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ARYA Atherosclerosis

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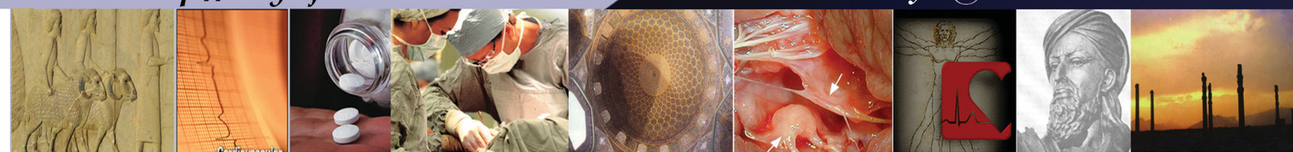

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Orthopedic problems: An underestimated hidden risk factor for development and progression of atherosclerosis; An inconspicuous joint link

Mohaddeseh Behjati[(1)]

Editorial

Date of submission: 12 Nov 2014, *Date of acceptance:* 13 May 2015

Introduction

Regular leisure time and occupational physical activity exerts beneficial effects on cardiovascular health.[1] Healthy life style and physical activity behaviors diminish overall rate of coronary artery disease (CAD) among both female and male gender.[2] Favorable effects of physical activity have been proven concerning cardiovascular disease (CVD) morbidity and mortality.[3] It improves cardiovascular function and compliance. Even modest physical activity minimizes the risk of CVD occurrence.[4]

Regular exercise impacts numerous health benefits in older people including improvement in blood pressure, osteoarthritis, osteoporosis, diabetes mellitus, lipid profile, CVD, neurocognition function, mood and overall morbidity and mortality.[3] Physical activity has beneficial dose-dependent effects on blood pressure via reaching a plateau level.[5] Cardioprotective effects of life-long physical activity and endurance exercise against cardiac insults are well-elucidated in both young and old age population.[6] Beneficial impacts of physical activity occur at various cellular organizations as mitochondria. Regular physical activity accompanies with cessation of cigarette smoking, decreased consumption of saturated fatty acids, reaching and maintenance of ideal body weight and decreased stress level which are all involved in achievement of cardiovascular health.[6]

Our ancestors were obligated to exert higher levels of physical activity in order to survive and that partly explains lower prevalence of this human-made disease in ancient nations. Modern life brought enhanced sitting time by facilitating achievement of daily requirements. Voluntary physical inactivation is a threat for majority of population, but by increasing the percentage of old age population, the ratio of people with involuntary physical inactivity will enhance dramatically. Physical activity behaviors might exist but converting it into action needs proper functioning of neuromusculoskeletal system. Therefore, this unintentional physical inactivity prohibits deriving cardiovascular benefits from physical activity. Thus, the aim of this article is to scheme an overview on inconspicuous link between orthopedic problems and CVD.

Orthopedic disorders bring great limitation for accomplishment of regular physical activity both in young and old people. Orthopedic problems are predisposing factors for lack of proper physical activity and alarming increase in sedentary habits. Considering the established association between physical activity and cardiovascular health, hints towards regular physical activity renders provocation of development and progression of atherosclerosis. Primarily, orthopedic insufficiency might prevent access to therapeutic pills and other therapeutic interventions. Thus, poor adherence and non-adherence to medical advises as effort to attend in follow-up sessions is another side of the coin. Depression related to impaired locomotion is also contributing to the progression of CVD.[7]

Since some of orthopedic disorders occur in the setting of underlying inflammatory conditions, the underlying inflammatory background bridges the gap between healthy and unhealthy cardiovascular system.[8] The delicate inter-relationship between vitamin D on both CVD and vitamin-D-deficiency-related bone disorders are also proposed. Heart failure is

1- Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Mohaddeseh Behjati, Email: behjati@med.mui.ac.ir

considered as an increased risk factor for development of subsequent orthopedic bone fracture.[9]

This is not the whole story. Orthopedic disorders are associated with CVDs in other ways. Some side effects of orthopedic problems are the leading causes of CVD, as occurrence of venous thromboembolism (VTE) after orthopedic surgeries or bed rest. Indeed, adverse side effects of applied medications as non-steroid anti-inflammatory drugs (NSAIDs) sand corticosteroids on cardiovascular system health should not be neglected. Figure 1 is schematic view for demonstration of links between orthopedic disorders and cardiovascular diseases.

Obviously, this could not be a primary risk factor for CVD. Since orthopedic disorders are mainly happening in old age as the same with CVD, these orthopedic problems could be considered as risk factor or even co-risk factors for development and progression of CVD. In better word, orthopedic problems could be considered as a secondary or tertiary risk factor for the onset and follow up of CAD. In brief, the current state of orthopedic disorders as secondary or tertiary risk factor for CVD is not definite due to the lack of clinical trials in this regard. Involuntary physical inactivity is not merely related to orthopedic problems, but each condition which compromise bodily locomotion should be considered as a risk factor for CVD. Considering this hidden risk factor, physicians should try to dampen the negative effects of this negative risk factor. But practically, the general advice of "having moderate intensity amounts of regular physical activity as walking through the park, running or cycling" should be avoided. The type of physical interventions should be personalized and physicians should advocate patients to find practical exercise prescription per case.

Conflict of Interests

Authors have no conflict of interests.

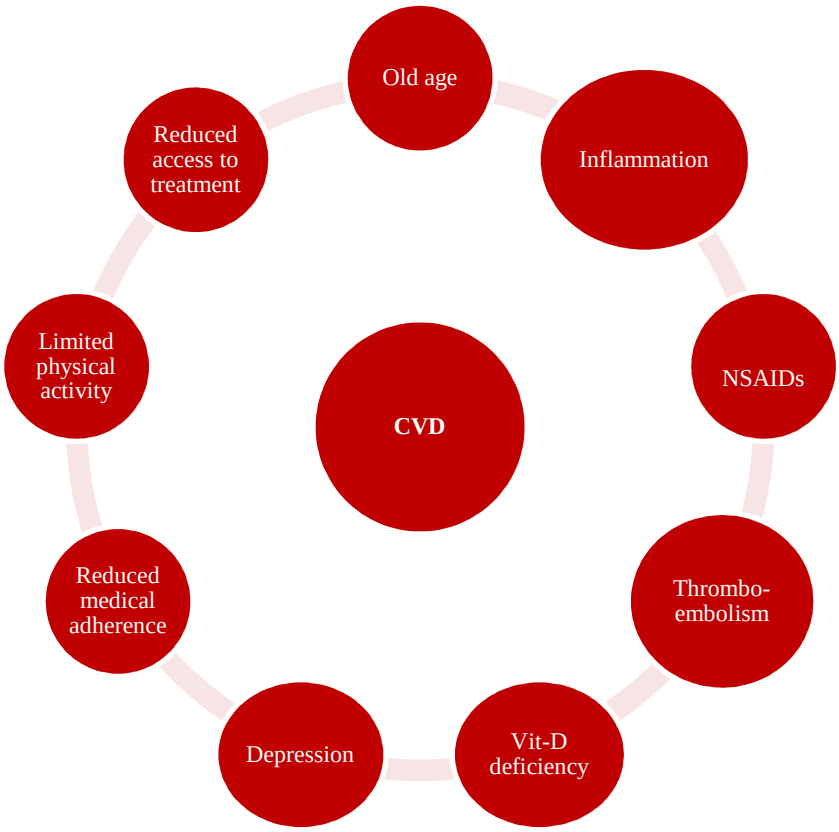

Figure 1. The schematic view for demonstration of links between orthopedic disorders and cardiovascular diseases (CVD)
NSAIDs: Non-steroid anti-inflammatory drugs

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Lipid peroxidation and antioxidant enzymes activity in controlled and uncontrolled Type 2 diabetic patients

Mahnaz Zarei[(1)], Zahra Farahnak[(1)], Mohammad Javad Hosseinzadeh-Attar[(2)], Mohammad Hassan Javanbakht[(3)], Payam Hosseinzadeh[(4)], Hoda Derakhshanian[(1)], Payam Farahbakhsh-Farsi[(3)], Mahmoud Djalali[(5)]

Original Article

Abstract

BACKGROUND: This study was designed to compare lipid peroxidation and antioxidant enzymes activity in Type 2 diabetes patients with good or weak glycemic control.

METHODS: In this case-control study, 62 Type 2 diabetic patients with glycated hemoglobin (HbA1c) between 6 and 8 were enrolled as the controlled group and 55 patients with HbA1c > 8 were selected as an uncontrolled group. Patients were all referred to Iranian Diabetes Association in Tehran, Iran, from 2010 onward. Groups were chosen by convenience sampling and were matched based on age, sex and duration of disease. Demographic questionnaire, two 24-hour food recall, HbA1c, insulin, malondialdehyde (MDA), superoxide dismutase (SOD), and catalase were measured in blood samples. Data were analyzed by Food Processor II and SPSS software.

RESULTS: A mean daily consumption of energy, carbohydrate, protein, and fat was not significantly different between two groups. MDA in the uncontrolled group was significantly higher than controlled group (2.03 ± 0.88 vs. 1.65 ± 1.01 nmol/ml; P = 0.030). A mean SOD was slightly higher in the uncontrolled group comparing to the control group (843.3 ± 101.9 vs. 828.0 ± 127.3 U/g Hb; P = 0.400).

CONCLUSION: These data suggest that MDA as a lipid peroxidation indicator is higher in uncontrolled diabetes probably due to chronic high blood sugar followed by higher oxidative stress.

Keywords: Antioxidant, Lipid Peroxidation, Diabetes Mellitus

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Introduction

Diabetes mellitus, one of the most common endocrine disorders, is known as high fasting blood sugar (FBS) more than 126 mg/dl threshold.[1] Hyperglycemia is a major factor in the development of diabetic complications.[2-4] However, the mechanism by which these changes occur is not clear. Glycosylated hemoglobin (HbA1c), which reflects long-term (2-3 months) control of blood glucose, is more reliable and valid compared with the FBS.[5] HbA1c < 7% is considered as well diabetes control according to the American Diabetes Association. The association has advised physicians and patients that when the HbA1c levels exceed 8% may be related to developing of diabetes micro- and macro-vascular complications,[6] and additional medical therapies are needed.[7] Hence, the HbA1c levels of 8% were considered in this study as cut-off point for allocating patients into two groups (controlled and uncontrolled). Chronically high blood sugar

1- Department of Cellular and Molecular Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
2- Associate Professor, Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
3- Assistant Professor, Department of Cellular and Molecular Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
4- Department of Nutrition and Biochemistry, The International Campus, Tehran University of Medical Sciences, Kish, Iran
5- Professor, Department of Cellular and Molecular Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
Correspondence to: Mahmoud Djalali, Email: mjalali87@yahoo.com

can be seen in patients with diabetes, and this may increase glycosylation and peroxidation processes which may lead to oxidative stress and resulting changes in structure and function of proteins and lipids.[8] In comparison with other cells, red blood cells are more prone to oxidative damage due to the high levels of iron and poly-unsaturated fatty acids and also their role in oxygen transportation.[9] Lipid hydroperoxides are degraded into the harmful aldehydes, such as malondialdehyde (MDA), in the presence of iron and copper ions. Therefore, MDA is considered as an indicator of lipid peroxidation and its value is used as indirect method of measuring free radicals.[10]

Superoxide dismutase (SOD) and catalase are important antioxidant enzymes which play a role in oxidant defense of body and often as the first line of defense against oxidative crisis.[11]

Some studies have previously evaluated the status of MDA and antioxidant enzymes in diabetic and healthy individuals.[12-14] However, this study was designed and performed for the first time to compare lipid peroxidation and antioxidant enzymes in Type 2 diabetes patients with good or weak control.

Materials and Methods

In this study, 62 Type 2 diabetic patients with HbA1c between 6 and 8 were enrolled as the controlled group and 55 patients with HbA1c > 8 were selected as uncontrolled group. Patients were all referred to Iranian Diabetes Association in Tehran, Iran, from 2010 onward. Groups were chosen by convenience sampling and were matched based on age, sex and duration of disease. A sample size of at least 50 patients in each group was estimated according to previous reports on leptin and adiponectin with the assumption of 80% power, and a 0.05 level of significance. The level of body mass index (BMI) was not different between groups. Inclusion criteria included fasting blood glucose above 126 mg/dl, HbA1c levels more than 6, the minimum age of 40 years, at least 3 years of diagnosed diabetes, consumption of oral hypoglycemic drugs, and consent for cooperation in this research study. Meanwhile, the exclusion criteria were insulin injections, supplementation with vitamins A, C, E and omega-3, history of hepatic, renal, cardiovascular, thyroid, or respiratory diseases. All the process was in the patient privacy and in accordance with Declaration of Helsinki-Ethical Principles for Medical Research.

Demographic data, including age, sex, and duration of diabetes, were recorded. Weight was measured using a digital scale (803, Seca Clara, Germany) with an accuracy of 100 g, in light clothes and without shoes. Height was measured without shoes using a stadiometer (206, Seca, Germany) with an accuracy of 0.1 cm. Hip and waist circumferences were measured using a measuring tape (201, Seca, Germany) with an accuracy of 0.1 cm. BMI was calculated using these recorded values [weight (kg)/height^2 (m)]. In addition, two 24-hour food recall questionnaires were completed by an expert nutritionist. Then, the average daily intakes of calorie, protein, carbohydrate, and fat were calculated. After recording the necessary information and before taking oral hypoglycemic drugs, 10 ml of venous blood was taken in 12-hours fasting state by a laboratory expert. Samples were centrifuged in 3000 rpm for 10 minutes. Blood glucose, HbA1c, insulin, MDA, SOD, and catalase were then measured in blood samples. HbA1c was measured by an ion exchange chromatography using a NycoCard® Reader II instrument (Catalog ref 1042184, Axis-Shield poC AS, Oslo, Norway) on ethylenediaminetetraacetic acid anticoagulated samples; insulin was measured using insulin kits and serum MDA values were determined by the spectrophotometric method described by Satoh using thiobarbituric acid. This measurement is based on the reaction of MDA with thiobarbituric acid to form 1:2 adduct, which has a stable pink color that absorbs maximally at 532 nm.[15] Measurements of SOD activity in erythrocytes were done spectrophotometrically using Randox Kit (Cat # SD125, Crumlin, UK). Catalase activity was determined using spectrophotometric method and measuring the decrease in hydrogen peroxide absorbance at 240 nm wavelength.[16]

Table 1. Demographic characteristics and hematological indices in controlled and non-controlled Type 2 diabetes groups

Variable	Group		Independent sample t-test
	Non-controlled Type 2 diabetes (n = 55)	Controlled Type 2 diabetes (n = 62)	
	Mean ± SD	Mean ± SD	P
Age (year)	54.27 ± 7.53	56.82 ± 7.61	0.080
Weight (kg)	74.16 ± 10.94	72.34 ± 10.61	0.360
BMI (kg/m^2)	29.49 ± 4.34	27.65 ± 3.89	0.080
Duration of diabetes (year)	10.89 ± 6.41	9.94 ± 6.75	0.430
Insulin (µU/ml)	13.53 ± 9.74	8.76 ± 7.17	0.510
Insulin resistance	6.96 ± 5.67	2.95 ± 2.64	< 0.001
FBS (mg/dl)	214.36 ± 68.22	136.15 ± 40.59	< 0.001
HbA1c (%)	8.88 ± 0.64	7.09 ± 0.58	< 0.001

The controlled group (62 patients with 6 < HbA1c ≤ 8) and uncontrolled group (55 patients with HbA1c > 8); BMI: Body mass index; FBS: Fasting blood sugar; HbA1c: Glycated hemoglobin; SD: Standard deviation

A SPSS software for Windows (version 13.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis of data. After normalizing the distribution of data by log transformation, independent t-test was used for comparing the means of quantitative variables in two groups. Furthermore, the nutritional data were analyzed by Food Processor FP II (version 2, Esha Research, salem, OR). P = 0.050 or less were considered as the statistically significant difference.

Results

In this study, 117 non-insulin dependent Type 2 diabetic patients of both sexes that had passed at least 3 years of diabetes onset from Iran Diabetes Association were involved. Participants were divided into the well-controlled (62 patients: 27 female, 35 male) and uncontrolled (55 patients: 34 female, 21 male) group. Of all participants, 52.1% (61 patients) were female and 47.9% (56 patients) were male. Patients' characteristics are shown in table 1. Mean MDA, catalase, and SOD values in the two groups are given in table 2. The table 2 indicates that MDA in the uncontrolled diabetes group was significantly higher than controlled diabetes group (P = 0.030). Mean SOD was slightly higher in the uncontrolled group comparing to the control group but was not statistically significant (P = 0.480). Catalase was not much different between the two groups (P = 0.940). According to table 3, the most important variable affecting the level of catalase is protein intake. However, no variable had statistically significant effect on the level of SOD. Mean daily consumption of energy, carbohydrate, protein, and fat was not significantly different between well controlled and uncontrolled diabetes groups.

Discussion

Results obtained in this study suggest that MDA in uncontrolled diabetes group was significantly higher than the control group. In some studies, elevated HbA1c in patients with diabetes was associated with increased lipid peroxidation, while such a relationship has not been seen in some other studies.[17-19] Ahmed et al.[20] have been found that high blood glucose levels lead to increased oxidative stress, and consequently, MDA levels may increase.

Table 2. Comparison of mean malondialdehyde (MDA), catalase and superoxide dismutase between controlled and non-controlled Type 2 diabetes groups

Variable	Group		Independent sample t-test
	Non-controlled Type 2 diabetes (n = 55)	Controlled Type 2 diabetes (n = 62)	
	Mean ± SD	Mean ± SD	P
MDA (nmol/ml)	2.01 ± 0.88	1.63 ± 1.01	0.030
Catalase (k/gHb)	205.12 ± 47.25	206.11 ± 80.49	0.940
SOD (U/gHb)	843.30 ± 101.90	828.00 ± 127.30	0.480

MDA: Malondialdehyde; SOD: Superoxide dismutase, Hb: Hemoglobin; SD: Standard deviation

Table 3. Comparison of mean energy, quantity and percent of carbohydrate, protein and fat intakes between controlled and non-controlled Type 2 diabetes groups

Variable	Group		Independent sample t-test
	Non-controlled Type 2 diabetes (n = 55)	Controlled Type 2 diabetes (n = 62)	
	Mean ± SD	Mean ± SD	P
Energy (kcal)	1330.22 ± 442.37	1416.21 ± 447.26	0.300
Carbohydrate (g)	196.37 ± 72.62	211.96 ± 80.02	0.270
Carbohydrate (%)	58.88 ± 8.16	59.56 ± 8.39	0.660
Protein (g)	53.08 ± 17.74	59.03 ± 19.72	0.090
Protein (%)	16.23 ± 3.12	16.97 ± 3.82	0.260
Fat (g)	40.71 ± 19.92	41.37 ± 17.16	0.850
Fat (%)	27.48 ± 8.72	26.39 ± 7.07	0.460

SD: Standard deviation

Seghrouchni et al.[21] have found that patients with Type 2 diabetes had a higher thiobarbituric acid reactive substances value than those with Type 1 diabetes. They have claimed that patients with Type 2 diabetes are more extendedly exposed to oxidative stress. In this study, the rate of catalase activity was not much different in the two groups (206.11 ± 80.49 vs. 205.12 ± 45.25). In Ahmed et al.[20] study the activity of catalase and SOD were significantly higher in the diabetic group than the healthy group.

Colak et al.[22] showed that anti-oxidative defense reduces in Type 2 diabetics, which negatively correlates with glucose concentrations and duration of diabetes and cardiovascular complications. In another study aiming to evaluate the effect of blood glucose control on catalase, catalase levels in patients with diabetes (HbA1c more than 8%), did not differ from healthy controls. However, after 3 months of hypoglycemic drugs consumption, catalase levels in patients with diabetes was less than the control group.[20]

In this study, subjects in both groups (controlled and uncontrolled diabetes) have been taking hypoglycemic agents (metformin or glibenclamide) and the strong sweeper effects of these drugs may have diminished the difference of catalase amount between the two groups.

Increase of free radicals in diabetes may increase antioxidant enzyme activities. In addition, high blood glucose can combine with the protein enzymes so that in patients with diabetes extracellular SOD is highly glycosylated comparing to healthy subjects.[23] Although, in some studies antioxidant enzymes such as SOD were inversely correlated with HbA1c, SOD in the present study was directly correlated with the level of FBS, HbA1c, and insulin resistance. However, these correlations were not statistically significant. In some other studies, no correlation was seen between SOD, FBS, and HbA1c. In present study higher SOD in uncontrolled diabetes group was an indicator of higher oxidative stress.

Other studies have evaluated the antioxidant status and SOD activity in patients with diabetes compared with healthy controls, but they did not found any significant differences between groups in terms of SOD activity.[22]

Furthermore, no significant relationship was observed between nutritional factors, MDA and SOD. It was previously reported that intake of antioxidant supplements can reduce reactive oxygen species and free radicals and may result in reducing lipid peroxidation.[24] In this study, vitamin supplements-such as vitamin A, C, E and omega-3 consumption-were among our exclusion criteria, so we had removed the effect of these confounding factors on the measurements and study results.[25] In this study, a mean percentage of protein intake was about 17% in both groups. The protein intake was the only nutritional factor which has affected the catalase level. The equal amount of protein intake in both groups was possibly one of the reasons that catalase was not so different between groups. This study encountered with a limited budget and sample

size. In future study, we can examine this variable with large sample size or with more sensitive indicator in diabetic patients.

Conclusion

MDA (lipid peroxidation indicator) is higher in uncontrolled diabetes (HbA1c > 8) probably due to chronic high blood sugar, followed by long and high oxidative stress. Furthermore, SOD is also higher in uncontrolled diabetes which might be an indicator of greater vascular damage in this group.

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Conflict of Interests

Authors have no conflict of interests.

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Comparison of health-related quality of life after percutaneous coronary intervention and coronary artery bypass surgery

Razieh Yazdani-Bakhsh[(1)], Mehdi Javanbakht[(2)], Masoumeh Sadeghi[(3)], Atefeh Mashayekhi[(4)], Hossein Ghaderi[(5)], Katayoun Rabiei[(6)]

Original Article

Abstract

BACKGROUND: Health-related quality of life (HRQOL) evaluation is an important measure of the impact of the disease. As more people with coronary heart disease (CHD) live longer, doctors and researchers want to know how they manage in day to day life. It looked like adults with CHD had a decrease QOL. The aim of this study was to comparison of HRQOL of patients who underwent percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) and to assess its main determinants in the whole sample of coronary artery disease (CAD) patients.

METHODS: The study was carried out to estimate HRQOL of 109 patients who underwent invasive coronary revascularization [PCI (n = 75) and CABG (n = 34)]. We applied HRQOL after 6 months and 2 years in both groups and scores were compared. The HRQOL data were obtained using MacNew Heart Disease questionnaire with dimensions emotional, physical and social that estimated. Data entry and analysis were performed by SPSS.

RESULTS: A total MacNew scale in CABG and PCI group in 6 months after treatment were 45.32 ± 13.75 and 53.52 ± 15.63, respectively (P = 0.010). After 2 years HRQOL mean changed to 51.176 ± 14.80 and 49.55 ± 16.22, respectively, in CABG and PCI group (P = 0.428). Our results in within-group analysis showed total MacNew scale and its subscales were changed significantly after 2 years in CABG and PCI group's scores were detected. We found in the whole sample of CAD patients those who had a higher level of income and education and were not either overweight or obese experienced better HRQOL.

CONCLUSION: Our results showed that patients who underwent PCI experienced significantly higher HRQOL in 6 months after revascularization but over 24 months follow-up no difference was observed between the two groups.

Keywords: Quality of Life, Percutaneous Coronary Intervention, Coronary Artery Bypass Graft, MacNew Scale, Iran

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Introduction

Coronary artery disease (CAD) is the result of the accumulation of atherosclerotic plaques within the walls of the coronary arteries leading to narrowing of the blood vessels, heart failure, angina pectoris, and myocardial infarction (MI). The CAD is the leading and the most common cause of morbidity and mortality in worldwide.[1-3] It is estimated that low- and middle-income countries contribute to about 80% of cardiovascular disease deaths in world.[4]

Recent data show a high prevalence of CAD and its risk factors such as cigarette smoking, diabetes mellitus, hypertension, dyslipidemia,

1- Health Management and Economic Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
2- Health Economics Research Unit, Institute of Applied Health Sciences, University of Aberdeen, Foresterhill, Aberdeen, Scotland
3- Professor, Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
4- Health Management and Economics Research Center AND School of Health Management and Information Sciences, Tehran University of Medical Sciences, Tehran, Iran
5- Department of Health Economics, School of Health Management and Information Sciences, Iran University of Medical Sciences, Tehran, Iran
6- Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Razieh Yazdani-Bakhsh, Email: razyazdany@gmail.com

low level of physical activity, and obesity among Iranian population.[5,6]

Although numerous studies have compared the outcomes of coronary revascularization between percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery but beyond the survival benefit of CABG and PCI, functional recovery is the expectation of patients who receive these treatments for relief of symptoms. Therefore, an importance of health-related quality of life (HRQOL) in clinical research has been extensively discussed over recent decades and there is an increasing recognition among clinicians and researchers that the impact of chronic illnesses and their treatments must be assessed in terms of their HRQOL in addition to more traditional measures of clinical outcomes—morbidity and mortality.[7,8] The HRQOL has also been used increasingly as a factor in cost effectiveness analysis and heath technology assessment that is used to determine the relative value for many of different forms of the treatment.[9] Hence, information on HRQOL of patients in different modes of coronary revascularization and its determinants is so important to defining a comprehensive plan of care. Since there are few studies regarding HRQOL of CAD in different therapeutic interventions in developing countries, therefore the main aim of this study was to comparison of HRQOL of patients who underwent CABG and PCI and to assess its main determinants in the whole sample of Iranian CAD patients.

Materials and Methods

A follow-up provident study was carried out after 6 and 24 months on patients who underwent coronary revascularization with either PCI or CABG. We identified between 20 March, 2010, and 20 September, 2010, about 389 patients underwent coronary revascularization at Chamran Heart Center of Isfahan, Iran. Before enrollment, the patients received detailed written and verbal information regarding the aims and protocol of the study and signed informed consent. If patients had ability to answer the questions, they filled it personally; otherwise a trained interviewer collected the necessary data through face-to-face interviews with respondents. The study has been approved by the Ethics Committee of the Isfahan University of Medical Sciences. Patients were excluded if they had prior PCI, CABG or also required valve surgery and passed < 6 months from their treatment. Finally among eligible patients, 109 [PCI (n = 75) and CABG (n = 34)] consented to enter the study. After treatment, 6 and 24 months QOL was evaluated to all participants of both groups.

The HRQOL data were obtained using MacNew Heart Disease HRQOL questionnaire that is a disease specific questionnaire designed to measure HRQOL in patients with cardiac disease, particularly MI and other types of ischemic heart disease.[10] The questionnaire validated and translated to Farsi by Asadi-Lari et al.[11] The MacNew consists of 27 questions that inquire about symptoms such as angina/chest pain, shortness of breath, fatigue, dizziness, and aching legs and finally summarized into three main domains, emotional, physical, and social wellbeing. Scoring of the MacNew is straight-forward the maximum possible score in any domain is 7 (high HRQOL) and the minimum is 1 (poor HRQOL). All scales were transformed so that they had a possible range of 0-100, with a higher score indicating a better level of functioning or HRQOL. Socio-demographic, clinical and comorbidity data were extracted from patients' medical records.

The continuous variables were expressed as a mean ± standard deviation and categorical variables as absolute numbers and percentages. We studied the association between and within groups in quantitative variables by paired Student's t-test and independent t-test. All statistical tests were two-sided and the significance level was set at 0.05. For QOL scores, distribution used Kolmogorov–Smirnov test. For the test of investigation, the relationship between data and demographics variables were analyzed by chi-square-test. A linear regression model was employed to examine the effect of variables and characters on QOL aspects in CAD patients. We used of Pearson correlation coefficient for study association of HRQOL with characteristics of patients. SPSS software for Windows (version

16.0, SPSS Inc., Chicago, IL, USA) was used to analysis the data.

Results

From all recruited patients 109 (after 6 months) and 106 persons (after 24 months) completed the questionnaire. One patient in CABG group and two patients in PCI group died during follow-up. Main characteristics of the studied patients are summarized in table 1. The two groups were tested for significant differences regarding socio-demographic and main comorbidity and clinical variables. As seen, the groups can be considered equivalent with no statistically significant differences between them (P > 0.050) except in education level (P = 0.009). The tests of HRQOL distribution were normal. The mean age of the patients in CABG and PCI group were 53.2 ± 5 and 51.2 ± 6.2 years, respectively,–did not show a significant difference (P = 0.207). Our results showed that, respectively, in CABG and PCI group (79.4%) and (85.3%) were male, (76.5%) and (50.7%) had < 6 grades education, (79.4%) and (86.7%) were employed, (47.1%)and (54.7%) were smoker, (26%) and (29.3%) had diabetes comorbidity, (32.4%) and (33.3%) had hypertension, (47.1%) and (52.0%) were overweight or obese, (38.2%) and (56.0%) had history of MI and (52.9%) and (53.3%) had hypercholesterolemia.

Between-group comparison results

Table 2 shows the mean difference scores for total and the three subscales of the MacNew in two groups 6 months and 2 years after revascularization. A cording to mean difference QOL score in 6 and 24 months after treatment by independent student's test in CABG and PCI were 8.20 ± 3.12 (P = 0.010) and 2.61 ± 3.28, respectively (P = 0.428). The overall QOL score in CABG and PCI group in 6 months after treatment were 45.32 ± 13.75 and 53.52 ± 15.63, respectively (P = 0.010). After 2 years these numbers changed to 51.17± 14.80 and 49.55 ± 16.22, respectively, in CABG and PCI group (P = 0.428). The highest score of the MacNew subscales was found in the physical (46.19 ± 14.87) and social (55.62 ± 16.75) subscales in CABG and PCI group (after 6 months). However, after 2 years, the best results of the MacNew subscales were related to the emotional subscales and the lowest score was related to physical dimension in both groups. The results showed significant different in 6 months after treatment (0.01), whereas HRQOL was not a significant difference between two groups (0.428) after 2 years (Table 2).

Table 1. Characteristics of patients in coronary artery bypass graft (CABG) (n = 34) and percutaneous coronary intervention (PCI) (n = 75) group

Indicator	CABG	PCI	P
	n (%)	n (%)	
Sex			
Male	27 (79.4)	64 (85.3)	0.438
Age			
< 50	8 (23.5)	29 (38.7)	0.123
≥ 50	26 (76.5)	46 (61.3)	
Education			
< 6 grade	26 (76.5)	38 (50.7)	0.009
≥ 6 grade	8 (23.5)	37 (49.3)	
Income			
Low	17 (50.0)	26 (34.7)	0.267
Middle	12 (35.3)	31 (41.3)	
High	5 (14.7)	18 (24.0)	
Employment			
Employed	27 (79.4)	65 (86.7)	0.328
Smoking	16 (47.1)	41 (54.7)	0.461
Diabetes	9 (26.5)	22 (29.3)	0.747
Hypertension	11 (32.4)	25 (33.3)	0.920
BMI			
< 25	18 (52.9)	36 (48.0)	0.626
≥ 25	16 (47.1)	39 (52.0)	
History of MI	13 (38.2)	42 (56.0)	0.086
Hypercholesterolemia	18 (52.9)	40 (53.3)	0.967

Chi-square test; CABG: Coronary artery bypass graft; PCI: Percutaneous coronary intervention; BMI: Body mass index; MI: Myocardial infarction

Within-group comparison results

Results of within-group by paired Student's t-test showed that in CABG group total MacNew scale were significantly increase (P = 0.001) but no significant in [emotional (P = 0.122), physical (P = 0.026), social (P = 0.064)]. While significantly decrease (0.016) in PCI group's scores and in subscale except of emotional (P = 0.244) difference significant on physical (P = 0.007) and social (P = 0.025) dimensions were detected (Table 3).

Table 2. The mean difference of MacNew Scale scores in coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) group 6 months and 2 years after revascularization (between-group comparison)

MacNew Scale	After 6 months	Mean ± SD	P	After 2 years	Mean ± SD	P
Total score						
CABG	45.32 ± 13.75	-8.20 ± 3.12	0.010	51.17 ± 14.80	2.61 ± 3.28	0.428
PCI	53.52 ± 15.63			49.55 ± 16.22		
Emotional						
CABG	46.15 ± 16.12	-7.60 ± 3.39	0.027	51.80 ± 17.20	0.65 ± 3.71	0.861
PCI	53.75 ± 16.53			51.14 ± 18.12		
Social						
CABG	45.29 ± 13.88	-10.33 ± 3.29	0.002	51.35 ± 15.10	0.47 ± 3.51	0.894
PCI	55.62 ± 16.75			50.88 ± 17.57		
Physical						
CABG	46.19 ± 14.87	-7.79 ± 3.39	0.024	50.39 ± 14.11	3.56 ± 3.32	0.285
PCI	53.46 ± 17.32			46.82 ± 16.72		

Comparison between group in 6 month and after 2 years (independent Student's t-test); CABG: Coronary artery bypass graft; PCI: Percutaneous coronary intervention; SD: Standard deviation

HRQOL of CAD Patients 6 months after revascularization

The mean total MacNew scale and emotional, social and physical subscale in CAD patients (sum of HRQOL options in both groups) were 50.96 ± 15.48, 51.38± 16.71, 52.39 ± 16.55 and 51.55 ± 16.72, respectively. Factors predictive in relation to the QOL were analyzed by linear regression.

Our results indicate that patients with male gender, those who had higher level of education and diabetes comorbidity, employed patients, those who had not hypertension, overweight, hypercholesterolemia and history of MI, those who were not smoker and patients with higher level of income experienced better HRQOL although these differences were only statistically significant in education, income and body mass index (BMI) variables ($P < 0.050$) (Table 4).

Correlation

Presents the correlations of HRQOL with characteristics of patients were shown in table 5. The correlations were significant at BMI, education, employee, sex hypertension in total HRQOL of PCI group whiles for dimensions and total HRQOL in CABG group, income and education display significant correlation (Table 5).

Table 3. Changes in the MacNew Scale and its subscale's scores in coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) group 2 years after revascularization (within-group comparison)

MacNew Scale	CABG		PCI	
	Mean ± SD	P	Mean ± SD	P
Total score				
After 6	45.32 ± 13.75	0.001	53.52 ± 15.63	0.016
After 24	51.36 ± 14.25		49.94 ± 16.46	
Emotional				
After 6	46.15 ± 16.12	0.122	53.75 ± 16.53	0.244
After 24	51.08 ± 16.94		51.36 ± 18.17	
Social				
After 6	45.29 ± 13.88	0.064	55.62 ± 16.75	0.025
After 24	50.44 ± 14.36		51.27 ± 17.77	
Physical				
After 6	46.19 ± 14.87	0.260	53.46 ± 17.32	0.007
After 24	49.49 ± 13.31		47.48 ± 18.04	

Paired Student's t-test; CABG: Coronary artery bypass graft; PCI: Percutaneous coronary intervention; SD: Standard deviation

Table 4. Linear regression analysis of coronary artery disease (CAD) patients 6 months after revascularization according to characteristics (n = 109)

Variable	Mean ± SD	Age	Sex	Education	Income	Employment	Smoking	Hypercholesterolemia	Hypertension	Diabetes	BMI	History of MI
Total MacNew	50.96 ± 15.48											
Score	Standard error	2.319	11.342	2.855	1.850	11.267	2.392	2.241	2.394	2.615	3.142	2.161
	Beta	0.021	-0.200	0.091	0.471	0.189	0.080	0.064	-0.105	0.112	-0.297	-0.011
	P	0.756	0.467	0.070	0.001	0.478	0.307	0.381	0.153	0.145	0.004	0.878
Emotional	51.38 ± 16.71											
subscale	Standard error	2.801	13.697	3.290	2.234	13.606	2.889	2.707	2.891	3.158	3.846	2.609
	Beta	-0.075	-0.258	-0.215	0.262	0.007	0.142	0.058	-0.055	0.096	-0.545	-0.053
	P	0.329	0.401	0.210	0.012	0.981	0.106	0.477	0.499	0.263	0.001	0.499
Social subscale	52.39 ± 16.55											
	Standard error	2.815	13.76	3.306	2.245	13.674	2.904	2.720	2.905	3.173	3.865	2.622
	Beta	0.044	-0.569	0.442	0.256	0.370	0.147	-0.074	-0.077	0.092	-0.354	0.072
	P	0.572	0.070	0.040	0.016	0.222	0.098	0.372	0.353	0.294	0.002	0.367
Physical	51.55 ± 16.72											
subscale	Standard error	2.858	13.975	3.518	2.279	13.883	2.948	2.762	2.949	3.222	3.924	2.662
	Beta	0.355	-0.349	-2.049	2.945	-0.113	1.664	-0.204	-1.694	0.920	-2.406	-0.134
	P	0.723	0.728	0.043	0.004	0.910	0.099	0.839	0.094	0.360	0.002	0.894

SD: Standard deviation; BMI: Body mass index; MI: Myocardial infarction

Table 5. Correlation of health-related quality of life (HRQOL) with characters

Variables	PCI				CABG			
	Emotional	Social	Physical	Total	Emotional	Social	Physical	Total
Age	0.026	0.074	0.136	0.059	0.092	0.294	0.274	0.213
Education	-0.092	0.122	0.159	0.265*	0.266	0.426*	0.507**	0.446*
Sex	-0.247	-0.172	-0.064	0.334**	0.172	0.312	0.263	0.229
Employee	-0.151	-0.080	-0.011	0.438**	0.172	0.312	0.263	0.229
Smoking	-0.018	-0.041	0.055	0.100	-0.135	0.113	0.086	-0.003
Hypertension	0.009	-0.107	-0.126	-0.236*	0.175	0.013	-0.052	0.093
Diabetes comorbidity	0.102	0.045	-0.016	-0.088	-0.017	0.113	0.128	0.086
BMI	-0.047	-0.033	-0.033	-0.373**	-0.083	-0.001	-0.062	-0.132
History of MI	-0.094	0.015	-0.003	-0.056	-0.233	-0.192	-0.208	-0.202
Income	0.209	0.177	0.190	0.015	0.374*	0.522**	0.555**	0.495**
Hypercholesterolemia	0.067	-0.021	0.045	0.014	0.052	0.044	-0.045	0.060

Pearson correlation coefficient; * Correlation is significant at the 0.05 level (two-tailed); ** Correlation is significant at the 0.01 level (two-tailed); PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; BMI: Body mass index; MI: Myocardial infarction

Discussion

In this study after proving similarity of patients in two groups in the aspect of socio-demographic and clinical characteristics, data analysis revealed that those who underwent PCI experienced significantly higher HRQOL in all dimensions of MacNew scale 6 months after revascularization but over 2 years follow-up there was not a significant difference between two groups. This finding is in agreement with results of a study that has been conducted recently by Loponen et al. to assess HRQOL after CABG and PCI in the management of stable CAD. They found that a 3 years survival was similar in the both groups and the HRQOL improved statistically in both groups until 6 months after treatment but deteriorated toward the end of the follow-up of 36 months. Despite initially more serious pre-operative morbidity, the CABG patients achieved an equal level of HRQOL when compared with PCI patients.[12]

The CAD imposes a high burden on communities in worldwide in terms of premature mortality, adverse effects on QOL and economic impacts on families and health systems.[2,12,13] It is evident that goal for the treatment of patients with the CAD is not just to prolong life but also to provide a better HRQOL. Therefore, the HRQOL has become an important measure of the outcome of care for patients with chronic diseases in the last two decades and it has also been found to be a predictor of health service utilization and mortality.[14,15] Hereupon, information on QOL of CAD patients in different modes of revascularization and its determinant is so important to defining a comprehensive plan of care.

Notwithstanding many studies have demonstrated that CABG and PCI provided a similar degree of protection against death and MI and shown that patients who undergo PCI are much more likely to have recurrent angina and to require repeat procedures[16] but few randomized trials have included HRQOL comparisons after PCI and CABG.

Our results in within-group analysis showed in both groups total MacNew scale and its subscales were changed significantly after 2 years. Norris et al. conducted other study to compare risk-adjusted HRQOL in 3392 patients with 1 year follow-up. Their results revealed that responders undergoing CABG reported significantly better HRQOL in all but one Seattle Angina Questionnaire dimension compared with who had either a PCI with or without stent.[13] A similar finding has been detected in other study that evaluated change in HRQOL after cardiac rehabilitation among 2441 patients.[17] In general and based on a comprehensive study conducted by Bravata et al.[18] to assess comparative effectiveness of PCI and CABG for CAD-11 randomized trials included in final analysis-they concluded HRQOL scores improved to a significantly greater extent after CABG than after PCI between 6 months and 3 years of follow-up but equalized thereafter.

Our results showed in the whole sample of CAD patients 6 months after revascularization, those who had higher level of income and education and were not either overweight or obese experienced better HRQOL while other covariates were not significantly associated with HRQOL. Several studies have been shown that educational and socioeconomic status are closely associated with the HRQOL.[19,20] Interestingly, age and sex, which are well known as predictors of HRQOL perception,[21,22] were not found to be determinant for HRQOL in our study. In accordance with our results, Durmaz et al.[23] found that sex and age were not important determinant for HRQOL.

Regarding clinical variables, previous MI, diabetes comorbidity, hypertension, and hypercholesterolemia were not found to be an important determinant for HRQOL. Since a number of studies have reported clinical predictors of HRQOL in CAD such as peripheral vascular disease, hypertension, and MI.[21,23,24] It seems the effect of clinical variables on the perception of health status was somewhat unique in this study and merits further investigation.

Since some may argued that generic HRQOL measuring instruments are not able to illustrate impact of different treatment methods and disease's effect on HRQOL's dimension of patients, therefore we used the MacNew Heart Disease HRQOL because it incorporates

domains that address a patient's attitudes toward coronary disease with specific questions regarding disease-specific symptoms and their attitude toward the illness that this is a strength of our study.

However, there are several limitations of our study that need to be considered in interpreting results. However our patients in two groups were similar but it is important to consider the differences among patients carefully when treatment outcomes are analyzed. It is difficult for case-mix adjustments to account adequately for these differences in analyzing patients' outcome in relation to CABG and PCI method. Moreover, since this study was carried out in only one province, our sample may not be representative of whole patients with CAD. Nonetheless, we have noted the paucity of information regarding HRQOL in CAD patients, particularly about two main modes of coronary revascularization in developing countries.

Conclusion

Our results showed that patients who underwent PCI experienced significantly higher HRQOL in 6 months after revascularization but over 2 years follow-up there was not a significant difference between two groups. Selecting an optimal method of coronary revascularization is complexes clinical decision-making process that needs clinicians incorporate a number of clinical factors, technical considerations, and patient preferences. Therefore in addition to clinical issues, patients' preferences for specific aspects of HRQOL should be considered and tradeoff must be discussed when informing patients about coronary revascularization choices.

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Conflict of Interests

Authors have no conflict of interests.

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Predictive role of adiponectin and high-sensitivity C-reactive protein for prediction of cardiovascular event in an Iranian cohort study: The Isfahan Cohort Study

Davoud Kazemi-Saleh[(1)], Pooya Koosha[(2)], Masoumeh Sadeghi[(3)], Nizal Sarrafzadegan[(4)], Reza Karbasi-Afshar[(5)], Mansoureh Boshtam[(6)], Shahram Oveis-Gharan[(7)]

Original Article

Abstract

BACKGROUND: Numerous studies have been conducted on the predictive effects of high-sensitivity C-reactive protein (hs-CRP) on cardiovascular events. Few studies have been conducted to investigate the effects of adiponectin for the prediction of the incident of cardiovascular events in the Middle East area. This study compared the predictive effect of hs-CRP and adiponectin on healthy volunteers for the prediction of cerebrovascular disease (CVD).

METHODS: This nested case-control in original Isfahan Cohort Study (ICS) was conducted from 2001 to 2011. Participants were selected from ICS. The case group included participants with CVD while the control group included participants without CVD. The level of hs-CRP and adiponectin was measured in the blood samples collected in the year 2007. Thereafter, the statistical analyses were performed to determine the predictive value of hs-CRP and adiponectin in CVD prediction.

RESULTS: The results showed that before the elimination of diabetes effect; there was a significant difference between the two groups, in terms of the mean of adiponectin (P = 0.019) and no significant difference was observed in hs-CRP levels (P = 0.673). However, after eliminating the factor of diabetes, there was no significant difference between the case and control groups in adiponectin and hs-CRP levels (P = 0.184, P = 0.946). The results showed that the odds ratio (OR) of the adiponectin level was 0.879 [95% confidence interval (CI): 0.719-1.075, P = 0.210] while the OR of hs-CRP was 1.045 (95% CI: 0.922-1.185, P = 0.491). Furthermore, it was shown that after adjustment for age, sex, and diabetes; the OR of adiponectine was 0.875 (95% CI: 0.701-1.091, P = 0.235) and that of hs-CRP was 1.068 (95% CI: 0.935-1.219, P = 0.333).

CONCLUSION: The results show that adiponectin and hs-CRP cannot be predictors for cardiovascular events in a healthy population. Risk factors such as diabetes limit the use of adiponectin as a CVD predictor.

Keywords: Adiponectin, High-Sensitivity C-Reactive Protein, Cardiovascular Disease

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Introduction

Cardiovascular disease (CVD) is the main cause of death worldwide.[1] Furthermore, in Iranian population, CVD is a major cause of morbidity and mortality.[2] The current evidence shows that fat tissue works not only as a storage source but also as an endocrine tissue.[3,4] Adiponectin is a recently introduced inflammatory cytokine and some studies revealed its important metabolic effects.[5] Few studies have reported on

1- Professor, Atherosclerosis Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
2- Resident, Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
3- Professor, Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
4- Professor, Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
5- Assistant Professor, Atherosclerosis Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
6- Research Assistant, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
7- Assistant Professor, Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan AND Department of Neurology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
Correspondence to: Masoumeh Sadeghi, Email: sadeghimasoumeh@gmail.com

adiponectin's anti-inflammatory and anti-atherogenic effects.[6] Some studies discussed the probable anti-atherogenic role of adiponectin while its real physiologic functions are still unknown.[7-10] On the other hand, high-sensitivity C-reactive protein (hs-CRP) has been proposed as a predictive factor for cardiovascular events.[11]

Adiponectin is a protein secreted by adipocytes, so its serum levels may differ with changes in body weight and visceral fat tissues. Lower levels of adiponectin (< 4 μg/ml) may be correlated with diabetes II, insulin resistance, hypertension (HTN), metabolic syndrome, dyslipidemia, and hyperuricemia. Adiponectin has also been mentioned as an anti-atherosclerotic agent. It has been investigated as a biomarker in association with weight gain disorders in some recent studies.[12]

CRP is an acute phase reactant which is synthesized in the liver by stimulation of cytokine interleukin-6 and is also a factor in atherosclerosis plaque development.[13] Several prospective and case-control studies conducted in the United States have shown that CRP is a risk factor for cardiovascular diseases and hs-CRP is a strong predictive factor of mortality and morbidity in cardiovascular patients.[14-17]

It is proposed that physiologic concentrations of adiponectin will inhibit the production of tumor necrosis factor in macrophages connected to the endothelium and thus, will avoid the expression of molecules such as E-selectin, vascular cell adhesion molecule 1, and intercellular adhesion molecule 1.[18-20] Hotta et al.[18] and Kumada et al.[21] showed that a reduction in adiponectin levels is associated with increased risk of cardiovascular events and will double the chance of disease independently.[12]

As a result of increasing rate of cardiovascular events in the Middle East, knowing more about predictive factors with higher predictive values and lower costs are essential. The purpose of this study was to explore the association of adiponectin and hs-CRP with the incidence of CVD events in adults who participated in the Isfahan Cohort Study (ICS).

Materials and Methods

This is a nested case-control study in the ICS conducted from 2001 to 2011. The ICS is a part of a community trial for prevention and control of CVD, named the Isfahan Healthy Program. In fact, the ICS is a population-based continuing longitudinal study of adults with 35 years or more which are residents in urban and rural places of three countries in central Iran.[22]

In the ICS, initially, the informed written consent is taken and then medical interview and physical examination were performed. After that, information about measurable characteristics of every participants and a fasting blood sample was taken which followed standard protocol and using tuned devices that are previously described.[23] All participants in ICS were followed by phone interview every 2 years using standard questionnaires.

For this nested case-control study, the case groups were selected among participants in ICS who had fatal, non-fatal myocardial infarction (MI) and stroke (ischemic) between September 2007 and September 2013, and before the year 2007, they had none of the diseases mentioned. The criteria for the diagnosis of MI were based on the following criteria which the patient who had two of three following characteristics considered MI: (1) Typical chest pain which prolonged for more 30 minutes, (2) ST-elevation for more than 40.1 mV in two contiguous leads, and (3) cardiac biomarkers increasing. The diagnosis of ischemic stroke was defined as rapid-onset focal neurological deficit which sustained for more than 24 hours.[22] The controls were selected among those without the aforementioned events but were matched with the case group during follow-up (density sampling) to make time for risk to be similar between each pair. For each case, the controls were chosen randomly from those members of the cohort who were at risk at the failure time (event date) of the case and matched in terms of age, sex, and hyperlipidemia (HLP). It is noteworthy that all patients in both groups had no history of vascular events such as MI and stroke at the baseline. Identifying the case and control groups were done using the information in the records. They were contacted according to their information in the documents and people with documented ischemic heart disease and stroke were identified.

Demographic data such as age, sex, marital

status, and cardiovascular risk factors such as diabetes (fasting blood sugar ≥ 126), HTN (systolic blood pressure ≥ 140, diastolic blood pressure ≥ 90), smoking, obesity (body mass index ≥ 30), and HLP (total cholesterol ≥ 200, triglyceride ≥ 150) were collected from the two groups. Blood samples of participants were collected in 2007 and stored at −70 °C in Isfahan Cardiovascular Research Center. Adiponectin and hs-CRP levels were measured using commercial kits (DRG, Germany) of radioimmunoassay (RIA) (human) adiponectin. Ethical approval was obtained from the Ethics Committee of Isfahan Cardiovascular Research Centre, the World Health Organization (WHO) collaborating center.

Numerical values were presented as a mean ± standard deviation (SD). Categorical factors were reported as number (percentage). T-test or Mann–Whitney test and Chi-square test were used to compare the case and control groups for quantitative and qualitative factors, respectively. The analysis of covariance was used to compare means of adiponectin or hs-CRP in the case and control groups while statistically controlling for diabetes, age, and sex. The conditional logistic regression was used to estimate the odds ratios (ORs). CVD events were assumed to be dependent on variables and adiponectin and hs-CRP as an independent variable while adjusting for age, sex and diabetes.[2]

The data were analyzed using the software package used for statistical analysis SPSS software (version 15.0, SPSS Inc., Chicago, IL, USA). $P < 0.050$ were considered as statistically significant.

Results

In this study, 39 patients with cardiovascular disease (cases) and 41 healthy individuals (controls) were included. From the 80 patients studied, 48 patients were males (60%) and 32 were females (40%). The sex distribution between the case and control groups was not significant.

As shown in table 1, the two groups showed no significant difference in terms of age. The other risk factors were also not significantly different in the case and control groups and only diabetes mellitus (DM) was different between the case and control groups ($P = 0.007$).

After the initial analysis of the results, comparison of adiponectin levels between the two groups showed that there were significant differences between the case and control groups ($P = 0.019$).

However, because the prevalence of diabetes differed significantly between the two groups, the factor of diabetes in the comparison between the two groups was adjusted. The results showed that there was no significant difference between the groups in levels of adiponectin ($P = 0.184$) and hs-CRP ($P = 0.946$). The results are shown in table 2.

Table 1. Comparison of demographic and risk factors between the case and control groups

Variable	Case (n = 39)	Control (n = 41)	P
Demographics			
Gender (%)			
Male	22 (56)	26 (63.4)	0.523*
Female	17 (44)	15 (36.6)	
Marital status			
Single	3 (7)	5 (12.0)	0.479*
Married	36 (93)	35 (86.0)	
Risk factors			
DM (%)	21 (53)	10 (24.3)	0.007*
HTN (%)	24 (61)	22 (53.6)	0.476*
HLP (%)	31 (79)	30 (73.1)	0.507*
Smoking (%)	6 (15)	7 (17.0)	0.761*
Triglyceride (mg/dl)	194.84 ± 110.86	164.56 ± 126.91	0.260**
BMI	27.42 ± 4.82	26.83 ± 3.29	0.523**
FBS (mg/dl)	129.77 ± 68.47	96.95 ± 26.94	0.006**
SBP (mmHg)	132.05 ± 22.16	130.70 ± 19.15	0.770**
DBP (mmHg)	80.76 ± 13.51	80.06 ± 10.14	0.790**
Cholesterol (mg/dl)	217.71 ± 38.84	214.89 ± 42.22	0.750**
Age	60.21 ± 9.64	60.42 ± 10.65	0.927**

* Chi-square; ** t-test; DM: Diabetes mellitus; HTN: Hypertension; HLP: Hyperlipidemia; BMI: Body mass index; FBS: Fasting blood sugar; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Table 2. Comparison of serum parameters between the two groups, with adjustment forconfounding risk factors (sex, diabetes, hypertension)

Variable	Case	Control	P*
Lab tests			
Adiponectin (µg/ml)	2.637 ± 2.375	3.303 ± 2.293	0.184
Hs-CRP (µg/ml)	3.671 ± 3.821	3.128 ± 3.288	0.946

* Analysis of covariance analysis; Hs-CRP: High-sensitivity C-reactive protein

They were also detrimentally associated with adiponectin and hs-CRP on CVD and obtained OR. The results showed that the OR of adiponectin level was 0.879 [95% confidence interval (CI): 0.719-1.075, P = 0.210] and OR of hs-CRP was 1.045 (95% CI: 0.922-1.185, P = 0.491). Moreover, the results showed that after adjustment for age, sex and diabetes, the OR of adiponectin was 0.875 (95% CI: 0.701-1.091, P = 0.235) and that of hs-CRP was 1.068 (95% CI: 0.935-1.219, P = 0.333).

Discussion

In this study, the association of adiponectin and hs-CRP with the incidence of cardiovascular events in adults who participated in the ICS was assessed. No prediction role of adiponectin and hs-CRP in CVD was observed.

Oliveira et al.[24] discussed adiponectin as an independent predictive factor for cardiovascular events. Another study conducted with 48 percutaneous coronary intervention-needed patients with coronary diseases (left anterior descending involvement) and a 66-month period of follow-up revealed that the lower serum levels of adiponectin are associated with future cardiovascular events.[25] Although, adiponectin as an adipocytokine has a considerable role in causing cardiovascular events, its clinical importance is still controversial.

A prospective study including 171 patients with ischemic stroke and 171 matched controls compared the serum levels of adiponectin in days 0, 3, 7 and 90 of the event across groups. Adiponectin serum level was significantly lower in the patients, and this level could predict an atheroemboli stroke (OR: 0.75; 95% CI: 0.58-0.91, P = 0.009). Adiponectin serum levels also had a positive correlation with the severity of the neurologic defect. The results of this study also showed that plasma levels of adiponectin may be different in the classification of stroke subtypes and is able to predict neurological defects and stroke outcome.[26]

Animal studies suggest that reduced adiponectin levels in the acute phase of ischemic stroke are a dynamic process. In a study of 31 patients with the first episode of stroke, at intervals of 24 hours, 2-4 days and 5-10 days after ischemic stroke, plasma adiponectin levels were measured three times. On the basis of their results, adiponectin levels were significantly lower in patients with ischemic stroke when compared with other causes of stroke. This may reflect the effect of adiponectin on the predictive value of the occurrence of ischemia.[27]

However, results of studies on the predictive effects of adiponectin on cardiovascular events are conflicting in some cases. In a prospective meta-analysis performed in Europe, the predictive value of adiponectin for cardiovascular events was studied. The relative risk of stroke in adiponectin levels higher than 5 µg/ml was about 1.10 with 95% CI: 0.89-1.37. The patients with higher levels of adiponectin have higher levels of high-density lipoprotein cholesterol and lower triglycerides and CRP.[28] The difference between the present study and studies in America can be attributed to differences in resource classification and naming of different kinds of stroke among various European and American resources.

The mechanism of action of adiponectin in predicting cardiovascular events remains unclear, and several hypotheses have been proposed. For example, adiponectin as an insulin sensitizing hormone was introduced with the assumption that the plasma adiponectin levels in metabolic disorders such as DM Type 2 is reduced and shows the relationship between adiponectin levels, increased risk of cardiovascular events and related deaths.[29]

Results of a cohort study on 4571 at risk African-Americans revealed that adiponectin is

more associated with stroke in females. This study showed that the mechanism of prediction of adiponectin is still unclear but hypotheses have been proposed that the production of this substance is in response to vascular inflammation and deals with atherosclerosis.[30]

Several large prospective epidemiological studies showed that hs-CRP is a strong predictor of cardiovascular events such as MI and stroke.[13] In a cohort study which was conducted with 1086 apparently healthy middle-aged men, participants in the quartile with the highest CRP values had 3 and 2 times the risk of MI and ischemic stroke, respectively, in contrast to subjects with the lowest CRP.[31]

The results of this study show that adiponectin and hs-CRP cannot be predictors for cardiovascular events in a healthy population. The difference between these results and the results of other studies could be because of diabetes which is a confounding factor.

This study had some limitations which could affect the results. One of the restrictions was the small sample size which had impact on the results. Another limitation of this study was the presence of confounding variables such as DM in both groups.

However, as mentioned, the use of adiponectin as an independent predictor of cardiovascular events continues to be associated with controversy. On the other hand, there is no population-based study to evaluate this effect. Future studies to examine the predictive effects of adiponectin as compared to other biomarkers with larger sample sizes are recommended.

Conclusion

The results of this study show that adiponectin and hs-CRP cannot be predictors for cardiovascular events in a healthy population. Risk factors such as diabetes, limit the use of adiponectin as a CVD predictor. Further studies with larger sample size should be conducted to determine the predictive role of adiponectin and hs-CRP in CVD.

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Conflict of Interests

Authors have no conflict of interests.

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What is role of sex and age differences in marital conflict and stress of patients under Cardiac Rehabilitation Program?

Saeid Komasi[(1)], Mozhgan Saeidi[(1)]

Original Article

Abstract

BACKGROUND: To investigate the role of sex and age differences in marital conflict and stress of patients who were under cardiac rehabilitation (CR) program.

METHODS: The data of this cross-sectional study were collected from the database of the CR Department of Imam Ali Hospital, Kermanshah, Iran. The demographics and medical data of 683 persons were collected from January 2003 and January 2010 using medical records, the Beck Anxiety Inventory, the Beck Depression Inventory, the Hudson's Index of Marital Stress, and the Structured Clinical Interview for axis I disorders. Data were analyzed through Analysis of Covariance and Bonferroni test.

RESULTS: About 74.8% of the subjects were male. After adjustment for age, educational level, anxiety, and depression-the findings showed that women in CR program had a higher level of marital stress compared to men (54.75 ± 2.52 vs. 49.30 ± 0.89; P = 0.042). Furthermore, it was revealed that women who aged 56-65 years and more experienced higher level of marital stress compared to younger patients (P < 0.050); however, no significant difference was observed between different age groups in male patients (P > 0.050).

CONCLUSION: Marital conflict and stress threaten healthiness of women who aged 56-65 years more prominently than does in males or younger patients. Regarding the effect of marital stress on recurrence of the disease and cardiac-related morbidity and mortality in women, providing effective education and interventions to this group of patients, especially older women and even their spouses could be one of the useful objectives of CR programs.

Keywords: Marital Conflict, Psychologic Stress, Sex Differences, Rehabilitation, Cardiac Disease

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Introduction

The protective and supportive effects of marriage on healthiness and well-being, in general, population have been demonstrated. It is stated that married individuals have better physical and psychological healthiness than single ones.[1] In patients with cardiovascular diseases (CVDs), as a subset of clinically encountered patients, the role of marriage and being married in the development of the disease and its outcomes has gained attention of the researchers in recent years.[2,3] Recent findings show that there is relationship between marital state and CVDs morbidity and mortality. The likelihood of premature death in single men and divorced women is significantly higher compared to other groups.[4] Furthermore, among married patients in age group of 45-64 years face premature death less likely in comparison to other groups.[5]

Even though these researches have indicated the positive role of being married on disease, it seems that the state of being married itself may have challenges which have not been investigated thoroughly in cardiac patients. One of these challenges is an inappropriate interaction between couples and marital stress. It has been stated that marital stress as a chronic between person stress decreases the immune function of the body, in particular, in older people. Marital stress, not only increases the risk of health problems such as CVDs,[6] but also challenges health behaviors of patients such as nutrition management.[7] Although the

1- Cardiac Rehabilitation Center, Imam Ali Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran
Correspondence to: Mozhgan Saeidi, Email: m_saeidi20@yahoo.com

mechanisms through which marital conflicts affect the healthiness of people,[8] it is evident that negative marital interactions are related to some cardiac reaction indices such as heart rate and systolic blood pressure in both males and females.[9] Marital stress not only increases the recurrence risk of cardiac events into 3-fold in a 5-year period[10] but also independently aggravates depression, anxiety, anger, and hostility in cardiac rehabilitation (CR) patients.[11,12] Marital stress also negatively affects the social relations of women.[13] It also predicts the risk of longer hospitalization after cardiac surgery in women[14] and in men.[15] In addition, appropriate quality of marital relationship especially in female patients with cardiac diseases inhibits systolic hypertension[16] and significantly predicts 4 to 8-year survival.[17,18]

Despite the aforementioned evidence, it is not yet clear exactly that which age or gender groups are affected more by marital stress. As negative aspects of marital relationship affect more significantly physiologic functions of women compared to men,[19] and survival of patients older than 64 years is at higher risk,[5] access to a response to this question is equivocal. Furthermore, designing of appropriate therapeutic procedures requires knowledge about the effect of sex and age on marital stress. Along with gender, age as one of the most important biomarkers among non-specific parameters of cardiac diseases has the highest effect on the disease evolution[20] and increasing age is associated with the risk of development and establishment of CVDs.[21] This issue shows the necessity of evaluation of marital stress in patients in different age groups. Therefore, here two questions arise and the current study was carried out with the purpose of answering to these two questions. The first question is that whether marital stress is higher in female or male patients in CR program? The second question is that which age group experiences the greatest level of marital stress?

Materials and Methods

In this cross-sectional study, the data were collected through the CR Department of Imam-Ali Hospital in Kermanshah, Iran. Kermanshah is located 525 km (326 miles) from Tehran in the western part of Iran. According to the 2011 census, its population is 851,405. People mostly speak Southern Kurdish and Persian. The city has a moderate and mountainous climate. Kermanshah is one of the western agricultural core of Iran that produces grain, rice, vegetable, fruits, and oilseeds; however, Kermanshah is emerging as a fairly important industrial city. Imam-Ali Hospital is a state specialized hospital for cardiology in Kermanshah, and the patients residing in Western Iran, in general, visit this hospital. The hospital includes intensive care unit and critical care unit Parts, Cardiac Surgery Department, Emergency Department, CR Unit, and Heart Research Center. Moreover, the governmental hospital has 214 beds. The database of this hospital is consists of data about different types of heart diseases especially cardiac surgery that has been enrolled in CR programs after the cardiac event had occurred. The demographic and medical data of the patients including the comorbidities, psychological health, and the early risk factors are registered in the database. The registration checklists are provided by heart health professionals and specialists under the supervision of Kermanshah University of Medical Sciences (KUMSs). The control center of the KUMS confirms the accuracy of the collected data 2 times in the year. Moreover, to evaluate the psychological state of the cardiac patients including anxiety, depression, and marital stress, standard tools such as the Beck inventories and structured clinical interview (SCID-I) for comorbidities are used in the start of CR in this center. In addition, the self-reported checklists for the illiterate patients were read by the psychologist of the ward and then the answers were registered.

1. Age between 30 and 85 years
2. Being married
3. Lack of substance abuse currently
4. The absence of stabilized psychosis.

We recognized 725 patients under CR enrolled in a 7-year period between January 2003 and January 2010. 22 patients were excluded due to the lack of inclusion criteria. Then, the data of other patients were used for the analysis. However, information of some of them was

confronted with missing data in some items which caused the SPSS software (version 20, SPSS Inc., Chicago, IL, USA) to exclude 20 patients. Thus, the sample size ultimately was declined to 683 persons. We did not perform sampling for selection of participants, but all patients in the mentioned period were enrolled - with the exception of patients without inclusion criteria. Given that there are 8 cells (four age groups × two genders × single dependent variable = 8) and it is recommended that would have existed in each cell 20 people,[22] as the result seems to be enough sample size 160 people. Thus, our sample size (n = 683) is appropriate. Furthermore, due to ethical considerations and after approval of the Ethics Committee of KUMS in January 2015, the patients data were used as confidential and anonymous to protect their privacy.

SCID-I assesses the axis I psychiatric disorders. This instrument is consists of 6 parts for assessments of diagnostic criteria of the 38 disorders such as anxiety and mood disorders and psychosis. The SCID-I done usually in one session and it takes between 45 and 90 minutes.[23] The reliability and validity of the tool for various disorders on axis I is appropriate. The Kappa values of the axis I disorders varied from 0.61 to 0.83, with a mean Kappa of 0.71 (0.60 for agoraphobia to 0.83 for specific and social phobia). Furthermore, the study results showed good inter-rater agreement of the axis I disorders.[24] The Kappa values of Persian version for various disorders are appropriate (0.60 and higher).[25]

- The Beck Anxiety Inventory is consists of 21 items, three scores awarded to each question, and its total score is calculated from 0 to 63. If the score is between 0 and 7, there is no anxiety; if the score is from 8 to 15, there is a mild anxiety; and if the score is from 16 to 25, the patient has moderate anxiety and ultimately; if the patient scores from 26 to 63, the patient suffers from severe anxiety. Cronbach's alpha of the inventory is 0.92, the credential using retest method with 1 week interval is 0.75, and the consistency of the items ranges from 0.30 to 0.76. The content validity revealed that it is suitable to measuring the intensity of anxiety.[26] In Iran, Kaviani and Mousavi were reported the inventory Cronbach's alpha 0.92 and they found that its validity and reliability is appropriate ($P < 0.001$).[27]
- The Beck Depression Inventory is a 21 items exam of 3 scores for each item. The score of this exam is varied from 0 to 63. Interpreting the results is determined as follows: 0-4 means depression denial; 5-9 equals to very mild depression; 10-18 means the patient has mild to moderate depression; if the patient scores from 19 to 29, it shows moderate to severe depression and the score more than 30 shows that the patients suffer from severe depression. Beck et al. discovered the retest reliability index in 1 week interval as 0.93.[28] Based on the results of a study in Iran, the inventory validity (convergent validity with general health questionnaire-28; r = 0.80) and reliability (Cronbach's alpha 0.92) is appropriate.[29]
- Hudson's index of marital stress is a 25 item scale that evaluates the severity of the marital conflict. 13 items of the scale are scored directly and 12 items are scored in reverse. Answers are graded based on the Likert 5-point (rarely to most of the time). The positively worded items were scored in the reverse such that 1 was rescored as 5, 2 as 4, 3 remained as 3, 4 as 2 and 5 as 1. The positively worded items were 1, 3, 5, 8, 9, 11, 13, 16, 17, 19, 20, 21, 23. After this, all the scores were summed up. Score higher than 30 means a considerable marital conflict. However, scores higher than 70 means strong and stable marital conflict. Cronbach's alpha of the scale items is 0.96 which it is indicator from suitable reliability.[30] Based on the results of Sanaei in Iran, the scale validity (content validity with enrich marital satisfaction scale; r = 0.86) is appropriate.[31]

We used percentage for report of nominal variables including baseline demographics and risk factors history. Then, these variables were compared between female and male using the chi-squared test. Mean and standard deviation (SD) used for continuous quantitative variables and independent t-test were used for comparison of mean scores of the baseline continuous variables including age, anxiety, and depression. Data normality and outliers were studied with used Kolmogorov–Smirnov test. In addition, preliminary checks were conducted to ensure that there was no violation of the other

assumptions of linearity and homogeneity of variances.[22] Then, the Analysis of Covariance (ANCOVA) and the Bonferroni test was used for comparison of marital stress among the sex and age groups. Applying the covariance analysis using the SPSS software for Windows (version 21.0, SPSS Inc., Chicago, IL, USA) software program, the effect of age, education level, anxiety, and depression in the sex groups was controlled. However, merely the effect of education level, anxiety, and depression was controlled to examine age groups. In the ANCOVA analysis was reported a mean and standard error (SE). The $P < 0.050$ concerned as significant level.

Results

Of the total 683 patients, 511 (74.8%) were male. The age ranges of female and male were 32-82 and 35-82 years, respectively. The total mean ± SD of marital stress was 50.77 ± 19.66. The baseline demographic and clinical variables of the participants are shown in table 1. The table results show significance different between female and male in term of education level, occupation, anxiety, and depression ($P < 0.001$). In addition, non-adjusted and adjusted means ± SE of marital stress of the sex groups are shown in table 2. It was revealed that marital stress is significantly higher among female compared to male, both before adjustment for age, education level, anxiety, and depression (57.53 ± 6.05 vs. 48.49 ± 2.96; $P < 0.001$) and after it (54.75 ± 2.52 vs. 49.30 ± 0.89; $P = 0.042$).

Table 1. Baseline demographic and clinical characteristics in the cardiac rehabilitation (CR) female and male

Characteristic	Total (n = 683)	Female (n = 172)	Male (n = 511)	P**,***
Demographic characteristics				
Education degree (%)				
Illiterate	36.6	64.5	27.2	< 0.001*
Less than diploma	33.8	24.4	37.0	
Diploma	16.7	6.4	20.2	
Academic	12.9	4.7	15.6	
Occupation (%)				
Market	40.4	0.6	53.8	< 0.001*
Clerk	10.7	1.7	13.7	
Retired	25.5	4.7	32.5	
Housewife	23.4	93.0	0.0	
Clinical characteristics				
Index procedure (%)				0.194
CABG	96.9	96.3	98.4	
VHD	1.1	1.3	0.1	
PCI	2.0	2.0	1.5	
Cardiac risk factors (%)				
Diabetes	37.6	34.8	37.9	0.645
Hypertension	30.7	34.8	30.2	0.475
Hyperlipidemia	57.7	56.1	57.9	0.780
Age (mean ± SD)	57.66 ± 9.21	56.97 ± 8.43	57.89 ± 9.46	0.2610
Anxiety (mean ± SD)	30.06 ± 11.85	36.87 ± 10.76	27.77 ± 11.31	< 0.001*
Depression (mean ± SD)	17.18 ± 3.40	18.51 ± 3.12	16.65 ± 3.36	< 0.001*

Significant difference between female and male for each characteristic * $P < 0.001$; ** Chi-square test performed for nominal and categorical variables; *** t-test performed for continuous variables; CABG: Coronary artery bypass graft surgery; VHD: Valvular heart disease; PCI: Percutaneous coronary intervention; SD: Standard deviation

Table 2. The compare of the marital stress mean between female and male before and after adjustment

Characteristics	Marital stress (mean ± SE) (Non-adjusted)	P	Marital stress (mean ± SE) (Adjusted)	P
Sex				
Female	57.53 ± 6.05	0.001*	54.75 ± 2.52	0.042**
Male	48.49 ± 2.96		49.30 ± 0.89	

Significant difference between female and male for each characteristic; * P < 0.010; ** P < 0.050; SE: Standard error

Table 3 presents the patients' marital stress in different age groups in either gender. The results of table show there is not different between non-adjusted means ± SE of female and male (P = 0.773). In addition, after adjustment for educational level, anxiety, and depression no significant difference was observed regarding marital stress between different age groups in male (P = 0.636). However, significant differences were observed in term of marital stress adjusted mean between different age groups in female (P < 0.001). The results of Bonferroni post-hoc test to find differences in marital stress between different age groups in either gender are presented in table 4. After adjustment for education level, anxiety, and depression, the results of the table show that female who aged 56-65 years had significantly higher level of marital stress compared to younger age groups including ≤ 45 years (76.40 ± 5.90 vs. 45.72 ± 7.69; P = 0.013) and 46-55 years (76.40 ± 5.90 vs. 48.77 ± 4.84; P = 0.002). Furthermore, it is obvious that no significant difference was seen between patients > 65 years with other age groups (P > 0.050).

Discussion

The study was done with the objective of finding difference in marital stress level between genders and also between different age groups of patients who were receiving CR program. The results showed that women experienced higher levels of marital stress compared to men. Plus, age did not have a role in marital stress among men. However, women who aged 56-65 years experienced higher level of marital stress compared to their younger counterparts. In justification of the observed results, it could be stated that women generally are more vulnerable to mental disorders including depression, stress, and anxiety.[32-34] Therefore, it can be expected that marital stress, as one of the items of general chronic stress, to be more severe in women. In support of this finding, the results of a study in 2014 showed that women were more likely to relate their cardiac condition to psychological risk factors, especially stress.[35] As there is relationship between perceived and real risk factors,[36] higher rate of stress reported by women seems natural.

Table 3. The compare of the marital stress in different age groups of female and male

Characteristics	Marital stress (mean ± SE) (Non-adjusted)	P	Marital stress (mean ± SE) (Adjusted)	P
Female				
Age (year)		0.102		0.001*
≤ 45 (n = 14)	44.93 ± 11.59		45.72 ± 7.69	
46-55 (n = 56)	55.27 ± 6.05		48.77 ± 4.84	
56-65 (n = 75)	60.61 ± 4.96		76.40 ± 5.90	
> 65 (n = 27)	60.22 ± 6.25		48.72 ± 10.64	
Male				
Age (year)		0.773		0.636
≤ 45 (n = 48)	49.94 ± 4.63		51.78 ± 4.61	
46-55 (n = 161)	48.14 ± 2.82		47.29 ± 1.35	
56-65 (n = 194)	49.10 ± 2.58		48.85 ± 1.37	
> 65 (n = 108)	47.28 ± 3.10		50.05 ± 2.73	

Significant difference between patients for each characteristic; * P < 0.010; SE: Standard error

Table 4. The multi-compare of the marital stress in different age groups before and after adjustment

Group (I)	Group (J)	Mean difference (SE) (Non-adjusted)	P	Mean difference (SE) (Adjusted)	P
Female					
≤ 45	46-55	-10.339 (6.918)	0.823	-3.048 (9.199)	0.999
	56-65	-15.685 (6.741)	0.131	-30.677 (9.871)	0.013*
	> 65	-15.294 (7.625)	0.280	-2.993 (13.139)	0.999
46-55	56-65	-5.345 (4.089)	0.999	-27.629 (7.544)	0.002**
	> 65	-4.954 (5.425)	0.999	0.055 (11.695)	0.999
56-65	> 65	0.391 (5.196)	0.999	27.684 (12.152)	0.144
Male					
≤ 45	46-55	1.801 (2.916)	0.999	4.492 (4.795)	0.999
	56-65	0.834 (2.858)	0.999	2.927 (4.809)	0.999
	> 65	2.660 (3.076)	0.990	1.728 (5.374)	0.999
46-55	56-65	-0.966 (1.890)	0.999	-1.565 (1.918)	0.999
	> 65	0.859 (2.205)	0.999	-2.764 (3.048)	0.999
56-65	> 65	1.825 (2.129)	0.999	-1.199 (3.046)	0.999

Significant difference between patients for each characteristic; * P < 0.050; ** P < 0.010; SE: Standard error

Women are more sensitive to familial stress than men and marital arguments affect their psychological and physiologic health more prominently.[11] They usually spend more time about thinking of marital relationship especially its negative aspects.[14] The rate of expressing anger of marital conflicts is fewer in women. This per se increases the risk of death from cardiac events four times.[37] In women, the quality of the marital relationship is generally affected by the perceived quality of the support by spouse[14] and if women perceive their spouse support more positively there will be less marital stress and better survival.[18] Therefore, it is obvious that gender is a factor that affects more negative perception of marital interactions in women. Due to stronger emotional responses in women, they report higher level of marital stress than men do.

Regarding the effect of age on marital stress, compatible with our results, Zare et al. reported that getting older and longer marriage duration is associated with decreased marital satisfaction in women.[38] Older women as a result of longer duration of their marriage and facing various difficulties throughout these years such as economic issues and problems with children[39] have spent more years with marital conflicts and possible disputes and since Iranian culture has a negative view toward divorce, social coercion to continue the marriage is probably followed by chronic marital stress.

Another justification is the educational level of these patients. Older patients have lower educational level compared to younger women and this state can lead to disagreement between couples and marital conflict.[38] In addition, since these women are illiterate or have a low level of education and have no job, they usually spend more time inside the household and spend less time in outdoor and leisure activities. This state leads to the feeling that home environment is repetitive in days after days, and therefore, women may feel pressure and inability to change the environment. Finally, older women have more physical problems and more limited range of motion which prohibit them from doing activities such as daily walking. Therefore, staying at home leads to nervousness and more marital disputes.

Overall, although CVD is a widespread problem throughout the world, marriage and marital relationship is primarily a cross-cultural issue. Our study participants were mostly Kurdish language that may have certain marital problems. Thus, the study results can help to increase the knowledge of health professionals both about this psychological risk factor and sex and age groups at risk and vulnerable.

Our study has several strengths and limitations. First, marital stress is one of the factors that has received less attention in previous studies. Other strength is the study of one of the aspects of general stress separately.

Using data from a large sample is other advantage our study. Conversely, one of the limitations of our study was that the data were collected from only one hospital. Therefore, caution is required in the generalizing results. The other limitation was lower number of female patients in the research. Therefore, it is recommended to survey more samples throughout the Iran and study more women in the upcoming studies. A third of our limitation was the retrospective nature of some of the collected data. In addition, there was no possibility to control for all confounding variables.

Conclusion

Marital stress threatens healthiness of women who aged 56-65 years more prominently than does in males or younger patients. Regarding the effect of marital stress on recurrence of the disease and cardiac-related morbidity and mortality in women, providing effective education and interventions to this group of patients, especially older women and even their spouses could be one of the useful objectives of CR programs.

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Conflict of Interests

Authors have no conflict of interests.

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Predicting metabolic syndrome using decision tree and support vector machine methods

Farzaneh Karimi-Alavijeh[(1)], Saeed Jalili[(2)], Masoumeh Sadeghi[(3)]

Original Article

Abstract

BACKGROUND: Metabolic syndrome which underlies the increased prevalence of cardiovascular disease and Type 2 diabetes is considered as a group of metabolic abnormalities including central obesity, hypertriglyceridemia, glucose intolerance, hypertension, and dyslipidemia. Recently, artificial intelligence based health-care systems are highly regarded because of its success in diagnosis, prediction, and choice of treatment. This study employs machine learning technics for predict the metabolic syndrome.

METHODS: This study aims to employ decision tree and support vector machine (SVM) to predict the 7-year incidence of metabolic syndrome. This research is a practical one in which data from 2107 participants of Isfahan Cohort Study has been utilized. The subjects without metabolic syndrome according to the ATPIII criteria were selected. The features that have been used in this data set include: gender, age, weight, body mass index, waist circumference, waist-to-hip ratio, hip circumference, physical activity, smoking, hypertension, antihypertensive medication use, systolic blood pressure (BP), diastolic BP, fasting blood sugar, 2-hour blood glucose, triglycerides (TGs), total cholesterol, low-density lipoprotein, high density lipoprotein-cholesterol, mean corpuscular volume, and mean corpuscular hemoglobin. Metabolic syndrome was diagnosed based on ATPIII criteria and two methods of decision tree and SVM were selected to predict the metabolic syndrome. The criteria of sensitivity, specificity and accuracy were used for validation.

RESULTS: SVM and decision tree methods were examined according to the criteria of sensitivity, specificity and accuracy. Sensitivity, specificity and accuracy were 0.774 (0.758), 0.74 (0.72) and 0.757 (0.739) in SVM (decision tree) method.

CONCLUSION: The results show that SVM method sensitivity, specificity and accuracy is more efficient than decision tree. The results of decision tree method show that the TG is the most important feature in predicting metabolic syndrome. According to this study, in cases where only the final result of the decision is regarded significant, SVM method can be used with acceptable accuracy in decision making medical issues. This method has not been implemented in the previous research.

Keywords: Machine Learning, Metabolic Syndrome, Decision Tree, Support Vector Machine

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Introduction

Nowadays, the health-care systems based on the intelligent systems have been drawing a lot of attention. Medical decision support systems which can be used for predicting diseases, and assisting physicians in the diagnosis and treatment decisions,[1,2] and etc., can be mentioned as a kind of intelligent system. A metabolic syndrome which has an upward trend due to industrialization of countries is one of the medical disorders. Lifestyle and dietary changes tending toward fast food, salty, and fatty food have increased metabolic syndrome in the communities.[3] Metabolic syndrome is a cluster

1- Department of Medical Informatics, School of Medical Sciences, Tarbiat Modares University, Tehran, Iran
2- Associate Professor, Department of Computer Engineering, School of Electrical and Computer Engineering, Tarbiat Modares University, Tehran, Iran
3- Professor, Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Masoumeh Sadeghi, Email: sadeghimasoumeh@gmail.com

of conditions including high blood pressure (BP), abdominal obesity and hyperlipidemia and insulin resistance. In many cases, these conditions are present simultaneously.[4]

It is estimated that about 20-25% of the world's adult population suffer from the metabolic syndrome which doubles the risk of mortality in individuals. Moreover, risk of heart attack is 3 times as many and Type 2 diabetes is 5 times as many compared to people without the metabolic syndrome.[4]

In Asian countries, the metabolic syndrome has become an important issue due to changes in diet and lifestyle. In Iran, the prevalence of metabolic syndrome is spectacularly increasing that according to recent estimates equals generally 33 and 10-11% in normal weight adults.[5,6]

In recent years, artificial intelligence has been considered as a new approach of problem modeling. Nowadays, artificial intelligence has frequently been utilized to predict, diagnose and help medical diagnosis. Support vector machines (SVMs) and decision tree have been utilized for diagnosis and prediction of diseases in the medical domain. H. X. Liu et al. used the SVM to the diagnosis of breast cancer.[7] SVM was also applied to predicting central nervous system (CNS) permeability of drug molecules.[8] Decision tree algorithms have been used to prediction of pancreatic cancer[9] and identification of metabolic syndrome.[10] So far, this study has been accomplished to predict metabolic syndrome using SVM and decision tree. The purpose of this research is to predict the metabolic syndrome using decision tree and SVM decision methods.

In this study, decision tree and SVM methods are used to predict the metabolic syndrome since they are easy to understand and have a great efficiency, respectively.

Materials and Methods

Data for this study included 2107 subjects participating in the research project of Isfahan Cohort Study (ICS).[11] The first phase of the research project of ICS began in January 2001 and lasted until October of 2001. In the first phase, 6323 people who have not been diagnosed of heart disease were randomly selected. The second phase, in 2007, was re-conducted. In Phase II, the 3284 of them, after 7 years of follow-up, were re-evaluated. Among the participants in this project 2107 cases who did not suffer from metabolic syndrome in the first phase were chosen according to ATPIII. In the second phase of the study, 596 of them were diagnosed to suffer from metabolic syndrome. According to the criteria of ATPIII, there must exist at least three components of five following components[12] for the diagnosis of metabolic syndrome:

1. Hypertriglyceridemia $\geq$ 150 mg/dl
2. Low- and high-density lipoprotein cholesterol (HDL-C) $<$ 40 mg/dl in men and HDL $<$ 50 mg/dl in women
3. Fasting glucose $\geq$ 100 or use of diabetes medication
4. BP $\geq$ 130/85 mmHg or treatment with BP medication
5. Waist circumference (WC) $\geq$ 95 cm in men and women
6. WC is considered 95 cm for the Iranian people.[13]

The features that have been used in this data set include: Gender, age, weight, body mass index (BMI), WC, waist-to-hip ratio (WHR), hip circumference (HC), physical activity, smoking history, hypertension, antihypertensive medication use, systolic BP, diastolic BP, fasting blood glucose, 2-hour blood glucose, triglycerides (TGs), total cholesterol, low-density lipoprotein (LDL), HDL-C, mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH).

The decision tree is a supervised machine learning technique. The results of this method can be presented in the form of a tree or a set of if-then rules.[14] The most significant feature in the decision tree method is the tree root. Other features are placed in the lower levels of tree in order of importance.[15] Finally, the leaves of the tree represent the classification result. This technique is widely used in various fields including the medical field. Many studies show that decision tree is an effective method in the analysis of medical data.[9,10,15-17] It has been applied in many studies because of its accurate and understandable results[18] which make the

decision tree more important than the other accurate methods.[19] After learning tree by starting from the root, and following the conditions in the intermediate nodes of the tree, we can easily follow the process of decision tree. Decision tree is one of the methods that have been employed to predict the metabolic syndrome; with this method, we can extract features that are effective in predicting the metabolic syndrome. Decision tree C4.5 tools use the entropy equation for determining the tree nodes. If S contains positive and negative examples of a target concept, the entropy of S will be defined by relation (1) relative to this Boolean classification. $P\oplus$ is the ratio of positive examples to all examples and $P\ominus$ is the ratio of negative examples to all examples.

$$\text{Entropy}(S) = -P_{\oplus}\log_2(P_{\oplus}) - P_{\ominus}\log_2(P_{\ominus}) \quad (1)$$

SVM

Another machine learning methods are SVM that can be used for classification and regression and recently has been widely used in the medical domain. Among them, studies in the following fields can be cited: diagnosis of heart diseases,[20] predicting diabetes[21] and diagnosis of breast cancer.[7,22] Unlike the decision tree method, SVM is more a liked a black box, in other words, the knowledge derived from SVM is not directly sensible by professionals. However, SVM accuracy in classification has been caused its variety of applications. In this approach, each data is a vector where its and dimensions is equal to the number of features to be considered and SVM creates a hyperplane that separates samples of two categories. Such of the induced, created hyperplane has a maximum distance between the margin samples of between two classes. Figure 1 represents the solution for a two features problem.

Remember that SVM kernel maps the data that are linearly inseparable to a non-linear feature space and then induces a hyperplane between two classes.[23] The advantage of this method is its implementation simplicity and, unlike the neural network does not get stuck in a local maximum.[8] However, the only thing that should be carefully regarded is selecting the kernel type in this method.[7] Type of selected kernel has a considerable impact on the prediction accuracy. The most commonly used kernels in SVM are the radial basis function (RBF), polynomial, sigmoid and linear. The C parameter must be set in all of them jointly. This parameter has an effect on the decision boundaries. As the value of C is increased, the distance between the boundaries of two classes is reduced. By changing C, a balance is established between the error and accuracy of the included hyperplane. Each kernel has its own parameters for setting which determines the degree of flexibility between the two classes. This study uses SVM method with polynomial kernel.

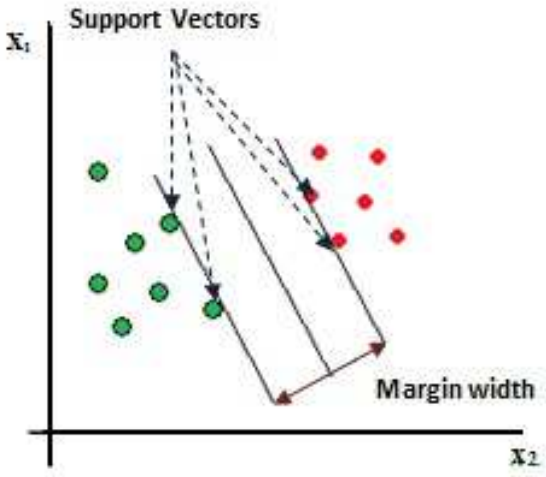

Figure 1. The induced line for the separation of positive and negative samples

Balance in data set is another subject that impacts the performance of machine learning methods. In the real world, especially in the medical field, the number of positive samples is much less than the negative samples.[24,25] On the other hand, in this field, accurate prediction and diagnosis of positive samples is very important. In medical issues, a high sensitivity is more important than high specificity. The lack of positive data causes the learned model is based on negative data which means they learn the classes containing negative data and ignore the minority positive samples. For example, in a dataset, if the number of positive samples would be 1%, the specificity and accuracy will be 100 and 99%, respectively, while it is the negative class that is learned. Instead of the positive class,[25] one-way to fix this problem is to balance the given data set can be used. In this research,

due to the unbalanced given data set Synthetic Minority Over-sampling Technique (SMOTE) method is used to balance the given data set. In this method, with the help of minima samples, a new synthetic data set is generated using the nearest neighbor.[24]

In general, there are several criteria to evaluate the success rate of a learning model. In this study, the criteria of sensitivity, specificity and accuracy are used. Furthermore, in this study, we have used 10-fold cross validation for performance evaluation of prediction metabolic syndrome.[26]

These criteria are calculated according to the values of the confusion matrix. The confusion matrix displays the results of predicting the classify problem samples compared to their original classes. In a problem with two classes including patient and healthy, there is a 2 × 2 confusion matrix. Four members of this matrix are numbers that show the true positive (TP), false positive (FP), true negative (TN), and false negative (FN). Criteria of sensitivity, specificity and accuracy are calculated using elements of the confusion matrix. Sensitivity as is shown in relation[3] is an accuracy rate of the right diagnosis in patients with metabolic syndrome. Specificity as is shown in relation[4] is the accuracy rate of right diagnosis of normal subjects. Accuracy as is shown in relation[5] is the rate of the right diagnosis of metabolic syndrome and healthy subjects.

$$\text{Sensitivity} = \frac{TP}{TP + FN} \quad (2)$$

$$\text{Specificity} = \frac{TN}{FP + TN} \quad (3)$$

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FN + FP} \quad (4)$$

We use 10-fold cross validation approach to validate the performance of predictive models.[14]

The experiments of research are conducted using the WEKA open source software (Waikato Environment for Knowledge Analysis, University of Waikato, New Zealand).

Results

We used ICS data set to determine the input factors (gender, age, weight, BMI, WC, WHR, HC, physical activity, smoking history, hypertension, antihypertensive medication use, systolic BP, diastolic BP, fasting blood glucose, 2-hour blood glucose, TGs, total cholesterol, LDL, HDL-C, MCV and MCH) (Table 1). Details of ICS study were reported previously.[27]

Table 1. Baseline subject characteristics in this study

Characteristics	Total (n = 2107) Mean (Min-Max)
Age	48.07 (34.0-86.0)
Weight	67.97 (39.0-120.0)
BMI	25.67 (14.96-39.9)
HC	99.77 (53.0-143.0)
WC	90.96 (52.0-131.0)
WHR	91.16 (0.7-1.2)
SBP	115.52 (75.0-200.0)
DBP	75.27 (20.0-150.0)
FBS	79.66 (41.0-298.0)
2-HP	97.22 (60.0-383.0)
HDL	48.48 (25.0-79.0)
LDL	125.70 (15.0-316.0)
TG	164.11 (47.0-726.0)
TCH	206.68 (76.0-450.0)
MCV	86.63 (44.0-106.0)
MCH	28.45 (0.0-42.3)

BMI: Body mass index; HC: Hip circumference; WC: Waist circumference; WHR: Waist-to-hip ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBS: Fasting blood sugar; HDL: High density lipoprotein; LDL: Low-density lipoprotein; TG: Triglycerides; TCH: Total cholesterol; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; 2-HP: 2-hour postprandial blood sugar

The results of the experimenting of the decision tree algorithm and SVM on ISC data set is presented in table 2. According to table 2, the sensitivity of the decision tree and SVM are 0.337 and 0.320, respectively. These sensitivity values are very low for predicting, so the result is not acceptable.

Table 2. The sensitivity, specificity and accuracy of the learning methods applied on the unbalanced Isfahan Cohort Study (ICS) data set

Method	Sensitivity	Specificity	Accuracy
Decision tree	0.337	0.917	0.75273
SVM	0.320	0.934	0.76032

SVM: Support vector machine

Table 3. The sensitivity, specificity and accuracy of the learning methods applied on the balanced Isfahan Cohort Study (ICS) data set

Method	Sensitivity	Specificity	Accuracy
Decision tree	0.758	0.72	0.739
SVM	0.774	0.74	0.757

SVM: Support vector machine

The lack of sensitivity is due to the ICS unbalanced data set. Following the lack of positive samples compared to with the negative samples, the model learns healthy subjects instead of patient subjects. To vanish this problem we used, SMOTE method to balance ICS data set. We applied decision tree and SVM method on the balanced ICS data set. The results are presented in table 3.

The value of the parameter C [$2^{(-5)}$, $2^{(-3)}$, ..., 2^{10}] with polynomial degree 2, 3 and 4 are used in SVM method. To determine the optimal value C, values between two consecutive C are tested again, after obtaining the highest value of C. Finally, the highest accuracy is obtained at C = 24. This accuracy is obtained with polynomial kernel of degree 4. Changes in accuracy, sensitivity and specificity based on C, is presented in figure 2.

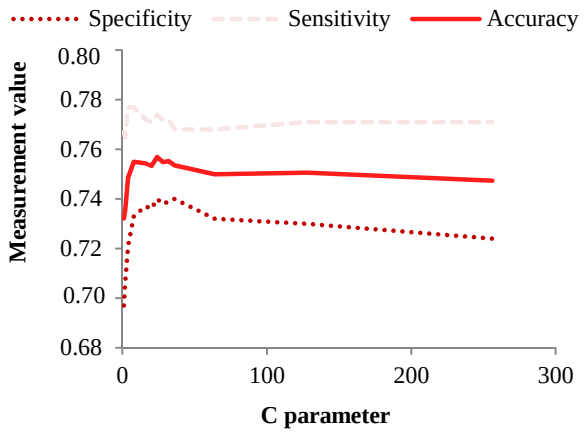

Figure 2. The sensitivity, specificity and accuracy of support vector machine, based on C in polynomial kernel of degree 4 applied on the balanced Isfahan cohort study data set

The decision tree method is studied for the confidence factor between 0.01 and 0.99. The best accuracy is obtained with a confidence factor equal to 0.06. Figure 3 shows the effectiveness of in sensitivity, specificity and accuracy of decision tree C4.5 with respect to changes of the confidence factor.

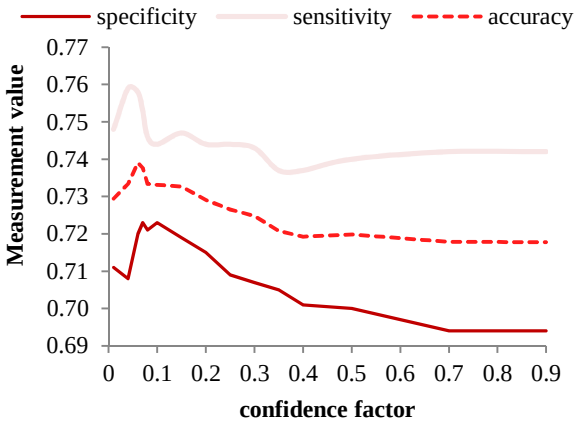

Figure 3. The sensitivity, specificity and accuracy of the decision tree C4.5 with different on faience factor applied on the balanced Isfahan Cohort Study data set

In this study, we have used four methods for performance evaluation of prediction metabolic syndrome. These methods are classification accuracy, analysis of sensitivity and specificity, and 10-fold cross validation.

Comparison of the decision tree and SVM methods based on figure 4 shows that SVM has better accuracy and efficiency than the decision tree. However, the advantages of decision tree in comparison with SVM are a high speed and low-cost learning and prediction. The decision tree generated in this study shows that TG is the main prognostic factor of metabolic syndrome. A combination of TGs + BMI is an accurate predictor for predicting. Moreover, according to the induced decision tree, a person with TGs > 223 and BMI ≥ 24.35, with probability 85%, will suffer the metabolic syndrome.

Discussion

The purpose of this study is comparing the prediction of metabolic syndrome using decision tree and SVM methods. The decision tree method is chosen because the induced tree is understandable and shows the process of prediction.

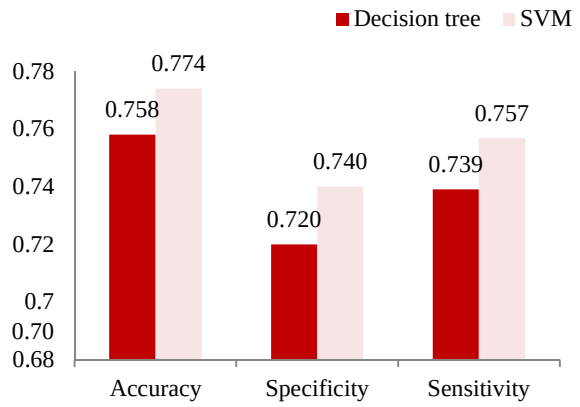

Figure 4. The sensitivity, specificity and accuracy of the learning methods applied on the balanced Isfahan cohort study data set
SVM: Support vector machine

According to studies, the method of SVM also has a high accuracy. The most significant feature in the decision tree method is the tree root. In the constructed decision tree, TGs represent the root. Therefore, TGs is the most important feature for classifying the metabolic syndrome. The derived results are corresponded with research by Worachartcheewan et al.[10] as "identification of metabolic syndrome using decision tree analysis." According to this study, participants had BMI ≥ 25. The results of this study show that TGs is an important feature for the diagnosis of metabolic syndrome and combining (TG + BP) and (TG + BP + glucose) are as an accurate predictor of metabolic syndrome. In another study by Lemieux et al.,[28] it is found that TGs is the most important feature for predicting the metabolic syndrome.

However, it is noted in other studies, using SVM is one of the most successful methods of classification. In our study, SVM method shows that it is more efficient than a decision tree method based on the criteria of sensitivity, specificity and accuracy. Note that, previously, SVM method is not used to predict metabolic syndrome.

Conclusion

One of the main objectives in the field of health is diseases prevention. One of the most effective actions to prevent diseases is prediction of disease in susceptible individuals. One of the effective methods for prediction of diseases is the use of methods of statistical inference and artificial intelligence. Statistical methods do not provide acceptable results in nonlinear and complex problems where features are dependent.[3] In recent years, machine learning techniques are frequently used in medical issues, and they acceptable results in predicting and diagnosing of diseases. Since to the metabolic syndrome is a precursor to heart disease and diabetes and increases the risk of these diseases so Predicting and analyzing the characteristics of this disorder, it can be an effective step in preventing these diseases. According to the results obtained in our study, increasing of TGs, BP, and BMI are regarded as the most important causes of this disorder. These factors are easily modifiable by changes in the lifestyle and the use of healthy eating.

Furthermore, due to the high efficiency of SVM method, this method can be used for prediction and generality issues related to the classification in the medical domain. According to the results of the two learning candidate methods, in other to have a more accurate prediction for new instances of the disorder we recommend to use SVM method. Prediction of ATPIII based metabolic syndrome using machine learning.

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Conflict of Interests

Authors have no conflict of interests.

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Reversible left bundle branch block should be mentioned in cardiac resynchronization therapy; A clinical case report

Ali Vasheghani-Farahani[(1)], Masih Tajdini[(2)], Seyed Abolfazl Mohsenizadeh[(2)], Seyed Mohammad Reza Hosseini[(3)]

Case Report

Abstract

BACKGROUND: Cardiac resynchronization therapy (CRT) is a medical device to help cardiac synchronized contractility by electrical impulses. Improvement of symptoms and left ventricular systolic function, reducing hospital admissions and mortality in patients with moderate to severe heart failure are the main benefits of administration of cardiac resynchronization therapy.

CASE REPORT: In this article, we describe a case of heart failure and left bundle branch block (LBBB) who was candidate for cardiac resynchronization therapy; but after managing hyperkalemia, left bundle branch block resolved, ejection fraction increased and cardiac resynchronization therapy implantation was canceled.

CONCLUSION: Exclusion of treatable causes is the first important step before any interventions. Now there is an important question; is cardiac resynchronization therapy effective in patients with heart failure and transient or intermittent left bundle branch block?

Keywords: Reversible Left Bundle Branch Block, Cardiac Resynchronization Therapy, Hyperkalemia

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Introduction

Wide QRS, mainly left bundle branch block (LBBB) is an independent predictor of adverse prognosis in patients with heart failure. Cardiac resynchronization therapy (CRT) is a medical device to help cardiac synchronized contractility by electrical impulses.[1]

CRT is indicated for patients who have left ventricular ejection fraction of less than 35 percent, LBBB with QRS duration of ≥ 120 ms (especially when is more than 150 ms) and New York Heart Association (NYHA) of class II, III, or ambulatory IV symptoms while receiving guideline-directed medical therapy (GDMT).[2]

Case Report

A 71-year-old woman referred to our clinic with dyspnea on exertion (DOE). Her dyspnea was progressed from class II to IV during the last month (based on NYHA classification). Past medical history was positive for hypertension and hypothyroidism. She was under heart failure regimen drugs [angiotensin II receptor blocker (ARB), aldosterone antagonist, digoxin, diuretic and beta blocker], and prednisolone for her thyroid-related ophthalmopathy condition.

On physical examination, holosystolic murmur in left sternal border (LSB) and coarse crackle on both lungs was heard. About + to ++ non-pitting edema was observed in lower limbs. Electrocardiogram (ECG) was in favor of normal sinus rhythm, left axis deviation, LBBB pattern with QRS duration of approximately 160 ms and wide base tall T waves in precordial leads (Figure 1).

Echocardiographic evaluations including tissue doppler imaging (TDI) and tissue synchronization imaging (TSI) were suggested significant intraventricular and interventricular dyssynchrony and ejection fraction of about 30 percent.

Due to these findings and based on 2012 American College of Cardiology Foundation/American Heart Association/Heart

1- Associate Professor, Tehran Heart Center AND Department of Cardiology, Tehran University of Medical Sciences, Tehran, Iran
2- Resident, Tehran Heart Center AND Department of Cardiology, Tehran University of Medical Sciences, Tehran, Iran
3- General Practitioner, Department of Radiology, Massachusetts General Hospital, Boston, MI
Correspondence to: Masih Tajdini, Email: drmasih84@yahoo.com

Rhythm Society (ACCF/AHA/HRS) Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities, the patient was candidate for CRT.

Routine laboratory tests such as electrolytes level, creatinine, complete blood count, coagulation tests, thyroid function tests and digoxin level were requested. All of aforementioned lab results were in normal ranges except potassium (k = 7.49 mEq/l), hemoglobin [10.3 g/l with mean corpuscular volume (MCV) of 85 fl] and creatinine (Cr = 1.52 mg/dl).

Therefore, acute treatment strategies were started for hyperkalemia. After treatment, the level of potassium was dropped to 4.3 mEq/l. Surprisingly, ECG converted to normal sinus rhythm with normal QRS duration and no ST-T changes (Figure 2). Echocardiography was done again and revealed an ejection fraction of about 40 percent.

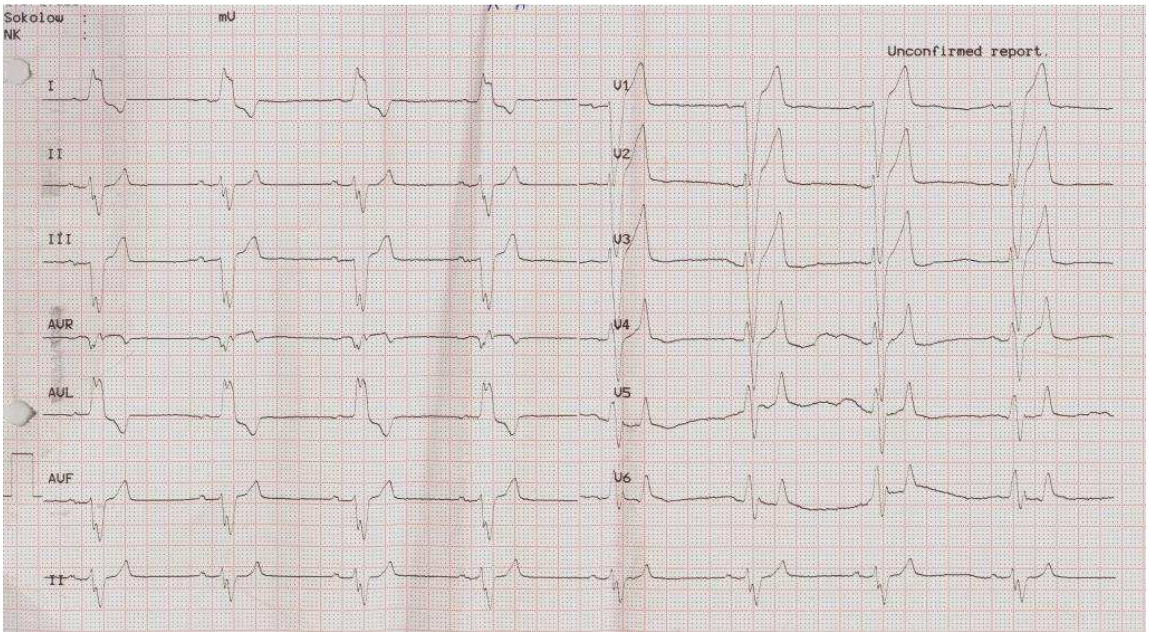

Figure 1. With this the patient was candidate for cardiac resynchronization therapy (CRT)

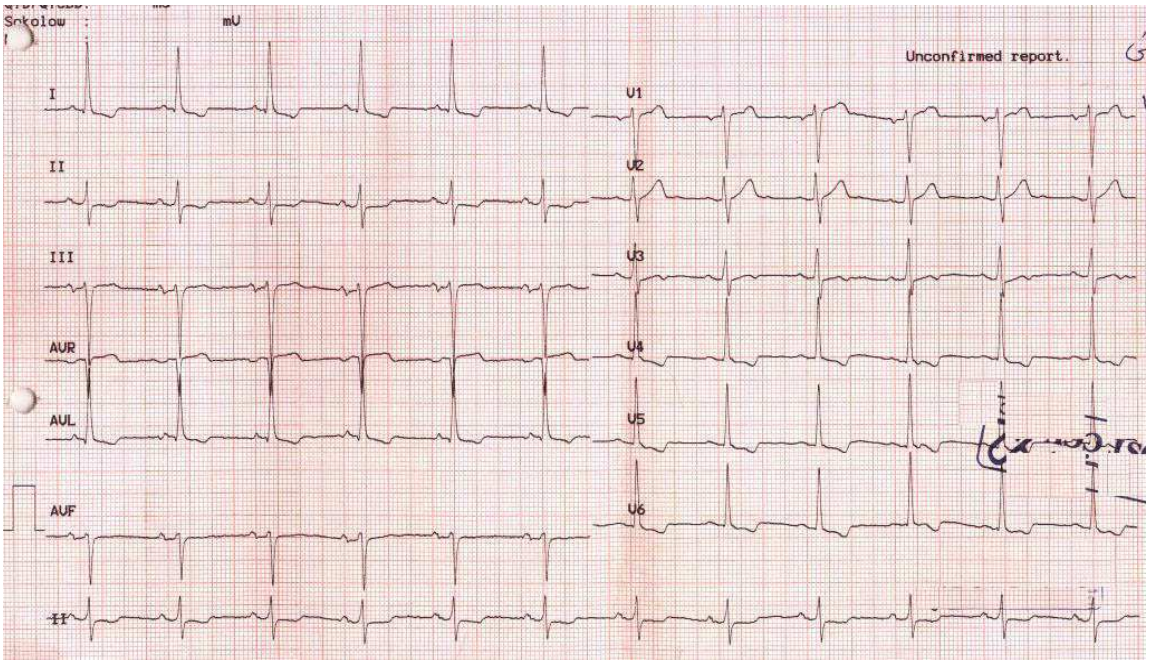

Figure 2. After potassium level correction

Discussion

Improvement of symptoms and left ventricular systolic function, reducing hospital admissions and mortality in patients with moderate to severe heart failure are the main benefits of CRT administration.[3]

Potassium level of more than 5.5 mEq/l is defined as hyperkalemia. Hyperkalemia has different causes but most often, it is due to renal impairment of potassium excretion, potassium sparing drugs (such as renin-angiotensin inhibitors and aldosterone antagonist diuretics) and cellular release of potassium. Hyperkalemia has different effects on ECG including narrow and tall T wave, shortening of QT interval, QRS widening, prolonged PR interval and loss of P wave.[4]

Based on our literature search, except hyperkalemia there are some causes of transient LBBB; a) Thyrotoxicosis, in a case report, LBBB in a young woman resolved by thyrotoxicosis treatment;[5] b) Rate-dependent bundle branch block that may happen with tachycardia in the settin of heart failure decompensation;[6] c) Acute carbon monoxide poisoning;[7] d) Vasospasm;[8] and e) Left coronary fistula.[9]

Our patient had transient LBBB due to hyperkalemia. We recognized chronic hyperkalemia as the main etiology of wide QRS in our patient. The ECG turned back to normal after K level was corrected. CRT was not a treatment of choice for this patient as result of acceptable ejection fraction and narrow QRS. So, exclusion of treatable causes is the first important step before any interventions. Now there is an important question; is CRT effective in patients with heart failure and transient or intermittent left bundle branch block?

Acknowledgments

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Conflict of Interests

Authors have no conflict of interests.

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Normal range of bleeding time in west of Iran

Hassan Mansouritorghabeh[1]

Letter to Editor

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Introduction

I read with great interest the contribution of Maleki et al. entitled "Normal range of bleeding time in urban and rural areas of Borujerd, west of Iran" that has been published in recent issue of ARYA Atherosclerosis.[1]

The bleeding time test (BTT) is an old in-vivo test for evaluation of platelets function and vascular integrity with low producibility.[2] Its procedure and performance is simple and due to its high dependence on operator skills, every laboratory should determine its reference range by itself and by one operator.[3] So, if you determine a reference range by a laboratory (an operator) it may not cover the same population tested by another laboratory (another operator) exactly.

The authors declared that participants were selected among patients referred to 9 rural and 16 urban medical centers. In an epidemiological study, to determine the reference range for a biologic parameter, it would be more logic and accurate to select participants among normal general population randomly to avoid any bias in results. The sampling methods in this regards have been fully addressed in biostatistics field.[4]

Besides, it is reported that all measurements of BTT were done by samplers in each medical center; as there were 25 medical centers for carrying out BTT, an important issue is how the authors are sure about standard incisions made by hand by various technicians while investigators did not use standard instrument for incision such as Template or Simplate.[5] As mentioned earlier, the results of BTT are highly dependent on operator's skill due to improperly performed puncture and can affect the results.

The difference of current reference range of BT in Borujerd that is different from worldwide reference range comprises that an important finding needs to be interpreted and addressed as this study has focused on reference range of BT in the region.

Owing to the authors cited "BT of the samples was determined according to Ivy simplate method considering national standard protocol in the selected persons" it would be cleared that according to Ivy protocol the BT is done directly on participants' forearms and there is no sample to be used in the procedure. In addition, there are four known different procedures that are in use for BTT; 1) The Duke method, 2) The Ivy method, 3) The Mielke method and 4) The simplate or surgicutt method. The former method is modified version of Ivy method and is done by a standard and sterile device (Figure 1) that makes a uniform incision. As the authors declared they have used a lancet for making an incision, naming Ivy simplate in the text is confusing.

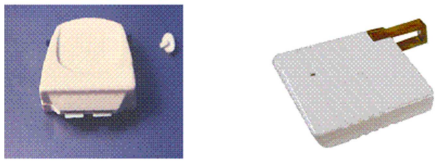

Figure 1. A schematic sample of incision devices are used in Ivy simplate or sugicutt method

Conflict of Interests

Authors have no conflict of interests.

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1- Allergy Research Center, Ghaem Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
Correspondence to: Hassan Mansouritorghabeh, Email: mansouritorghabeh@mums.ac.ir

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