet enriched in legumes; HDWL: Hypocaloric diet without legumes; T_1: Before intervention; T_2: Three weeks after intervention; T_3: Six weeks after intervention; WHR: Waist to hip ratio; TC: Total cholesterol; LDL-C: Low density lipoprotein-cholesterol; hs-CRP: High sensitivity C-reactive protein; TAC: Total antioxidant capacity; SE: Standard error

Discussion

This clinical trial explored the effects of high-legume hypocaloric diet on cardiovascular risk factors among women with central obesity. We observed that HDEL did not affect fasting concentrations of TC, while HDWL increased it. In the previous studies both high-legume hypocaloric diets and high-legume isocaloric diets led to greater declines in both TC and LDL-C compared to diets without legumes.[5,12] In this study, the mean legume intake at baseline diet was 2.94 servings per week (increased to 2 servings per day in intervention period) compared to 1serving per week in Hermsdorff et al. study (increased to 4 servings per week in intervention period),[6] and 1.3 servings per week in Zhang et al.[5] and Hartman et al.[7] study (increased to 3 servings per day in isocaloric diet and 3.8 servings per day in hypocaloric diet in intervention period). In fact, the baseline legume intake in our study was almost 3 times more than baseline legume intake in previous RCTs. The inconsistency of the results of the current study can be attributed to the participants' higher legumes intake at baseline in comparison to other studies. In the two recent RCTs, the intake of legumes even after intervention reached to the baseline level of the our study.[6,12] In HDWL group which participants consumed legume-less diet in intervention period, fasting concentration of TC increased because of replacing legumes with animal foods. In HDWL group adverse effects of legumes-less diet on TC were not compensated by beneficial effects of low-calorie diet.

We observed that both hypocaloric diets (HDEL and HDWL) reduced hs-CRP in 3 weeks and returned it to basal values after 6 weeks. In previous isocaloric and hypocaloric diets legumes favorably improved CRP concentrations compared with legume-less diets after 4 and 8 weeks.[6,7] If the fasting concentration of hs-CRP was being measured after 3 and 6 weeks in previous studies, probably we would not be observing any contradiction among studies. In general, our study did not show any advantage to legumes in reducing hs-CRP. With precise scrutiny of previous studies we can see that there was a direct correlation between hs-CRP and TC.[6] We did not observe any reduction in TC in HDEL group because of high consumption of legumes at baseline, therefore, any expectation for reduction of hs-CRP would not be reasonable. On the other hand, it seems that lowering the calorie intake and weight is more effective in reducing hs-CRP than diet composition.[24] Since the results showed the significant effect of both diets on hs-CRP was disappeared after adjustment for WC and/or weight. Consistent with this study, Belza et al. did not find any reduction in hs-CRP after 8 weeks via weight reducing hypocaloric diet and only hs-CRP reduction was observed after 16 weeks.[25] In our study, it seems that in the first half of the study hypocaloric diets did not increase plasma levels of free fatty acids but in the second half of the study enhanced it. High plasma levels of free fatty acids in the second half of the study probably produced acute-phase reactants and cytokines in the liver and masked the beneficial effects of the weight reducing hypocaloric diets on hs-CRP.

It seems that there is no linear correlation between higher intake of legumes and low fasting concentration of TC, LDL-C and hs-CRP meaning that its beneficial effects reaches to a plateau. This conclusion has been confirmed by Kabagambe et al. study in which the consumption of 1/3 cup (86 gr) cooked beans decreased myocardial infarction risk by 38% and more amounts showed no beneficial effects.[9] The baseline level of legume intake in the our study is almost equal to what Kabagambe et al. defined as beneficial level. Although no positive effect was found by increasing legume intake, omitting usual consumption of legumes raised TC.[9]

Two meta-analyses have confirmed the beneficial effects of legumes on TC and LDL-C. Based on these studies, the beneficial effects of legumes can be mediated via soluble fiber, plant protein, oligosaccharides, isoflavones, phospholipids, fatty acids, phytosterols, saponins and other components. They also concluded that legumes can probably decrease the risk of CVD.[26,27]

In this study, none of the two interventions had any effect on NO_x and MDA however HDEL increased TAC only in the first-half of the study. In Crujeiras et al. study, high-legume hypocaloric diet reduced MDA compared to basal values and had no effect on MDA and TAC compared to legume-less hypocaloric diet.[12] Inconsistent results of the two studies can be related to high basal consumption of legumes in our study and/or MDA measurement methods. We measured MDA using a modified version of the Yagi et al.[19] protocol based on the thiobarbituric acid reaction, while Crujeiras et al. used Kits for its measurement.[12]

Consistent with many hypocaloric diets both of interventional diets reduced waist to hip ratio (WHR) and, the study showed privilege to legume less diet in reduction of WHR. Probably bloating

due to legumes caused this result.

To our knowledge, this is the first research investigated a legume based hypocaloric diet exclusively in women. The advantage of our study was the special population of the study which their mean usual intake of legumes was almost threefold of the usual intakes of the previous RCTs.[6,7] This study provides an opportunity to find the effects of legume enriched diet on CVD risk factors in participants who consumed high legumes at baseline. Our study had two limitations. First, the participants' reasons for leaving the study were not evaluated. Second, we could not provide food to the participants. Third, we did not blind participants and researchers due to the nature of the study.

Conclusion

We concluded that both hypocaloric diets reduced hs-CRP in 3 weeks and returned it to basal values after 6 weeks ($P = 0.004$). HDWL significantly reduced WHR (3.2%, $P = 0.01$) and increased TC (6.3%, $P < 0.01$). Despite the significant effect of HDEL on increasing TAC in 3 weeks (4%, $P = 0.05$), the level of TAC remained the same in 6 weeks. None of the diets have any significant effects on NO_x and MDA. It seems that there is not reverse linear correlation between intake of legumes and fasting concentration of TC, LDL-C and hs-CRP meaning that its beneficial effects reaches to a plateau. Planning long-term studies with different servings of legumes, study on diverse population with different usual intakes of legumes, and study of these aspects in high-legumes isocaloric diets are necessary for validating the results of the present study.

Acknowledgments

This work was supported by Tabriz University of Medical Sciences (Grant no. 5.4.8491), Nutrition Research Center (Grant no. 5.71.2419) and Liver and Gastrointestinal Disease Research Center (Grant no. GT-660). We thank the participants of this study for their enthusiastic support.

Conflict of Interests

Authors have no conflict of interests.

References

1. World Health Organization. Fact sheets [Online]. [cited 2012]; Available from: URL: http://www.who.int/mediacentre/factsheets/fs317/en/index.html
2. Grundy SM. Obesity, metabolic syndrome, and cardiovascular disease. J Clin Endocrinol Metab 2004; 89(6): 2595-600.
3. Azizi F, Azadbakht L, Mirmiran P. Trends in overweight, obesity and central fat accumulation among Tehranian adults between 1998-1999 and 2001-2002: Tehran lipid and glucose study. Ann Nutr Metab 2005; 49(1): 3-8.
4. Messina MJ. Legumes and soybeans: overview of their nutritional profiles and health effects. Am J Clin Nutr 1999; 70(3 Suppl): 439S-50S.
5. Zhang Z, Lanza E, Kris-Etherton PM, Colburn NH, Bagshaw D, Rovine MJ, et al. A high legume low glycemic index diet improves serum lipid profiles in men. Lipids 2010; 45(9): 765-75.
6. Hermsdorff HH, Zulet MA, Abete I, Martinez JA. A legume-based hypocaloric diet reduces proinflammatory status and improves metabolic features in overweight/obese subjects. Eur J Nutr 2011; 50(1): 61-9.
7. Hartman TJ, Albert PS, Zhang Z, Bagshaw D, Kris-Etherton PM, Ulbrecht J, et al. Consumption of a legume-enriched, low-glycemic index diet is associated with biomarkers of insulin resistance and inflammation among men at risk for colorectal cancer. J Nutr 2010; 140(1): 60-7.
8. Wiseman H, O'Reilly JD, Adlercreutz H, Mallet AI, Bowey EA, Rowland IR, et al. Isoflavone phytoestrogens consumed in soy decrease F(2)-isoprostane concentrations and increase resistance of low-density lipoprotein to oxidation in humans. Am J Clin Nutr 2000; 72(2): 395-400.
9. Kabagambe EK, Baylin A, Ruiz-Narvarez E, Siles X, Campos H. Decreased consumption of dried mature beans is positively associated with urbanization and nonfatal acute myocardial infarction. J Nutr 2005; 135(7): 1770-5.
10. Bazzano LA, He J, Ogden LG, Loria C, Vupputuri S, Myers L, et al. Legume consumption and risk of coronary heart disease in US men and women: NHANES I Epidemiologic Follow-up Study. Arch Intern Med 2001; 161(21): 2573-8.
11. Duane WC. Effects of legume consumption on serum cholesterol, biliary lipids, and sterol metabolism in humans. J Lipid Res 1997; 38(6): 1120-8.
12. Crujeiras AB, Parra D, Abete I, Martinez JA. A hypocaloric diet enriched in legumes specifically mitigates lipid peroxidation in obese subjects. Free Radic Res 2007; 41(4): 498-506.
13. Aranceta J. Spanish food patterns. Public Health Nutr 2001; 4(6A): 1399-402.
14. Ayatollahi SM. Nutritional assessment of lactating women in Shiraz in relation to recommended dietary allowances. East Mediterr Health J 2004; 10(6): 822-7.
15. McCrory MA, Hamaker BR, Lovejoy JC,

Eichelsdoerfer PE. Pulse consumption, satiety, and weight management. Adv Nutr 2010; 1(1): 17-30.
16. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients). Washington, DC: National Academies Press; 2005.
17. Harrison SP, Barlow IM. Immunoturbidimetric C-reactive protein kit adapted to the Technicon RA-1000. Clin Chem 1988; 34(1): 172.
18. Miranda KM, Espey MG, Wink DA. A rapid, simple spectrophotometric method for simultaneous detection of nitrate and nitrite. Nitric Oxide 2001; 5(1): 62-71.
19. Yagi K. A simple fluorometric assay for lipoperoxide in blood plasma. Biochem Med 1976; 15(2): 212-6.
20. Benzie IF, Strain JJ. The ferric reducing ability of plasma (FRAP) as a measure of "antioxidant power": the FRAP assay. Anal Biochem 1996; 239(1): 70-6.
21. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001; 285(19): 2486-97.
22. Panagiotakos DB, Pitsavos C, Yannakoulia M, Chrysohoou C, Stefanadis C. The implication of obesity and central fat on markers of chronic inflammation: The ATTICA study. Atherosclerosis 2005; 183(2): 308-15.
23. Esmaillzadeh A, Kimiagar M, Mehrabi Y, Azadbakht L, Hu FB, Willett WC. Dietary patterns and markers of systemic inflammation among Iranian women. J Nutr 2007; 137(4): 992-8.
24. Clifton PM. Diet and C-reactive protein. Curr Atheroscler Rep 2003; 5(6): 431-6.
25. Belza A, Toubro S, Stender S, Astrup A. Effect of diet-induced energy deficit and body fat reduction on high-sensitive CRP and other inflammatory markers in obese subjects. Int J Obes (Lond) 2009; 33(4): 456-64.
26. Anderson JW, Major AW. Pulses and lipaemia, short- and long-term effect: potential in the prevention of cardiovascular disease. Br J Nutr 2002; 88(Suppl 3): S263-S271.
27. Bazzano LA, Thompson AM, Tees MT, Nguyen CH, Winham DM. Non-soy legume consumption lowers cholesterol levels: a meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis 2011; 21(2): 94-103.

How to cite this article: Safaeiyan A, Pourghassem-Gargari B, Zarrin R, Fereidooni J, Alizadeh M. **Randomized controlled trial on the effects of legumes on cardiovascular risk factors in women with abdominal obesity.** ARYA Atheroscler 2015; 11(2): 117-25.

Comparing the effect of whole body massage by a specialist nurse and patients' relatives on blood cortisol level in coronary patients

Mohsen Adib-Hajbaghery[1], Rahman Rajabi-Beheshtabad[2], Abolfazl Ardjmand [3]

Original Article

Abstract

BACKGROUND: Cardiovascular diseases such as acute coronary syndrome and myocardial infarction are often accompanied by severe anxiety over the likelihood of death. Cortisol has been known as a stress hormone. However, there are controversies about the effect of massage therapy on blood cortisol level. Furthermore, no study is available on the difference between massage applied by a nurse specialist or by patients' relatives on blood cortisol level. This study was aimed to compare the effect of massage applied by a nurse specialist and patients' relatives on blood cortisol level among the patients admitted in coronary care unit (CCU).

METHODS: In a randomized controlled trial, ninety patients hospitalized at CCU were randomly placed in three groups: massage by a nurse; massage by patients' relatives and control group. The two massage groups received a session of whole body massage. The control group received the routine care. Data were analyzed using analysis of variance, chi-square and Fischer exact tests, Kruskal–Wallis and Wilcoxon Signed Ranks tests.

RESULTS: The mean age of participants was 58.43 ± 14.23 years. None of the participants had the history of massage therapy. In the group massaged by a nurse, the median blood cortisol level was 281.90 nanomoles, which were decreased to 197.00 after the intervention ($P < 0.007$). The median blood cortisol level in the group massaged by the patients' relatives and the control group did not affect significantly.

CONCLUSION: Massage therapy decreased the blood cortisol level in the group that received massage by a specialist nurse. It can be recommended that massage therapy be used in patients admitted in CCU.

Keywords: Massage Therapy, Nurses, Relatives, Acute Coronary Syndrome, Myocardial Infarction, Cortisol

Date of submission: 8 Nov 2013, ***Date of acceptance:*** 30 Dec 2014

Introduction

Acute coronary syndrome (ACS) and myocardial infarction (MI) are major reasons for admission in coronary care units (CCU).[1] Studies showed that 50-90 % of patients with ACS or MI experience great anxiety over the likelihood of death.[2-7] This anxiety increases the myocardial oxygen demand and also the risk of cardiac dysfunction, dysrhythmia, ischemia, and the likelihood of death.[8]

Given the negative impacts of anxiety on the body, anxiety reduction methods should be used for the relaxation of cardiac patients. Among these methods, medicinal treatments are yet the main method for lowering anxiety in patients admitted in CCU.[9] However, considering the side-effects of drugs, alternative methods such as massage therapy may be used to decrease anxiety.[10-13]

Some studies have shown that massage therapy could decrease anxiety and consequently reduce the blood cortisol level.[14-17] However,, there are contradicting studies in this regard.[18,19] It is believed that circulating levels of stress hormones such as cortisol, before and after exposure to various situations may be reflective of the stressful situation.[20] However, Nijm et al. have reported that normal cortisol pattern is markedly attenuated after coronary artery diseases.[21]

Given the existing controversies about the effect of massage therapy on blood cortisol and also the fact that no study is available about the difference

1- Professor, Trauma Nursing Research Center, Kashan University of Medical Sciences, Kashan, Iran
2- Department of Nursing, Dehdash Imam Khomeini Hospital, Yasouj University of Medical Sciences, Yasouj, Iran
3- Assistant Professor, Physiology Research Center, Kashan University of Medical Sciences, Kashan, Iran
Correspondence to: Mohsen Adib-Hajbaghery, Email: adib1344@yahoo.com

of massage therapy applied by nurses or by patients' relatives, the present study was conducted to compare the effect of massage therapy applied by nurse and patients' relatives on blood cortisol level among the patients admitted in CCUs.

Materials and Methods

This randomized controlled trial study was conducted on 90 patients hospitalized at a CCU in the Kashan University of Medical Sciences, Iran.

The sample size was calculated based on a pilot study on seven subjects in which the mean blood cortisol of 333.89 nanomoles was decreased to 278.77 nanomoles after massage therapy. The difference in the response was 55.12 ± 93.25 nanomoles. Then with a power of 0.80 and the type 1 error of 0.05, a number of 24 patients were estimated to be required in each group. However, a number of 30 patients were selected in each of the three groups.

Sampling was carried out through convenience method and the patients were randomly assigned into the three groups including control group and two intervention groups (i.e. the group received massage by a nurse and the group received massage by patients' relatives) till the sample size were completed in three groups.

For this purpose, the numbers 1-90 were entered in the SPSS for Windows (version 11.5, SPSS Inc., Chicago, IL, USA). Then, using "Random sample of cases," in the "Data menu" and "Select Cases," the numbers were randomly assigned to three groups of 30 random cases (i.e., the control group, group of massage by a nurse and the group of massage by relatives.

The eligibility criteria were: being male, literate, and hospitalized in CCU, having an established diagnosis of ACS or acute MI, willing to take part in the study. Moreover, the absence of following qualifications were also considered as additional inclusion criteria: a history of cardiac arrest during the recent 72 h, being on Warfarin, having a coagulating disorder, a known psychological disorder, a cardiac pacemaker, an established hepatitis, jaundice, adrenal gland disorder, skin problem, fever, limb amputation, bone fracture in recent 2 months, deep vein thrombosis, a dialysis fistula in limbs, and a history of - massage therapy.

Exclusion criteria were: a reduction in the level of consciousness, hemodynamic instability, decreased heart rate below 60 beats/min, severe dyspnea, and inability to complete the massage therapy session.

The eligible patients were identified through referring to the two CCUs of Shahid Beheshti Hospital, Kashan, Iran, and on reviewing their hospitalization records and consultation with the physician on a daily basis and invited to the study while being briefed about the research objectives. Overall, from 178 patients, which were assessed, 88 ones were excluded due to not meeting the eligibility criteria (22 ones), declining to participate (39 ones) and other reasons (27 ones). Finally, 90 patients were participated in this study. Figure 1 shows the flow diagram of the trial.

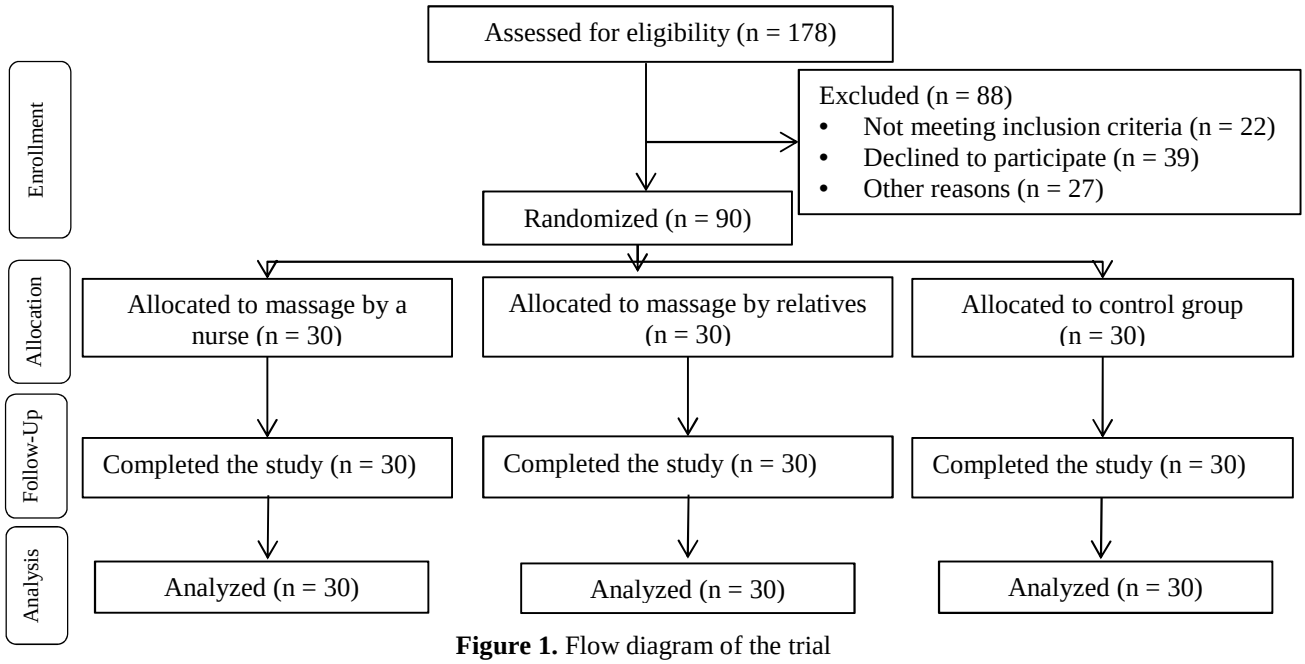


Figure 1. Flow diagram of the trial

The data collection instrument was consisted of seven questions on demographic characteristics (age, marital status, occupation, education level of patient and his selected relatives) and a table for recording the blood cortisol level both before and after receiving the massage. The medical diagnosis and the history of hospitalization of the participants were extracted from the patients' files.

In the intervention groups, massage therapy was performed in a private room or after providing a private situation for the patient in the third day of hospitalization (after passing the acute phase of disease) and issuing the permission by the concerned doctor and obtaining the patient's informed consent. Following the selection of patients and filling in the demographic questionnaire, the blood samples were obtained of each patient for measuring the blood cortisol level.

For each individual in the group received massage by a nurse specialist, a session of whole body massage was performed in about 60 min. The process of massage therapy is shown in table 1. The techniques used in massage therapy were consisted of static massage, superficial stretching technique, stretching massage, lymph vacuuming technique, latitudinal rubbing technique and myofascial releasing technique,[22] which were accompanied with effleurage of almond oil.[23]

Thirty minutes before and 15 min after the termination of massage therapy (while patient was relax at least for 15 min), the blood sample was obtained for measuring the cortisol level. For this purpose, 4 mm of blood were taken from the patient's arm in a test tube, which was then immediately kept in an ice box and transferred to the lab. All patients were massaged in the evening work shift. The blood cortisol level was determined by Immunotech Kits (Beckman Coulter Co. Czech) and following the instructions given by the manufacturing company and using the Gama Counter (Genesys Gamma-1TM, LTI Co. (Laboratory Technologies INE, USA). All patients were monitored during the massage therapy session.

In the second group (received massage by a relative), a male relative of each patient was selected through consulting with the patient, which then was trained on massage technique performed it to his patient according to the explained guidelines. All stages for data collection in this group were also the same as the first group. Training each of the relatives was carried out in an individual 2 h session in a private room on a human mannequin by the nurse specialist in massage therapy.

No intervention was done for the control group and the patients in this group received the routine care of the CCU. Blood samples were taken in this group at intervals similar to intervention groups and following completion of the informed consent. All the demographic and clinical data of this group was also obtained as for the intervention groups.

This study was approved by the Institutional Review Board and the Research Ethics Committee of the Kashan University of Medical Sciences. All the participants signed a written informed consent and were assured of the confidentiality of their individual information and of the voluntary nature of participating in the study. Data collection was conducted after coordination with the head nurses and the treating doctor. The research objective was explained to all participants.

Data analysis was performed using SPSS. Shapiro–Wilk test was used to determine if the data (i.e., age and cortisol) are normally distributed. The age of participants was normally distributed but this was not the case for cortisol. Then, analysis of variance was employed to compare the mean age in the three groups. Kruskal–Wallis test was used to compare the cortisol levels of the three groups. Wilcoxon Signed Ranks test was used for comparing the pre- and post-intervention cortisol levels. Chi-square and Fischer's exact tests were used to analyze the nominal and categorized data. In all tests, the level of significance was considered to be < 0.05.

Results

The mean age in the group that received massage by the nurse was 57.5 ± 11.1 years, whereas it was 61.1 ± 13.6 and 56.6 ± 17.3 in the group that received massage by relatives and the control group, respectively ($P = 0.533$). Moreover, 93% in the group that received massage by the nurse and 96% and 86.7% of the group that received massage by relatives and the control group were married ($P = 0.163$). Overall, 76.7% of the selected relatives were the patients' sons and the others were their brothers or friends. Also, no significant differences were observed between the three groups in terms of demographic variables ($P > 0.050$) (Table 2).

The median blood cortisol level before the intervention in the group that received massage by the nurse was 281.90 nanomoles, which it was decreased to 197.00 after the intervention ($P < 0.007$). However, the median blood cortisol level did not change significantly either in the control group or in the group that received massage

by the patients' relatives. The Kruskal–Wallis test did not reveal a significant difference between the cortisol level in the three groups either before or after the intervention (Table 3).

Table 1. The massage protocol

Preparations
All patients were massaged in the evening shift (between the 16-19 pm., while the patient was lying in prone and then supine position
Each part of the body was effleuraged with almond oil before the massage
A standardized massage protocol was used for all patients
The pressure applied for a massage was based on the patient's request
A few strokes (with palm or the outer margin of the hand) were applied on each part after the massage
Each part was wrapped in/covered with a towel after the massage.
The patients were recommended to have a shower after three hours or after the night sleep
Back massage (including scapular and auxiliary region)
Symmetrically pressing the patient's back in several points with palm of hands (both sides of the vertebral column, from iliac crest up to shoulders and back to the iliac crest (3 times)
Symmetric, triple, branched and back and forth thumb massages across the back muscles
Triple, branched thumb massage in the posterior side of auxila
The peri-scapular muscles are massaged with branched thumb movements (with the opposite hand)
Symmetric, triple, branched thumb massages of peri-scapular muscles with both of hands
Hand massage
Stretching thumb massage from the wrist up to shoulder and back to the wrist (3 times)
Triple, branched and back and forth, thumb massage from the wrist up to shoulder and then from to shoulder to wrist
Paw the palm (7 times). Then, branched thumb massage from the wrist down (7 times)
Triple stretching massages of each finger from the first phalange to the tip of the finger
Triple back and forth and 'M' shape massage on the dorsal side of the hand
Triple 'O' movement on each phalange
Pressure on the co4 point for 5 s
Leg massage (the posterior side, in prone position)
Pressing the posterior side of thigh and leg with palm of hand. Start from the ankle up to hip and back to the ankle (3 times)
Stretching thumb massage on the posterior side of thigh and leg. Starting from the ankle up to hip and back to the ankle (3 times)
Massaging the posterior side of thigh and leg muscles with triple, branched, and back and forth thumb movements
Massaging the plantar surface of the foot with wolf paw and 'C' shape movements of thumb (each for 7 times) and stretching thumb massage from ankle to the fingers and back to the ankle (3 times). Apply triple thumb pressures to all pressure points on the plantar surface of the foot (each for 5 s)
Leg massage (the front side)
Pressing the anterior side of thigh with palm of hand. Starting from knee up to hip and back to the knee (3 times)
Stretching thumb massage of anterior side of thigh and leg. Starting from the ankle up the inguinal region and back to the ankle (3 times)
Massaging the anterior side of thigh and leg with triple, branched, and back and forth thumb movements
Massaging the plantar surface of the foot with wolf paw and 'C' shape movements of thumb (each for 7 times) and stretching thumb massage from fingers to ankle and back to the gingers (3 times). Then massaging the tips of fingers with 'O' shape movements of thumb and again apply triple thumb pressures to all pressure points on the plantar surface of the foot (each for 3 s)
Triple semi-circular movements around the malleolar areas with the thumb (6 times)
Massaging the posterior side of foot with branched, oblique and 'M' shape movements of the thumb (each for 3 times)
Pressing all the pressure points in the outer margin of the foot (each for 5 s)
Smooth downward massage from knee to the fingers tip with palm of hands (7-10 times)
Massage of abdomen and axila
Smooth pressing on the suprapubic region with palm of hand. Keep for ten seconds
Stretching thumb massage across the rectus abdominal muscle from the rib cage down to the pubis and then back toward the rib cage (3 times)
Circular abdominal massage with both palms of the hands (10 times)
Massaging the lateral side of the chest with branched movements of thumb. Start from the last rib up to the arm pit and back to the last rib (3 times)
Neck and shoulder massage
Smooth front to back massage on the neck and shoulder (10 times)
Stretch the neck muscles from the mastoid down to the shoulder (7 times)
Triple pressures on all the pressure points with thumb. Start from the shoulder joint to the occiput and back to the shoulder joint

Table 2. Comparison of the participants' characteristics between intervention and control group

Variables	Group			P
	Massage by nurse	Massage by relatives	Control	
	n (%)	n (%)	n (%)	
Medical diagnosis				
Acute coronary syndrome	28 (93.3)	19 (63.3)	25 (83.3)	0.342
Myocardial infarction	2 (6.6)	11 (36.6)	5 (16.6)	
Patients' level of education				
Elementary	20 (66.7)	21 (70.0)	21 (70.0)	0.533
High school or higher level	10 (33.3)	9 (30.0)	9 (30.0)	
History of hospitalization				
Yes	25 (83.3)	18 (60.0)	19 (63.3)	0.501
No	5 (16.7)	12 (40.0)	11 (36.7)	
Companions' level of education				
Elementary	-	4 (13.3)	-	-
High school	-	26 (86.6)	-	
Satisfaction of massage				
Very much	24 (80.0)	15 (50.0)	-	0.073
Highly	4 (13.3)	14 (46.7)	-	
Moderately	2 (6.7)	1 (3.3)	-	
Age (year) (mean ± SD)	57.5 ± 11.1	61.1 ± 13.6	56.6 ± 17.3	0.432

SD: Standard division

Table 3. The median and interquartile range of the blood cortisol level in the three groups before and after the intervention*

Time	Group			P**
	Massage by nurse	Massage by relatives	Control	
Before, median (Q3-Q1)	281.90 (530.32-171.05)	303.90 (465.07-182.72)	265.40 (434.60-124.00)	0.677
After, median (Q3-Q1)	197.00 (383.77-142.32)	211.55 (383.07-165.97)	296.70 (441.42-137.87)	0.502
Test results***	P = 0.007 Z = -2.70	P = 0.102 Z = -1.55	P = 0.848 Z = -0.19	

* Nanomoles; ** Kruskal–Wallis test; ***Wilcoxon Signed Ranks test

Discussion

This study was aimed to compare the effect of massage applied by a nurse specialist and the patients' relatives on blood cortisol level among the patients admitted in CCU. Findings of the present study show that whole body massage given either by the nurse or patient's companion decrease the blood cortisol level. However, no statistically significant difference was found among the three groups after the intervention. This finding was congruent with Billhult et al. who reported no significant difference between the salivary cortisol level in the control and intervention groups.[18] In addition, by examining the effect of massage therapy on blood cortisol, Moyer et al. reported that massage therapy had only little effect on blood cortisol level.[14] The decrease in blood cortisol level seen in the intervention groups of the current study suggests that the method applied has been clinically effective; however, the sample size may seem too small to reveal a significant difference among the three groups. Moreover, other variables might have been involved, which were out of the researcher's control and were effective on the level of cortisol.

The present study indicates that blood cortisol level was significantly decreased after the massage therapy in the group, which received massage by a nurse. This finding was in line with Field et al. who indicated that massage leads to a decrease in blood cortisol level.[16] Besides, Lindgren et al. examined the physiological responses to massage among the healthy individuals and reported that salivary cortisol was significantly decreased after massage compared to the pre- and 1 h post-massage.[15]

Although changes in blood cortisol level did not find to be statistically significant in the group, which received massage by patient companion, the cortisol level was decreased compared to the pre-intervention time. The difference seen in this case might be relevant to the difference in massage givers' skill.

In general, the findings indicate that massage as an external stimulant may decrease the cortisol level as a stress hormone. Then, it could be expected that this modality may be effective for decreasing patients' anxiety. In the agreement with our study, previous studies have also reported that hypothalamus-hypophysis-adrenal axis is activated

during the anxiety related to internal and external stimulants.[24] Thus, it could be supposed that massaging may alleviate anxiety, which then leads to a decrease in the blood cortisol level.[14]

Limitations and recommendations for further studies

While the person who performed massage was the same for the group that received massage by a nurse, the other intervention group was massaged by their relatives and these relatives may have different characters, which may biased the results in this group. Moreover, we measured the blood cortisol level 15 min after the application of massage, but as the changes in blood cortisol level may be seen in different time point after the application of massage, it is recommended that another study be conducted for examining the blood cortisol level several times after massaging. Doing in this way, the durability of blood cortisol reduction is pinpointed. In this study, firstly the participants were selected through convenience sampling and then they were randomly assigned into the three groups. Hence, a study with randomized block sampling is recommended.

Conclusion

This study indicated that after massage therapy, the cortisol level decreased significantly in the group that received massage by a nurse. Regarding the effects of the massage therapy on lowering anxiety and cortisol levels and also its relaxing effect, it could be recommended that massage therapy, as a non-pharmacological method be used in patients admitted in CCU. Moreover, as an educational suggestion it is recommended that this theme can be added to the nursing curriculum.

Acknowledgments

The researchers would like to express their gratitude to the directors and personnel of CCUs in Shahid Beheshti Hospital of the Kashan University of medical sciences for their kind cooperation in the study. This study was approved as a thesis in Master of Science in nursing and supported by Kashan University of Medical Sciences with grant number 9077. This study was also registered at Iranian Registry of Clinical Trials (IRCT). The registration number of the study is IRCT201112048296N1.

Conflict of Interests

Authors have no conflict of interests.

References

1. Michalopoulou A, Tsios A, Vitos M, Liapi P, Mpizas L. Admissions to the coronary care unit (ccu): comparison with international data. Hospital Chronicles 2008; 3(4): 182-6.
2. Stromberg A, Jaarsma T. Thoughts about death and perceived health status in elderly patients with heart failure. Eur J Heart Fail 2008; 10(6): 608-13.
3. Kulkarni HS, Kulkarni KR, Mallampalli A, Parkar SR, Karnad DR, Guntupalli KK. Comparison of anxiety, depression, and post-traumatic stress symptoms in relatives of ICU patients in an American and an Indian public hospital. Indian J Crit Care Med 2011; 15(3): 147-56.
4. Chulay M, Burns SM. AACN essentials of progressive care nursing. New York, NY: McGraw-Hill, Medical Pub. Division; 2007.
5. Abolhasani S. Effects of sensuous stimulation on anxiety in the patients hospitalized in coronary care unit. Sci J Kurdistan Univ Med Sci 2007; 12(2): 46-52. [In Persian].
6. Huffman JC, Smith FA, Blais MA, Januzzi JL, Fricchione GL. Anxiety, independent of depressive symptoms, is associated with in-hospital cardiac complications after acute myocardial infarction. J Psychosom Res 2008; 65(6): 557-63.
7. Beyraghi N, Tonekaboni SH, Vakili GH. Anxiety and depression in patients admitted in cardiac care unit, Taleghani Hospital, Tehran, Iran, 2003. Hormozgan Med J 2006; 9(4): 261-4. [In Persian].
8. Ulvik B, Bjelland I, Hanestad BR, Omenaas E, Wentzel-Larsen T, Nygard O. Comparison of the Short Form 36 and the Hospital Anxiety and Depression Scale measuring emotional distress in patients admitted for elective coronary angiography. Heart Lung 2008; 37(4): 286-95.
9. Rincon HG, Granados M, Unutzer J, Gomez M, Duran R, Badiel M, et al. Prevalence, detection and treatment of anxiety, depression, and delirium in the adult critical care unit. Psychosomatics 2001; 42(5): 391-6.
10. Wang AT, Sundt TM, Cutshall SM, Bauer BA. Massage therapy after cardiac surgery. Semin Thorac Cardiovasc Surg 2010; 22(3): 225-9.
11. Castro-Sanchez AM, Mataran-Penarrocha GA, Granero-Molina J, Aguilera-Manrique G, Quesada-Rubio JM, Moreno-Lorenzo C. Benefits of massage-myofascial release therapy on pain, anxiety, quality of sleep, depression, and quality of life in patients with fibromyalgia. Evid Based Complement Alternat Med 2011; 2011: 561753.
12. Frazier SK, Moser DK, Daley LK, McKinley S, Riegel B, Garvin BJ, et al. Critical care nurses' beliefs about and reported management of anxiety. Am J Crit Care 2003; 12(1): 19-27.
13. Nerbass FB, Feltrim MI, Souza SA, Ykeda DS, Lorenzi-Filho G. Effects of massage therapy on

sleep quality after coronary artery bypass graft surgery. Clinics (Sao Paulo) 2010; 65(11): 1105-10.
14. Moyer CA, Seefeldt L, Mann ES, Jackley LM. Does massage therapy reduce cortisol? A comprehensive quantitative review. J Bodyw Mov Ther 2011; 15(1): 3-14.
15. Lindgren L, Rundgren S, Winso O, Lehtipalo S, Wiklund U, Karlsson M, et al. Physiological responses to touch massage in healthy volunteers. Auton Neurosci 2010; 158(1-2): 105-10.
16. Field T, Hernandez-Reif M, Diego M, Schanberg S, Kuhn C. Cortisol decreases and serotonin and dopamine increase following massage therapy. Int J Neurosci 2005; 115(10): 1397-413.
17. Field T, Deeds O, Diego M, Hernandez-Reif M, Gauler A, Sullivan S, et al. Benefits of combining massage therapy with group interpersonal psychotherapy in prenatally depressed women. J Bodyw Mov Ther 2009; 13(4): 297-303.
18. Billhult A, Lindholm C, Gunnarsson R, Stener-Victorin E. The effect of massage on cellular immunity, endocrine and psychological factors in women with breast cancer -- a randomized controlled clinical trial. Auton Neurosci 2008; 140(1-2): 88-95.
19. McVicar AJ, Greenwood CR, Fewell F, D'Arcy V, Chandrasekharan S, Alldridge LC. Evaluation of anxiety, salivary cortisol and melatonin secretion following reflexology treatment: a pilot study in healthy individuals. Complement Ther Clin Pract 2007; 13(3): 137-45.
20. Moraska A, Pollini RA, Boulanger K, Brooks MZ, Teitlebaum L. Physiological adjustments to stress measures following massage therapy: a review of the literature. Evid Based Complement Alternat Med 2010; 7(4): 409-18.
21. Nijm J, Kristenson M, Olsson AG, Jonasson L. Impaired cortisol response to acute stressors in patients with coronary disease. Implications for inflammatory activity. J Intern Med 2007; 262(3): 375-84.
22. Shiri M. Massage therapy. Tehran: Aeeizh Publication; 2010. p. 48-62. [In Persian].
23. Young R, Gutnik B, Moran RW, Thomson RW. The effect of effleurage massage in recovery from fatigue in the adductor muscles of the thumb. J Manipulative Physiol Ther 2005; 28(9): 696-701.
24. McEwen BS. Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. Eur J Pharmacol 2008; 583(2-3): 174-85.

How to cite this article: Adib-Hajbaghery M, Rajabi-Beheshtabad R, Arjmand A. **Comparing the effect of whole body massage by a specialist nurse and patients' relatives on blood cortisol level in coronary patients.** ARYA Atheroscler 2015; 11(2): 126-32.

Inhibitory potential of pure isoflavonoids, red clover, and alfalfa extracts on hemoglobin glycosylation

Mohsen Hosseini[(1)], Sedigheh Asgary[(1)], Somayeh Najafi[(1)]

Original Article

Abstract

BACKGROUND: Non-enzymatic glycosylation of hemoglobin is complications of diabetes. Antioxidant system imbalance can result in the emergence of free radicals' destructive effects in the long-term. Red clover (Trifolium pratense L.) and alfalfa (Medicago sativa L.) contain isoflavonoids and have antioxidant activity. This experimental study evaluated the inhibitory activity of pure isoflavonoids (daidzein and genistein), red clover and alfalfa extracts on hemoglobin glycosylation.

METHODS: This study was performed in Iran. Stock solution of hydroalcoholic extracts of red clover and alfalfa in concentrations of 1 and 10 g/100 ml and stock solution of daidzein and genistein in concentrations of 250 ng, 500 ng, 25 µg and 250 µg/100 ml were prepared as case groups. Control group was without hydroalcoholic extracts of plants and pure isoflavonoids. All experiments were performed in triplicate. Hemoglobin was prepared and antioxidant activities were investigated to estimate degree of nonenzymatic hemoglobin glycosylation.

RESULTS: There was no significantly difference between used extracts (extract of red clover and alfalfa) and control of the hemoglobin glycosylation but using daidzein ($P = 0.046$, 0.029 and 0.021, respectively) and genistein ($P = 0.034$, 0.036 and 0.028) significantly inhibited ($P < 0.050$) this reaction in 25 µg/100 ml, 250 and 500 ng/100 ml concentrations when compared to control. in 25 µg/100 ml, 250 ng and 500 ng/100 ml concentrations percentage of inhibition were 32, 80 and 74.5% respectively with used of daidzein and were 21, 83 and 76% respectively with consumption of genistein.

CONCLUSION: According to decrease of glycation of hemoglobin with isoflavonoids, two used plant in this study containing isoflavonoid may be useful on diabetes.

Keywords: Glycosylation, Genistein, Medicago sativa, Trifolium

Date of submission: 21 Nov 2014, ***Date of acceptance:*** 3 Feb 2015

Introduction

The non-enzymatic glycation of hemoglobin having been established and shown to be significantly increased in diabetes.[1] Measurement of glycated hemoglobin has proven to be particularly useful in monitoring the effectiveness of therapy in diabetes.[1,2] The major factor responsible for the elevated basal glucose level in the diabetic group was a decreased efficiency in the tissue uptake of glucose.[3]

Control of plasma glucose could prevent the progression of most of the complications of diabetes and hemoglobinA1c is the most important criterion controlling these long-term complications.[4] Dramatically increase of the worldwide prevalence of type 2 diabetes is a true challenge for modern medicine. Thus, dietary supplements that can modulate glucose homeostasis would be desirable.[5] Use of medicinal plants for amelioration of various metabolic disorders is finding favor with researches owing to their lesser side-effects.[6] Despite considerable progress in the treatment of diabetes by oral hypoglycemic agents, search for newer drugs continues because the existing synthetic drugs have several limitations.[7] The herbal drugs with antidiabetic activity are yet to be commercially formulated as modern medicines, even though they have been acclaimed for their therapeutic properties in the traditional systems of medicine.[7] The plants provide a potential source of hypoglycemic drugs because many plants and plant-derived compounds have been used in the treatment of diabetes.[7] Several investigators have implicated the role of free radical mediated pathology in diabetes mellitus.[8,9]

1- Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Sedigheh Asgary, Email: sasgary@yahoo.com

Since the glycosylation of protein is an oxidative reaction[10] Therefore, antioxidants should be able to prevent this reaction. Antioxidants have attracted attention in recent years in scavenging and combating the effects of free radicals.[11,12] Recently, a great deal of interest has been directed toward the bioactivity of flavonoids as dietary sources of antioxidants.[13]

Red clover (Trifolium pratense L.) and alfalfa (Medicago sativa L.) (belongs to the leguminosae family) have been used traditionally as a medicine.[14,15] These plants contain high concentrations of isoflavonoids[16] such as genistein and daidzein.[17,18] Isoflavonoids are secondary metabolites that can be divided into isoflavones and pterocarpans.[19] Certain isoflavones found in red clover leaves include daidzein, genistein, pratensein and prunetin.[20,21] Several in vitro, animals and human studies have shown isoflavones to have antidiabetic properties.[21-24]

In the studies, effects of red clover and alfalfa were investigated on diabetes, for example, the results of Gray and Flatt[14] demonstrated the presence of anti-hyperglycemic, insulin-releasing and insulin-like activity in alfalfa.

According to the effect of isoflavonoids on diabetes treatment, this experimental study aimed to assessment the inhibitory activity of pure isoflavonoids (daidzein and genistein), red clover and alfalfa and on hemoglobin glycosylation.

Materials and Methods

This study was performed in Iran. Red Clover and alfalfa collected before sprouting from Semirum District, Isfahan, Iran. The plant specimen was authenticated and deposited at the Herbarium of the College of Sciences, Isfahan University. The aerial parts of the plants were dried in the shade, and whole parts of the plants were crushed in a miller.[25] Pure isoflavonoids (daidzein and genistein) were purchased from Sigma (Sigma Chemical Co., USA).

A total of 50 g of dried plants material was soaked in 85% aqueous-methanol (1/10, w/v) for 12 h. The extract was filtered through a Buchner funnel. The plant residue was re-extracted then with 50% methanol for additional 6 h. The resulting extracts were evaporated in vacuum to one-third of the original volume. Chlorophyll, oil and carbon were extracted using decanter and chloroform.[26]

1 ml prepared plant extract was evaporated in Benmary 40 °C[27] then was dissolved in Dimethyl sulfoxide (Sigma Chemical Co., USA) to obtain a stock solution.[28] Plants stock solution was prepared in concentrations of 1 and 10 g/100 ml.[29]

Daidzein and genistein stock solution were prepared in concentrations of 250 ng, 500 ng, 25 µg and 250 µg/100 ml in methanol and were used to investigate antioxidant effect on hemoglobin glycosylation.

These stocks were used as case group. Control group was without hydroalcoholic extracts of plants and pure isoflavonoids.

Freshly blood was taken from healthy volunteers and was separated by centrifugation at 3000 rpm for 10 min. Erythrocytes were washed with 5 vol of the phosphate buffered saline three times. The buffy coat was carefully removed with each wash. At the last washing, the cells were centrifuged at 2800 rpm for 5 min to obtain packed cells with a constant volume. The upper layers (containing hemoglobin) were taken with a dropper.[30] The hemoglobin concentrations were estimated by Drabkin and Austin[31] method.

The antioxidant activities of two hydroalcoholic extracts and pure flavonoids were investigated by estimating the degree of nonenzymatic hemoglobin glycosylation.

The assay was performed with adding 60 mg/100 ml of hemoglobin solution, and 1 ml of gentamycin (20 mg/100 ml), in 0.01 M phosphate buffer (pH 7.4) in absence and presence of 2 g/100 ml concentration of glucose for 72 h. The mixture was incubated in dark at room temperature for 72 h. Degree of glycosylation of hemoglobin was measured colorimetrically at 443 nm. Rate of absorption with control was considered as 100% glycosylation.[32,33] The experiment was performed in triplicate.[34,35]

The glycosylation of hemoglobin percentage was calculated according to the following equation:

Percentage of hemoglobin glycosylation = $(A-B)/C\times100$

Where A was the absorbance in the presence of the extracts or flavonoids without glucose, B was the absorbance of the extracts or flavonoids in the presence of the glucose and C was the absorbance of the control.[36]

Statistical evaluation was conducted with SPSS for Windows (version 14, SPSS Inc., Chicago, IL, USA) and values were expressed as mean ± standard deviation. Independent samples t test was applied to compare groups means. Difference between concentrations in the case group was carried out using the analysis of variance (one-way ANOVA) and Duncan's post-hoc. $P < 0.050$ were considered statistically significant.

Results

As shown in table 1, inhibitory activity of both hydroalcoholic extracts in 1 and 10 g/100 ml concentrations had no statistically significant difference with control group although percentage of inhibition with alfalfa extract was more than red clover extract in both of used concentrations.

Table 2 illustrates the effect of daidzein and genistein on the inhibition percent of hemoglobin glycosylation. Daidzein in 25 µg/100 ml, 250 and 500 ng/100 ml concentrations can significantly inhibit (P = 0.046, 0.029 and 0.021, respectively) glycosylation of hemoglobin in comparison with control group.

Hemoglobin glycosylation had a significant difference in 25 and 250 µg/100 ml concentrations of daidzein and genistein as compared to 250 ng and 500 ng/100 ml concentrations.

The highest inhibitory activity of hemoglobin glycosylation was 80% in 250 ng/100 ml concentration. Genistein significantly inhibited (P = 0.034, 0.036 and 0.028 respectively) hemoglobin glycosylation in 25 µg/100 ml, 250 ng and 500 ng/100 ml concentrations as compared to control group. Percentage of hemoglobin glycosylation inhibition with using of genistein in 250 ng/100 ml concentration was highest (83%).

Discussion

Despite insulin therapy, diabetic patients suffer from some chronic clinical complications due to high blood glucose which induces non-enzymatic glycosylation of natural proteins such as hemoglobin, lens proteins, biomembrane proteins, albumin, collagen and myelin.[37]

Glycated hemoglobin has attained significant prominence in the modern world of the medicinal biology due to its use as a scale in the long-term control of diabetes mellitus.[38,39] There are several herbs, roots, fruits and other plant materials that are used to treat diabetes throughout the world.[40]

Table 1. Effect of red clover and alfalfa extract on inhibition percentage of haemoglobin glycosylation

Group		Concentration (g/100 ml)	Absorption (means ± SD)	Inhibition percentage of haemoglobin glycosylation	P
Case	Red clover	1	0.319 ± 0.06	3	0.265
		10	0.309 ± 0.30	6	0.153
	Alfalfa	1	0.301 ± 0.02	8	0.092
		10	0.291 ± 0.11	11	0.075
Control		-	0.326 ± 0.07	0	

Independent samples t test were applied to compare groups means; SD: Standard deviation

Table 2. Effect of daidzein and genistein on inhibition percent of haemoglobin glycosylation

		Concentration (ng or µg/100 ml)	Means ± SD of absorption (confidence interval)	Inhibition percent of haemoglobin glycosylation	P
Daidzein	Case	250 ng	0.066 ± 0.04*	80.0	0.021
		500 ng	0.083 ± 0.20*	74.5	0.029
		25 µg	0.272 ± 0.40*,**,§	32.0	0.046
		250 µg	0.310 ± 0.02**,§	5.0	0.122
	Control	0	0.316 ± 0.10	0.0	
Genistein	Case	250 ng	0.056 ± 0.06*	83.0	0.028
		500 ng	0.078 ± 0.09*	76.0	0.036
		25 µg	0.260 ± 0.20*,**,§	21.0	0.034
		250 µg	0.322 ± 0.60**,§	2.0	0.201
	Control	0	0.316 ± 0.10	0.0	

* Significant difference between used concentration of daidzein in comparison with control; ** Each significant difference with 250 ng; § Each significant difference with 500 ng; P values are significant P < 0.050; Independent samples t-test were applied to compare groups means; Difference between concentrations in case group were applied using the analysis of variance and Duncan's post-hoc; SD: Standard deviation

According to our results, extracts of plant (red clover and alfalfa) in used concentrations can't inhibit glycosylation of hemoglobin while daidzein and genistein in 25 µg/100 ml, 250 and 500 ng/100 ml concentrations significantly reduced its. In our study, increasing of plant extract amount containing most of isoflavonoid may considerably inhibit hemoglobin glycosylation.

Alfalfa has an antihyperglycemic property and insulin-releasing action[41] that is known in both of animal and human studies.[14,42] These activates of alfalfa extracts may be useful for type 2 diabetes and especially important for patients with "pre-diabetic" state for diabetes prevention. These patients already manifest abnormalities of glucose metabolism and could benefit from a low-risk, inexpensive, food-based intervention.[5]

According to Daisy and Rajathi orally administered aqueous extracts (400 mg/kg body weight) of Clitoria ternatea leaves (leguminosae family) and flowers significantly reduced glycosylated hemoglobin in rats.[43] In the other study by Amer et al.,[44] daily intake of Trifolium alexandrinum extract (leguminosae family) in drinking water for 4 weeks immediately caused significant decreases in glycated hemoglobin levels in diabetic rats. They expressed these effects may be due to the presence of a high content of flavonoids, which acts synergistically as antioxidants.

In the study carried out by James et al.,[25] the subsequent administration of Hibiscus cannabinus methanolic leaf (containing antioxidant) extract inhibit hemoglobin glycosylation, where a concentration of 20 mg/ml of the extract gave a significant inhibition by yielding hemoglobin concentration of 1.877 ± 0.40 µg/ml. This observed effect might be attributed by the presence of bioactive compounds in the plant extract such as flavonoids, alkaloids, phenols and sterols. This needs further investigation specific bio active compound responsible for such activities.[25] The main isoflavones in red clover are biochanin A and formononetin, which are both abundantly found in leaves.[17]

Winiarska et al.[5] and Asgary et al.[45] and Asgary et al.[46] carried out different studies on the effect of antioxidants on hemoglobin glycosylation. In one of these researches,[46] they measured the inhibition percentage of haemoglobin glycosylation in the presence of three different concentrations (0.5, 5, 10 microg/ml) of several flavonoids. The results demonstrated that biochanin A (isoflavonoid) inhibited haemoglobin glycosylation 100%. They expressed antioxidants able to prevent haemoglobin glycosylation reaction. According to their studies, plants containing flavonoids can be utilized to inhibit or treat complication of diabetes.

In the study by Adisa et al.,[47] inhibitory effect of flavonoid-rich methanolic extract of cnestis ferruginea on glycosilation was investigated in concentrations of 10, 20, 30 µg/ml and hemoglobin glycosylation reduced in these concentrations.

In the animal study by Kamalakkannan and Prince,[48] flavonoids effect was investigated in diabetic rats. In their study, Rutin (a polyphenolic flavonoid) was orally administered to rats for a period of 45 days, and this flavonoid significantly decreased glycosylated hemoglobin in them.

Selvaraj et al.[49] investigated the effect of lipoic acid and taurine antioxidants on glycosylation of hemoglobin. They revealed glycated hemoglobin levels were higher in erythrocytes incubated with 50 mmol/l glucose concentrations than in erythrocytes incubated with 5 mmol/l glucose and the increase in glycated hemoglobin levels was blocked significantly when erythrocytes were pretreated with either lipoic acid or taurine (25, 50, 100, 150 µmol/l). They mentioned antioxidants can partially inhibit the formation of glycated hemoglobin by lowering the levels of lipid peroxides. Based on the favorable efficiency of these herbal medicines containing isoflavonoid on diabetes, additional studies are needed to investigate effect of the other extraction assays and the other concentrations of these plants on glycosylation of hemoglobin.

Further studies are needed to identify the effect of other concentrations of red clover and alfalfa extracts on inhibition of hemoglobin glycosylation.

Conclusion

This suggests that the isoflavonoids inhibit hemoglobin glycosylation. Isoflavonoids could be improved diabetes by inhibition this reaction. These components exert beneficial effects on glycosylation of hemoglobin through their antioxidative actions, therefore, two used plant in this study containing isoflavonoid may be useful in minimizing glycation of hemoglobin.

Acknowledgments

The authors gratefully acknowledge authorities at the Isfahan Cardiovascular Research Center for financial support of this study.

Conflict of Interests

Authors have no conflict of interests.

References

1. Gasser A, Forbes JM. Advanced glycation: implications in tissue damage and disease. Protein Pept Lett 2008; 15(4): 385-91.
2. University of Michigan Health System. Hemoglobin A1c Fact Sheet [Online]. [cited 2007]; Available from: URL: http://www.med.umich.edu/mdrtc/cores/ChemCore/hemoa1c.htm
3. Grayson BE, Seeley RJ, Sandoval DA. Wired on sugar: the role of the CNS in the regulation of glucose homeostasis. Nat Rev Neurosci 2013; 14(1): 24-37.
4. Haddadinezhad S, Ghazaleh N. Relation of fasting and postprandial and plasma glucose with hemoglobinA1c in diabetics. Int J Diabetes Dev Ctries 2010; 30(1): 8-10.
5. Winiarska H, Dworacka M, Borowska M, Iewicz-Koz³owska TB, Gorecki P, Mœcisz A. The effects of plant extracts of Medicago sativa and Trigonella foenum-graecum on postprandial glucose levels in type 2 diabetic rats. Herba polonica 2007; 53(5): 34-44.
6. Kavishankar GB, Lakshmidevi N, Mahadeva Murthy S, Prakash HS, Niranjana SR. Diabetes and medicinal plants-A review. Int J Pharm Biomed Sci 2011; 2(3): 65-80.
7. Wadkar KA, Magdum CS, Patil SS, Naikwade NS. Antidiabetic potential and Indian medicinal plants. Journal of Herbal Medicine and Toxicology 2008; 2(1): 45-50.
8. Gupta M, Chari S. Proxidant and antioxidant status in patients of type II Diabetes Mellitus with IHD. Indian J Clin Biochem 2006; 21(2): 118-22.
9. Alamdari DH, Paletas K, Pegiou T, Sarigianni M, Befani C, Koliakos G. A novel assay for the evaluation of the prooxidant-antioxidant balance, before and after antioxidant vitamin administration in type II diabetes patients. Clin Biochem 2007; 40(3-4): 248-54.
10. Tabesh M, Hariri M, Askari G, Ghiasvand R, Tabesh M, Heydari A, et al. The Relationship Between Vegetables and Fruits Intake and Glycosylated Hemoglobin Values, Lipids Profiles and Nitrogen Status in Type II Inactive Diabetic Patients. Int J Prev Med 2013; 4(Suppl 1): S63-S67.
11. Block KI. Antioxidants and cancer therapy: furthering the debate. Integr Cancer Ther 2004; 3(4): 342-8.
12. Lamson DW, Brignall MS. Antioxidants and cancer, part 3: quercetin. Altern Med Rev 2000; 5(3): 196-208.
13. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. Oxid Med Cell Longev 2009; 2(5): 270-8.
14. Gray AM, Flatt PR. Pancreatic and extra-pancreatic effects of the traditional anti-diabetic plant, Medicago sativa (lucerne). Br J Nutr 1997; 78(2): 325-34.
15. Barentsen R. Red clover isoflavones and menopausal health. J Br Menopause Soc 2004; 10 (Suppl 1): 4-7.
16. Dixon RA. Phytoestrogens. Annu Rev Plant Biol 2004; 55: 225-61.
17. Horn-Ross PL, Barnes S, Lee M, Coward L, Mandel JE, Koo J, et al. Assessing phytoestrogen exposure in epidemiologic studies: development of a database (United States). Cancer Causes Control 2000; 11(4): 289-98.
18. Tolleson WH, Doerge DR, Churchwell MI, Marques MM, Roberts DW. Metabolism of biochanin A and formononetin by human liver microsomes in vitro. J Agric Food Chem 2002; 50(17): 4783-90.
19. Saviranta NM, Anttonen NJ, von Wright A, Karjalainen RO. Red clover (Trifolium pratense L.) isoflavones: determination of concentrations by plant stage, flower colour, plant part and cultivar. Journal of the Science of Food and Agriculture 2008; 88(1): 125-32.
20. Klejdus B, Sterbova D, Stratil P, Kuban V. Identifikace a charakterizace isoflavonu v rostlinnych extraktech za pouzitýkombinace HPLCs hmotnostnim detektorem a detektorem s diodovym polem (HPLC-DAD-MS). Chemicke´ Listy 2003; 97(7): 530-9.
21. Wu Q, Wang M, Simon JE. Determination of isoflavones in red clover and related species by high-performance liquid chromatography combined with ultraviolet and mass spectrometric detection. J Chromatogr A 2003; 1016(2): 195-209.
22. Jayagopal V, Albertazzi P, Kilpatrick ES, Howarth EM, Jennings PE, Hepburn DA, et al. Beneficial effects of soy phytoestrogen intake in postmenopausal women with type 2 diabetes. Diabetes Care 2002; 25(10): 1709-14.
23. Shen P, Liu MH, Ng TY, Chan YH, Yong EL. Differential effects of isoflavones, from Astragalus membranaceus and Pueraria thomsonii, on the activation of PPARalpha, PPARgamma, and adipocyte differentiation in vitro. J Nutr 2006; 136(4): 899-905.
24. Shim JY, Kim KO, Seo BH, Lee HS. Soybean isoflavone extract improves glucose tolerance and raises the survival rate in streptozotocin-induced diabetic rats. Nutr Res Pract 2007; 1(4): 266-72.
25. James SA, Auta R, Goje D. In vitro study on inhibition of glycosylation of methanolic leaf extract of hibiscus cannabinus. Science World Journal 2011; 6(3): 7-9.
26. Houcher Z, Boudiaf K, Benboubetra M, Houcher B. Effects of methanolic extract and commercial oil of Nigella sativa L. on blood glucose and antioxidant capacity in alloxan-induced diabetic rats.

PTERIDINES 2007; 18(18): 8-18.
27. Tajabadipour A, Afshari H, Hokmabadi H. Recognition and Determination of Contaminated Pistachios to Aflatoxin in Processing Stage. International Journal of Nuts and Related Sciences 2011; 2(2): 27-30.
28. Krenn L, Unterrieder I, Ruprechter R. Quantification of isoflavones in red clover by high-performance liquid chromatography. J Chromatogr B Analyt Technol Biomed Life Sci 2002; 777(1-2): 123-8.
29. Lu T, Sheng H, Wu J, Cheng Y, Zhu J, Chen Y. Cinnamon extract improves fasting blood glucose and glycosylated hemoglobin level in Chinese patients with type 2 diabetes. Nutr Res 2012; 32(6): 408-12.
30. Koenig RJ, Blobstein SH, Cerami A. Structure of carbohydrate of hemoglobin AIc. J Biol Chem 1977; 252(9): 2992-7.
31. Drabkin DL, Austin H. Harold spectrophotometric studies: I. spectrophotometric constants for common hemoglobin derivatives in human, dog, and rabbit blood. J Biol Chem 1932; 98: 719-33.
32. John A, Steven DA. Microsomal lipid peroxidation. Methods in Enzymology 1984; 30: 302-8.
33. Benzie IF, Strain JJ. The ferric reducing ability of plasma (FRAP) as a measure of "antioxidant power": the FRAP assay. Anal Biochem 1996; 239(1): 70-6.
34. Lu X, Wang J, Al-Qadiri HM, Ross CF, Powers JR, Tang J, et al. Determination of total phenolic content and antioxidant capacity of onion (Allium cepa) and shallot (Allium oschaninii) using infrared spectroscopy. Food Chemistry 2011; 129(2): 637-44.
35. Mohammadi-Motlagh HR, Mostafaie A, Mansouri K. Anticancer and anti-inflammatory activities of shallot (Allium ascalonicum) extract. Arch Med Sci 2011; 7(1): 38-44.
36. Parker KM, England JD, Da CJ, Hess RL, Goldstein DE. Improved colorimetric assay for glycosylated hemoglobin. Clin Chem 1981; 27(5): 669-72.
37. Garber AJ. Diabetes mellitus. In: Stein JH, Eisenberg JM, Editors. Internal Medicine. Philadelphia, PA: Mosby; 1998.
38. Jeffcoate SL. Diabetes control and complications: the role of glycated haemoglobin, 25 years on. Diabet Med 2004; 21(7): 657-65.
39. Sen S, Kar M, Roy A, Chakraborti AS. Effect of nonenzymatic glycation on functional and structural properties of hemoglobin. Biophys Chem 2005; 113(3): 289-98.
40. Modak M, Dixit P, Londhe J, Ghaskadbi S, Devasagayam TP. Indian herbs and herbal drugs used for the treatment of diabetes. J Clin Biochem Nutr 2007; 40(3): 163-73.
41. Gallagher AM, Flatt PR, Duffy G, Abdel-Wahab YHA. The effects of traditional antidiabetic plants on in vitro glucose diffusion. Nutrition Research 2003; 23(3): 413-24.
42. Asgary S, Naderi GA, Shams Ardekani MR, Sahebkar A, Airin A, Aslani S, et al. Chemical analysis and biological activities of Cupressus sempervirens var. horizontalis essential oils. Pharm Biol 2013; 51(2): 137-44.
43. Daisy P, Rajathi M. Hypoglycemic Effects of Clitoria ternatea Linn. (Fabaceae) in Alloxan-induced Diabetes in Rats. Tropical Journal of Pharmaceutical Research 2009; 8(5): 393-8.
44. Amer M, El-Habibi e, El-Gendy A. Effects of Trifolium alexandrinum extracts on streptozotocin-induced diabetes in male rats. Ann Nutr Metab 2004; 48(5): 343-7.
45. Asgary S, Naderi G, Sarrafzadegan N, Ghassemi N, Boshtam M, Rafie M, et al. Anti-oxidant effect of flavonoids on hemoglobin glycosylation. Pharm Acta Helv 1999; 73(5): 223-6.
46. Asgary S, Naderi GA, Zadegan NS, Vakili R. The inhibitory effects of pure flavonoids on in vitro protein glycosylation. J Herb Pharmacother 2002; 2(2): 47-55.
47. Adisa RA, Oke J, Olomu SA, Olorunsogo O. Inhibition of human haemoglobin glycosylation by flavonoid containing leaf extracts of Cnestis ferruginea. Journal of the Cameroon Academy of Sciences 2004; 4: 351-9.
48. Kamalakkannan N, Prince PS. Antihyperglycaemic and antioxidant effect of rutin, a polyphenolic flavonoid, in streptozotocin-induced diabetic wistar rats. Basic Clin Pharmacol Toxicol 2006; 98(1): 97-103.
49. Selvaraj N, Bobby Z, Sathiyapriya V. Effect of lipid peroxides and antioxidants on glycation of hemoglobin: an in vitro study on human erythrocytes. Clin Chim Acta 2006; 366(1-2): 190-5.

How to cite this article: Hosseini M, Asgary S, Najafi S. **Inhibitory potential of pure isoflavonoids, red clover, and alfalfa extracts on hemoglobin glycosylation.** ARYA Atheroscler 2015; 11(2): 133-8.

Validation of a simplified food frequency questionnaire for the assessment of dietary habits in Iranian adults: Isfahan Healthy Heart Program, Iran

Noushin Mohammadifard[1], Firouzeh Sajjadi[2], Maryam Maghroun[3], Hassan Alikhasi[1], Farzaneh Nilforoushzadeh[1], Nizal Sarrafzadegan[1]

Original Article

Abstract

BACKGROUND: Dietary assessment is the first step of dietary modification in community-based interventional programs. This study was performed to validate a simple food frequency questionnaire (SFFQ) for assessment of selected food items in epidemiological studies with a large sample size as well as community trails.

METHODS: This validation study was carried out on 264 healthy adults aged ≥ 41 years old living in 3 district central of Iran, including Isfahan, Najafabad, and Arak. Selected food intakes were assessed using a 48-item food frequency questionnaire (FFQ). The FFQ was interviewer-administered, which was completed twice; at the beginning of the study and 2 weeks thereafter. The validity of this SFFQ was examined compared to estimated amount by single 24 h dietary recall and 2 days dietary record. Validation of the FFQ was determined using Spearman correlation coefficients between daily frequency consumption of food groups as assessed by the FFQ and the qualitative amount of daily food groups intake accessed by dietary reference method was applied to evaluate validity. Intraclass correlation coefficients (ICC) were used to determine the reproducibility.

RESULTS: Spearman correlation coefficient between the estimated amount of food groups intake by examined and reference methods ranged from 0.105 (P = 0.378) in pickles to 0.48 (P < 0.001) in plant protein. ICC for reproducibility of FFQ were between 0.47-0.69 in different food groups (P < 0.001).

CONCLUSION: The designed SFFQ has a good relative validity and reproducibility for assessment of selected food groups intake. Thus, it can serve as a valid tool in epidemiological studies and clinical trial with large participants.

Keywords: Validity, Reliability, Food Frequency Questionnaire, Dietary Intake, Food

Date of submission: 30 Aug 2014, ***Date of acceptance:*** 8 Jan 2015

Introduction

Non-communicable diseases (NCD), including cardiovascular diseases (CVD) and cancers are the principal causes of mortality in Iran along with worldwide.[1,2] Dietary behaviors have a main effect in the CVD risk, and prevention.[3] Thus, nutrition assessment is the first step of dietary modification in community-based interventional programs.[4] However, the biggest challenge in nutrition epidemiological studies is the inaccuracy of dietary information assessed by using various dietary assessment methods.[4] Some dietary assessment methods need several recalls, which are time and cost consuming, much human resources demanding and have high recall bias, which makes them inappropriate in a large population.[4] Thus, development of the alternative method to avoid subject fatigue and use feasible dietary assessment method is the essential components in population-based studies.[5]

Food frequency questionnaire (FFQ) is a simple, inexpensive, quick completion with low recall bias for applying in a large population surveys.[4] FFQs provide the information about the frequency and sometimes the portion size of a defined food items list.[6] This method measures usual intake over a middle or long-term period and monitors usual dietary behaviors.[7] In addition, the FFQ can rank persons according to their food intake, which is usually sufficient for the purposes in health survey.[8]

1- Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
2- Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
3- Hypertension Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Noushin Mohammadifard, Email: nmohammadifard@gmail.com

However, reducing the food items in FFQ makes it more practicable.[6] Therefore, using a simple FFQ (SFFQ) without specific portion is another approach to have more feasibility particularly for nutritional epidemiologic studies in a large population and community trials, which could reduce the burden on respondents.[9] Previously, SFFQ was validated to use in nutrition survey in other societies.[9] However, FFQs should be adapted for each study population according to their dietary patterns and culture.[10]

Although some studies validated different FFQs for various objectives in Iranian population, in best of our knowledge there is no validated SFFQ in Iranian population.[11,12] Therefore, we required a SFFQ to assess dietary pattern and nutrition improvement in large samples. This study was performed to validate a SFFQ for using in epidemiological studies and community trails with a large population.

Materials and Methods

Subjects were recruited from the participants of the Isfahan Cohort Study, Iran, who had been selected through cluster random sampling among adult population aged ≥ 35 years in Isfahan, Najafabad and Arak, Iran, district in 2001.[13] They were followed 2 years apart for cardiovascular events assessment by telephone interview. In addition repeated measurements including behavioral, biochemical and physical characteristics were carried out in the subject who had not any events in 2007.[14] Among them 300 healthy volunteer aged ≥ 41 years who accepted to complete second FFQ after 2 weeks included in the current validation study. They were included if they were non-diabetic and had no history of CVD, hypercholesterolemia, renal, thyroid, hematological, or mental diseases. Those on special diets and pregnant or lactating women were excluded. Excluding all the under- and over-reporting of dietary intake (daily energy intake < 800 or > 5000 Kcal), our sample size of n = 264 was selected from this subsample.

The FFQ was completed twice; at the beginning of the study and 2 weeks thereafter. The total number of samples studied was 300. The initial FFQ was accompanied by a demographic questionnaire and a 24 h diet recall, which were administered by trained dietitian. The respondents or one of their family members were also trained to complete two self-reported diet records in the same week. The study protocol was approved by the research council of the Isfahan Cardiovascular Research Center (ICRC).

Detailed home interviews were carried out by trained health professionals at study baseline to obtain required information about participants' general characteristics, including socioeconomic and demographic characteristics as well as data on dietary behaviors, smoking and physical activity status.[15,16] Physical activity was assessed by means of a validated Baeck physical activity questionnaire. A trained interviewer measured standing height without shoes and recorded to the nearest 0.5 cm at the baseline visit. Body weight was measured with the subjects wearing light clothes, without shoes and recorded to the nearest 0.5 kg. Body mass index (BMI) was calculated as body weight (kg)/height (m^2).

A 48-item FFQ was designed based on the nutrition questionnaire of Countrywide Integrated Non-communicable Disease Intervention program to assess usual food intakes contributing in prevention or occurrence of CVD and relevant risk factors. Face and content validity of the questionnaire were assessed by an expert panel, consisting of five nutritionists. The FFQ was tested in pilot for clarity and comprehensiveness among 30 adults who were not entered in the main study participants and had the same characteristics to study population.

Participants reported their frequency consumption of several food items over the last preceding year on a daily, weekly or monthly basis in an open-ended format. Subjects were also requested to choose the "never/seldom" response if they never consumed a given food item. The reported frequency of each food item was converted into a daily consumption. Seldom and never were calculated as "zero."

All participants also completed a single 24 h recall and 2 food records for 3 non-consecutive days, including 2 weeks days and 1 weekend during a week. We used two dietary assessment methods as the gold standard, because completing three 24 h dietary recalls were difficult. Hence, a single 24 h recall was completed by interviewing to train participants for self-reporting 2 dietary records.

In the case of mixed dishes, to estimate the serving size of each person, the total amount of cooked food as well as the number of persons who consumed it was collected and the amount of the food intake for each person was then calculated. The participants were asked to complete two self-reported food records. If he/she was illiterate and was not able to complete the questionnaire, a family member was requested and trained to do it. The samples were followed by phone to verify and complete self-reported food records. First trained

nutritionists rechecked and grouped the food items into the same 13 groups in both SFFQ and dietary reference method, which were presented in table 1. Then, they entered the data including the frequency (time/week) consumption of foods groups based on the SFFQ and reference method, as well as the quantitative amount of food groups, intake based on dietary reference method. To estimate quantitative amount of foods intake, gram weights of food intakes were determined based on the previously established weights of the measure.[17] Food groups extracted from reference dietary assessment method were similar to FFQ item.

The data were analyzed using SPSS for Windows (version 11.5, SPSS Inc., Chicago, IL, USA).The distributions of dietary intake values were examined for normality by the Kolmogorov–Smirnov test. All foods were non-normally distributed; therefore, non-parametric tests were performed. Validation of the FFQ was determined using Spearman correlation coefficients between daily frequency consumption of food groups, which assessed by the FFQ and the qualitative amount of daily food groups intake accessed by dietary reference method. Participants were divided into four groups based on frequency consumption of food groups assessed by the FFQs or dietary reference method. Then, the frequencies of subjects in the same, adjacent, one quartile apart and opposite quartiles of 2 dietary assessment methods were estimated. Intraclass correlation coefficients (ICC) were used to determine the reproducibility of 2 FFQs. $P < 0.05$ was considered as significant.

Results

The study sample was consisted of 264 subjects including 127 males and 137 females. Table 2 shows the baseline characteristic including mean of age, BMI and total daily physical activity as well as frequency of ever smoker, educational level and urbanization in total participants.

Table 3 shows Spearman's rank correlation coefficients between frequency of various food groups derived from SFFQ compared to the qualitative amount of those from the reference method based on genders. The significant Spearman's rank correlation coefficients ranged from 0.239 in beverages ($P = 0.046$) to 0.480 in plant protein ($P < 0.001$). The Spearman's rank correlation coefficients were no significant for pickles, sweets, grains and animal fat in the total population. There were significant Spearman's rank correlation coefficients varied from 0.253 for beverages ($P = 0.042$) to 0.473 for plant protein ($P < 0.001$) in male and 0.278 for animal protein ($P = 0.009$) to 0.491 for plant protein ($P < 0.001$) in females. The Spearman's rank correlation coefficients were no significant for pickles, sweets, grains and animal fat in male and for pickles, sweets, grains, animal fat and beverages in female (Table 3).

Table 4 illustrates that the reliability of the SFFQ was between [ICC (95% confidence interval) = 0.47 (0.25-0.70)] for grain and [ICC (95% CI) = 0.69 (0.48-0.85)] for dairy products in total population, [ICC (95% CI) = 0.47 (0.26-0.69)] for grain and [ICC (95% CI) = 0.68 (0.48-0.92)] for non-HVO in male and [ICC (95% CI) = 0.45 (0.32-0.59)] for beverages and [ICC (95% CI) = 0.69 (0.47-0.91)] for HVO in female.

The cross-classification frequency consumption of food groups between the SFFQ and the reference method revealed that from 28% (pickles) to 50% (nuts) of participants were classified in the same quartile of two methods, from 3 % (dairy products) to 13% (grain) categorized in the opposite quartile (Table 5).

Table 1. Studied food and food groups in the validation study

Hydrogenated vegetable oils	Hydrogenated vegetable oil, hard margarine
Non-hydrogenated vegetable oils	Non- hydrogenated vegetable oil, olive oil and soft margarine
Animal fats	Ghee, butter, cream, visceral fat and liver, kidney, heart and other organ meats
Fast foods	Frankfurter, sausages, hamburger , pizza and canned food
Animal proteins	Red meat, poultry, fish and egg
Plant proteins	Lentil, pea, bean, mung pea and soy protein
Fruits and vegetables	fruits, fresh fruit juices, raw, cooked and dried vegetables
Grains	Bread, rice and potato
Dairy products	Cheese, low and whole fat milk and yogurt
Sweets	Sweet, chocolate, biscuit, cake, cookie and jam
Nuts	Walnut, almond, hazelnut, pistachio and seeds
Beverages	Coke, diet coke, canned fruits and industrial fruit juices
Pickles	Sour and salty pickles

Table 2. Baseline characteristics of study population based on gender

Characteristic	Mean ± SD	n (%)
Age (year)	55.3 ± 9.6	
BMI (kg/m^2)	26.8 ± 3.7	
Daily physical activity (METs minute/day)	1133.1 ± 548.9	
Ever smoker [n (%)]		41 (15.5)
Education [n (%)]		
Illiterate		45 (17.0)
Primary school		118 (45.0)
> Primary school		101 (38.0)
Urbanization		224 (85.0)

SD: Standard division; BMI: Body mass index; MET: Metabolic equivalents

Table 3. Spearman's rank correlation coefficients between frequency of food consumption accessed by simplified food frequency questionnaire and quantitative amount of food intake assessed by mean of single 24 h recall and two food records based on gender

	Male		Female		Total	
	Spearman's correlation coefficients	P	Spearman's correlation coefficients	P	Spearman's correlation coefficients	P
HVO	0.324	< 0.001	0.346	< 0.001	0.352	< 0.001
Non-HVO	0.315	< 0.007	0.322	0.006	0.319	0.008
Animal fat	0.192	0.231	0.116	0.314	0.205	0.211
Animal protein	0.308	0.008	0.278	0.009	0.294	0.007
Dairy products	0.457	< 0.001	0.467	< 0.001	0.467	< 0.001
Plant protein	0.473	< 0.001	0.491	< 0.001	0.480	< 0.001
Grains	0.183	0.227	0.127	0.270	0.226	0.134
Nuts	0.465	< 0.001	0.479	< 0.001	0.468	< 0.001
Fruits and vegetables	0.328	0.006	0.315	0.009	0.338	< 0.001
Fast foods	0.334	0.005	0.319	0.007	0.326	0.003
Sweets	0.108	0.315	0.097	0.441	0.113	0.174
Beverages	0.253	0.042	0.108	0.416	0.239	0.046
Pickles	0.091	0.433	0.084	0.508	0.105	0.378

HVO: Hydrogenated vegetable oil

Table 4. Reproducibility of the simplified food frequency questionnaire for foods/food based on gender

Food/food groups (time/day)	ICC (95% CI)		
	Male	Female	Total
HVO	0.64 (0.42-0.85)	0.69 (0.47-0.91)	0.66 (0.44-0.89)
Non-HVO	0.68 (0.48-0.92)	0.67 (0.46-0.90)	0.67 (0.45-0.91)
Animal fat	0.53 (0.34-0.71)	0.57 (0.35-0.73)	0.59 (0.36-0.75)
Animal protein	0.61 (0.46-0.79)	0.63 (0.47-0.79)	0.67 (0.49-0.83)
Dairy products	0.65 (0.48-0.83)	0.68 (0.45-0.84)	0.69 (0.48-0.85)
Plant protein	0.56 (0.34-0.72)	0.59 (0.36-0.75)	0.61 (0.39-0.78)
Grains	0.47 (0.26-0.69)	0.46 (0.22-0.66)	0.47 (0.25-0.70)
Nuts	0.64 (0.40-0.89)	0.65 (0.39-0.92)	0.67 (0.40-0.93)
Fruits and vegetables	0.52 (0.29-0.76)	0.58 (0.31-0.79)	0.51 (0.28-0.74)
Fast foods	0.65 (0.42-0.88)	0.62 (0.40-0.85)	0.64 (0.41-0.86)
Sweets	0.55 (0.32-0.76)	0.60 (0.34-0.87)	0.59 (0.34-0.88)
Beverages	0.48 (0.31-0.64)	0.45 (0.32-0.59)	0.49 (0.36-0.63)
Pickles	0.59 (0.37-0.80)	0.63 (0.42-0.85)	0.61 (0.40-0.82)

ICC (95% CI): Intra class correlation coefficient (95% confidence interval); HVO: Hydrogenated vegetable oil

Table 5. Cross classification frequency consumption of food groups between the simplified food frequency questionnaire and the mean of single 24 h recall and 2 days dietary records

Food/food groups (time/day)	Same quartile	Adjacent quartile	One quartile apart	Opposite quartile
HVO	46	26	21	7
Non-HVO	48	31	16	5
Animal fat	29	35	26	10
Animal protein	42	36	16	6
Dairy products	49	37	11	3
Plant protein	47	38	11	4
Grains	32	32	23	13
Nuts	50	37	8	5
Fruits and vegetables	41	39	14	6
Fast foods	43	33	15	9
Sweets	35	41	18	6
Beverages	30	43	19	8
Pickles	28	39	24	9

HVO: Hydrogenated vegetable oil

Discussion

We assessed the validity of a SFFQ to estimate the habitual dietary pattern and its improvement in epidemiological studies or community trials with a large sample of Iranian adults as well as its ability to rank individuals based on their consumption of specific foods and food groups. This SFFQ was developed by comparing with one 24 h recall and 2 days diet record to evaluate food groups intake. In addition, we investigated the short-term reliability of the non-quantitative FFQ by comparing two FFQ over a 2 weeks period.

Our design was relatively the same as validation study a FFQ which was develop to assess food groups in New Zealand adolescents[18] and Huang et al.'s study which was carried out in Taiwanian elderly to evaluate validation of a SFFQ compared to 2 or 3 24 h recall for using in the Nutrition and Health Survey.[9] We found that the SFFQ, as short as 48-items, could provide good estimations of dietary intake frequency as measured dietary reference method. In the validation study, the correlation coefficients of food intake between examined and reference method should be ≥ 0.3, preferably more than 0.4 and optimally 0.5-0.7 [4,8]. Thus, a majority of the questions in this FFQ had an acceptable correlation and can be applied to rank individuals according to several important food intakes.

The relative validity for specific food groups including plant protein, dairy products and nuts was good and for HVO, non-HVO, fruits and vegetables and fast foods were reasonable in both genders. In addition, the validity of animal protein was acceptable in men and moderate in women. In contrast, validity for animal fat, sweets, beverages, and pickles were relatively poor in both genders. Huang et al.'s study reported the Spearman's rank correlation coefficients between SFFQ frequencies and weight of food intakes calculated from 24 h recall ranged from −0.291 for total grains to 0.620 for dairy products in males and −0.014 for whole grains to 0.812 for dairy products for females.[9]

The validity of a FFQ which was performed to calculate the intake of specific food groups in Brazilian was high for dairy products and soy products; however, it was moderate for legumes and processed meat and poor for the meat group.[19] Another FFQ which was developed to assess food groups the consumption had optimal validity for fruits, vegetables and naturals juice.[20] The validity of a FFQ, which was develop in German population compared to two 24 h dietary recalls revealed a reasonable to good agreement in ranking of participants based on their intake for most food groups. The correlation coefficients ranged from 0.15 to 0.80.[21] In agreement to our findings sweets and biscuits, beverages and meat had low validity. The inconsistencies between the validity of different FFQ might be relevant to various reference methods, sample size, culture of the populations in different studies.[22] Disagreement might be seen mostly in food that is consumed seldom. Therefore, this issue may be solved by completing more recalls as a reference method.[4] Moreover, the differences between 24 h recall and FFQ are expected because the FFQ belongs to long-term memory, and the 24 h recall short-term memory.[8]

Consistent to our findings in Eysteinsdottir et al. study[23] the correlation coefficients of dairy product,

fruits and vegetables were higher than 0.3 in both genders, whereas it was no significant for soft drinks/sweetened juices. They used 3 days food record as a reference method, which was relatively like our study. In addition, the relative validity of FFQ against to 2 h recalls in Jackson et al.'s study varied from 0.27 to 0.56 and reliability in this study was good and correlation coefficients between 0.50-0.88.[24] SFFQ without reporting portion size leads to diminish the difficulty of participants. Furthermore using portion size does not improve the validity.[9] Pietinen et al.[25] and Wakai et al.[26] designed SFFQs which had reasonable validity to estimate food intake in Finnish and Japanese people, respectively.

It was noted that splitting the frequency consumption of foods with a narrow distribution of answers may improve the validity since the global questions lead to intake underestimation.[10] Thus, there was no overestimation in our results. Nonetheless most of the previous studies reported that an overestimation is a common concern in FFQ compared with other dietary assessment methods.[27,28] This inconsistency probably was due to using short lists of foods without portion size. Furthermore, the validity in food items consumed occasionally had a poor validity.[29]

According to the Fleiss's study that was reported the values from 0.40 to 0.75 of ICC as "fair to good,"[30] the short-term reliability of this SFFQ over a 2 weeks was reasonable. Our finding was in agreement with the results of Wong et al. in New Zealand that was carried out the reliability of a non-qualitative FFQ during the 2 weeks period.[18] The short-term period of study might be the reason of relatively higher reliability of this study.

Several studies have shown relatively good reliability of FFQ with different interval period. The reliability of FFQ administered about 2 years apart in the Shu et al.'s study ranged from 0.37 to 0.66 for food groups.[27] Zhang and Ho reported that the reproducibility of two FFQ administered in 1 year apart was between 0.30 and 0.68.[29] Hence, comparing to previous validation studies our findings show relatively good reproducibility for food groups.[28,31,32]

Moreover, one of the main objectives of diet-disease relation epidemiological studies is ranking the participants to the correct category. Thus, we examined the cross-classification of the SFFQ compared to reference method and it revealed that this SFFQ could classified the participants correctly with the mean percentage of participants assigned into the same quartile by the two methods was 40%, which was in lined with the finding of Zhang and Ho that was reported 43% for food groups.[29]

Conclusion

We concluded that the relative validity of the developed SFFQ compared to reference method and it's reproducibility were reasonably good in estimating food groups and satisfactory for evaluating the relationship of diet with risk of disease in both genders. In addition, it is applicable for ranking population based on food groups consumption and may be utilized in future population-based studies to assess dietary patterns of Iranian adults population as well as community trials, which evaluate the impact of nutrition intervention for NCD prevention.

Strengths and limitations

This study had several strengths including using interviewer-administered FFQ instead of self-administered which was improved the quality of data;[28] as participants were randomly selected sample, this study might have no selection bias, hence generalizability of these findings to all populations may be more possible; this study had ideal sample since previous studies suggested that between 100 and 200 should be used;[4] non-quantitative design and approximately short FFQ which make it is practical for administering in time-limited or population-based surveys with large sample size when the exact amount of food intakes are not reasonable.

However, there were several limitations in the design and validation of this SFFQ. Firstly, the reproducibility was examined in 2 weeks apart, which is a short period and might be overestimate the reliability. It is impossible to achieve an accurate estimate of nutrients intake by this SFFQ due to lack of portion size data and limited food items. Another consideration is that the 24 h recall and dietary records were collected within 1 week. Hence, it could not cover seasonal variation in food intake. In addition repeated 24 h recall monthly during a year is the ideal dietary reference method. However it was not feasible in our study, therefore we applied the minimum dietary recall or record that was possible.

Acknowledgments

This program was conducted by Isfahan Cardiovascular Research Center, a World Health Organization (WHO) Collaborating Center in collaboration with Isfahan Provincial Health Office, both affiliated to Isfahan University of Medical Sciences. We are thankful to collaborating teams in ICRC, Isfahan Provincial Health Office, Najaf-

Abad Health Office and Arak University of Medical Sciences.

Conflict of Interests

Authors have no conflict of interests.

References

1. Araujo F, Gouvinhas C, Fontes F, La VC, Azevedo A, Lunet N. Trends in cardiovascular diseases and cancer mortality in 45 countries from five continents (1980-2010). Eur J Prev Cardiol 2013; 21(8): 1004-17.
2. Ghassemi H, Harrison G, Mohammad K. An accelerated nutrition transition in Iran. Public Health Nutr 2002; 5(1A): 149-55.
3. LeFevre ML. Behavioral counseling to promote a healthful diet and physical activity for cardiovascular disease prevention in adults with cardiovascular risk factors: U.S. preventive services task force recommendation statement. Ann Intern Med 2014; 161(8): 587-93.
4. Willett W. Nutritional Epidemiology. Oxford, UK: Oxford University Press; 1998.
5. Subar AF. Developing dietary assessment tools. J Am Diet Assoc 2004; 104(5): 769-70.
6. Cade J, Thompson R, Burley V, Warm D. Development, validation and utilisation of food-frequency questionnaires - a review. Public Health Nutr 2002; 5(4): 567-87.
7. Vuckovic N, Ritenbaugh C, Taren DL, Tobar M. A qualitative study of participants' experiences with dietary assessment. J Am Diet Assoc 2000; 100(9): 1023-8.
8. Haftenberger M, Heuer T, Heidemann C, Kube F, Krems C, Mensink GB. Relative validation of a food frequency questionnaire for national health and nutrition monitoring. Nutr J 2010; 9: 36.
9. Huang YC, Lee MS, Pan WH, Wahlqvist ML. Validation of a simplified food frequency questionnaire as used in the Nutrition and Health Survey in Taiwan (NAHSIT) for the elderly. Asia Pac J Clin Nutr 2011; 20(1): 134-40.
10. Andersen LF, Solvoll K, Johansson LR, Salminen I, Aro A, Drevon CA. Evaluation of a food frequency questionnaire with weighed records, fatty acids, and alpha-tocopherol in adipose tissue and serum. Am J Epidemiol 1999; 150(1): 75-87.
11. Esfahani FH, Asghari G, Mirmiran P, Azizi F. Reproducibility and relative validity of food group intake in a food frequency questionnaire developed for the Tehran Lipid and Glucose Study. J Epidemiol 2010; 20(2): 150-8.
12. Mohammadifard N, Omidvar N, Houshiarrad A, Neyestani T, Naderi GA, Soleymani B. Validity and reproducibility of a food frequency questionnaire for assessment of fruit and vegetable intake in Iranian adults. J Res Med Sci 2011; 16(10): 1286-97.
13. Sarraf-Zadegan N, Sadri G, Malek AH, Baghaei M, Mohammadi FN, Shahrokhi S, et al. Isfahan Healthy Heart Programme: a comprehensive integrated community-based programme for cardiovascular disease prevention and control. Design, methods and initial experience. Acta Cardiol 2003; 58(4): 309-20.
14. Sarrafzadegan N, Talaei M, Sadeghi M, Kelishadi R, Oveisgharan S, Mohammadifard N, et al. The Isfahan cohort study: rationale, methods and main findings. J Hum Hypertens 2011; 25(9): 545-53.
15. Mohammadifard N, Sarrafzadegan N, Nouri F, Sajjadi F, Alikhasi H, Maghroun M, et al. Using factor analysis to identify dietary patterns in Iranian adults: Isfahan Healthy Heart Program. Int J Public Health 2012; 57(1): 235-41.
16. Talaei M, Rabiei K, Talaei Z, Amiri N, Zolfaghari B, Kabiri P, et al. Physical activity, sex, and socioeconomic status: A population based study. ARYA Atheroscler 2013; 9(1): 51-60.
17. Ghafarpour M, Houshiarrad A, Kianfar H. Food Album. Tehran: Iran: Institute of Nutrition sciences and Food Technology; 2005. [In Persian].
18. Wong JE, Parnell WR, Black KE, Skidmore PM. Reliability and relative validity of a food frequency questionnaire to assess food group intakes in New Zealand adolescents. Nutr J 2012; 11: 65.
19. Ishihara J, Iwasaki M, Kunieda CM, Hamada GS, Tsugane S. Food frequency questionnaire is a valid tool in the nutritional assessment of Brazilian women of diverse ethnicity. Asia Pac J Clin Nutr 2009; 18(1): 76-80.
20. Slater B, Enes CC, Lopez RV, Damasceno NR, Voci SM. Validation of a food frequency questionnaire to assess the consumption of carotenoids, fruits and vegetables among adolescents: the method of triads. Cad Saude Publica 2010; 26(11): 2090-100.
21. Bohlscheid-Thomas S, Hoting I, Boeing H, Wahrendorf J. Reproducibility and relative validity of food group intake in a food frequency questionnaire developed for the German part of the EPIC project. European Prospective Investigation into Cancer and Nutrition. Int J Epidemiol 1997; 26(Suppl 1): S59-S70.
22. Bhakta D, dos SS, I, Higgins C, Sevak L, Kassam-Khamis T, Mangtani P, et al. A semiquantitative food frequency questionnaire is a valid indicator of the usual intake of phytoestrogens by south Asian women in the UK relative to multiple 24-h dietary recalls and multiple plasma samples. J Nutr 2005; 135(1): 116-23.
23. Eysteinsdottir T, Thorsdottir I, Gunnarsdottir I, Steingrimsdottir L. Assessing validity of a short

food frequency questionnaire on present dietary intake of elderly Icelanders. Nutr J 2012; 11: 12.
24. Jackson MD, Walker SP, Younger NM, Bennett FI. Use of a food frequency questionnaire to assess diets of Jamaican adults: validation and correlation with biomarkers. Nutr J 2011; 10: 28.
25. Pietinen P, Hartman AM, Haapa E, Rasanen L, Haapakoski J, Palmgren J, et al. Reproducibility and validity of dietary assessment instruments. II. A qualitative food frequency questionnaire. Am J Epidemiol 1988; 128(3): 667-76.
26. Wakai K, Egami I, Kato K, Lin Y, Kawamura T, Tamakoshi A, et al. A simple food frequency questionnaire for Japanese diet--Part I. Development of the questionnaire, and reproducibility and validity for food groups. J Epidemiol 1999; 9(4): 216-26.
27. Shu XO, Yang G, Jin F, Liu D, Kushi L, Wen W, et al. Validity and reproducibility of the food frequency questionnaire used in the Shanghai Women's Health Study. Eur J Clin Nutr 2004; 58(1): 17-23.
28. Chen Y, Ahsan H, Parvez F, Howe GR. Validity of a food-frequency questionnaire for a large prospective cohort study in Bangladesh. Br J Nutr 2004; 92(5): 851-9.
29. Zhang CX, Ho SC. Validity and reproducibility of a food frequency Questionnaire among Chinese women in Guangdong province. Asia Pac J Clin Nutr 2009; 18(2): 240-50.
30. Fleiss JL. The design and analysis of clinical experiments. New Jersey, NJ: Wiley; 1986.
31. Ogawa K, Tsubono Y, Nishino Y, Watanabe Y, Ohkubo T, Watanabe T, et al. Validation of a food-frequency questionnaire for cohort studies in rural Japan. Public Health Nutr 2003; 6(2): 147-57.
32. Torheim LE, Barikmo I, Hatloy A, Diakite M, Solvoll K, Diarra MM, et al. Validation of a quantitative food-frequency questionnaire for use in Western Mali. Public Health Nutr 2001; 4(6): 1267-77.

How to cite this article: Mohammadifard N, Sajjadi F, Maghroun M, Alikhasi H, Nilforoushzadeh F, Sarrafzadegan N. **Validation of a simplified food frequency questionnaire for the assessment of dietary habits in Iranian adults: Isfahan Healthy Heart Program, Iran.** ARYA Atheroscler 2015; 11(2): 139-46.

Echocardiographic changes after aortic valve replacement: Does the failure rate of mitral valve change?

Arezoo Khosravi[(1)], Hadi Sheykhloo[(2)], Reza Karbasi-Afshar[(1)], Amin Saburi[(3)]

Original Article

Abstract

BACKGROUND: Since some degrees of functional mitral regurgitation (MR) may be seen in patients who are candidate for undergoing isolated aortic valve replacement (AVR), determining the effectiveness of AVR surgery on MR rate improvement can be effective in designing a protocol to deal with patients with functional MR. The purpose of this study was to examine the echocardiographic changes after AVR surgery with a focus on changes in MR.

METHODS: The research was conducted as a before-after observational study on patients hospitalized in Baqiyatallah Hospital, Tehran, Iran, who were undergone AVR surgery between 2011 and 2012. After selecting the patients and obtaining informed consent to participate in the project, transthoracic echocardiographic data were collected by a specialist in Cardiology Echocardiography using ViVid 7 device before and till one week after AVR surgery. The MR rate was measured using methods; including Color Flow Doppler, PISA, Vena Cava Width and Effective Regurgitant Orifice.

RESULTS: Finally, the study was conducted on 85 patients (mean age = 56.23 ± 6.10 years, 27 women = 31.8%). Of 21 patients with preoperative MR more than mild (moderate, mild to moderate), 20 patients (95%) showed at least one degree decrease in MR. Among 64 patients who had mild MR before the surgery, 29 patients improved (45%), that this difference was statistically significant (P < 0.001).

CONCLUSION: The study results showed that in patients with preoperative MR degree higher than mild, after AVR the MR rate improved 24 times more than those who had preoperative MR degree equivalent to mild and lower. However, these changes are not affected by other echocardiographic changes and patients demographic characteristics.

Keywords: Echocardiography, Heart Valve Prosthesis Implantation, Mitral Valve Regurgitation

Date of submission: 12 Sep 2014, ***Date of acceptance:*** 21 Jan 2015

Introduction

Aortic valve stenosis is one of the most common heart valve diseases that its effective and decisive treatment is valve replacement.[1] Patients requiring treatment for aortic stenosis (AS) also often have some degree of mitral regurgitation (MR).[2] In most patients, the severity of MR is in mild to moderate range, and it seems that with aortic valve gradient decrease, the severity of MR will also improve; however, with severe MR, mitral valve replacement or repair is also indicated.[3]

MR is one of the most common valvular disorders with an incidence of 7%. The main causes of MR include mitral valve prolapse, rheumatic heart disease, infective endocarditis, mitral ring calcification, cardiomyopathy, and ischemic heart disease.[1] MR can be also associated with AS and aortic regurgitation (AR). MR is associated with poor clinical outcome and can lead to atrial fibrillation, heart failure, and the need for replacement or repair of mitral valve.[2] It has been shown in several studies conducted in other countries that if the severity of functional MR rate is higher than average, mitral valve replacement or repair should be performed simultaneously with AVR; however, if the functional MR is less than moderate or lower, a conservative approach in the treatment of

1- Assistant Professor, Department of Cardiology, Cardiovascular Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
2- Cardiologist, Department of Cardiology, Cardiovascular Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
3- Birjand Atherosclerosis and Coronary Artery Research Center, Birjand University of Medical Sciences, Birjand AND Chemical Injuries Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
Correspondence to: Amin Saburi, Email: aminsaburi@yahoo.com

functional MR would be useful.[4] Since the simultaneous replacement of aortic and mitral valves is associated with increased mortality, especially in elderly patients, therefore, surgical treatment for functional MR should be selected in a very precise approach and in specific cases.[5]

Since some degrees of functional MR may be seen in patients who are candidate for undergoing isolated AVR, determining the effectiveness of AVR surgery on MR rate improvement can be effective in designing a protocol to deal with patients with functional MR.[6-8] Thus, for the first time in Iran, in this study, we examined the severity degree of MR before and after AVR to provide a protocol based on that on how to treat functional MR associated with aortic disease.

Materials and Methods

The research was conducted as one group before after prospective study on patients hospitalized in Baqiyatallah Hospital, Tehran, Iran, between 2011 and 2012 who was undergone AVR surgery. All patients with AS who were candidates for valve replacement were studied. The following individual candidates for valve replacement were enrolled.[1] Adults with symptomatic severe AS, asymptomatic severe AS cases, if ejection fraction (EF) < 50%, the patient candidate for coronary artery bypass graft surgery (CABG) or any other cardiac surgery or having significant MR.

Patients with the following conditions were excluded from the study:

- Patients who were candidate for transcatheter aortic valve implantation
- Any structural mitral valve diseases
- A history of infective endocarditis
- A history of CABG surgery
- Severe functional MR that has been treated by mitral valve repair (MVR)
- A history of tricuspid valve replacement or repair

Necessary comments and points about the project were given to patients, and after obtaining informed consent for participating in the project, they were included. The study imposed no cost to the patients. The study plan was approved by the Ethics and Scientific Committee of Baqiyatallah University of Medical Science.

After patient selection based on meeting the study inclusion criteria, the necessary explanations were provided for them, and transthoracic echocardiography was performed using ViVid 7 echocardiography before and one week after AVR by one specialist in Cardiology Echocardiography department. MR rate was measured using methods of Color Doppler Flow, PISA, Vena Contracta Width and Effective Regurgitant Orifice. In echocardiographic examination, the normal sizes of left atrial (LA), left ventricular end-systolic diameter (LVESD) and left ventricular end-diastolic diameter (LVEDD) were, respectively, considered as 3.8 cm, 2.4-4.2 cm, 5.4 cm and left ventricular function (LVF) ≥ 50% as well as pulmonary artery pressure (PAP) < 30 mmHg (R). MR improvement was considered as a reduction of at least one degree of the MR severity.

Echocardiographic findings associated with grading of MR severity, the left ventricular hypertrophy (LVH), and the AS were determined. LVH was diagnosed using echocardiographic findings though measuring ventricular septum thickness.

Data were entered into SPSS for Windows (version 19, SPSS Inc., Chicago, IL, USA), and the relevant tables and graphs were extracted. Descriptive statistics was expressed as percentage (%) in qualitative variables and expressed in quantitative variables by mean and standard deviation. The difference between the frequencies of the qualitative variables was measured by chi-square test and McNemar test. Comparing the quantitative variables between groups, t-test and ANOVAs were used. Paired t-test or Wilcoxon also were used for comparing the quantitative variable within group before and after the intervention. $P < 0.050$ was considered statistically significant.

Results

A total of 85 patients were enrolled in this study that 27 patients (31.8%) were female. The mean age of participants was 56 ± 6.1 years that the youngest person was 16 years old, and the oldest was 79 years old. Table 1 shows the patients characteristics in demographic and clinical data. In 61 patients (71%), mechanical aortic valves and in the remaining patients, biological valves were used. In pre-operative echocardiography, 55 patients (64.7%) had normal left ventricular ejection fraction (LVEF) regarding left ventricular systolic function; however, mild, moderate, and severe systolic dysfunction were reported in 14 patients (16.5%), 13 patients (15.3%), and 3 patients (3.5%), respectively. These values after surgery were reported, respectively, as 49 patients (57.6%) with normal LVEF, 21 patients (24.7%) with mild systolic dysfunction, 11 patients (12.9%) with moderate dysfunction and 4 patients (4.7%) with severe dysfunction that such changes were statistically significant ($P = 0.030$).

Table 1. Demographic, clinical, and para-clinical characteristics of patients

Item	Mean ± SD	n (%)
Male	-	58 (68.0)
Smoking	-	19 (16.0)
Angina	-	23 (22.0)
DOE FC I	-	1 (0.9)
DOE FC II	-	70 (68.0)
DOE FC III	-	6 (5.8)
AF	-	3 (2.6)
Syncope	-	2 (1.9)
DM	-	14 (12.0)
HTN	-	45 (39.0)
Dyslipidemia	-	20 (17.0)
Renal failure	-	2 (1.7)
Age (year)	56.0 ± 6.10	-
LVEF	47.8 ± 8.00	-
PA pressure (mmHg)	25.6 ± 11.10	-
LA size (cm)	3.9 ± 7.00	-
LV wall thickness (cm)	0.2 ± 1.24	-
LVEDD (cm)	0.7 ± 5.46	-
LVESD (cm)	0.7 ± 3.90	-

DOE FC: Dyspnoea on exertion functional class; AF: Atrial fibrillation; DM: Diabetes mellitus; HTN: Hypertension; LVEF: Left ventricular ejection fraction; PAP: Pulmonary-artery pressure; LA: Left atrial; LV: Left ventricular; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; SD: Standard deviation

Preoperative LVEF mean was as 47.8% and became as 47% after surgery. The preoperative mean LVEDD was as 5.46 ± 0.77 cm and postoperatively as 5.1 cm. This LVEDD decrease was statistically significant ($P < 0.001$). Other echocardiographic findings are given in Table 2, 3. In addition to MR degree, tricuspid regurgitation (TR) degree, aortic insufficiency (AI) severity, and AS severity were changed after AVR which these changes were statistically significant ($P < 0.001$) (Table 2). Moreover, In addition to LVEF and LVEDD, interventricular septum diameter (IVSD), aortic valve mean gradient (AVMG), and aortic valve pressure gradient (AVPG) were changed significantly ($P < 0.050$) (Table 3).

Among studied subjects, of 21 patients with preoperative MR more than mild (moderate, mild to moderate), 20 patients (95%) showed at least one degree decrease in MR. Among 64 patients who had mild MR before the surgery, the MR improved in 29 patients (45%) that these changes were statistically significant ($P < 0.001$) (Figure 1). On the other word, 33 patients (38.8%) had no MR after surgery

Table 2. Qualitative echocardiography characteristics before and after aortic valve replacement (AVR)

Item (%)	Sub-group	Before (85 cases)	After (85 cases)	P
LVEF dysfunction	No	55 (64.7)	49 (57.6)	0.109
	Mild	14 (16.5)	21 (24.7)	
	Moderate	13 (15.3)	11 (12.9)	
	Severe	3 (3.5)	4 (4.7)	
AS severity	No	23 (27.1)	79 (92.9)	< 0.001
	Mild	6 (7.1)	5 (5.9)	
	Mild to mod	2 (2.4)	1 (1.1)	
	Moderate	11 (12.9)	-	
	Mod to severe	10 (11.8)	-	
	Severe	33 (38.8)	-	
AI severity	No	3 (3.5)	62 (72.9)	< 0.001
	Mild	12 (14.1)	21 (24.7)	
	Mild to Mod	10 (11.8)	2 (2.4)	
	Moderate	15 (17.6)	-	
	Mod to severe	21 (24.7)	-	
	Severe	24 (28.2)	-	
MR severity	No	-	33 (38.8)	< 0.001
	Mild	64 (75.3)	52 (61.2)	
	Mild to Mod	20 (23.5)	-	
	Moderate	1 (1.2)	-	
LVH	No	24 (28.2)	26 (30.6)	0.096
	Mild	42 (49.4)	43 (50.6)	
	Moderate	17 (20)	14 (16.5)	
	Severe	2 (2.4)	2 (2.4)	
TR	No	10 (11.8)	16 (18.8)	< 0.001
	Mild	70 (82.4)	67 (78.8)	
	Mild to Moderate	4 (4.7)	2 (2.4)	
	Moderate	1 (1.2)	-	
PAH	No	63 (74.1)	67 (78.8)	0.052
	Mild	12 (14.1)	12 (14.1)	
	Moderate	8 (9.4)	4 (4.7)	
	Severe	2 (2.4)	2 (2.4)	

Based on McNemmar; LVEF: Left ventricular ejection fraction; AS: Aortic stenosis; AI: Aortic insufficiency; MR: Mitral regurgitation; LVH: Left ventricular hypertrophy; TR: Tricuspid regurgitation; PAH: Pulmonary arterial hypertension

Table 3. Quantitative echocardiography characteristics before and after aortic valve replacement (AVR)

Item*	Before (85 cases)	After (85 cases)	P
LVEF	47.80 ± 8.20	47.00 ± 7.83	0.038
LVEDD (cm)	5.46 ± 0.77	5.17 ± 0.63	< 0.001
LVESD (cm)	3.73 ± 0.79	3.90 ± 2.42	0.530
IVSD (cm)	1.24 ± 0.22	1.21 ± 0.20	< 0.001
AVMG (mmHg)	35.62 ± 25.98	12.25 ± 5.16	< 0.001
AVPG	55.22 ± 38.74	20.93 ± 8.75	0.009
Mean PAP (mmHg)	25.67 ± 11.17	24.89 ± 9.95	0.260
LA size (cm)	3.89 ± 0.76	3.89 ± 0.71	0.980

* All quantitative items were described as mean ± SD; SD: Standard deviation; LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; IVSD: Inter-ventricular septum diameter; AVMG: Aortic valve mean gradient; AVPG: Aortic valve pressure gradient; PAP: Pulmonary-artery pressure; LA: Left atrial

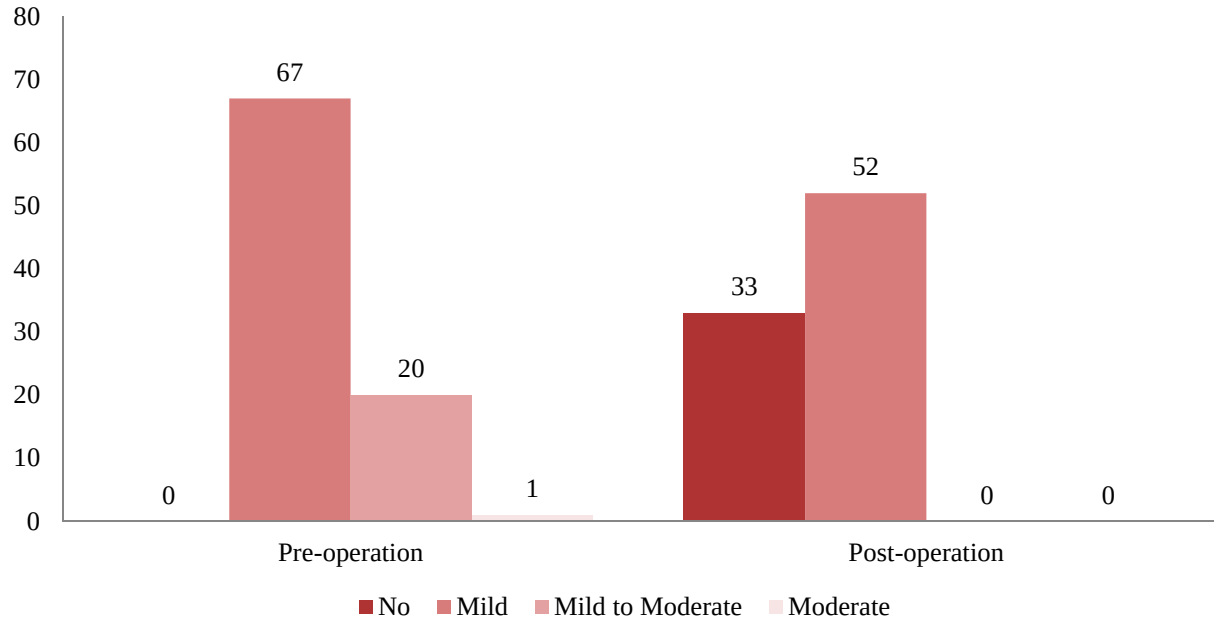


Figure 1. Mitral regurgitation frequency before and after aortic valve replacement
* Based on McNemmar test

versus all patients before surgery had degrees of MR. This means that in those with preoperative MR higher than a mild degree, the improvement in MR rate after AVR was 24 times more than those who had preoperative MR equivalent to mild and lower. Between two groups of MR improved and not improved, neither demographics variable (age, gender) and nor echocardiographic characters showed statistically significant differences (P > 0.050).

Discussion

Our study showed that MR rate has decreased in 50 patients (58%) after AVR. There are some similar studies which evaluate the impact of AVR on MR severity.

In a study in the United States by Barreiro et al. conducted in 2004 on 408 patients, the improvement rate of functional MR after AVR was reported as 81.8%.[4] In a review study by Matsumura et al. in Canada, the improvement in functional MR was observed after isolated AVR.[9] In Waisbren et al.[3] and Tunick et al.[10] studies, the improvements rates in functional MR were reported at about 66% and 64% after AVR, respectively.

In a retrospective study by Tunick et al. that had reviewed MR rates before and after AVR in echocardiographic reports of 44 patients, 60% of patients showed postoperative reduced MR and it remained unchanged in 27% and had become worse in 13%.[10] Although improvement of functional MR has been shown in these studies after isolated AVR,

however, in a study on 27 patients by Brasch et al., MR echocardiography improvement was not seen in 52% of patients.[11]

Based on the current study results, LVEF of patients shows decrease after AVR, which is statistically significant. Injection Lindeboom study conducted in The Netherlands, the patients' LVEF after CABG or AVR surgeries was improved from 46% to 55% during 3-18 days. Furthermore, end-diastolic dimensions of LA and LVEDD considerably reduced.[12]

One of the limitations of this study was the short period of post-operative evaluation. Due to the fact that in our study, echocardiography was performed during the same hospitalization period and at one week after the operation for LVEF assessment after surgery, thus, reduced LVEF at this period time might have been due to anesthetic drugs effects, cardiopulmonary pump, and during cardiac surgery and its complications. Therefore, accurate assessment of LVEF should be done periodically in order to make accurate assessments on actual LVEF of patient and AVR effect on left LVF.

In our study, the mean LV end-diastolic diameter and the mean LV end-systolic diameter decrease after AVR surgery that the change is significant only regarding LVEDD. Furthermore, the LA size remained unchanged after AVR, but the severity of TR, AR, LVH, and PAP rate showed reduction.

Comparing the variables before and after surgery, it was found that changes in LVEF, LVEDD, IVSD, AVMG, and AVPG after surgery were statistically significant, but changes in PAP, LVESD, and LA size were not significant.

As mentioned before, reduced LVEDD size after surgery was considered statistically significant that such a factor can cause a reduction in MR after operation by reducing mitral valve annulus size; however, in our study, the mitral valve size annulus was not measured in all patients before and after the surgery, which can be considered in future studies.

However, LVESD size is a more reliable index for reduction of postoperative MR, which was not significant in our study, perhaps because of the LVEF reduction in a short period after AVR. However, if we measured LVESD 3-6 months after surgery, perhaps these changes would become significant to justify MR reduction.[13]

Furthermore, postoperative reduced IVSD can cause reduced MR through reducing LV wall stress and omission of pressure and volume effects on LV and reducing LVEDP that further studies are needed to confirm these hypotheses.

The strength of our study is that any intervening factors such as CABG and repair or replacement of mitral and tricuspid valves that could have reduced the postoperative MR rate were excluded, so that patients undergoing revascularization were excluded from the study.

The study results showed no significant association between age, sex, patient's symptoms, preoperative risk factors, valve type (mechanical or biological), LVEDD size, LVESD, IVSD, LA, LVEF rate, PAP, AVMG, AVPG, and AI rate before the surgery improvement in MR, which could be due to low sample size.

However, the relationship between severity of preoperative MR and MR improvement rate after AVR was significant. The results show that in patients who are candidate for AVR, if preoperative rate of functional MR failure is at most moderate, MR rate will reduce after AVR in 58% of cases. This change especially occurs when preoperative MR is more than Mild (at maximum: moderate) so that improvement rate in these patients is approximately 24 times higher than those with mild preoperative MR.

Conclusion

Similar to previous studies, our results also showed improvement in functional MR following AVR surgery. Thus, performing surgery on aortic valve is associated with higher mortality and morbidity, especially in elderly, a conservative approach in cases with moderate functional MR that are candidate for AVR is recommended and after AVR, the patients should be evaluated for further therapeutic approach. Therefore, more coordination is needed between cardiovascular surgeons and cardiologists to determine indications for MV repair or MVR with the AVR.

Acknowledgments

We would like to thank all patients for their good cooperation

Conflict of Interests

Authors have no conflict of interests.

References

1. Bonow RO, Mann DL, Zipes DP, Libby P. Braunwald's Heart Disease: A Textbook of

Cardiovascular Medicine. 9th ed. Philadelphia, PA: Elsevier Health Sciences; 2011. p. 1468-78, 1499-514.
2. Gleyzolle B, James S, Orton C, Monnet E. Correction of Acute Functional Mitral Regurgitation: Development of a New Epicardial Device. Circulation 2012; 120: S822.
3. Waisbren EC, Stevens LM, Avery EG, Picard MH, Vlahakes GJ, Agnihotri AK. Changes in mitral regurgitation after replacement of the stenotic aortic valve. Ann Thorac Surg 2008; 86(1): 56-62.
4. Barreiro CJ, Patel ND, Fitton TP, Williams JA, Bonde PN, Chan V, et al. Aortic valve replacement and concomitant mitral valve regurgitation in the elderly: impact on survival and functional outcome. Circulation 2005; 112(9 Suppl): I443-I447.
5. Unger P, Magne J, Vanden Eynden F, Plein D, Van CG, Pasquet A, et al. Impact of prosthesis-patient mismatch on mitral regurgitation after aortic valve replacement. Heart 2010; 96(20): 1627-32.
6. Unger P, Plein D, Van CG, Cosyns B, Pasquet A, Henrard V, et al. Effects of valve replacement for aortic stenosis on mitral regurgitation. Am J Cardiol 2008; 102(10): 1378-82.
7. Unger P, Plein D, Cosyns B, Van Camp G, Xhaet O, Henrard V, et al. Does Mitral Regurgitation Regress After Aortic Valve Replacement For Aortic Stenosis? A Prospective Multicenter Study. Circulation 2007; 116: II_447.
8. Alghamdi AA, Elmistekawy EM, Singh SK, Latter DA. Is concomitant surgery for moderate functional mitral regurgitation indicated during aortic valve replacement for aortic stenosis? A systematic review and evidence-based recommendations. J Card Surg 2010; 25(2): 182-7.
9. Matsumura Y, Gillinov AM, Toyono M, Oe H, Yamano T, Takasaki K, et al. Echocardiographic predictors for persistent functional mitral regurgitation after aortic valve replacement in patients with aortic valve stenosis. Am J Cardiol 2010; 106(5): 701-6.
10. Tunick PA, Gindea A, Kronzon I. Effect of aortic valve replacement for aortic stenosis on severity of mitral regurgitation. Am J Cardiol 1990; 65(18): 1219-21.
11. Brasch AV, Khan SS, DeRobertis MA, Kong JH, Chiu J, Siegel RJ. Change in mitral regurgitation severity after aortic valve replacement for aortic stenosis. Am J Cardiol 2000; 85(10): 1271-4.
12. Lindeboom JE, Jaarsma W, Kelder CJ, Morshuis WJ, Visser CA. Mitral valve repair is not always needed in patients with functional mitral regurgitation undergoing coronary artery bypass grafting and/or aortic valve replacement. Netherlands heart Journal 2005; 13(5): 175-80.
13. Pai RG, Varadarajan P. Prognostic Implications of Mitral Regurgitation in Patients with Severe Aortic Regurgitation. Circulation 2010; 122(suppl 1): S43-S47.

How to cite this article: Khosravi A, Sheykhloo H, Karbasi-Afshar R, Saburi A. **Echocardiographic changes after aortic valve replacement: Does the failure rate of mitral valve change?** ARYA Atheroscler 2015; 11(2): 147-52.

Evaluating the impact of fractional flow reserve-guided percutaneous coronary intervention in intermediate coronary artery lesions on the mode of treatment and their outcomes: An Iranian experience

Alireza Khosravi[(1)], Mohammad Reza Pourbehi[(2)], Masoud Pourmoghaddas[(1)], Afshin Ostovar[(3)], Mohammad Reza Akhbari[(4)], Fereshteh Ziaee-Bideh[(3)], Jafar Golshahi[(5)], Shahin Shirani [(6)]

Original Article

Abstract

BACKGROUND: Today, the fractional flow reserve (FFR) guides the physician to select suitable patients with intermediate severity coronary lesions in angiography that should be treated or not with stent. The aim of this study was to evaluate the impact of using FFR in the selection of appropriate treatment strategy in angiographic intermediate coronary lesions and their short-term outcome in a sample of Iranian population.

METHODS: In a prospective cohort, 34 patients who had intermediate coronary artery lesion(s), defined as having a 40-70% diameter stenosis, as determined by visual estimation or quantitative coronary angiography were enrolled through a convenience sampling method. All patients underwent FFR measurement to decide whether percutaneous coronary intervention should be performed. The results of visual assessment, quantitative coronary angiography, and functional assessment of the severity of coronary stenosis were compared. Significant stenosis was defined as FFR < 0.80. All patients were followed for 6 months for the incidence of major advanced cardiac events.

RESULTS: In this study, 34 patients (22 male and 12 female) with mean age of 57 ± 8 (range 45-70) were included. In 26.47% (9/34) of patients, FFR was < 0.80, they underwent coronary angioplasty. The correlation between visual estimation and quantitative assessment of lesion diameter was 0.804 (P < 0.001). During the follow-up period, no major advanced cardiac events were reported. In addition, 5.88 (2/34) of patients had a left main (LM) lesion with FFR > 0.80 and stenting was done to the other vessels with significant coronary lesions.

CONCLUSION: Measurement of FFR is a useful approach in making clinical decisions about revascularization procedures in patients with moderate coronary artery lesion severity, especially in LM and multivessel disease. This study showed that not only FFR can change treatment plan of the patients, but also it would improve clinical outcomes.

Keywords: Fractional Flow Reserve Myocardial, Coronary Stenosis, Coronary Angiography

Date of submission: 16 Nov 2014, ***Date of acceptance:*** 10 Feb 2015

Introduction

Intermediate coronary artery lesions are defined as a diameter narrowing of ≥ 40% to ≤ 70%[1] and is reported in about one third to half of coronary angiograms.[2] The clinical significance and management strategy of these lesions are important.[3] Visual estimation of coronary lesion severity in routine coronary angiography may be inaccurate because of two-dimensional views and inter/interobservervariability.[3,4] Quantitative coronary angiograms are better suited, but they also have the same limitations in assessing coronary artery stenosis.[1] In patients with angina pectoris and moderate coronary artery stenosis severity, as assessed by visual estimation in a coronary angiogram, decision making for the

1- Interventional Cardiology Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
2- Assistant Professor, The Persian Gulf Nuclear Medicine Research Center AND Department of Interventional Cardiology, Bushehr University of Medical Sciences, Bushehr, Iran
3- Assistant Professor, The Persian Gulf Tropical Medicine Research Center, Bushehr University of Medical Sciences, Bushehr, Iran
4- Heart Failure Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
5- Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
6- Hypertension Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Mohammad Reza Pourbehi, Email: mr_purbehi@yahoo.com

selection of treatment strategies, stenting, or medical follow-up is a dilemma, and evaluation and treatment of lesions are challenging.[3] In a considerable number of patients, coronary artery revascularization is performed without definite evidence that coronary stenosis is causing symptoms.[5,6] In recent years, technical advances have provided new diagnostic devices to catheterization laboratories to evaluate the severity of coronary artery lesions. One of the diagnostic modalities for assessment of the functional importance of intermediate coronary lesion is fractional flow reserve (FFR), which is carried out by intracoronary pressure guide wires.[7,8] Based on the pressure-flow analysis of coronary stenosis during maximal flow reserve,[9] the concept of a myocardial FFR has been developed as an invasively determined index of the functional severity of coronary stenosis in intermediate lesion.[10-13] FFR is defined as the ratio of maximum coronary blood flow in a stenotic area to maximum blood flow in the same vessel that is completely normal.[10,14] In other words, FFR can be derived from the ratio of the mean distal coronary artery pressure (post stenotic-Pd) to the aortic pressure (Pa) during maximal hyperemia (FFR = Pd/Pa).[10,15] This index is independent of changes in systemic blood pressure, heart rate, and left ventricular function, and it is unaffected by conditions known to increase the baseline myocardial flow.[2,12] The normal value of the index is 1.0, regardless of the patient or the specific vessel studied.[13] The FFR has been shown to correlate well with other noninvasive tests for the detection of ischemia.[16-18] In contrast to most other invasive indexes, FFR has a direct clinical relevance.[10,13,14,19] For these reasons, FFR may be regarded as a gold standard for the evaluation of the physiological significance of intermediate coronary stenosis in catheterization laboratories, with extensive validation in randomized controlled trials.[6]

We believe using FFR have been shown to improve patient outcomes in the short- and long-term[2,20,21] reduce the number of stents implanted by approximately 30% and are cost effective.[21] Therefore, without using these devices, stents (usually drug eluting stents) may be inserted in non-significant lesions wrongly.[3]

Our center (Chamran Heart Hospital, Isfahan, Iran) has been using intracoronary pressure guide wires since January 2013. Therefore, the purpose of this study was to describe our experiences with the use of this device.

This study aimed to evaluate the impact of FFR in decision making for revascularization in patients with intermediate coronary stenosis and relevant angina in an Iranian population. It aimed to determine the complications associated with the use of FFR devices also.

Materials and Methods

The patient population consisted of 34 stable angina patients who consecutively underwent FFR assessment to decide whether to perform percutaneous coronary intervention (PCI) for de novo intermediate coronary lesions between January and December 2013. All cases were selected from patients who came to our center for coronary angiography as outpatients. An intermediate coronary artery lesion was defined as a 40-70% diameter[1] stenosis through the visual estimation of two cardiologists separately. If their estimation was different, opinion of third cardiologist was considered as a final decision. A single operator blinded to clinical and FFR data performed an off-line quantitative coronary angiogram on moderate coronary lesions to determine lesion length. For this study, the target vessel was a lesion in the proximal or mid part of a major epicardial coronary artery with a reference vessel diameter larger than 2.5 mm. Patients were excluded if they were in the setting of ST elevation of myocardial infarction for primary PCI; in the setting of acute coronary syndrome; had a major life-threatening illness; experienced contraindication to adenosine and anticoagulant or antiplatelet, or had prior coronary artery bypass surgery. Patients were eligible for enrollment if they had at least one intermediate lesion in their coronary artery tree. The cutoff value of FFR in the FFR-guided PCI group was 0.80.[2,14,22] PCI was done if the FFR was > 80% and all implanted stents were commercially available third-generation drug-eluting stents. The patients gave us informed consent.

Major advanced cardiac events defined as death, myocardial infarction, and ischemic driven target vessel revascularization (TVR) at 6 months follow-up of all the patients were evaluated. During the follow-up period, all patients in the vascularized group received appropriate doses of Aspirin, metoprolol, an angiotensin-converting enzyme inhibitor, nitrate, and clopidogrel.

Immediately after coronary angiography with standard technique,[2] the coronary artery was selectively engaged with a 6F guiding catheter without side holes, and 200 μg nitroglycerin was administered intracoronary. A 0.014" pressure guide

wire was calibrated at zero, advanced into the coronary artery, and positioned distal to the stenosis to be measured. FFR was determined during maximum hyperemia using the ratio Pd/Pa; Pd represents mean coronary pressure distal to the stenosis segment measured via the pressure wire, and Pa represents mean Pa measured via the guiding catheter. Maximum hyperemia was induced by intracoronary adenosine (≥ 30 μg in the right and ≥ 40 μg in the left coronary artery).[23]

All selected patients underwent coronary angiography by standard techniques via femoral approach. Coronary angiography was performed in multiple orthogonal views. Patients requiring FFR performance were chosen based on a visual estimation of coronary lesion severity by at least two cardiologists in each coronary artery. If patients were eligible for the study, informed consent was obtained. A single operator blinded to clinical and FFR data performed an off-line quantitative coronary angiogram on coronary moderate lesions. The most severe narrowing in no foreshortening view was used for quantitative coronary measurements (Siemens software, Siemens Healthcare GmbH, Germany); lesion length was obtained and recorded.

All patients were followed for about 6 months, and the primary outcome was defined as a composite of major adverse cardiac event (MACE), defined as death, myocardial infarction, and ischemia-driven TVR at 12 months after the index procedure. Death was defined as all-cause mortality. The diagnosis of myocardial infarction was based on either the development of new pathological Q-waves in two contiguous electrocardiogram leads and/or cardiac enzyme level elevation 3 times the upper limit of normal value. TVR included target lesion PCI and bypass surgery of the target lesion. TVR was performed only in the presence of symptoms and/or signs of ischemia[3], so MACEs were recorded, if present.

All values are expressed as mean ± standard deviation for continuous variables or as counts and percentages for categorical variables. All variables were compared using an appropriate statistical test. Kolmogorov-Smirnov test was used to evaluate if the distribution of data was normal. Pearson correlation coefficient tests were used for the correlation between quantitative variables and linear regression curves were drawn using the least square method. Independent t-test was used to compare means of vessel diameter and a minimal luminal diameter between patients with FFR ≥ 0.80 and those with lower values. Statistical significance was assessed as $P < 0.050$ using a two-tailed probability analysis. All data were analyzed SPSS software for Windows (version 20, SPSS Inc., Chicago, IL, USA).

Results

From the beginning of the January to 31 December 2013, 10,000 angiography and interventional procedures were carried out in our center. Of these, 34 patients (22 male and 12 female) with mean age 57 ± 8 (range 45-70) who were undergoing clinically indicated coronary angiography and met inclusion criteria were enrolled in the study and underwent FFR assessment, pending informed consent from the patient and their physician. Clinical characteristic of all patients, including age, sex, ordinary atherosclerotic risk factors, and so on, were summarized in table 1.

FFR measurements were done in 34 patients. There were no significant differences in reference vessel diameter and a minimal luminal diameter between patients with FFR ≥ 0.80 and those with lower values ($P = 0.332$ and $P = 0.724$, respectively). Angiography data, numbers of diseased vessels, type of involved vessel, lesion length, extent of stenosis, and FFR values are shown in table 1, as well.

In 26.47% (9/34) of the patients, FFR was lower than 0.8 and they underwent coronary angioplasty and stenting with a drug-eluting stent. Two patients (5.88 %) had FFR above 0.80 in the intermediate lesion and stenting of the other vessel with significant lesions (stenosis > 70%) was done. For the other patients, the FFR was more than 80% and revascularization was not performed. In this study, three cases (8.82%) of left main (LM) with intermediate lesions were enrolled. If the FFR measurements showed no significant LM disease, revascularization protocol would change from urgent coronary bypass graft surgery to stenting of the other vessel with significant lesions.

The correlation coefficient between FFR and lesion length and FFR and luminal stenosis was -0.599 ($P < 0.001$) and -0.430 ($P = 0.011$), respectively. The correlation between visual estimation of lesion diameter and quantitative measurement of lesion diameter was 0.804 ($P < 0.001$). Visual estimation of lesion diameter and FFR showed a correlation of -0.576 ($P < 0.001$), as shown in figure 1.

During 6 months follow-up period no any MACEs were reported in both groups.

Table 1. Baseline characteristics of the patients (n = 34)

Variables	n (%)	Mean ± SD
Sex		
Female	12 (35.3)	-
Male	22 (64.7)	-
Age		
Female	-	59.50 ± 10.30
Male	-	56.20 ± 8.40
Total	-	57.50 ± 9.20
Risk factors		
DM	10 (29.4)	-
HTN	19 (55.9)	-
DLP	15 (44.1)	-
Smoking	14 (41.2)	-
FH	10 (29.4)	-
LVEF	-	51.76 ± 4.58
Angina class		
I	10 (29.4)	-
II	18 (53.0)	-
III	5 (14.7)	-
IV	1 (2.9)	-
Angiography results		
Visual estimation	-	-
Diameter stenosis	-	59.60 ± 8.00
QCA		
Reference diameter	-	31.50 ± 0.49
Diameter stenosis	-	56.60 ± 7.80
Lesion length	-	15.00 ± 4.80
FFR	-	0.86 ± 0.09
Treatment strategy		
PCI on target vessel	9 (26.5)	-
Medical	23 (67.6)	-
PCI on non-target vessel	2 (5.9)	-
Number of diseased vessels		
Single vessel	25 (83.5)	-
Two vessels	8 (23.5)	-
Three vessel	1 (2.9)	-
Type of diseased vessel		
LM	3 (8.8)	-
LAD	29 (25.3)	-
LCX	4 (11.8)	-
RCA	9 (26.5)	-

SD: Standard deviation; DM: Diabetes mellitus; HTN: Hypertension; DLP: Dyslipidemia; FH: Familial hypercholesterolemia; LVEF: Left ventricular ejection fraction; QCA: Quantitative coronary angiography; FFR: Fractional flow reserve; PCI: Percutaneous coronary intervention; LM: Left main; LAD: Left anterior descending; LCX: Left circumflex; RCA: Right coronary artery

Significant complications did not occur during coronary adenosine administration, except for a transient severe bradycardia in nine patients and a transient complete heart blockage in one case. One lesion was not studied with pressure guide wires in the first attempt due to guide wire cross failure; the failed guide wire was then substituted with the next wire. Successful FFR measurements increased progressively after the early months of using pressure guide wires and increasing operator experience. The mean procedure time for the FFR measurement of a single lesion was 25 minutes (15-45), a period that included calibration, equalization, and hyperemia induction. This timeframe was not significantly different versus single vessel angioplasty, but in the cases of multivessel disease or vessels with multiple lesions, this was important. In the current study, misclassification of lesions with angiographic assessment alone amounted to more than 25%.

Discussion

This study demonstrated a new experience of an Iranian center in the use of pressure guide wires as a new technology for the assessment of intermediate coronary stenosis.

Routine coronary angiography is not accurate in assessing the functional significance of coronary stenosis when compared with FFR, not only in the 50-70% category, but also in the 70-90% category of angiographic severity.[4] This is because of inter-/intra-observer variability that is about 27% and 15%, respectively, in this study. In our study all PCI was done by new third generation drug eluted stents, therefore, good outcomes and low MACEs in follow-up period may be for this reason, however, more participants are needed to evaluate this subject. A prominent physician from our center refused to use FFR measurements in the assessment of coronary lesion severity because of cost, time constraints, radiation exposure, and a higher likelihood of volume of contrast. This study, along with Leesar et al., showed that FFR procedures for measurement are safe, resulting in decreased radiation exposure, and no change in the amount of contrast in comparison to conditions with inappropriate stenting.[24]

Despite the fact that myocardial single photon emission tomography (SPECT) has shown a high sensitivity of 90% or greater in the detection of multivessel coronary artery disease, accuracy is limited in the identification of each individual stenosis. Detection of reversible perfusion abnormalities,

especially of the culprit lesion, might fail in cases of a missing reference area, and the allocation of perfusion defects to target vessels is a well-known problem in these patients.[25] In our study, some of the cases involved multivessel disease, so myocardial perfusion SPECT may not be useful for the functional assessment of intermediate lesions. Leesar et al. showed that the FFR significantly shortens the duration of hospitalization compared with stress perfusion scintigraphy.[24]

Technical developments have made newer and better-designed tools available for coronary interventionist procedures. Sometimes, the complexity of devices, their cost, their limited field of application, or the scant yield of relevant information in an interventionist procedure mean that new devices are used only for research in few hemodynamic laboratories, or in sporadic cases with unusual presentation or evolution.[26] In the present study, the FFR was used in < 0.5% of the interventionist procedures in our center, but it had a great negative impact on the need to do revascularization in the patient with intermediate lesions. It has an indication in about 30% of cases. Previous studies have shown that FFR above 0.75-0.80 was a strong predictor of favorable clinical outcomes in patients with intermediate LM disease.[27-31]

One of the major findings of the present study is the effect of FFR measurement in intermediate lesions of LM or proximal left anterior descending (LAD) or left circumflex (LCX). If FFR showed insignificant lesions in LM, proximal lesions of LAD or LCX can change the strategy for revascularization, [coronary artery bypass grafting (CABG) or stenting] medical treatment. This study showed that lesion length with a severity of lesion stenosis predicted lower FFR. Thus, FFR measurement is appropriate to identify patients with intermediate LM stenosis in whom deferral of revascularization may be associated with excellent outcomes.[32]

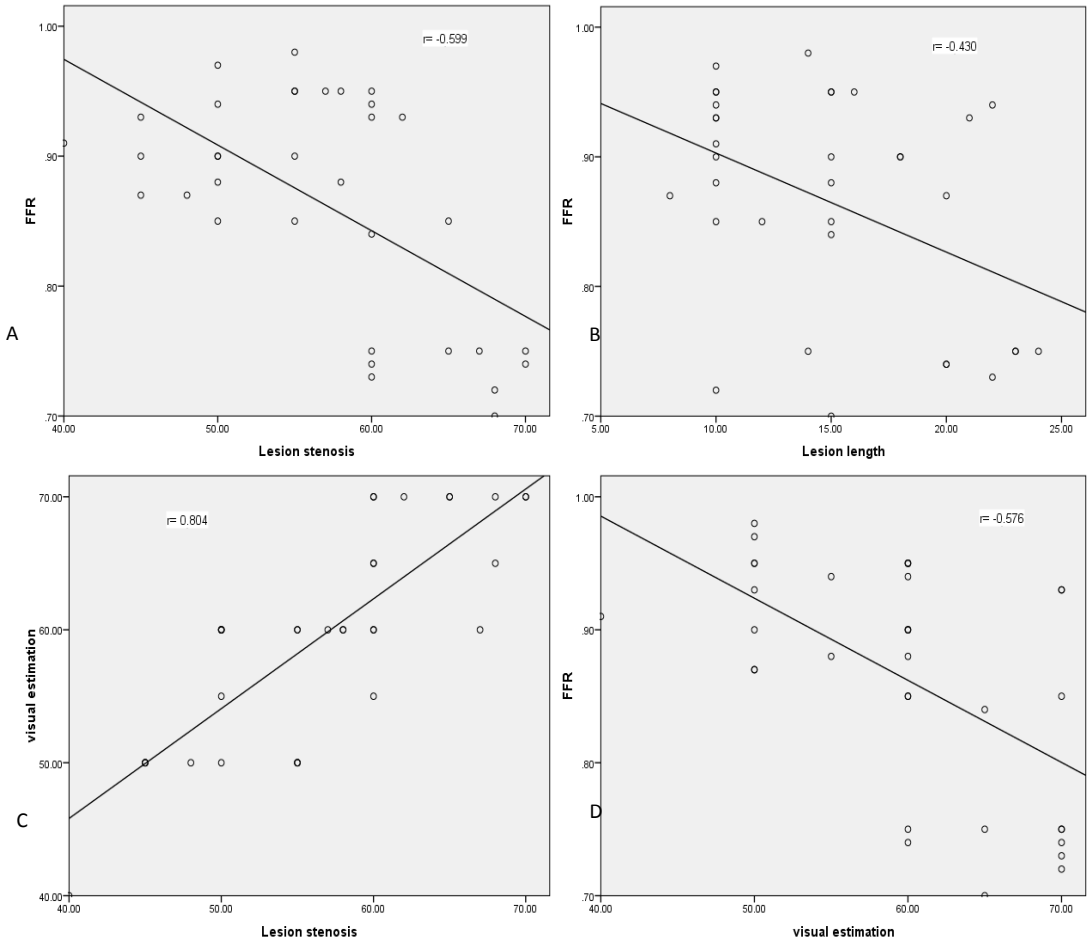


Figure 1. Scatter plots and linear regression curves of fractional flow reserve versus visual and quantitative indices of coronary lesions
FFR: Fractional flow reserve

In this study, from 35 patients coronary stenting was done in only 9 (26.5%) lesions that FFR showed significant stenosis, so this procedure prevented from inappropriate stenting of others (73.5%). The therapeutical decisions were changed from PCI or CABG in 23 patients (67.5%) to medical treatment. The treatment approach was changed from urgent CABG to Medical treatment or PCI on other lesions in three cases that had LM coronary artery lesions but without significant FFR findings. The current study with a low sample size showed that not only FFR can change treatment plan of the patients, but also it would improve clinical and economical outcomes by lowering inappropriate stenting.[4]

Limitations

The presence of small vessel disease, diffuse coronary artery disease, and left ventricular hypertrophy restrict the hyperemia induced by pharmacologic vasodilatation, so decreasing distal coronary pressure and the calculation of FFR measurements is limited.[33] This study included a relatively small number of patients and a short course follow-up for event recording.

Conclusion

Measurement of FFR during coronary angiography is a useful method of assessing whether an intermediate coronary lesion based on a routine angiography is functionally significant and may be responsible for future cardiac events. Although this procedure is underused in catheterization laboratories, it is believed that FFR is a useful approach in clinical decision making about revascularization procedures in patients with moderate coronary artery lesion severity, especially in cases of LM and multivessel disease. This procedure had a significant negative effect in coronary revascularization in these patients. Therefore, this study is a good foundation for the increased use of functional assessments in our and other catheterization laboratories, and it should be a basis for new randomized trials.

Acknowledgments

We would like to thank the personnel of the Interventional and Catheterization Angiography Laboratory of Isfahan Chamran Heart Hospital. This study was approved and supported by Isfahan Medical School, Isfahan University of Medical Sciences. This paper is a part of fellowship thesis in School of Medicine Isfahan University of Medical Sciences.

Conflict of Interests

Authors have no conflict of interests.

References

1. Iguchi T, Hasegawa T, Nishimura S, Nakata S, Kataoka T, Ehara S, et al. Impact of lesion length on functional significance in intermediate coronary lesions. Clin Cardiol 2013; 36(3): 172-7.
2. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, Veer M, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009; 360(3): 213-24.
3. Nam CW, Yoon HJ, Cho YK, Park HS, Kim H, Hur SH, et al. Outcomes of percutaneous coronary intervention in intermediate coronary artery disease: fractional flow reserve-guided versus intravascular ultrasound-guided. JACC Cardiovasc Interv 2010; 3(8): 812-7.
4. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. J Am Coll Cardiol 2010; 55(25): 2816-21.
5. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003; 349(14): 1315-23.
6. Kern MJ, Donohue TJ, Aguirre FV, Bach RG, Caracciolo EA, Wolford T, et al. Clinical outcome of deferring angioplasty in patients with normal translesional pressure-flow velocity measurements. J Am Coll Cardiol 1995; 25(1): 178-87.
7. Kern MJ, Puri S, Craig WR, Bach RG, Donohue TJ. Hemodynamic rounds series II: Coronary hemodynamics for angioplasty and stenting after myocardial infarction: use of absolute, relative coronary velocity and fractional flow reserve. Cathet Cardiovasc Diagn 1998; 45(2): 174-82.
8. Pijls NH, Kern MJ, Yock PG, De Bruyne B. Practice and potential pitfalls of coronary pressure measurement. Catheter Cardiovasc Interv 2000; 49(1): 1-16.
9. Gould KL, Kirkeeide RL, Buchi M. Coronary flow reserve as a physiologic measure of stenosis severity. J Am Coll Cardiol 1990; 15(2): 459-74.
10. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. Circulation 1993; 87(4): 1354-67.
11. De Bruyne B, Paulus WJ, Pijls NH. Rationale and application of coronary transstenotic pressure gradient

measurements. Cathet Cardiovasc Diagn 1994; 33(3): 250-61.
12. Pijls NH, Bech GJ, el Gamal MI, Bonnier HJ, De Bruyne B, Van Gelder B, et al. Quantification of recruitable coronary collateral blood flow in conscious humans and its potential to predict future ischemic events. J Am Coll Cardiol 1995; 25(7): 1522-8.
13. Pijls NH, Van Gelder B, Van der Voort P, Peels K, Bracke FA, Bonnier HJ, et al. Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. Circulation 1995; 92(11): 3183-93.
14. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek JKJ, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med 1996; 334(26): 1703-8.
15. De Bruyne B, Baudhuin T, Melin JA, Pijls NH, Sys SU, Bol A, et al. Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography. Circulation 1994; 89(3): 1013-22.
16. Bartunek J, Marwick TH, Rodrigues AC, Vincent M, Van Schuerbeeck E, Sys SU, et al. Dobutamine-induced wall motion abnormalities: correlations with myocardial fractional flow reserve and quantitative coronary angiography. J Am Coll Cardiol 1996; 27(6): 1429-36.
17. Bartunek J, Van Schuerbeeck E, De Bruyne B. Comparison of exercise electrocardiography and dobutamine echocardiography with invasively assessed myocardial fractional flow reserve in evaluation of severity of coronary arterial narrowing. Am J Cardiol 1997; 79(4): 478-81.
18. Caymaz O, Fak AS, Tezcan H, Inanir SS, Toprak A, Tokay S, et al. Correlation of myocardial fractional flow reserve with thallium-201 SPECT imaging in intermediate-severity coronary artery lesions. J Invasive Cardiol 2000; 12(7): 345-50.
19. Lederman SJ. Brief review: Fractional flow reserve. ACC Curr J Rev 1997; 34-5.
20. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012; 367(11): 991-1001.
21. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, Van't Veer M, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol 2007; 49(21): 2105-11.
22. De Bruyne B, Pijls NH, Bartunek J, Kulecki K, Bech JW, De Winter H, et al. Fractional flow reserve in patients with prior myocardial infarction. Circulation 2001; 104(2): 157-62.
23. McGeoch RJ, Oldroyd KG. Pharmacological options for inducing maximal hyperaemia during studies of coronary physiology. Catheter Cardiovasc Interv 2008; 71(2): 198-204.
24. Leesar MA, Abdul-Baki T, Akkus NI, Sharma A, Kannan T, Bolli R. Use of fractional flow reserve versus stress perfusion scintigraphy after unstable angina. Effect on duration of hospitalization, cost, procedural characteristics, and clinical outcome. J Am Coll Cardiol 2003; 41(7): 1115-21.
25. Hacker M, Rieber J, Schmid R, Lafougere C, Tausig A, Theisen K, et al. Comparison of Tc-99m sestamibi SPECT with fractional flow reserve in patients with intermediate coronary artery stenoses. J Nucl Cardiol 2005; 12(6): 645-54.
26. Lopez-Palop R, Pinar E, Lozano I, Carrillo P, Cortes R, Pico F, et al. Clinical utilization of the coronary pressure wire. Rev Esp Cardiol 2002; 55(3): 251-7.
27. Bech GJ, Droste H, Pijls NH, De Bruyne B, Bonnier JJ, Michels HR, et al. Value of fractional flow reserve in making decisions about bypass surgery for equivocal left main coronary artery disease. Heart 2001; 86(5): 547-52.
28. Lindstaedt M, Yazar A, Germing A, Fritz MK, Holland-Letz T, Mugge A, et al. Clinical outcome in patients with intermediate or equivocal left main coronary artery disease after deferral of surgical revascularization on the basis of fractional flow reserve measurements. Am Heart J 2006; 152(1): 156-9.
29. Jimenez-Navarro M, Hernandez-Garcia JM, Alonso-Briales JH, Kuhlmorgen B, Gomez-Doblas JJ, Garcia-Pinilla JM, et al. Should we treat patients with moderately severe stenosis of the left main coronary artery and negative FFR results? J Invasive Cardiol 2004; 16(8): 398-400.
30. Jasti V, Ivan E, Yalamanchili V, Wongpraparut N, Leesar MA. Correlations between fractional flow reserve and intravascular ultrasound in patients with an ambiguous left main coronary artery stenosis. Circulation 2004; 110(18): 2831-6.
31. Courtis J, Rodes-Cabau J, Larose E, Potvin JM, Dery JP, Larochelliere RD, et al. Usefulness of coronary fractional flow reserve measurements in guiding clinical decisions in intermediate orequivocal left main coronary stenoses. Am J Cardiol 2009; 103(7): 943-9.
32. Kang SJ, Lee JY, Ahn JM, Song HG, Kim WJ, Park DW, et al. Intravascular ultrasound-derived predictors for fractional flow reserve in intermediate left main disease. JACC Cardiovasc Interv 2011; 4(11): 1168-74.
33. de Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med 2014; 371(13): 1208-17.

How to cite this article: Khosravi A, Pourbehi MR, Pourmoghaddas M, Ostovar A, Akhbari MR, Ziaee-Bideh F, et al**. Evaluating the impact of fractional flow reserve-guided percutaneous coronary intervention in intermediate coronary artery lesions on the mode of treatment and their outcomes: An Iranian experience.** ARYA Atheroscler 2015; 11(2): 153-9.

Rare post-operative complications of large mediastinal tumor resection

Mohsen Mirmohammadsadeghi[(1)], Amir Mirmohammadsadeghi[(2)]

Case Report

Abstract

BACKGROUND: There are some reports in the literature, which suggest that cardiac tamponade drainage may transiently affect systolic function and also cause acute respiratory distress syndrome (ARDS). We did not find any reports of acute ventricular failure and ARDS secondary to mediastinal tumor resection without tamponade.

CASE REPORT: Here we report a 48-year-old woman presenting with massive pericardial effusion without tamponade in whom tumor was resected through median sternotomy using cardiopulmonary bypass. ARDS and acute heart failure were two rare complications that happened at the end of the operation secondary to a sudden decompression of the heart from tumor pressure.

CONCLUSION: ARDS and acute heart failure are two rare complications, which can happen after large mediastinal tumor resection.

Keywords: Heart Failure, Acute Respiratory Distress Syndrome, Mediastinal Neoplasms, Pericardium

Date of submission: 15 May 2014, ***Date of acceptance:*** 12 Jan 2015

Introduction

There are some reports in the literature, which suggest that cardiac tamponade drainage may transiently affect systolic function and also may cause acute pulmonary edema. Both cardiogenic and non-cardiogenic pulmonary edemas are reported in different cases as the cause of sudden deterioration in oxygenation after pericardiocentesis. Different etiologies of tamponade are reported, which are mostly malignant and one case of traumatic pericardial effusion.[1-5] In our case, a large anterior mediastinal tumor obviously compressing anterior elements of the heart caused massive pericardial effusion without tamponade and its resection caused sudden both ventricular failure and pulmonary edema.

Case Report

A 48-year-old female was consulted for recurrence of massive pericardial effusion. Pericardial window through left thoracotomy had been done 3 months ago for cardiac tamponade. The fluid cytology was negative. This time she had orthopnea without pulsus paradoxus. Laboratory data were normal. Chest X-ray (CXR) showed abnormal borders of the heart. Echocardiography revealed recurrence of massive pericardial effusion without right ventricular (RV) collapse. Ejection fraction was normal, and a suspicious mass on RV was reported. In computed tomography scan a large (10 × 7 cm) superior mediastinal mass containing calcific density foci suggesting mesenchymal origin was mentioned with pericardial effusion (Figure 1).

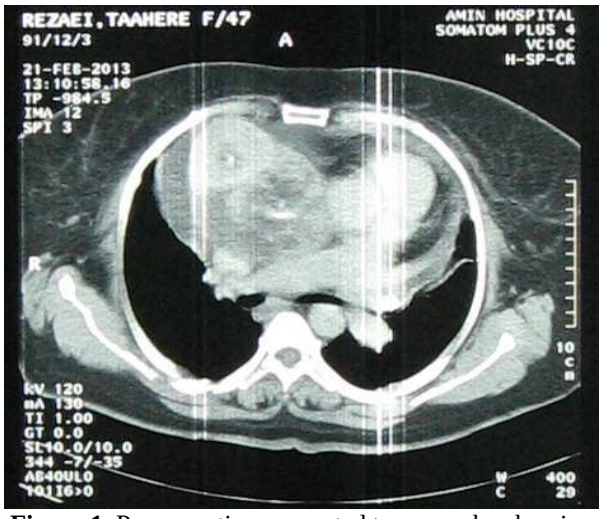


Figure 1. Pre-operative computed tomography showing a large (10 × 7 cm) superior mediastinal mass containing calcific density foci

1- Associate Professor, Department of Cardiovascular Surgery, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
2- Assistant Professor, Department of Cardiovascular Surgery, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Amir Mirmohammadsadeghi, Email: am_sadeghi@med.mui.ac.ir

Hence, she was prepared for operation. As midsternotomy was done a large whitish mass obscuring and compressing the heart was seen (Figure 2). After early dissections, although it had severe adhesions to superior vena cava, right atrium (RA), RV and specially aorta it seemed to be resectable. Cardiopulmonary bypass (CPB) was established through the femoral artery and RA cannulation after releasing RA from the tumor. The highly vascularized tumor was resected encapsulated only after careful dissections separating it from adhesive cardiac elements specially aorta. She came off CPB with low dose inotrope. But while hemostasis was being done oxygen saturation began to decrease and cardiac contractions became weak with sudden ventricular fibrillation, which was resistant to internal shocks and medications.

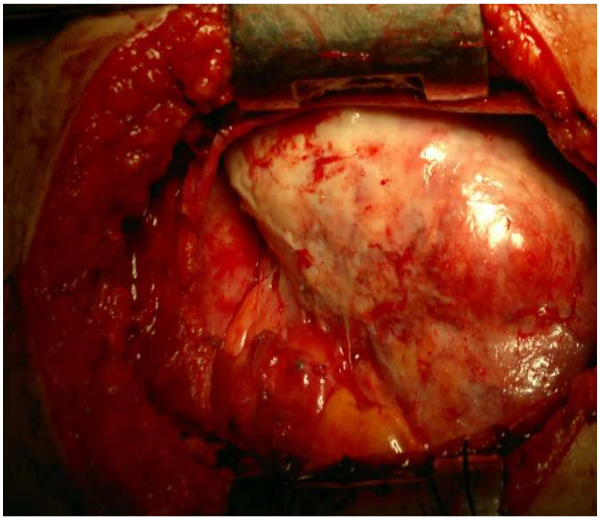


Figure 2. Intraoperative image of a large whitish extra-cardiac tumor obscuring superior vena cava, right atrium, aorta and pulmonary artery

During 15 min of internal cardiac massage about 15-20 internal shocks were given with various drugs. At last, heart began to contract in sinus rhythm again. Bleeding points were packed, and she was brought to intensive care unit after only closing the skin. Although high dose inotropes and 100% FiO_2 were supplied, oxygen saturation was about 60%. CXR showed patchy densities in both lungs similar to acute respiratory distress syndrome (ARDS). Echocardiography showed moderate RV dilatation and dysfunction with left ventricular (LV) ejection fraction of about 50%. Respiratory support for ARDS and inotropic support for RV failure was continued. After the 3rd post-operative day, arterial oxygen saturation began to rise and inotrope requirements were decreased. A multidrug-resistant Klebsiella pneumonia complicated the weaning course and tracheostomy was done. Pneumonia responsed to empirical fluconazole prescription. Furthermore, she was complicated with acute illness myopathy, which she could hardly move her extremities. Pathology report was 14 × 10 × 8 cm solid to cystic tumor, which after checking immunohistochemistry examinations solitary fibrous tumor was diagnosed. She was transferred from intensive care unit (ICU) on 3rd post-operative day and was discharged from hospital on 33rd post-operative day. Myopathy nearly completely resolved after 3 months of physiotherapy, but moderate RV failure did not resolve after 3 months despite no clinical symptoms.

Discussion

Pericardial effusion drainage either percutaneously or surgically may cause sudden ventricular failure either on the right heart or on the left heart in about 4.8% of the patients 1. Different terms are used for this complication, which we prefer "pericardial decompression syndrome."[1] Among some mechanisms, which are suggested for this complication is sudden decrease of pericardial pressure, which can lead to disproportionate increase in end-diastolic volume of the right ventricle compared with left ventricle and a temporary mismatch of the ventricular outputs.[2,3] Also, the presence of high peripheral vasoconstriction and volume overload may cause acute LV wall stress and LV failure after decompression.[2,3] Other mechanisms such as myocardial stunning because of a mismatch of oxygen distribution across the myocardial wall and altered coronary blood flow because of increased pericardial pressures are also mentioned.[2,3]

Another complication, which may happen early after sudden cardiac tamponade decompression is pulmonary edema.[2,4] It is hypothesized that LV dysfunction following pericardiocenthesis and preload increase causes the problem.[2,4]

In this case, patient was presented with recurrence of massive pericardial effusion secondary to large anterior mediastinal tumor. In contrast to all reported cases, this case had no cardiac tamponade and were the first case in which external tumor pressure was the cause of this complication.[1-5] The cardiac failure was mainly on the right side and although she clinically improved after 3 days RV failure and dilatation remained in moderate severity even after 3 months. In contrast to our case in some

reports ventricular function has been completely resolved; may be chronic tumor pressure on myocardium causes fibrosis and partially reversible myocardial damage. The pulmonary edema was non-cardiogenic ARDS and was presented with decreased PaO_2 and diffuse patchy densities on the CXR. The same as some case reports our patient improved clinically by day 3, but in some other reports the patients did not survive.[2,5]

We suggest ventricular failure and ARDS be kept in mind as possible early intraoperative complications of decompression of the heart from extra-cardiac tumor pressure.

Acknowledgments

The authors would like to thank all members of the Chamran Heart Center operating room in Isfahan, Iran.

Conflict of Interests

Authors have no conflict of interests.

References

1. Angouras DC, Dosios T. Pericardial decompression syndrome: a term for a well-defined but rather underreported complication of pericardial drainage. Ann Thorac Surg 2010; 89(5): 1702-3.
2. Karamichalis JM, Gursky A, Valaulikar G, Pate JW, Weiman DS. Acute pulmonary edema after pericardial drainage for cardiac tamponade. Ann Thorac Surg 2009; 88(2): 675-7.
3. Bernal JM, Pradhan J, Li T, Tchokonte R, Afonso L. Acute pulmonary edema following pericardiocentesis for cardiac tamponade. Can J Cardiol 2007; 23(14): 1155-6.
4. Shenoy MM, Dhar S, Gittin R, Sinha AK, Sabado M. Pulmonary edema following pericardiotomy for cardiac tamponade. Chest 1984; 86(4): 647-8.
5. Sunday R, Robinson LA, Bosek V. Low cardiac output complicating pericardiectomy for pericardial tamponade. Ann Thorac Surg 1999; 67(1): 228-31.

How to cite this article: Mirmohammadsadeghi M, Mirmohammadsadeghi A. **Rare post-operative complications of large mediastinal tumor resection.** ARYA Atheroscler 2015; 11(2): 160-2.

Long-term pulmonary functional status following coronary artery bypass grafting surgery

Hamid Rouhi-Boroujeni[(1)], Hojjat Rouhi-Boroujeni[(2)], Parnia Rouhi-Boroujeni[(3)], Morteza Sedehi[(4)]

Short Communication

Abstract

BACKGROUND: The present study aimed to describe the long-term alterations of pulmonary function and also to describe its association with post-operative pain after coronary artery bypass grafting (CABG) surgery.

METHODS: In this prospective study, thirty non-smoker male patients undergoing isolated on-pump CABG were consecutively included in this study. Pulmonary function measurements were performed, in a sitting position, preoperatively, a week postoperatively, and 6 months after the surgery using a Medical Graphics PF/Dx pulmonary function system. Pain was determined by using visual analog scale (VAS) pain scores with a standardized questionnaire's.

RESULTS: Regarding functional class, all patients had New York Heart Association (NYHA) Class II to III. A week after operation, a severe restrictive pulmonary impairment was revealed with a mean decrease in VC to 60.9 ± 9.2% and in forced expiratory volume in one second (FEV1) to 64.6 ± 12.2% of pre-operative values ($P < 0.001$). Regarding sternotomy related pain, the mean pain VAS score was preoperatively 3.3 ± 1.5 that reached to 6.2 ± 2.5 and 4.8 ± 2.2 1 week and 6 months after the operation ($P < 0.001$). The trend of the changes in pain score within 6 months of operation was significantly similar to the trend of the changes in some pulmonary function indices such as FEV% and residual volume (RV).

CONCLUSION: A significant reduction is expected in most pulmonary functional parameters following CABG despite normal pulmonary function state preoperatively. Severe pain originated from sternotomy may be an important factor related to pulmonary dysfunction following CABG.

Keywords: Pulmonary Functional, Coronary Artery Bypass Grafting, Post-Operative Pain

Date of submission: 19 May 2014 ***Date of acceptance:*** 18 Oct 2014

Introduction

The development of pulmonary functional problems such as atelectasis, reduce of oxygenation, and also severe decrease of function parameters such as lung volumes are common findings in patients who undergoing surgical revascularization.[1,2] The correct etiologies of these pulmonary changes remained questioned, however, seems to be multifactorial probably related to anesthesia reactions, diaphragmatic dysfunction, sensitivity to medications, changes in hemodynamic parameters, intra-operative events, and post-operative pain.[3-6] The decrease in pulmonary function was firstly described that suggested as the consequences of post-operative pain rose from sternotomy.[7-9] Thereafter, various studies focused the main reasons for appearing pulmonary dysfunction. Some could show significantly reducing dynamic lung volumes and also expiratory flow rates occurred early after coronary revascularization; while pulmonary dysfunction has been also reported long-term after this procedure in a few studies.[10,11] Moreover, there are a few published evidences on the long-term alterations of pulmonary function following coronary artery bypass grafting (CABG) surgery.[12,13] Hence, the present study aimed to describe the long-term alterations of pulmonary function and also to describe its association with post-operative pain after CABG surgery.

1- Clinical Biochemistry Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran
2- Member of Student Research Committee, Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran
3- Department of Pharmacology, School of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran
4- Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran
Correspondence to: Hojjat Rouhi-Boroujeni, Email: dr_rohib@yahoo.com

Materials and Methods

Study design and participants: In this prospective study, 30 nonsmoker male patients undergoing isolated on-pump CABG were consecutively included in the study. Those who had unstable angina, previous cardiac surgery or severe renal dysfunction were excluded. Informed consent was obtained from each participant and Ethical Committee of Shahrekord University, Iran, approved the study.

Operation was conducted on general anesthesia with the same anesthesia protocols for all with cardiopulmonary bypass through a median sternotomy. Postoperatively, the patients were ventilated with a positive end-expiratory pressure of 5 cm H_2O and an inspired oxygen concentration of 60 to 80%. After extubation, all subjects received pain relief with morphine and paracetamol according to their needs along with routine post-operative protocol. The patients also received basic post-operative care as conventionally used at our hospital. Pain was measured by an 11-point pain scale (0, no pain, 10, maximal imaginable pain).[12] Pulmonary function tests were performed in the usual manner on PODs 7 and 14 by portable spirometer (Autospiro AS-303, Minato Medical Science Co Ltd., Osaka, Japan). Recovery rates of forced vital capacity (FVC), vital capacity (VC), and forced expiratory volume in one second (FEV1) were expressed by the percent of predicted values that were calculated by numbers of resected pulmonary segments:

Predicted value (ml) = pre-operative value (ml) * (19-the number of resected segment)/19

Pulmonary function measurements were performed, in a sitting position, preoperatively, a week postoperatively, and 6 months after the surgery using a Medical Graphics PF/Dx Pulmonary Function System. In this regard, the highest value of two or three technically satisfactory maneuvers was retained for measurement of VC, inspiratory capacity (IC), FEV1 and peak expiratory flow rate (PEFR). FEV% was calculated as FEV1 in percentage of VC. Functional residual capacity (FRC) and residual volume (RV) were measured with the single-breath nitrogen was Hout technique. Total lung capacity (TLC) was also calculated as VC + RV. The single-breath carbon monoxide diffusing capacity (DLCO) was measured according to the method previously described.[14] The DLCO values were corrected using the standard equation on hemoglobin concentration.[15] On above three-time points of surgery, sternotomy wound pain was also quantified at rest using a continuous unmarked visual analog scale (VAS) ranged from 0 (no pain) to10 (worst imaginable pain).

Statistical analysis: Results were presented as mean ± standard deviation for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. The one-way repeated-measures ANOVA and post-hoc Bonferroni test were used. For the statistical analysis, the statistical software SPSS for Windows (version 20, SPSS Inc., Chicago, IL, USA) was used. $P = 0.05$ or less were considered statistically significant.

Results

The average age of the patients was 67.75 ± 10.25 years, and the mean body mass index was 25.58 ± 4.41 kg/m^2. Regarding functional class, all patients had New York Heart Association (NYHA) class II to III. Furthermore, mean left ventricular ejection fraction was 61.95 ± 12.22%. Before surgery, all patients had normal lung function related to the reference values of VC as 92.6 ± 13.4% of predicted and FEV1 as 98.8 ± 20.4% of predicted. A week after operation, a severe restrictive pulmonary impairment was revealed with a mean decrease in VC to 60.9 ± 9.2% and in FEV1 to 64.6 ± 12.2% of pre-operative values ($P < 0.001$). Six month after surgery, reduction in some parameters including PEFR, FRC, TLC and DLCO were still found compared to pre-operative values ($P < 0.001$), whereas no significant abnormality was shown in FEV, RV and DLCO/VA ($P = 0.543$, $P = 0.765$ and $P = 0.064$, respectively) as shown in table 1. Regarding sternotomy related pain, the mean pain VAS score was preoperatively 3.3 ± 1.5 that reached to 6.2 ± 2.5 and 4.8 ± 2.2 1 week and 6 months after operation. The trend of the changes in pain score within 6 months of operation was significantly similar to the trend of the changes in some pulmonary function indices such as FEV% and RV.

Discussion

Our study could show a significant reduce in most pulmonary functional parameters following CABG despite normal pulmonary function state preoperatively. Also, to determine the association between sternotomy related pain score and changes in these parameters, we could show a similarity between the trends of the changes in some pulmonary function indices and pain score following CABG. On the other hand, pulmonary function state can be potentially affected by post-sternotomy pain severity. Of course, post-operative pain is not only predictor for post-operative pulmonary dysfunction. In some previous studies,

Table 1. Pulmonary function and pulmonary diffusing capacity data preoperatively, on the 7th post-operative day and 6 months after coronary artery bypass grafting (CABG)

	Pre-operative	1 week after	6 months after	P
VC	64.1 ± 0.4	60.9 ± 9.2*	61.4 ± 0.6*	
IC	3.7 ± 0.2	2.2 ± 0.1*	2.2 ± 0.3*	< 0.001
FEV1	73.4 ± 0.5	64.6 ± 12.2*	68.4 ± 0.2*	
FEV	74.4 ± 8.2	78.2 ± 8.9	72.2 ± 7.8	0.543
PEFR	557.3 ± 125.1	354.7 ± 118.9*	477.2 ± 127.5*	< 0.001
FRC	3.3 ± 0.6	2.2 ± 0.7*	2.8 ± 0.5*	0.020
RV	2.2 ± 0.6	1.7 ± 0.4	2.0 ± 0.6	0.765
TLC	6.6 ± 0.2	4.4 ± 0.5*	5.8 ± 0.3*	< 0.001
DLCO	23.3 ± 5.8	15.5 ± 3.1*	22.5 ± 5.5*	
DLCO/VA	3.3 ± 0.6	3.8 ± 0.8	3.8 ± 0.7	0.064
VAS score	3.3 ± 1.5	6.2 ± 2.5*	4.8 ± 2.2*	< 0.001

* Significant P value obtained by Tukey Post hoc; VC: Vital capacity; IC: Inspiratory capacity; FEV1: Forced expiratory volume in one second; PEER: Peak expiratory flow rate; FRC: Functional residual capacity; RV: Residual volume; TLC: Total lung capacity; DLCO: Single-breath carbon monoxide diffusing capacity; VAS: Visual analogue scale

aging has been also shown as a strong predictor for pulmonary dysfunction after major surgeries. It has been demonstrated that a decrease in pulmonary function is to be expected for reasons of ageing in longtime after surgery. According to reference values,[16,17] the normal reduction is for VC and FEV1 about 20-30 and for FRC 10 ml per year in nonsmokers. Also, the type of arteries or veins used as grafts may also be another determinant for deterioration of pulmonary functional state as previously by Vargas et al.[2] study. In their study, on the first post-operative day, the FVC decreased to 33% of the pre-operative value in the saphenous vein graft group and to 29% in the internal mammary artery group. The spirometry gradually improved, but after 10 days, the FVC remained reduced. Although the decreases in FVC tended to be greater in the internal mammary artery group, there was no significant difference in the two groups. The changes in FVC were not significantly related to age, smoking history, anesthesia or pump time. In another study by Westerdahl et al.,[18] 4 months postoperatively, the patients still showed a significant decrease (6-13% of pre-operative values) in VC, IC, FEV1, peak expiratory flow rate (PEER), FRC, TLC, and DLCO. RV and DLCO per litre of alveolar volume had returned to the pre-operative level. Four months postoperatively, the median values for sternotomy pain while taking a deep breath was 0.2 and while coughing 0.3 on a 10 cm visual analogue pain scale. In another study by Ergun and Sirlak[19] in the results the post-operative PFT values were significantly decreased. However, the RV, RV% and RV/TLC values were not changed significantly. In the investigation by Shenkman et al.,[11] a more pronounced decrease in pulmonary function is described after cardiac surgery. No static lung volumes or dilution capacity were measured, but the FVC was reduced by an average of 25% in FEV1 and PEFR 3-4 months after surgery. FEF50, FEF75 and maximal voluntary ventilation did not recover at all 3.5 months postoperatively compared to 3 weeks after surgery. This indicates that pulmonary function after cardiac surgery is long lasting, and may even be permanent.

Many factors that may have an influence on the impairment have been suggested. Altered mechanics after opening of the thorax, reduced rib cage expansion and uncoordinated chest wall motion may possibly persist for several months. Both respiratory muscle weakness and alterations in chest wall mechanics induced by surgery may contribute to these changes.[9,20] Basal atelectasis develops early during anesthesia and possibly will persist into the post-operative period.[21] We could show that severe pain originated from sternotomy may be an important factor related to pulmonary dysfunction following CABG beside other factors related to the chest wall deformation or pulmonic dynamic changes.

Acknowledgments

This study was approved and supported by the Shahrekord University of Medical Sciences.

Conflict of Interests

Authors have no conflict of interests.

References

1. Tenling A, Hachenberg T, Tyden H, Wegenius G, Hedenstierna G. Atelectasis and gas exchange after cardiac surgery. Anesthesiology 1998; 89(2): 371-8.

2. Vargas FS, Terra-Filho M, Hueb W, Teixeira LR, Cukier A, Light RW. Pulmonary function after coronary artery bypass surgery. Respir Med 1997; 91(10): 629-33.
3. Cohen AJ, Moore P, Jones C, Miner TJ, Carter WR, Zurcher RP, et al. Effect of internal mammary harvest on postoperative pain and pulmonary function. Ann Thorac Surg 1993; 56(5): 1107-9.
4. Schuller D, Morrow LE. Pulmonary complications after coronary revascularization. Curr Opin Cardiol 2000; 15(5): 309-15.
5. Taggart DP. Respiratory dysfunction after cardiac surgery: effects of avoiding cardiopulmonary bypass and the use of bilateral internal mammary arteries. Eur J Cardiothorac Surg 2000; 18(1): 31-7.
6. Meyerson J, Thelin S, Gordh T, Karlsten R. The incidence of chronic post-sternotomy pain after cardiac surgery--a prospective study. Acta Anaesthesiol Scand 2001; 45(8): 940-4.
7. Braun SR, Birnbaum ML, Chopra PS. Pre- and postoperative pulmonary function abnormalities in coronary artery revascularization surgery. Chest 1978; 73(3): 316-20.
8. Ferdinande P, Lauwers P, Van BL, Van de Walle J. Pulmonary function tests before and after open heart surgery. Acta Anaesthesiol Belg 1980; 31(Suppl): 127-36.
9. Shapira N, Zabatino SM, Ahmed S, Murphy DM, Sullivan D, Lemole GM. Determinants of pulmonary function in patients undergoing coronary bypass operations. Ann Thorac Surg 1990; 50(2): 268-73.
10. Johnson D, Hurst T, Thomson D, Mycyk T, Burbridge B, To T, et al. Respiratory function after cardiac surgery. J Cardiothorac Vasc Anesth 1996; 10(5): 571-7.
11. Shenkman Z, Shir Y, Weiss YG, Bleiberg B, Gross D. The effects of cardiac surgery on early and late pulmonary functions. Acta Anaesthesiol Scand 1997; 41(9): 1193-9.
12. DeLoach LJ, Higgins MS, Caplan AB, Stiff JL. The visual analog scale in the immediate postoperative period: intrasubject variability and correlation with a numeric scale. Anesth Analg 1998; 86(1): 102-6.
13. Grimby G, Soderholm B. Spirometric Studies in Normal Subjects. Acta Medica Scandinavica 1963; 173(2): 199-206.
14. Blakemore WS, Forster RE, Morton JW, Ogilvie CM. A standardized breath holding technique for the clinical measurement of the diffusing capacity of the lung for carbon monoxide. J Clin Invest 1957; 36(1 Part 1): 1-17.
15. Cotes JE, Chinn DJ, Quanjer PH, Roca J, Yernault JC. Standardization of the measurement of transfer factor (diffusing capacity). Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 1993; 16: 41-52.
16. van Belle AF, Wesseling GJ, Penn OC, Wouters EF. Postoperative pulmonary function abnormalities after coronary artery bypass surgery. Respir Med 1992; 86(3): 195-9.
17. Hedenstrom H, Malmberg P, Fridriksson HV. Reference values for lung function tests in men: regression equations with smoking variables. Ups J Med Sci 1986; 91(3): 299-310.
18. Westerdahl E, Lindmark B, Almgren SO, Tenling A. Chest physiotherapy after coronary artery bypass graft surgery-a comparison of three different deep breathing techniques. J Rehabil Med 2001; 33(2): 79-84.
19. Ergun A, Sirlak M. Pulmonary function test before and after operation of coronary artery by-pass surgery. Tuberk Toraks 2003; 51(1): 17-22.
20. Locke TJ, Griffiths TL, Mould H, Gibson GJ. Rib cage mechanics after median sternotomy. Thorax 1990; 45(6): 465-8.
21. Lundquist H, Hedenstierna G, Strandberg A, Tokics L, Brismar B. CT-assessment of dependent lung densities in man during general anaesthesia. Acta Radiol 1995; 36(6): 626-32.

How to cite this article: Rouhi-Boroujeni H, Rouhi-Boroujeni H, Rouhi-Boroujeni P, Sedehi M. **Long-term pulmonary functional status following coronary artery bypass grafting surgery.** ARYA Atheroscler 2015; 11(2): 163-6.