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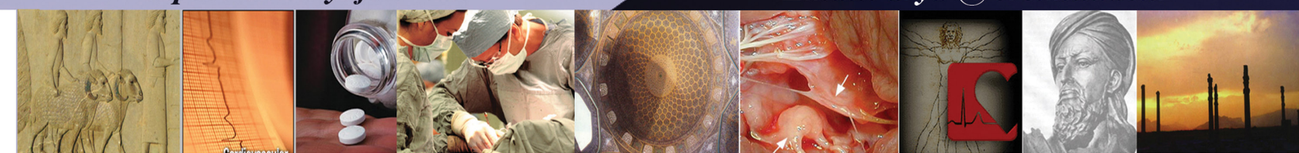

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2. Bonow RO, Mann DL, Zipes DP, Libby P. Braunwald's Heart Disease E-Book: A Textbook of Cardiovascular Medicine. 7th ed. Philadelphia, PA: Elsevier Health Sciences; 2007. p. 1976, 1981, 1982.

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Evaluation of the return to work and its duration after myocardial infarction

Seyyed Jalil Mirmohammadi[1], Seyyed Mahmoud Sadr-Bafghi[2], Amir Houshang Mehrparvar[1], Marjan Gharavi[3], Mohammad Hossein Davari[3], Maryam Bahaloo[4], Mehrdad Mostaghaci[3], Seyyed Ali Sadr-Bafghi[5], Pedram Shokouh[6]

Original Article

Abstract

BACKGROUND: The evaluation of the ability for return to work among patients after myocardial infarction (MI) is subject to controversy. Understanding various factors, which may affect return to work process, will help in promoting effective communication between physicians and patients. Return to work is dependent on such factors as patients' functional capacity, MI expansion, cardiac muscle function, some psychiatric variables, job satisfaction, economic status, and age. In this study, we aimed to assess the frequency of return to work after first MI attack, and factors affecting it.

METHODS: This was a follow-up study performed in Yazd, Iran from September 2007 until September 2010 on 200 patients suffering from their first MI attack. Patients were assessed 6 months and 1-year after MI regarding their cardiac function. Job satisfaction was evaluated by Direct Support Professional job satisfaction questionnaire.

RESULTS: Seventy-seven percent of MI patients returned to work after 1-year. Mean time for return to work was 46.00 ± 4.12 days. Sixty percent of patients returned to work during the first 50 days after MI and 50% of them during 40 days after MI. The most common reason for not returning to work was patient's decision.

CONCLUSION: This study showed that a considerable numbers of patients returned to work after 1-year. The only factors which affected the rate of return to work were left ventricular function after MI and job satisfaction.

Keywords: Myocardial Infarction, Return to Work, Left Ventricular Function, Job Satisfaction

Date of submission: 01 Jan 2013, ***Date of acceptance:*** 26 Jun 2013

Introduction

The evaluation of the ability for return to work among patients after myocardial infarction (MI) is subject to controversy. In the studies during 1960s, about 12-28% of MI patients returned to their previous jobs.[1] In the first decade of the 21st century, despite many advances in the diagnosis and treatment of MI in the last 40 years, this rate was almost similar to the last century.[2]

It has been estimated that in the European Union, 90 million working days are lost a year due to coronary artery diseases morbidity.[3] Return to work following acute coronary events may have both economic benefits and improve the quality of life.[4] Lack of early return to work may cause depression.[5]

Understanding various factors, which may affect return to work process will help in promoting effective communication between physicians and patients.[6] Return to work is dependent on such medical factors as patient's functional capacity, MI expansion, cardiac muscle function, some psychiatric variables (e.g., anxiety and depression)[7] and some non-medical factors, for example, job satisfaction, economic status,[2] and age, illness perception, history of heart failure, and physician's recommendation.[6] Job satisfaction acts independent from socio-demographic factors.[4] In a study, it was shown that 1-year after returning to work, subjects showed more

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positive affect, and less somatic complaints.[8]

It is estimated that in 40-50% of cases not returning to work cannot be explained by patients' physical limitations.[9] Although physicians pay more attention to the medical factors, psychological and non-medical factors have a significant effect on return to work.[10,11] Some studies have shown that early return to work after MI is safe,[12] but the decision for return to work is yet controversial.

There are few studies in this regard in our country, and since about 50% of cases of MI are below 65 years old, the period of employment is an important issue.

This study was designed to assess the frequency of return to work after the first MI attack, and its influencing factors.

Materials and Methods

This was a follow-up study performed in Yazd, Iran from September 2007 until September 2010. Subjects were 200 patients younger than 65 years old suffering from their first MI attack who were employed before MI and were followed for 1-year. A questionnaire including demographic data, economic status, and occupational information was filled for each subject. For evaluating cardiac muscle function, echocardiography was performed for each subject after MI (device: GE vivid 7, USA). Job satisfaction was evaluated by Direct Support Professional job satisfaction questionnaire.

Data were analyzed by SPSS for Windows (version 17, SPSS Inc., Chicago, IL, USA) using Student's t-test and chi-square test. Level of significance was set at 0.05. An informed consent was obtained from each subject. This study was approved by Ethics Committee of Shahid Sadoughi University of Medical Sciences (Yazd, Iran).

Results

One hundred and seventy-four cases (out of 200 cases) returned for follow-up. From these subjects, 134 cases (77%) returned to work after 1-year. Mean (± standard deviation) time for return to work was 46.00 ± 4.12 days. Sixty percent of patients returned to work during the first 50 days after MI and 50% of them during 40 days after MI. The most common reason for not returning to work was patient's decision. Table 1 shows the frequency of different reasons for not returning to work. Among those who returned to work, most subjects returned to their previous job (99.2%).

Table 1. Frequency of reasons for not returning to work

Reason	Number	Percent
Retirement	4	10.0
Physician's order	3	7.5
Physician's recommendation	9	22.5
Patient's decision	18	45.0
Disease complications	1	2.5
Dismissal	1	2.5
Unknown	4	10.0

There was not any significant difference in return to work between shift workers and others (P = 0.670). Regular exercise before MI had a positive effect on return to work, so as 86.7% of those with previous regular exercise history returned to work, compared to 78.3% of those without regular exercise, but the difference was not statistically significant (P = 0.440). Table 2 shows the effect of job satisfaction on return to work. Chi-square test failed to show a significant difference in returning to work according to the level of job satisfaction (P = 0.350), although those with a high level of job satisfaction returned to work significantly higher than those with low and moderate level of job satisfaction (P = 0.027 and P = 0.042 for comparison with low and moderate levels of satisfaction).

Left ventricular ejection fraction (LVEF) had a significant effect on return to work (P = 0.007). Table 3 shows the effect of LVEF on return to work.

Table 4 shows the frequency of return to work in different age groups. In spite of the difference observed, it was not statistically significant (P = 0.410).

Table 2. Frequency of return to work according to the level of job satisfaction

Return to work	Job satisfaction			Total
	Low	Moderate	High	
Yes, n (%)	10 (71.4)	71 (74.7)	43 (84.3)	124 (77.5)
No, n (%)	4 (28.6)	24 (25.3)	8 (15.7)	36 (22.5)

Table 3. Frequency of return to work according to left ventricular ejection fraction

Return to work	LVEF (%)			Total
	< 40	41-50	> 50	
Yes, n (%)	18 (66.7)	33 (80.5)	34 (97.1)	85 (82.5)
No, n (%)	9 (33.1)	8 (19.5)	1 (2.9)	18 (17.5)

LVEF: Left ventricular ejection fraction

Table 4. Frequency of return to work according to age

Return to work	Age (year)			Total
	≤ 40	41-59	≥ 60	
Yes, n (%)	16 (88.9)	97 (77.6)	12 (70.6)	125 (78.1)
No, n (%)	2 (11.1)	28 (22.4)	5 (29.4)	35 (21.9)

Work load before MI did not have a significant effect on return to work (P = 0.210). The frequency of return to work was 82.0%, 81.7%, and 66.7% for those with mild, moderate, and heavy work load, respectively.

Drug abuse, smoking, income, and job title did not have any significant effect on return to work (P = 0.230, 0.230, 0.620, and 0.710, respectively).

Discussion

In the assessment of MI patients for return to work, prognosis, functional capacity, and psychosocial status should be evaluated. Prognosis is defined by such factors as other diseases, electrocardiogram findings, exercise tolerance test, thallium scan, and angiography.[13-15]

LVEF is one of the most important predictors of return to work in these patients. In the present study, more than 95% of subjects with LVEF > 50% returned to work, and there was a significant relationship between LVEF and return to work.

The effect of MI on the quality of life is completely understood. Frequency and time of return to work is a representative of their life quality and economic effects of the disease.

Studies have found a frequency of 63-94%, 58-80%, 85-87%, and 90% for return to work after MI in the USA, Sweden, Belgium, and Denmark, respectively.[16] Our study showed a frequency of 77% for return to work, which is almost consistent with studies in other parts of the world.

Five percent of MI cases are subjects under 40 years old, and 45% are in subjects under 65 years old, so a considerable number of MI patients are in the years of employment; therefore, it may affect personal and social life of the patient and may lead to important socioeconomic outcomes.

Psychosocial factors are among the most important identifiers of return to work and most studies on this issue have shown this relationship in MI patients.[17] Psychological changes after MI are complex and are individualized. Fear from recurrent MI and probable death may prevents the patient from return to work.[18] Most studies show an important effect for psychosocial factors in return to work of MI patients.[17,18] In our study, those with a high level of job satisfaction returned to work more frequently than other workers consistent with some other studies.[4,10,19] In the current study, office workers were the job group who returned to work most frequently.

Mean time of return to work in this study was 6 weeks, which is similar to the results of other studies. Kovoor et al. in Australia showed that return to work during 2 weeks after MI in low-risk patients comparing 6 weeks in high-risk patients is harmless, and they could not find a significant difference between two groups regarding cardiovascular complications.[20] Another study showed that MI complications are related to the physician's and employee's understanding from disease severity.[13]

In the study conducted by Isaaz et al. 24% did not return to work, and there was not a significant difference between these individuals and others regarding LV function, the interval between the onset of pain and percutaneous coronary intervention, and length of hospitalization; although age, marital status and work load significantly affected return to work.[21] Our results were inconsistent with the results of this study, because in our study, the only factor which significantly affected the return to work was LVEF.

Geographical differences have been observed in return to work, which is dependent on the working conditions in each country.[22]

Rehabilitation, age, educational level, and such psychological conditions as depression and anxiety, job satisfaction and comorbidities such as diabetes mellitus have been shown in different studies to be effective in return to work.[16,23,24]

In the current study, patient understands about his (her) disease and physician's advice was the most frequent reasons for not returning to work, which was consistent with Dennis et al. study.[23] In a study in Austria, authors have shown that patients' rehabilitation, age, educational status, social support, and job satisfaction were the factors which were most frequently related to return to work.[14]

To the best of our knowledge, this was the first study in our country about return to work among MI patients; although there were some limitations: in 1-year period, we could only find < 200 individuals and they were employed in different jobs so it may lack the appropriate power to show some associations. The information about subject's job was according to the self-report of the individuals, so we did not have access to the details of their jobs.

Conclusion

This study showed that a considerable numbers of patients returned to work after 1-year. The only factors which affected the rate of return to work were LV function after MI and job satisfaction

Conflict of Interests

Authors have no conflict of interests.

References

1. Wigle RD, Symington DC, Lewis M, Connell WF, Parker JO. Return to work after myocardial infarction. Can Med Assoc J 1971; 104(3): 210-2.
2. Brisson C, Leblanc R, Bourbonnais R, Maunsell E, Dagenais GR, Vezina M, et al. Psychologic distress in postmyocardial infarction patients who have returned to work. Psychosom Med 2005; 67(1): 59-63.
3. Leal J, Luengo-Fernandez R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged European Union. Eur Heart J 2006; 27(13): 1610-9.
4. Fiabane E, Argentero P, Calsamiglia G, Candura SM, Giorgi I, Scafa F, et al. Does job satisfaction predict early return to work after coronary angioplasty or cardiac surgery? Int Arch Occup Environ Health 2013; 86(5): 561-9.
5. Mital A, Desai A, Mital A. Return to work after a coronary event. J Cardiopulm Rehabil 2004; 24(6): 365-73.
6. Slebus FG, Jorstad HT, Peters RJ, Kuijer PP, Willems JH, Sluiter JK, et al. Return to work after an acute coronary syndrome: patients' perspective. Saf Health Work 2012; 3(2): 117-22.
7. Bhattacharyya MR, Perkins-Porras L, Whitehead DL, Steptoe A. Psychological and clinical predictors of return to work after acute coronary syndrome. Eur Heart J 2007; 28(2): 160-5.
8. Boudrez H, de Backer G. Recent findings on return to work after an acute myocardial infarction or coronary artery bypass grafting. Acta Cardiol 2000; 55(6): 341-9.
9. Lewin R. Return to work after MI, the roles of depression, health beliefs and rehabilitation. Int J Cardiol 1999; 72(1): 49-51.
10. Mittag O, Kolenda KD, Nordman KJ, Bernien J, Maurischat C. Return to work after myocardial infarction/coronary artery bypass grafting: patients' and physicians' initial viewpoints and outcome 12 months later. Soc Sci Med 2001; 52(9): 1441-50.
11. Soderman E, Lisspers J, Sundin O. Depression as a predictor of return to work in patients with coronary artery disease. Soc Sci Med 2003; 56(1): 193-202.
12. McBurney CR, Eagle KA, Kline-Rogers EM, Cooper JV, Smith DE, Erickson SR. Work-related outcomes after a myocardial infarction. Pharmacotherapy 2004; 24(11): 1515-23.
13. Cherrington CC, Moser DK, Lennie TA, Kennedy CW. Illness representation after acute myocardial infarction: impact on in-hospital recovery. Am J Crit Care 2004; 13(2): 136-45.
14. Korzeniowska-Kubacka I, Piotrowicz R. Cardiological rehabilitation-a chance of returning to work. Med Pr 2005; 56(4): 325-7.
15. Waszkowska M, Szymczak W. Return to work after myocardial infarction: a retrospective study. Int J Occup Med Environ Health 2009; 22(4): 373-81.
16. Hamalainen H, Maki J, Virta L, Keskimaki I, Mahonen M, Moltchanov V, et al. Return to work after first myocardial infarction in 1991-1996 in Finland. Eur J Public Health 2004; 14(4): 350-3.
17. DeBusk RF, Dennis CA. Occupational work evaluation of patients with cardiac disease: a guide for physicians. West J Med 1982; 137(6): 515-20.
18. Mayou RA, Gill D, Thompson DR, Day A, Hicks N, Volmink J, et al. Depression and anxiety as predictors of outcome after myocardial infarction. Psychosom Med 2000; 62(2): 212-9.
19. Saari LM, Judge TA. Employee attitudes and job satisfaction. Human Resource Management 2004; 43(4): 395-407.
20. Kovoor P, Lee AK, Carrozzi F, Wiseman V, Byth K, Zecchin R, et al. Return to full normal activities including work at two weeks after acute myocardial infarction. Am J Cardiol 2006; 97(7): 952-8.
21. Isaaz K, Coudrot M, Sabry MH, Cerisier A, Lamaud M, Robin C, et al. Return to work after acute ST-segment elevation myocardial infarction in the modern era of reperfusion by direct percutaneous coronary intervention. Arch Cardiovasc Dis 2010; 103(5): 310-6.
22. Abbas AE, Brodie B, Stone G, Cox D, Berman A, Brewington S, et al. Frequency of returning to work one and six months following percutaneous coronary intervention for acute myocardial infarction. Am J Cardiol 2004; 94(11): 1403-5.
23. Dennis C, Houston-Miller N, Schwartz RG, Ahn DK, Kraemer HC, Gossard D, et al. Early return to work after uncomplicated myocardial infarction. Results of a randomized trial. JAMA 1988; 260(2): 214-20.
24. Yonezawa R, Masuda T, Matsunaga A, Takahashi Y, Saitoh M, Ishii A, et al. Effects of phase II cardiac rehabilitation on job stress and health-related quality of life after return to work in middle-aged patients with acute myocardial infarction. Int Heart J 2009; 50(3): 279-90.

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Glycemic control in type 2 diabetes mellitus prevents coronary arterial wall infection

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Original Article

Abstract

BACKGROUND: Diabetes mellitus (DM) is a very well-known risk factor for development of atherosclerosis, and it has been hypothesized that poor glycemic control and hyperglycemia plays a major role in this process. In the current study, we aimed to evaluate the associates of poor glycemic control in Iranian patients who have already undergone coronary artery bypass grafting (CABG), with especial focus on the inhabitation of infectious agents within the coronary arterial wall.

METHODS: In January 2010, 52 consecutive patients with type 2 DM who undergone CABG at the Department of Cardiovascular Surgery of Baqiyatallah University of Medical Sciences (Tehran, Iran) were included into this cross-sectional study and biopsy specimens from their coronary plaques were taken and analyzed by polymerase chain reaction (PCR) methods for detecting *Helicobacter* species, cytomegalovirus (CMV) and *Chlamydia pneumoniae*, and their potential relation to the glycemic control status in these patients.

RESULTS: Compared to that in diabetic patients with mean fasting blood sugar (FBS) levels FBS < 126, atherosclerotic lesions in type 2 diabetic patients with poor glycemic control (FBS > 126) were significantly more likely to be positive for CMV PCR test (41% vs. 9%, respectively; P = 0.05). In laboratorial test results, mean triglyceride level was significantly higher among patients of poor glycemic control (168 ± 89 vs. 222 ± 125 mg/dl, respectively; P = 0.033). Hypertension was also significantly more prevalent in this population (73% vs. 36%, respectively; P = 0.034).

CONCLUSION: Type 2 diabetic patients with poor glycemic control can be at higher risk for developing CMV infection in their coronary arterial wall, which can promote atherosclerosis formation process in this patient population. According to the findings of this study, we recommend better control of serum glucose levels in type 2 diabetic patients to prevent formation/progression of atherosclerosis.

Keywords: Diabetes Mellitus, Hyperglycemia, Coronary Artery, Cytomegalovirus, Infection

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Introduction

Coronary artery disease (CAD) is the one of the leading cause of mortality and morbidity all over the world, which represents a high fatality highlighting the need for evaluating risk factors and associations. Diabetes mellitus (DM) is forerunning risk factor for cardiovascular disease (CVD) development and one of the best known predictive factors for mortality in this patient population especially among women.[1,2]

In patients with type 2 DM previous prospective studies have shown an association between the degree of hyperglycemia and increased risk of cardiovascular complications.[3,4] It has been demonstrated that poor glycemic control in diabetic patients is associated with clinical complications including the myocardial infarction.[5]

Patients with DM have a two-fold to three-fold increased incidence of diseases related to atheroma; nevertheless, factors inducing an excessive risk for diabetes in inducing CVD or its clinical

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complications are not fully revealed; although hyperglycemia as well as diabetic dyslipidemia is likely to be major contributor.[6] For patients with type 1 DM, previous prospective studies have shown an association between glycemia and the progression of cardiovascular complications and deaths.[7] Patients with type 2 DM have high levels of dyslipidemias, including increased levels of triglyceride, decreased levels of high-density lipoprotein (HDL) cholesterol, and smaller absolute elevations of low-density lipoprotein (LDL) cholesterol levels relative to non-diabetic patients.[8]

It has been suggested that atherosclerosis is primarily a chronic inflammatory disease. A potential link between infectious agents and atherosclerosis has been debated for more than a century.[9] After the introduction of Coxsackie B4 virus, as a possible infectious etiology of coronary arteritis,[10] several other infective agents have been reportedly detected in the arterial plaque samples such as herpes simplex virus (HSV) and cytomegalovirus (CMV). The first bacterium that was proposed to play a role in the coronary artery diseases and myocardial infarction is *Chlamydia pneumoniae*[11] and since then, several other studies were conducted to determine potential roles of bacterial infections such as the *C. pneumoniae* and other agents in the development of coronary atheromas among, which periodontal microbes and *Helicobacter pylori* were more frequently studied.[12]

Patients with DM are at an increased risk for CAD and frequently require coronary artery bypass grafting (CABG). However, few studies have been conducted to investigate that whether this risk enhancement is due to an increased risk of inhabitation of infection within the coronary arterial walls or can it be attenuated with a better control of hyperglycemia? In the current study, which we believe that is the first in the current literature, the relationship between poor glycemic control in patients with type 2 DM and different factors, including infective agents' inhabitation in the coronary arterial wall, has been evaluated in our CABG patient population.

Materials and Methods

Study participants

Until January 2010, 52 consecutively selected type 2 DM patients who were admitted to the Department of Cardiovascular Surgery of Baqiyatallah University of Medical Sciences (Tehran, Iran) with different complaints and manifestations of ischemic heart disease, and who underwent CABG surgery were included into this cross-sectional study and biopsy specimens from their coronary plaques were taken and analyzed for existence of atherosclerotic plaques and DNA of *Helicobacter* species (H. spp.), *C. pneumoniae*, and CMV. Inclusion criteria included: (1) cardiovascular patients on the list of CABG, (2) they should have documented history of type 2 diabetes, and (3) they should be under observation for their diabetes. Diagnosis of type 2 DM was performed when fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl) or 2-h plasma glucose ≥ 11.1 mmol/l (200 mg/dl), according to the current WHO definition criteria, in all patients.

Data acquisition

Data on demographics, smoking habit, lipid profile, and medical history were recorded for all subjects. Acute coronary syndrome was defined as positive documented history for previous episode(s) for unstable angina and/or myocardial infarction. A positive "family history" was defined when a positive history was reported on at least one first and/or second family members before the age of 56.[13]

Definition of the study groups

For stratifying fasting blood sugar (FBS) levels of our patients as high and normal, we used two approaches: in the first and the second approach, cut-off points of 110 (Stratus I) and 126 (Stratus II) mg/dl were used for categorization. In the third approach, patients with FBS levels of lower than 110 and higher than 126 were compared (Stratus III) (data not shown).

Laboratorial evaluations

Fibrinogen concentrations were measured by using the Clauss method with commercial reagents (Mahsa-yaran, Tehran, Iran). C-reactive protein (CRP) was measured by turbidimetric method. Lipid concentration levels were determined using standard procedures at Baqiyatallah Hospital Central Laboratory (Tehran, Iran) for all patients.

Polymerase chain reaction (PCR)

Tissue samples were dissected in the operating room and stored under sterile conditions. Atherosclerotic plaques were confirmed and reported by a pathologist for all the specimens. Artery specimens were placed in microcentrifuge tubes without using binding buffer. Transport vials were sealed in the operating room and opened only in the laminar airflow safety cabinet at the microbiology laboratory. All of the specimens were kept at −20° C until processing. For preparation of genomic DNA and polymerase chain reaction (PCR), DNA was extracted from endoarterectomy specimens by using the QIAamp tissue mini-kit (Qiagen Inc., Valencia, CA, USA). The DNA absorbed in the QIAamp spin column was eluted

with 55 µL of Tris-EDTA and then subjected to the PCR. DNA from each of the three infective agents were extracted using a commercially available kit (Qiagen, Hilden, Germany) and analyzed using conventional methods.

Ethical considerations

This study was approved by the Local Committee of the University Research Review Board (URRB) of Baqiyatallah University of Medical Sciences (Tehran, Iran). All subjects provided written informed consent to participate in the study and were assured that their personal information will remain anonymous and confidential.

Statistical analysis

Data were analyzed using SPSS for Windows (SPSS 17.0, Corp., Chicago, IL, USA). Chi-square test, Student's t-test, and Kruskal-Wallis test were used where appropriate. All statistical analyses were performed at the 0.05 significance level.

Results

Characteristics of the study participants are summarized in table 1. Twenty-eight (53.8%) of the study population were males, and the remaining 24 (46.2%) were females. Mean age at surgery was 61.0 ± 8.9 years old. Mean body mass index (BMI) was 27.7 ± 3.4 kg/m^2. Mean FBS was 187.0 ± 70.4 mg/dl. According to Stratus I, 49 (94%) of patients had out of range FBS; while based on the second and third strata 41 (79% and 93%, respectively) had FBS over 126 mg/dl.

A history of unstable angina or myocardial infarction was confirmed in 20 (38.5%) patients. The number of patients whose biopsy specimens from atherosclerotic lesions were reported positive by PCR analysis for H. spp., CMV, and *C. pneumoniae* were 13 (25.0%), 16 (30.8%), and 8 (15.4%), respectively.

When FBS cut-off point has been defined at the level of 110 mg/dl, no significant difference has been observed regarding any of the study variables, therefore, the cut-off was raised to 126 mg/dl; and patients with in-range (< 126) and out-range (> 126) FBS were comparable regarding their age (P = 0.761), mean weight (P = 0.743), mean BMI (P = 0.477), mean fibrinogen value (P = 0.639), mean cholesterol total (P = 0.635), mean LDL levels (P = 0.979), and mean HDL levels (P = 0.674). Moreover, patients of the two groups were comparable regarding gender (P = 0.190; χ^2 = 2.00), CRP positive rate (P = 0.705; χ^2 = 0.54), smoking (P = 0.424; χ^2 = 0.58), and acute coronary syndromes (P = 0.393; χ^2 = 1.17). Prevalence of positive PCR tests for H. spp. and *C. pneumoniae*

Table 1. Comparison of the study parameters in diabetic patients with or without proper glycemic control (fasting blood sugar cut-off: 126 mg/dl)

Parameters	Stratus II (cut-off FBS = 126 mg/dl)		
	In range	Out range	P
Mean age ± SD (year)	60.5 ± 9.8	59.9 ± 8.9	0.761
Mean weight ± SD (kg)	75.3 ± 11.6	76.0 ± 10.0	0.743
Mean BMI ± SD (kg/m^2)	27.5 ± 3.3	28.0 ± 3.7.0	0.477
Biochemical examinations			
Triglyceride (mean ± SD)	168.3 ± 89.3	221.9 ± 124.7	0.033
Fasting blood glucose (mean ± SD)	102.6 ± 12.7	199.1 ± 64.9	-
Fibrinogen (mean ± SD)	207.2 ± 48.1	200.8 ± 58.9	0.639
Cholesterol total (mean ± SD)	174.8 ± 41.4	179.3 ± 42.7	0.635
LDL cholesterol (mean ± SD)	98.4 ± 38.2	98.2 ± 37.8	0.979
HDL cholesterol (mean ± SD)	41.8 ± 12.5	42.9 ± 10.2	0.674
CRP (%)	12 (29.3)	2 (18.2)	0.705
Medical history			
Hypertension (%)	4 (36.4)	30 (73.2)	0.034
Smoking (%)	7 (17.1)	3 (27.3)	0.424
Acute coronary syndromes (%)	3 (42.9)	17 (65.4)	0.393
PCR test positive (%)			
CMV	1 (9.1)	17 (41.5)	0.050
Helicobacter spp.	8 (72.7)	31 (75.6)	0.562
C. pneumonia	3 (27.3)	5 (12.5)	0.343
Gender male (%)	8 (72.7)	20 (48.8)	0.190

FBS: Fasting blood sugar; SD: Standard deviation; BMI: Body mass index; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; CRP: C-reactive protein; PCR: Polymerase chain reaction; CMV: Cytomegalovirus; C. pneumonia: Chlamydia pneumonia

were also equal in the two groups (P = 0.562; χ^2: 0.38 and P = 0.343; χ^2: 1.52, respectively).

Atherosclerotic lesions in patients with out-range FBS were significantly more likely to be positive for CMV PCR test (P = 0.05; χ^2: 3.08). In laboratorial test results, mean triglyceride level was significantly higher among the out of range patients (P = 0.033). Hypertension was also significantly more prevalent in the out-range FBS group (P = 0.034; χ^2: 5.19).

Discussion

Several authors have recommended a significant role for inflammatory mechanisms in the pathogenesis of coronary artery disease, although due to its unclear mechanisms and associations, existence of such relationship is under doubt. Epidemiological studies have suggested associations between several infective agents affecting coronary arterial wall and atherosclerosis formation.[14,15] On the other hand, DM is one of the best known risk factor for atherosclerosis development. To the best of our knowledge, there is no study in the current literature evaluating a potential association between DM and infective agents complicating coronary artery walls. In the current study, we evaluated any potential association between hyperglycemia due to a poor DM control and three infective agents, H. spp., CMV, and *C. pneumoniae*, in atherosclerosis lesions in our Iranian patient population undergoing CABG.

Several authors have previously investigated associations of the three mentioned infective agents with arterial atherosclerosis. H. spp. are one of the most frequently investigated infections whose associations with atherosclerosis are very well-demonstrated;[16,17] although contradictory results have also been reported.[18] Moreover, several authors have issued *C. pneumoniae* replication in atherosclerotic arterial wall.[19] On the other hand, some others even have suggested a positive relationship between *C. pneumoniae* infection and metabolic disorders, which can provide an explanation for its potential atherosclerogenic activity.[20] The same association was also found for CMV infection.[21] In the current study, we did not find any association between poor glycemic control in type 2 diabetic patients and *C. pneumoniae* or H. spp.; nevertheless, a positive association was found for CMV inhabitation in coronary artery wall. This association provides two hypotheses: CMV can deteriorate glucose control in diabetic patients, or poor glycemic control in type 2 diabetic patients endangers coronary artery to CMV infection.

Previous studies have shown that CMV infection can affect glucose metabolism. Evidence suggests that CMV infection increases glucose uptake.[22,23] On the other hand, both in naïve and transplant pancreatic cells, it has been demonstrated that CMV infection can increase immunogenicity, which can reduce beta-cell survival.[24] This survival disturbance is to such an extent that some studies have suggested a role for CMV infection in inducing type I diabetes;[25] and post-transplant DM.[26] On the other hand, in type 2 diabetes in which beta-cells are alive and functional, a CMV-induced damage can reduce insulin availability and deteriorate glucose control.

There is data scarcity on the second hypothesis, in which poor glycemic control was introduced as the reason for higher CMV infection risk. However, a study on periodontal infective agents found no association between poor glycemic control in type 2 diabetic patients and CMV infection.[27] On the other hand, in a case study, development of CMV associated colitis was reported in a case of diabetic ketoacidosis.[28] In this article, authors proclaim that immunosuppression induced by hyperglycemia-ketoacidosis can be considered as the precedent to infection. Several studies have suggested that hyperglycemia can make infections.[29-31] As we also mentioned above, the association does not make it clear that what of them, hyperglycemia or infection, was the first factor, and which is the consequence.[32]

This study has some limitations. First of all, the sample size is limited; although as a premier study and due to its very strong methodology, we believe that this limitation would not hurt the credibility of our findings. However, future studies can more strongly corroborate or rule out our results.

Conclusion

To the best of our knowledge, our study is the first study that correlates hyperglycemia with CMV infection in the coronary arterial wall in diabetic patients. This study suggests that diabetic patients should undergo strict glycemic control to prevent atherosclerosis promotion. Further studies with prospective approaches are needed to confirm our findings.

Conflict of Interests

Authors have no conflict of interests.

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References

1. Ismail-Beigi F. Clinical practice. Glycemic management of type 2 diabetes mellitus. N Engl J Med 2012; 366(14): 1319-27.
2. Jackson CA, Jones NR, Walker JJ, Fischbacher CM, Colhoun HM, Leese GP, et al. Area-based socioeconomic status, type 2 diabetes and cardiovascular mortality in Scotland. Diabetologia 2012; 55(11): 2938-45.
3. Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet 2009; 373(9677): 1765-72.
4. Genuth SM, Backlund JY, Bayless M, Bluemke DA, Cleary PA, Crandall J, et al. Effects of prior intensive versus conventional therapy and history of glycemia on cardiac function in type 1 diabetes in the DCCT/EDIC. Diabetes 2013; 62(10): 3561-9.
5. Pacilli A, de Cosmo S, Trischitta V, Bacci S. Role of relationship between HbA1c, fibrinogen and HDL-cholesterol on cardiovascular disease in patients with type 2 diabetes mellitus. Atherosclerosis 2013; 228(1): 247-8.
6. Purnell JQ, Zinman B, Brunzell JD. The effect of excess weight gain with intensive diabetes mellitus treatment on cardiovascular disease risk factors and atherosclerosis in type 1 diabetes mellitus: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) study. Circulation 2013; 127(2): 180-7.
7. McVeigh GE, Gibson W, Hamilton PK. Cardiovascular risk in the young type 1 diabetes population with a low 10-year, but high lifetime risk of cardiovascular disease. Diabetes Obes Metab 2013; 15(3): 198-203.
8. Kataoka Y, Shao M, Wolski K, Uno K, Puri R, Tuzcu EM, et al. Multiple risk factor intervention and progression of coronary atherosclerosis in patients with type 2 diabetes mellitus. Eur J Prev Cardiol 2013; 20(2): 209-17.
9. Osler W. Diseases of the arteries. In: Osler W, McCrae T, Editors. Modern medicine, its theory and practice. Philadelphia, PA: Lea & Febiger; 1908. p. 426-47.
10. Sohal RS, Burch GE, Chu KC, Leiderman E, Colcolough HL. Ultrastructural changes in cardiac capillaries of Coxsackie virus B4-infected mice. Lab Invest 1968; 19(4): 399-405.
11. Kuo CC, Shor A, Campbell LA, Fukushi H, Patton DL, Grayston JT. Demonstration of Chlamydia pneumoniae in atherosclerotic lesions of coronary arteries. J Infect Dis 1993; 167(4): 841-9.
12. Beck J, Garcia R, Heiss G, Vokonas PS, Offenbacher S. Periodontal disease and cardiovascular disease. J Periodontol 1996; 67(10 Suppl): 1123-37.
13. Ketterer MW, Denollet J, Chapp J, Thayer B, Keteyian S, Clark V, et al. Men deny and women cry, but who dies? Do the wages of "denial" include early ischemic coronary heart disease? J Psychosom Res 2004; 56(1): 119-23.
14. Jha HC, Srivastava P, Divya A, Prasad J, Mittal A. Prevalence of Chlamydophila pneumoniae is higher in aorta and coronary artery than in carotid artery of coronary artery disease patients. APMIS 2009; 117(12): 905-11.
15. Kilic A, Onguru O, Tugcu H, Kilic S, Guney C, Bilge Y. Detection of cytomegalovirus and Helicobacter pylori DNA in arterial walls with grade III atherosclerosis by PCR. Pol J Microbiol 2006; 55(4): 333-7.
16. Sulewska A, Modrzejewski W, Kovalchuk O, Kasacka I, Jackowski R, Hirnle T, et al. Attempts to detect Helicobacter pylori in atherosclerotic plaques. Rocz Akad Med Bialymst 2004; 49(Suppl 1): 239-41.
17. Izadi M, Fazel M, Sharubandi SH, Saadat SH, Farahani MM, Nasseri MH, et al. Helicobacter species in the atherosclerotic plaques of patients with coronary artery disease. Cardiovasc Pathol 2012; 21(4): 307-11.
18. Deniset JF, Cheung PK, Dibrov E, Lee K, Steigerwald S, Pierce GN. Chlamydophila pneumoniae infection leads to smooth muscle cell proliferation and thickening in the coronary artery without contributions from a host immune response. Am J Pathol 2010; 176(2): 1028-37.
19. Dabiri H, Rezadehbashi M, Badami N, Aghanouri R, Ahmadi H, Khoramizadeh MR, et al. Detection of Chlamydia pneumoniae in atherosclerotic plaques of patients in Tehran, Iran. Jpn J Infect Dis 2009; 62(3): 195-7.
20. Yi L, Wang DX, Feng ZJ. Detection of human cytomegalovirus in atherosclerotic carotid arteries in humans. J Formos Med Assoc 2008; 107(10): 774-81.
21. Izadi M, Fazel M, Saadat SH, Nasseri MH, Ghasemi M, Dabiri H, et al. Cytomegalovirus localization in atherosclerotic plaques is associated with acute coronary syndromes: report of 105 patients. Methodist Debakey Cardiovasc J 2012; 8(2): 42-6.
22. Yu Y, Maguire TG, Alwine JC. Human cytomegalovirus activates glucose transporter 4 expression to increase glucose uptake during infection. J Virol 2011; 85(4): 1573-80.
23. Yu Y, Clippinger AJ, Alwine JC. Viral effects on metabolism: changes in glucose and glutamine utilization during human cytomegalovirus infection. Trends Microbiol 2011; 19(7): 360-7.
24. Smelt MJ, Faas MM, de Haan BJ, Hofstede J, Cheung CW, van der Iest H, et al. Rat pancreatic

beta cells and cytomegalovirus infection. Pancreas 2010; 39(1): 47-56.
25. Zanone MM, Favaro E, Quadri R, Miceli I, Giaretta F, Romagnoli R, et al. Association of cytomegalovirus infections with recurrence of humoral and cellular autoimmunity to islet autoantigens and of type 1 diabetes in a pancreas transplanted patient. Transpl Int 2010; 23(3): 333-7.
26. Leung Ki EL, Venetz JP, Meylan P, Lamoth F, Ruiz J, Pascual M. Cytomegalovirus infection and new-onset post-transplant diabetes mellitus. Clin Transplant 2008; 22(2): 245-9.
27. Casarin RC, Duarte PM, Santos VR, Lima JA, Gagnon G, Casati MZ, et al. Influence of glycemic control on Epstein-Bar and Cytomegalovirus infection in periodontal pocket of type 2 diabetic subjects. Arch Oral Biol 2010; 55(11): 902-6.
28. Izumi K. Diabetic ketoacidosis with cytomegalovirus-associated colitis. Intern Med 2009; 48(5): 343-6.
29. Pomposelli JJ, Baxter JK, Babineau TJ, Pomfret EA, Driscoll DF, Forse RA, et al. Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. JPEN J Parenter Enteral Nutr 1998; 22(2): 77-81.
30. Khaodhiar L, McCowen K, Bistrian B. Perioperative hyperglycemia, infection or risk? Curr Opin Clin Nutr Metab Care 1999; 2(1): 79-82.
31. Guvener M, Pasaoglu I, Demircin M, Oc M. Perioperative hyperglycemia is a strong correlate of postoperative infection in type II diabetic patients after coronary artery bypass grafting. Endocr J 2002; 49(5): 531-7.
32. Weis M, Kledal TN, Lin KY, Panchal SN, Gao SZ, Valantine HA, et al. Cytomegalovirus infection impairs the nitric oxide synthase pathway: role of asymmetric dimethylarginine in transplant arteriosclerosis. Circulation 2004; 109(4): 500-5.

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Comparison of the effect of different intensity exercise on a bicycle ergometer on postprandial lipidemia in type II diabetic patients

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Original Article

Abstract

BACKGROUND: Postprandial lipid clearance failure and lipoprotein disorders, which are independent risk factors for cardiovascular diseases are well-recognized in type II diabetes. Reduction of fats through exercise has been proved, though the mechanism is not well-defined, and the effects of different intensity exercise on postprandial lipidemia in diabetes type II is unknown. This study aims to find these effects using a cycle ergometer.

METHODS: On three different days, 15 type II diabetics (10 women and 5 men, with a mean age 42.07 ± 6.05 years, weight 94.64 ± 4.37 kg, height 159.78 ± 9.09 cm, and body mass index 29.83 ± 3.93 kg/m^2), consumed a full fat breakfast (750-800 kcal, 85% fat), and 150 min later, blood samples were taken from them to measure their lipid profile. The 1st day was the control day, without any exercises. Seven days later, 90 min after enriched breakfast, they did 30 min of exercise on the cycle ergometer with intensity of 55-70% of maximum heart rate (HRmax), and 14 days later, 90 min after enriched breakfast, they did 30 min of exercise with intensity of 70-85% of HRmax.

RESULTS: According to Friedman non-parametric test, high-density lipoprotein (HDL) cholesterol serum level significantly increased after 30 min of moderate intensity exercise ($P > 0.05$, from 39.4 ± 5.2 to 48.6 ± 9.3), while this increase was insignificant after a higher intensity exercise. Neither intensity levels had any significant effects on triglyceride or on low-density lipoprotein cholesterol.

CONCLUSION: Results showed that moderate intensity exercise was more effective in increasing HDL cholesterol level in type II diabetics.

Keywords: Postprandial Lipidemia, Resistance Exercise, Bicycle Ergometer, Type II Diabetes

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Introduction

Since the middle of the 20th century, the rapid increase in prevalence of diabetes has become a major concern for the World Health Organization,[1,2] and over 246 million current number of diabetes is forecast to increase to 380 million by 2025.[3] Diabetes is a group of metabolic diseases. Over the past three decades, postprandial hyperlipidemia has been the most common diabetes disorder, responsible for pancreatic disorders, insulin resistance, and type II diabetes,[4,5] as well as high incidence of cardiovascular diseases (CVDs).[6] Postprandial lipid increase includes triglyceride (TG) rich lipoproteins, increased very low-density lipoprotein (LDL), and increased less dense, smaller LDL particles in plasma.[6,7] It has been over 30 years since the publication of information identifying relationship between postprandial hyperlipidemia, and CVDs and atherosclerosis.[7,8]

There have been numerous studies on advantages of consistent aerobic exercises on postprandial lipid reduction,[9-16] showing effects remaining 11-18 h after eating fatty food.[16-18] However, no research has been conducted into the effect of different intensity exercise on postprandial lipidemia in diabetes type II patients.[19-23] This study aims to investigate the effect of different intensity of exercises on reducing postprandial lipidemia in patients with diabetes type II.

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Materials and Methods

This applied, cross-sectional, and semi-experimental study was conducted on type II diabetic patients attending Isfahan Cardiovascular Research Center in 2010, with age ranging from 30 to 50 years. After completion of a questionnaire containing such information as age, gender, body mass index, medical history, including kidney, liver, eye, and CVDs; insulin intake, physical activity and diet. Based on blood pressure and electrocardiogram and normal laboratory standards and after completing a consent form, 15 type II diabetic patients (5 males and 10 females) were selected. Those with diabetes complications such as retinopathy, CVDs, skin diseases, joint diseases, and lipid disorders were excluded from the study.

Preliminary tests

Physical examination and measurements of weight, height, body mass index (BMI) were carried out, and under specialist's supervision, treadmill exercise test was conducted according to Bruce protocol and maximum intensity exercise for each patient was determined during the rest after 5-15 min of exercise. Exercise intensity was found by Carnen method as follows:

Heart rate at reserve (HRR) = HR_{max} − heart rate at rest (HR_{rest})

Target heart rate (THR) (intensity %) = HR_{rest} + (intensity %) (HR_{max} – HR_{rest})

Or

THR (intensity %) = HR_{rest} + (intensity %) HRR.

According to exercise test and medical examination, all patients were healthy in cardiovascular terms.

Main tests

Seven days after an exercise test, all patients participated in a 3-day study protocol with 7 days interval. On each day, blood samples were taken 150 min after enriched breakfast. The 1st day was a control day with no exercise. On the other 2 days, 90 min after breakfast, patients exercised on the ergometer bicycle with different intensities for 30 min.

The 1st day

Full fat breakfast included; 150 g bread, 25 g butter, 100 g cream cheese, and 200 ml milk (85% fat), and no exercise. Blood samples were taken 150 min after enriched breakfast.

The 2nd day

Seven days later, 90 min after the same type of enriched breakfast, patients exercised on a cycle ergometer for 30 min with 55-75% maximum heart rate (HRmax) intensity.

The 3rd day

Much the same as the 2nd day, but with 70-85% HRmax intensity.

Exercise sessions and intensities

Each 30 min session involved 5 min of warm-up, 20 min of exercise with specified intensity, and 5 min of cooling down. Caronen method was used according to each patient's intensity result from exercise test, and under specialist's supervision, bicycle ergometer resistance was altered accordingly.

Blood sampling

To determine lipoprotein and lipidemia indices, 10 cc of blood was taken from the antecubital vein of the left arm in seating position, 150 min after enriched breakfast on each day of the test. Blood samples were immediately cooled down to 4° C and centrifuged at 2000 rpm for 15 min, separating its serum. Serum total cholesterol, TG, high-density lipoprotein (HDL) cholesterol, and glucose were measured using Pars Azmoon Company kits, and LDL cholesterol was measured using Randox Company kit.

Data analysis

The SPSS for windows (version 16, SPSS Inc., Chicago, IL, USA) was used for data analysis in two stages; descriptive with mean ± standard deviation and inferential statistics using non-parametric Friedman test. Significance level was set at $P > 0.05$ for all patients.

Results

Participants' characteristics

Fifteen type II diabetic patients (5 men and 10 women) with a mean age of 42.07 ± 6.05 years, BMI of 29.83 ± 3.93 kg/m^2, and with 1.0 ± 0.8 years since their diagnosis with type II diabetes were studied. Exercise test results, biochemical, and clinical details of patients are presented in table 1.

Postprandial lipidemia response after moderate and high intensity physical activity

The mean serum HDL cholesterol increased somewhat after enriched breakfast, and increased significantly after moderate intensity exercise. High intensity exercise increased HDL cholesterol only a little (Table 2). According to the Friedman test, there was a significant difference between the two levels of exercise intensity for serum HDL cholesterol. In fact, moderate intensity exercise increased postprandial HDL more than high intensity exercise (Figure 1). After intake of fat-enriched breakfast, patients' plasma TG concentration increased, but reduced again after exercise (Table 2). Moderate intensity exercise reduced mean TG level more than high intensity (Figure 2). But, the difference between exercise

intensities in reducing TG was insignificant according to Friedman test (P ≥ 0.274) (Table 2).

There was no significant difference in mean postprandial serum LDL level after high and moderate intensity exercise (P < 0.05), though, high intensity exercise more reduced LDL than moderate intensity (Figure 3).

Discussion

In recent years, not only has postprandial hyperlipidemia been taken as the most common sign and risk factor of CVDs and athrosclerosis in type II diabetes, it is also now being taken as the main predictor of CVDs. The relationship between postprandial hyperlipidemia and level of exercise remains unclear,[21-23] in spite of recent studies on the role of exercise in treatment and prevention of postprandial hyperlipidemia.[19-24] Hence, this study attempted to find a suitable exercise intensity level for treatment of this disorder in type II diabetic patients, by comparing two exercise intensity levels.

Table 1. Biochemical and clinical details and exercise test results of type II diabetic patients

Variables	Mean ± SD (n = 15)
Age (year)	42.07 ± 6.05
Height (cm)	159.78 ± 9.09
Weight (kg)	94.64 ± 4.37
BMI (kg/m^2)	29.83 ± 3.93
WHR	0.87 ± 0.46
BP (mmHg)	122.60 ± 13.65
BS (mg/dl)	167.06 ± 59.71
TG (mg/dl)	195.93 ± 77.30
Total cholesterol (mg/dl)	184.46 ± 33.32
LDL cholesterol (mg/dl)	113.92 ± 30.21
HDL cholesterol (mg/dl)	39.40 ± 5.27
HbA1c (%)	8.12 ± 1.51

SD: Standard deviation; BMI: Body mass index; WHR: Waist-to-hip circumference ratio; BP: Blood pressure; BS: Blood sugar; TG: Triglyceride; LDL: Low-density lipoprotein; HDL: High-density protein; HbA1c: Hemoglobin A1c

Table 2. Mean and standard deviation of biochemical blood indices before and after breakfast and after 30 min of moderate and high intensity exercise, with Friedman test results, mean scores, and chi-square test and significance level

Variables	Number	Mean ± SD	Mean score	Chi-squared	Significance P > 0.05
Postprandial TG	15	324.53 ± 144.36	2.17		
Postprandial TG and moderate exercise	15	240.93 ± 122.98	1.67	2.586	0.274
Postprandial TG and maximum exercise	15	304.86 ± 141.07	2.17		
Postprandial LDL cholesterol	15	106.26 ± 14.14	2.27		
Postprandial LDL cholesterol and moderate exercise	15	105.46 ± 25.25	1.97	1.932	0.381
Postprandial LDL cholesterol and maximum exercise	15	100.93 ± 18.79	1.77		
Postprandial HDL cholesterol	15	42.06 ± 4.97	1.53		
Postprandial HDL cholesterol and moderate exercise	15	42.06 ± 4.97	1.53	9.404	0.009
Postprandial HDL cholesterol and maximum exercise	15	48.60 ± 9.30	2.60		

SD: Standard deviation; TG: Triglyceride; LDL: Low-density lipoprotein; HDL: High-density lipoprotein

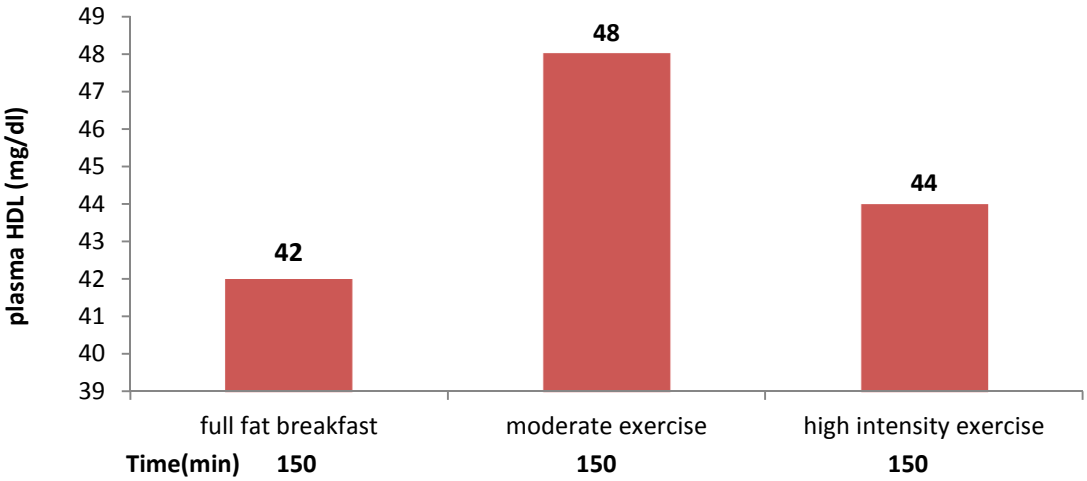

Figure 1. Comparison mean postprandial high-density lipoprotein (HDL) cholesterol concentrations levels, with 30 min of moderate and high intensity exercise

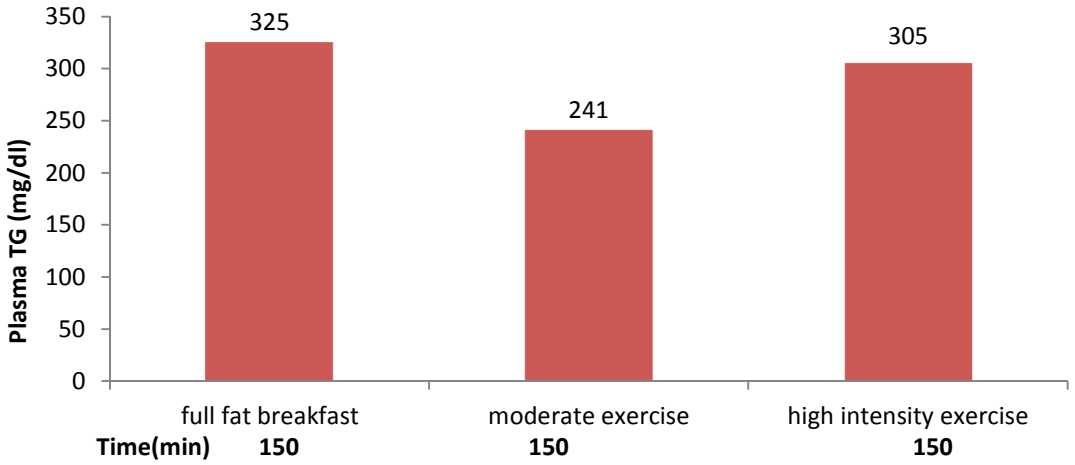

Figure 2. Comparison mean postprandial triglyceride (TG) concentrations levels, with 30 min of moderate and high intensity exercise

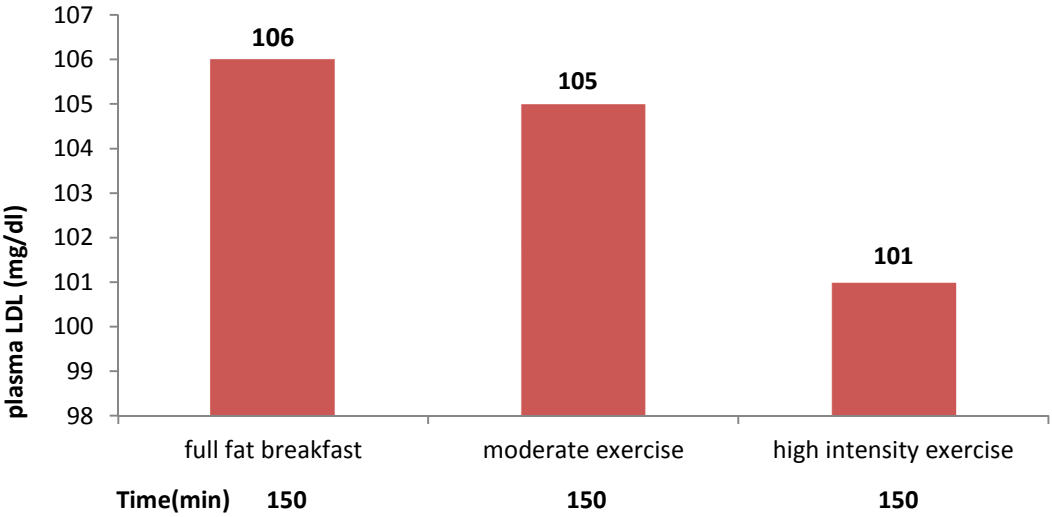

Figure 3. Comparison mean postprandial low-density lipoprotein (LDL) cholesterol concentrations levels, with 30 min of moderate and high intensity exercise

The main finding of this study showed that the serum postprandial HDL cholesterol increased significantly with moderate intensity exercise (Table 2). In contrast, serum HDL did not significantly increase with high intensity exercise (Figure 1). This finding agrees with that of previous studies with regards to the effect of regular aerobic exercise on HDL cholesterol increase.[11] Lipid oxidation[11-27] increased muscular and liver lipoprotein,[12-28] reduced TG concentration,[25-27] increased half-life of HDL cholesterol and its function during regular low-intensity aerobic exercise in patients with type II diabetes[28] are among the main reasons for increased postprandial HDL cholesterol after exercise. Although some studies attributed this increase to TG plasma and lipid metabolic disorders as well as to liver function abnormalities and inadequate and indistinct exercise intensity.[29] Recently, other studies have shown HDL cholesterol can be increased with intensive exercise, believing this to be due to reduction in blood TG resistance, increased insulin sensitivity, and reduced muscle and liver insulin resistance after intensive exercise.[17,30,31] Intensive exercise duration and the effect of consistent exercise and patients' adjustment to it are reasons for differing results of this study.

Another finding was with regards to TG serum level. The difference between exercise intensities in reducing TG was insignificant (Table 2). In fact, moderate intensity exercise reduced mean postprandial TG level in type II diabetic patients more than high intensity exercise. Nonetheless, it was statistically insignificant (Figure 2).

A study in 2006 showed that regular aerobic exercise significantly improved TG concentration due to increased muscle blood circulation and gradual increase in muscle lipid oxidation during exercise.[32] In a similar study, Trenell et al.[17] and Tobin et al.[27] found that a course of regular moderate intensity aerobic exercise can reduce postprandial TG concentration just as well as insulin secretion. This was thought to be due to type II diabetic patients' adjustment to regular aerobic exercise. The effect of adjustment over a few months in previous studies and the small sample size in this study are the reason for the differences.

In other studies,[3,30-34] no significant relationship was found between postprandial serum TG variations and high intensity exercise, which was thought to be due to metabolic differences in type II diabetic patients,[30] increased muscle blood circulation, greater distribution of fatty acids released from adipose tissue onto active muscles during and after strenuous exercise.[32] Other researchers have reported postprandial TG reduction through increased muscular lipoprotein lipase after an intense walking exercise.[3,17,26-34] Again, duration and inadequate number of exercise sessions for effective adjustment caused the differences between the results of this study and those of previous studies.

The last finding of this study showed that one session of high intensity exercise reduced postprandial LDL cholesterol more than one session of moderate intensity exercise. Though it was not statistically significant (Table 2), its importance cannot be undermined (Figure 3). This was also illustrated in previous studies,[3,17,27-35] no significant reduced postprandial LDL cholesterol was found a period of high intensity exercise in type II diabetic patients,[27,30] and emphasized on such reasons as oxidation disorders in liver metabolism, reduced liver LDL receptors, reduced postprandial blood lipid clearance in type II diabetic patients. However, Cohen et al. found a reduction in LDL cholesterol after 14 months of intense physical activity.[34] Also, Harrison et al. showed intensive exercise could reduce LDL cholesterol concentration and level. They considered increased oxidation in liver metabolism and LDL receptors the reasons for this.[30] Therefore, duration and infrequent sessions of high intensity exercise are thought to have made the difference between this and previous studies.

Conclusion

According to the results of this study, moderate intensity aerobic exercise reduces HDL cholesterol level more than high intensity exercise, and postprandial TG serum level is reduced more with regular, consistent, moderate intensity exercise than with high intensity exercise. However, long-term adjustment of the body to regular exercise reduces TG most in type II diabetic patients. Postprandial LDL cholesterol reduction occurred more with high intensity, regular aerobic exercise than with moderate intensity exercise. Generally, postprandial lipid reduction in type II diabetes is best achieved through a combined regular aerobic and consistent exercise.

Acknowledgments

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Conflict of Interests

Authors have no conflict of interests.

References

1. Regensteiner JG, Reusch JE, Stewart KJ, Veves A. Diabetes and Exercise. Berlin, Germany: Springer; 2009. p. 317.
2. Burns N, Finucane FM, Hatunic M, Gilman M, Murphy M, Gasparro D, et al. Early-onset type 2 diabetes in obese white subjects is characterised by a marked defect in beta cell insulin secretion, severe insulin resistance and a lack of response to aerobic exercise training. Diabetologia 2007; 50(7): 1500-8.
3. Zanuso S, Jimenez A, Pugliese G, Corigliano G, Balducci S. Exercise for the management of type 2 diabetes: a review of the evidence. Acta Diabetol 2010; 47(1): 15-22.
4. Kommoju UJ, Reddy BM. Genetic etiology of type 2 diabetes mellitus: a review. International Journal of Diabetes in Developing Countries 2011; 31(2): 51-64.
5. Skoczynska A, Kreczynska B, Poreba R. Postprandial lipemia in diabetic men during hypolipemic therapy. Pol Arch Med Wewn 2009; 119(7-8): 461-8.
6. Enkhmaa B, Ozturk Z, Anuurad E, Berglund L. Postprandial lipoproteins and cardiovascular disease risk in diabetes mellitus. Curr Diab Rep 2010; 10(1): 61-9.
7. Carstensen M, Thomsen C, Gotzsche O, Holst JJ, Schrezenmeir J, Hermansen K. Differential postprandial lipoprotein responses in type 2 diabetic men with and without clinical evidence of a former myocardial infarction. Rev Diabet Stud 2004; 1(4): 175-84.
8. Lievre MM, Moulin P, Thivolet C, Rodier M, Rigalleau V, Penfornis A, et al. Detection of silent myocardial ischemia in asymptomatic patients with

diabetes: results of a randomized trial and meta-analysis assessing the effectiveness of systematic screening. Trials 2011; 12: 23.
9. Codario RA. Type 2 Diabetes, Pre-Diabetes, and the Metabolic Syndrome. Berlin, Germany: Springer; 2010. p. 367.
10. Ferreira AP, Ferreira CB, Souza VC, Cordova CO, Silva GC, Nobrega OT, et al. The influence of intense intermittent versus moderate continuous exercise on postprandial lipemia. Clinics (Sao Paulo) 2011; 66(4): 535-41.
11. Colberg SR. Physical activity: the forgotten tool for type 2 diabetes management. Front Endocrinol (Lausanne) 2012; 3: 70.
12. Hurren NM, Balanos GM, Blannin AK. Is the beneficial effect of prior exercise on postprandial lipaemia partly due to redistribution of blood flow? Clin Sci (Lond) 2011; 120(12): 537-48.
13. Praet SF, van Loon LJ. Exercise therapy in type 2 diabetes. Acta Diabetol 2009; 46(4): 263-78.
14. Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, et al. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. Diabetes Care 2010; 33(12): e147-e167.
15. Morrato EH, Hill JO, Wyatt HR, Ghushchyan V, Sullivan PW. Physical activity in U.S. adults with diabetes and at risk for developing diabetes, 2003. Diabetes Care 2007; 30(2): 203-9.
16. Wagner H, Degerblad M, Thorell A, Nygren J, Stahle A, Kuhl J, et al. Combined treatment with exercise training and acarbose improves metabolic control and cardiovascular risk factor profile in subjects with mild type 2 diabetes. Diabetes Care 2006; 29(7): 1471-7.
17. Trenell MI, Hollingsworth KG, Lim EL, Taylor R. Increased daily walking improves lipid oxidation without changes in mitochondrial function in type 2 diabetes. Diabetes Care 2008; 31(8): 1644-9.
18. Rimbert V, Boirie Y, Bedu M, Hocquette JF, Ritz P, Morio B. Muscle fat oxidative capacity is not impaired by age but by physical inactivity: association with insulin sensitivity. FASEB J 2004; 18(6): 737-9.
19. MacEneaney OJ, Harrison M, O'Gorman DJ, Pankratieva EV, O'Connor PL, Moyna NM. Effect of prior exercise on postprandial lipemia and markers of inflammation and endothelial activation in normal weight and overweight adolescent boys. Eur J Appl Physiol 2009; 106(5): 721-9.
20. Kadoglou NP, Iliadis F, Angelopoulou N, Perrea D, Ampatzidis G, Liapis CD, et al. The anti-inflammatory effects of exercise training in patients with type 2 diabetes mellitus. Eur J Cardiovasc Prev Rehabil 2007; 14(6): 837-43.
21. Okada S, Hiuge A, Makino H, Nagumo A, Takaki H, Konishi H, et al. Effect of exercise intervention on endothelial function and incidence of cardiovascular disease in patients with type 2 diabetes. J Atheroscler Thromb 2010; 17(8): 828-33.
22. Conn VS, Hafdahl AR, Moore SM, Nielsen PJ, Brown LM. Meta-analysis of interventions to increase physical activity among cardiac subjects. Int J Cardiol 2009; 133(3): 307-20.
23. Holt RG, Cockram C, Flyvbjerg A, Goldstein BJ. Textbook of Diabetes. New Jersey, NJ: Wiley; 2010. p. 1119.
24. Singhal A, Trilk JL, Jenkins NT, Bigelman KA, Cureton KJ. Effect of intensity of resistance exercise on postprandial lipemia. J Appl Physiol (1985) 2009; 106(3): 823-9.
25. Nicklas B. Endurance Exercise and Adipose Tissue. London, UK: Taylor & Francis; 2001. p. 179.
26. Castaneda C, Layne JE, Munoz-Orians L, Gordon PL, Walsmith J, Foldvari M, et al. A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. Diabetes Care 2002; 25(12): 2335-41.
27. Tobin LW, Kiens B, Galbo H. The effect of exercise on postprandial lipidemia in type 2 diabetic patients. Eur J Appl Physiol 2008; 102(3): 361-70.
28. Zois C, Tokmakidis SP, Volaklis KA, Kotsa K, Touvra AM, Douda E, et al. Lipoprotein profile, glycemic control and physical fitness after strength and aerobic training in post-menopausal women with type 2 diabetes. Eur J Appl Physiol 2009; 106(6): 901-7.
29. Harrison M, O'Gorman DJ, McCaffrey N, Hamilton MT, Zderic TW, Carson BP, et al. Influence of acute exercise with and without carbohydrate replacement on postprandial lipid metabolism. J Appl Physiol (1985) 2009; 106(3): 943-9.
30. Harrison M, Murphy RP, O'Connor PL, O'Gorman DJ, McCaffrey N, Cummins PM, et al. The endothelial microparticle response to a high fat meal is not attenuated by prior exercise. Eur J Appl Physiol 2009; 106(4): 555-62.
31. Miyashita M, Burns SF, Stensel DJ. Accumulating short bouts of brisk walking reduces postprandial plasma triacylglycerol concentrations and resting blood pressure in healthy young men. Am J Clin Nutr 2008; 88(5): 1225-31.
32. Middlebrooke AR, Elston LM, Macleod KM, Mawson DM, Ball CI, Shore AC, et al. Six months of aerobic exercise does not improve microvascular function in type 2 diabetes mellitus. Diabetologia 2006; 49(10): 2263-71.
33. Mensink M, Blaak EE, van Baak MA, Wagenmakers AJ, Saris WH. Plasma free Fatty Acid uptake and oxidation are already diminished in subjects at high risk for developing type 2 diabetes. Diabetes 2001; 50(11): 2548-54.

34. Cohen ND, Dunstan DW, Robinson C, Vulikh E, Zimmet PZ, Shaw JE. Improved endothelial function following a 14-month resistance exercise training program in adults with type 2 diabetes. Diabetes Res Clin Pract 2008; 79(3): 405-11.
35. Galbo H, Tobin L, van Loon LJ. Responses to acute exercise in type 2 diabetes, with an emphasis on metabolism and interaction with oral hypoglycemic agents and food intake. Appl Physiol Nutr Metab 2007; 32(3): 567-75.

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Prognostic value of the high-mobility group box-1 in young patients with chest pain

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Original Article

Abstract

BACKGROUND: Atherosclerosis is accepted as an inflammatory disease. Evidence suggests that inflammation evoked by injury plays a pathogenic role in all stages of atherosclerosis. This study aimed to investigate whether the high-mobility group box-1 (HMGB1) a proinflammatory cytokine/nuclear protein, which is derived from both injured endothelium and activated macrophages/monocytes, could contribute to the progression of atherosclerosis and other cardiovascular diseases.

METHODS: This study was designed as case–control. A total of 135 patients who referred to the hospital due to angina pectoris had the diagnosis of unstable angina and were candidates of angiography were recruited in this study. Forty patients who had coronary artery disease confirmed by angiography were considered as case group and control group consists of 40 persons who had no plaque, and 55 persons were excluded according to the exclusion criteria. At first, a questionnaire was filled for each patient including demographic factors and their medical history. Then a blood sample was taken to assess the level of HMGB1. Data were analyzed using SPSS, Student's independent t-test, and chi-square tests.

RESULTS: The mean plasma level of HMGB1 in the case group was 27.1 ± 2.9 ng/ml, while it was 19.6 ± 1.9 ng/ml in control groups (P = 0.03). The odds ratio for coronary artery plaque associated with high (> 15.03 ng/ml) levels of HMGB1 was 2.50 (95% confidence interval, 1.02-6.17, P = 0.03).

CONCLUSION: Increased plasma HMGB1 concentration may be associated with an increased risk of coronary atherosclerosis.

Keywords: High-Mobility Group Box-1, Coronary Artery Diseases, Inflammation, Biomarkers

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Introduction

The cardiovascular disease has long been an issue that causes severe loss in population, especially those conditions associated with arterial malfunction, being attributable to atherosclerosis, and subsequent thrombotic formation.[1]

Atherosclerosis is an inflammatory condition that affects the arterial wall and is characterized by progressive thickening due to the accumulation of lipids.[2]

Our understanding of the role of inflammation in the initiation and progression of atherosclerosis has evolved considerably in recent years. This has led to advances in both diagnostic and prognostic approaches, as well as a novel treatment modalities targeting inflammatory and immune mediators.[3]

The high-mobility group box-1 (HMGB1) protein, also known as amphoterin, expressed in almost all eukaryotic cells and recently identified as a potent proinflammatory mediator when present extracellularly.[4,5]

HMGB1 has been suggested to be involved in the pathogenesis of several vascular diseases such as systemic vasculitis and atherosclerosis.[6]

HMGB1 is expressed in endothelial cells, smooth muscle cells and microvessels of the adventitia.[7] Previous studies have shown that in human atherosclerotic lesions from the aorta, carotid and coronary arteries the expression of HMGB1 is noticeably increased in the nuclei and in

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the cytoplasm of macrophages and smooth muscle cells localized near the intima.[7,8] Intense HMGB1 expression has also been observed in areas adjacent to the necrotic core of atherosclerotic lesions and release of HMGB1 from necrotic cells, inducing local inflammation.[7,9]

HMGB1 may be released from several cell types in the atherosclerotic plaque including smooth muscle cells, endothelial cells, foam cells, macrophages, and activated platelets.[10,11]

HMGB1 promotes smooth muscle cells proliferation, migration to the intimal layer, their release of C-reactive protein as well as matrix metalloproteinases (MMPs) (MMP2, MMP3, and MMP9) in atherosclerotic plaques.[8,10,11]

In this study, by using HMGB1 measurements and angiographic investigation of coronary plaques in patients with unstable angina, we can consider the correlation of inflammation and plaque and then we can relate HMGB1 as an inflammatory marker with high-risk unstable patients that need more intensive medical or interventional follow-up.

Materials and Methods

This study was approved by Ethics Committee in Isfahan University of Medical Science (288294). In this case–control study, we recruit 135 consecutive patients fewer than 55 years old that referred to Chamran Hospital (Tehran, Iran) due to unstable angina and underwent coronary artery angiography in 2010. Unstable angina is defined as angina at rest with an accelerating pattern (with more frequency, higher intensity or longer duration), rest angina or an angina, which has newly developed.[12]

Patients with a history of myocardial infarction, surgery and/or percutaneous transluminal coronary angioplasty, valvular disease, anemia, fever, thyroid abnormalities, and renal failure, inflammatory and rheumatologic diseases or patients taking related medications including corticosteroid were excluded from the study. Letters of consent were taken from patients regarding all steps of study.

A questionnaire including information about demographic factors, history of above-mentioned diseases, drug consumption, and smoking was filled for those patients who met the inclusion criteria.

Finally, 40 patients who had coronary artery disease (CAD) confirmed by angiography were considered as case group and 40 patients with chest pain without any coronary complications in their angiography were selected as a control group.

History of diabetes was defined as history of twice fasting blood sugar of higher than 126 mg/dl or once plus a clinical sign hyperlipidemia was determined as low-density lipoprotein higher than 160 mg/dl or triglyceride higher than 150 (mg/dl) and hypertension was blood pressure higher than 140/90 mm Hg.

On the day of angiography, blood samples were collected after 10-12 h fasting. The serums were separated and were stored in −80° C in the freezer and angiography was done with Judkins standard.

HMGB1 level was measured simultaneously in all samples in Applied Physiology Research Center. The HMGB1 enzyme-linked immunosorbent assay (ELISA) kit was from immuno biological laboratory (IBL) International (Hamburg, Germany-Cat. Number: ST51011).[13]

HMGB1 ELISA is a Sandwich-enzyme immunoassay for the quantitative determination of HMGB1 in serum and plasma. The microtiter strips were coated with purified anti-HMGB1 antibody. HMGB1 in the sample binds specifically to the immobilized antibody and is recognized by a second enzyme marked antibody. After substrate reaction, the HMGB1 concentration was determined by the color intensity in 450 nm wavelength. HMGB1 concentration is obtained by optical density and standard curve.

In the last step, all patients underwent coronary artery angiography according to Judkins standard protocol. The degree of stenosis in each epicardial coronary arteries was evaluated by the cardiologist who was blind about laboratory test results of the patients. Atherothrombotic plaques were classified into simple and complex according to Ambrose et al. criteria.[14]

In order to determine the appropriate cut-off point of HMGB1 levels for identifying the risk of coronary plaque, the sensitivity, specificity, and likelihood ratio were calculated at different levels of HMGB1 using receiver operating characteristics (ROC) curve.

Data were analyzed using SPSS for Windows (version 18, SPSS Inc., Chicago, IL, USA) using Student's independent t-test, and chi-square. The odds ratio (OR) was calculated from multivariate logistic regression.

Results

The demographic characteristics of patients have been illustrated in table 1. There was no significant difference in age, sex, body mass index and history of hypertension, hyperlipidemia diabetes, and smoking between groups ($P < 0.05$).

The HMGB1 levels was 19.6 ± 1.9 ng/ml in controls and 27.1 ± 2.9 ng/ml in cases, there is a significant difference between groups ($P = 0.002$) (Figure 1).

Table 1. Basic characteristics of the study population

Characteristics	Case	Control
Age (year)	49.6 ± 6.6	48.4 ± 6.5
Body mass index (kg/m^2)	27.0 ± 6.7	25.6 ± 5.1
Male (%)	62.5	46.2
Hypertension (%)	30.3	29.5
Hyperlipidemia (%)	50.7	44.1
Diabetes (%)	22.8	16.6
Smoking (%)	15.9	13.6

Values are expressed as mean ± SD or number (%); There was no significant difference between case and control groups (P < 0.05); SD: Standard deviation

The sensitivity, specificity, positive and negative predictive value of different levels of HMGB1 using ROC curve were 83.3%, 72.2%, 75.0%, and 71.3%, respectively.

The ROC curve analysis, applied to HMGB1 level, showed the best diagnostic profile with an area under the curve of 0.81 and 0.89, respectively. The best cut-off points were 15.03 ng/ml. The sensitivity, specificity, and accuracy were 88.9%, 83.3%, and 86.1%, respectively.

Crude odd ratio (ORs) for significant coronary artery plaque was calculated for HMGB1 above the 50th percentile. Estimated risk of association between significant coronary artery plaque associated with high (> 15.03 ng/ml) levels of HMGB1 was 2.50 (95% confidence interval, 1.02-6.17, P = 0.03).

Discussion

HMGB1 has been implicated in the pathogenesis of inflammatory vascular diseases including systemic vasculitis and atherosclerotic disease. Furthermore, HMGB1 is expressed in atherosclerotic lesions by several cell types contributing to the development of the atherosclerotic plaque. HMGB1 levels are significantly increased in patients with subclinical CAD and in those who develop acute ischemic events in cardiac and cerebral vascular beds. Experimental studies showed that HMGB1 has a significant effect, potentiating the inflammatory response as well as damage in the acute phase and participating in tissue remodeling during the late phase after ischemic injury. Targeting HMGB1 may be an attractive therapeutic modality for inflammatory vascular diseases.[15]

In our study, patients with CAD had upper plasma HMGB1 levels than control groups, and there were significant difference in HMGB1 levels between two groups.

Previous studies have been shown that HMGB1 stimulate vascular endothelial cells to express and secret cell adhesion molecules, monocyte chemotatic protein 1, and other inflammatory cytokines.[16,17]

In the other hand, study on apolipoprotein E-deficient mice that fed with a high-fat diet has been shown that HMGB1 has an importance role in the development of atherosclerosis.

Using antibodies against HMGB1 result in reduced inflammation and plaque progression in apolipoprotein E-deficient mice.[18]

Yang et al.[19] and Haraba et al.[20] showed that hyperlipidemia stimulates the extracellular release of

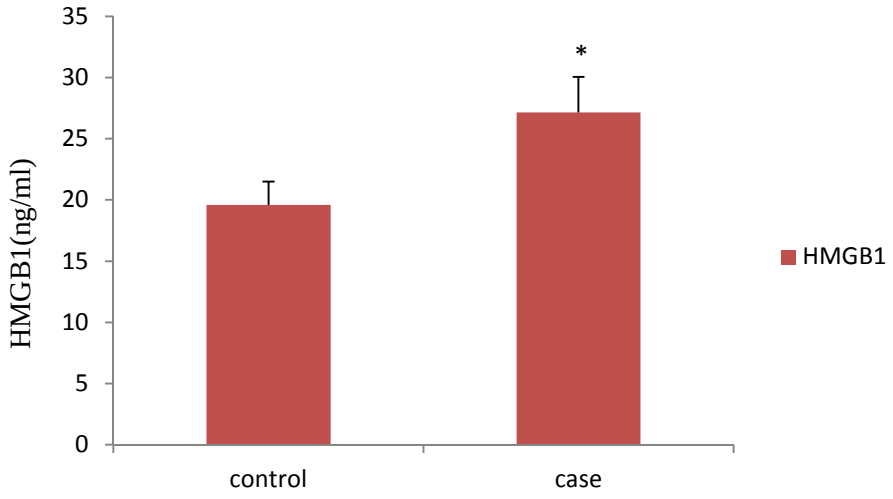

Figure 1. Serum levels of high-mobility group box-1 protein in case and control group
* Significantly different from control group (P = 0.002)
HMGB1: High-mobility group box-1

the HMGB1 protein in hyperlipidemic hamsters. Furthermore, it has been shown that statins attenuate HMGB1-induced vascular endothelial activation.

In contrast, a beneficial effect of HMGB1 has been demonstrated after ischemic limb injury in diabetic and non-diabetic mice. HMGB1 expression was lower in ischemic limbs of diabetic mice, and this lower expression was associated with a diminished perfusion recovery after injury. Administration of HMGB1 significantly improved blood flow and capillary density in ischemic muscles of diabetic mice, and this beneficial effect was associated with an increased expression of vascular endothelial growth factor.[21]

Conclusion

The results of the present study show significantly higher levels of plasma HMGB1 in angiographically documented coronary plaque than healthy individuals. Increased plasma HMGB1 concentration may be associated with an increased risk of coronary atherosclerosis.

HMGB1 can reflect the coronary artery atherosclerosis in patients with unstable angina. Hence, it can be used as diagnostic factors, and as an independent factor for risk stratification in young patients with chest pain. However, future studies with larger sample size are needed in order to determine accurate cut-point value in CAD patients and healthy population.

Conflict of Interests

Authors have no conflict of interests.

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References

1. Wang W, Lee Y, Lee CH. Review: The physiological and computational approaches for atherosclerosis treatment. Int J Cardiol 2013; 167(5): 1664-76.
2. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med 1999; 340(2): 115-26.
3. Wong BW, Meredith A, Lin D, McManus BM. The biological role of inflammation in atherosclerosis. Can J Cardiol 2012; 28(6): 631-41.
4. Erlandsson HH, Andersson U. Mini-review: The nuclear protein HMGB1 as a proinflammatory mediator. Eur J Immunol 2004; 34(6): 1503-12.
5. Guo ZS, Liu Z, Bartlett DL, Tang D, Lotze MT. Life after death: targeting high mobility group box 1 in emergent cancer therapies. Am J Cancer Res 2013; 3(1): 1-20.
6. de Souza AW, Westra J, Limburg PC, Bijl M, Kallenberg CG. HMGB1 in vascular diseases: Its role in vascular inflammation and atherosclerosis. Autoimmun Rev 2012; 11(12): 909-17.
7. Kalinina N, Agrotis A, Antropova Y, DiVitto G, Kanellakis P, Kostolias G, et al. Increased expression of the DNA-binding cytokine HMGB1 in human atherosclerotic lesions: role of activated macrophages and cytokines. Arterioscler Thromb Vasc Biol 2004; 24(12): 2320-5.
8. Inoue K, Kawahara K, Biswas KK, Ando K, Mitsudo K, Nobuyoshi M, et al. HMGB1 expression by activated vascular smooth muscle cells in advanced human atherosclerosis plaques. Cardiovasc Pathol 2007; 16(3): 136-43.
9. Scaffidi P, Misteli T, Bianchi ME. Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. Nature 2002; 418(6894): 191-5.
10. Porto A, Palumbo R, Pieroni M, Aprigliano G, Chiesa R, Sanvito F, et al. Smooth muscle cells in human atherosclerotic plaques secrete and proliferate in response to high mobility group box 1 protein. FASEB J 2006; 20(14): 2565-6.
11. Degryse B, Bonaldi T, Scaffidi P, Muller S, Resnati M, Sanvito F, et al. The high mobility group (HMG) boxes of the nuclear protein HMG1 induce chemotaxis and cytoskeleton reorganization in rat smooth muscle cells. J Cell Biol 2001; 152(6): 1197-206.
12. Sadeghi M, Pourmoghaddas M, Tavasoli A, Roohafza H. Is there any relationship between C-reactive protein level and complex coronary plaques in patients with unstable angina? ARYA Atheroscler 2010; 6(1): 31-4.
13. Davis K, Banerjee S, Friggeri A, Bell C, Abraham E, Zerfaoui M. Poly (ADP-ribosyl) ation of high mobility group box 1 (HMGB1) protein enhances inhibition of efferocytosis. Mol Med 2012; 18: 359-69.
14. Ambrose JA, Tannenbaum MA, Alexopoulos D, Hjemdahl-Monsen CE, Leavy J, Weiss M, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 1988; 12(1): 56-62.
15. de Souza AW, Westra J, Limburg PC, Bijl M, Kallenberg CG. HMGB1 in vascular diseases: Its role in vascular inflammation and atherosclerosis. Autoimmun Rev 2012; 11(12): 909-17.
16. Fiuza C, Bustin M, Talwar S, Tropea M, Gerstenberger E, Shelhamer JH, et al. Inflammation-promoting activity of HMGB1 on human microvascular endothelial cells. Blood 2003; 101(7): 2652-60.
17. Treutiger CJ, Mullins GE, Johansson AS,

Rouhiainen A, Rauvala HM, Erlandsson-Harris H, et al. High mobility group 1 B-box mediates activation of human endothelium. J Intern Med 2003; 254(4): 375-85.
18. Kanellakis P, Agrotis A, Kyaw TS, Koulis C, Ahrens I, Mori S, et al. High-mobility group box protein 1 neutralization reduces development of diet-induced atherosclerosis in apolipoprotein e-deficient mice. Arterioscler Thromb Vasc Biol 2011; 31(2): 313-9.
19. Yang J, Huang C, Yang J, Jiang H, Ding J. Statins attenuate high mobility group box-1 protein induced vascular endothelial activation: a key role for TLR4/NF-kappaB signaling pathway. Mol Cell Biochem 2010; 345(1-2): 189-95.
20. Haraba R, Suica VI, Uyy E, Ivan L, Antohe F. Hyperlipidemia stimulates the extracellular release of the nuclear high mobility group box 1 protein. Cell Tissue Res 2011; 346(3): 361-8.
21. Biscetti F, Straface G, de Cristofaro R, Lancellotti S, Rizzo P, Arena V, et al. High-mobility group box-1 protein promotes angiogenesis after peripheral ischemia in diabetic mice through a VEGF-dependent mechanism. Diabetes 2010; 59(6): 1496-505.

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The relationships between cortisol levels, insulin levels, and thyroid hormones with 24-h urinary sodium excretion in never treated essential hypertensive patients

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Original Article

Abstract

BACKGROUND: To study the relationship between cortisol, insulin, and thyroid hormone levels with 24-h urinary sodium (Na) excretion levels in essential hypertensive patients.

METHODS: All patients underwent history taking, physical examination, blood pressure (BP) measurement, 12 lead electocardiographic evaluation, routine urine analysis, biochemical analysis including measurement of cortisol, insulin, and thyroid hormone levels, 24-h urine collection to measure urinary Na and protein excretion and creatinine clearance.

RESULTS: In total, 68 newly diagnosed hypertensive patients were included. Spearman correlation analysis revealed that 24-h urinary Na excretion was correlated with insulin levels ($\rho = -0.473$, $P < 0.0001$), serum cortisol levels ($\rho = -0.404$, P= 0.0010) and creatinine clearance ($\rho = 0.407$, P: 0.0010). Linear regression of independent factors has revealed that systolic BP ($B = 0.004$, CI = 0.001-0.008, P = 0.0170), body mass index ($B = 0.014$, CI = 0.005-0.023, P = 0.0030), being male ($B = 0.077$, CI = 0.001-0.153, P = 0.0480), creatinine clearance ($B = 0.003$, CI = 0.001-0.006, P = 0.0120) and insulin levels ($B = -0.008$, CI = −0.014 to −0.002, P = 0.0070) were independently related with logarithmically converted 24-h Na excretion.

CONCLUSION: In conclusion, we found that insulin but not cortisol and thyroid hormone levels were independently related with 24-h urinary Na excretion in newly diagnosed essential hypertensive patients.

Keywords: Cortisol, Hypertension Insulin, Sodium, Thyroid

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Introduction

High blood pressure (BP) is a major public health challenge and one of the most important preventable risk factor for stroke, cardiovascular, and renal disease.[1] Experimental, observational, and clinical data have indicated that dietary salt intake is closely related with BP[2] and various guidelines recommend to lower Na daily intake.[3,4] It is well-known that 24-h urine sodium (Na) excretion is an appropriate and most reliable method to estimate daily Na consumption.[5,6] Various hormones influence Na handling in renal tubules. Apart from renin angiotensin and sympathetic system other hormones been shown to play a role in tubule handling of Na. For example, insulin,[7,8] glucocorticoids (GCs),[9] and thyroid hormones[10-12] have all shown to be antinatriuretic and increase Na reabsorption along nephron segments. However, to the best of our knowledge no study has evaluated the relationship between insulin, cortisol, and thyroid hormone levels with 24-h urinary Na excretion in hypertensive patients comprehensively although these hormones can be measured easily and routinely in everyday clinical practice. Hence, the current study is conducted to analyze the relationships between insulin, cortisol, and thyroid hormone levels with 24-h urinary Na excretion in never treated newly diagnosed essential hypertensive patients.

Materials and Methods

The current study was conducted in the outpatient nephrology unit of a State Hospital. The study was in accordance with the declaration of Helsinki and Local Ethical Approval and informed consent was obtained before enrolment. Study population consisted of patients with newly diagnosed hypertensive that was hitherto treated. All patients firstly underwent following procedures: history

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taking, physical examination, BP measurement, 12 lead electocardiographic evaluation routine urine analysis, fasting blood samples for biochemical analysis (including measurement of insulin, cortisol, and thyroid function tests), 24-h urine collection to measure urinary Na and protein excretion and creatinine clearance. An information leaflet along with a urine container was given to all subjects, and they also received a verbal explanation about how to collect a proper 24-h urine sample. After excluding the first morning urine sample of the collection day, urine was collected over 24 h, which included the first urine sample of the next morning. During the sampling period, subjects were instructed to keep urine samples in a dark and cool place. At the end of the collection period, the urine containers were taken to the laboratory within 2-4 h. Since erroneous estimations of salt intake may occur according to problems in collecting 24-h urine samples participants with urinary creatinine out of reference levels were excluded.[13]

Patients with diabetes mellitus, coronary artery disease, heart failure, rhythm problems, liver disease, nephrotic syndrome, urinary tract infection were excluded. None of the patients reported any alcohol intak.

BP measurement

Seated clinic BP was measured manually with a mercury column sphygmomanometer and an appropriate size cuff after 5 min of rest according to American Heart Association guidelines.[14] Hypertension was defined as systolic BP between ≥ 140 mmHg and diastolic BP ≥ 90 mmHg.[3]

Laboratory analysis

The routine laboratory parameters were measured after 10-12 h of fasting. The laboratory parameters including fasting blood glucose, urea, creatinine, uric acid, Na, potassium, hemoglobin, albumin, calcium, phosphorus, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), insulin, and cortisol levels. Twenty four hours urinary Na and protein levels were also measured.

The levels of fasting glucose, urea, creatinine, and uric acid, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were determined by using commercially available assay kits with an autoanalyzer (Architect® c16000, Abbott Diagnostics, Abbott Park, IL, USA). Hemoglobin was measured by automated blood analyzer (CELL-DYN 3700 cell counter Abbott Diagnostics Division, Abbott Laboratories, IL, USA). Serum Na and potassium and urine Na were measured by direct potentiometric method by ion specific electrodes. Twenty four hours protein excretion was measured by benzethonium chloride method by (Architect® c16000, Abbott Diagnostics, Abbott Park, IL, USA). Albumin was measured by bromcresol purple method. TSH, FT3, FT4 insulin, and cortisol levels were assayed by direct chemiluminescence method (Advia Centaur XP, Siemens, Dublin, Ireland).

Statistics

Statistical analysis was performed using SPSS for Windows (version 15.0; SPSS Inc., Evanston, IL, USA). Results were considered statistically significant if two-tailed P value was < 0.05. Data were checked for normality. Pearson's correlation coefficient r and Spearman's correlation coefficient ϱ was used for correlations. Linear regression analysis was performed to analyze the independent factors related with logarithmically converted 24-h urinary Na excretion. Variables tested for significance included age, sex, smoking status, body mass index, systolic BP, diastolic BP, 24 h creatinine clearance and protein excretion, TSH, FT3, FT4 insulin, and cortisol.

Results

Initially, 94 patients were enrolled. One patient with coronary artery disease, one patient with heart failure, three patients with diabetes, two patients with chronic liver disease, two patients with nephrotic syndrome, two patients with atrial fibrillation, two patients with urinary tract infection, five patients who did not want to participate, and eight patients with incomplete 24-h urine calculation were excluded from the study. The final patient population consisted of never treated 68 newly diagnosed hypertensive patients. The demographic and laboratory parameters of the patients were shown in table 1.

Spearman correlation analysis revealed that 24-h urinary Na excretion was correlated with insulin levels ($\varrho = -0.473$, $P < 0.0001$), serum cortisol levels ($\varrho = -0.404$, $P = 0.0010$), and creatinine clearance ($\varrho = 0.407$, $P = 0.0010$). There was also a negative correlation between logarithmically converted 24-h urinary Na excretion and logarithmically converted serum insulin ($r = -0.487$, $P < 0.0001$) (Figure 1).

Linear regression of independent factors (as mentioned above) has revealed that systolic BP, BMI, gender, creatinine clearance, and insulin levels were related with logarithmically converted 24-h Na excretion (as a dependent parameter) (Table 2).

Table 1. The demographic and laboratory parameters of 68 essential hypertensive patients

Parameter*	Mean ± SD	n (%)
Smoker/non-smoker (n)		19/49
Male/female (n, %)		34/34 (50, 50)
Body mass index (kg/m^2)*	27.90 ± 5.30	
Age (year)*	49.70 ± 14.20	
Systolic blood pressure (mmHg)*	147.90 ± 11.70	
Diastolic blood pressure (mmHg)*	92.90 ± 8.70	
Serum glucose (mmol/l) (mean ± SD)*	5.82 ± 0.86	
Serum urea (mg/dl)*	30.00 ± 13.50	
Creatinine (µmol/l)*	74.30 ± 17.70	
Hemoglobin (g/l)*	128.90 ± 13.70	
Sodium (mmol/l)*	139.40 ± 4.40	
Potassium (mmol/l)*	4.65 ± 0.65	
Albumin (g/l)*	42.70 ± 4.80	
Total cholesterol (mmol/l)*	5.03 ± 1.18	
LDL-C (mmol/l)*	3.08 ± 0.87	
HDL-C (mmol/l)*	1.15 ± 0.35	
Triglyceride (mmol/l)*	1.80 ± 1.07	
Uric acid (µmol/l)*	390.20 ± 179.60	
Thyroid stimulating hormone (mU/l)*	1.92 ± 1.24	
FT3 (pg/ml)*	2.94 ± 0.83	
FT4 (ng/dl)	1.23 ± 0.18	
Insulin (µU/ml)*	11.70 ± 7.90	
Cortisol (nmol/l)*	454.70 ± 160.10	
24-h urinary Na excretion (mEq/day)*	143.80 ± 57.40	
Creatinine clearance (ml/min)/1.73 m^{2*}	82.00 ± 20.90	
24-h urinary protein excretion (mg/day)*	222.30 ± 334.40	

* Mean ± SD; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; FT3: Free triiodothyronine; FT4: Free thyroxine; SD: Standard deviation

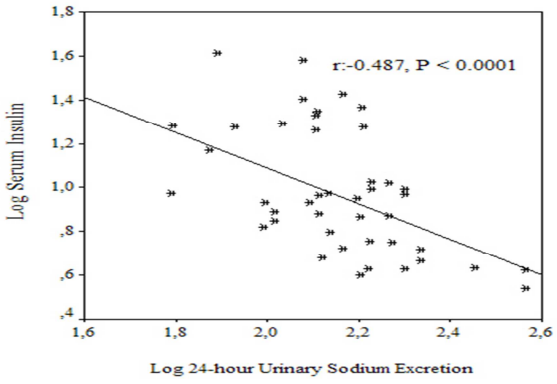

Figure 1. The scatter plot graphic between logarithmically converted 24 h urinary sodium excretion and logarithmically converted serum insulin levels

Table 2. Independent factors related with logarithmically converted 24-h Na excretion

Parameter	Beta	P
Age	0.309	0.189
Gender	0.267	0.048
Body mass index	0.428	0.003
Smoking status	−0.226	0.338
Systolic blood pressure	0.357	0.017
Diastolic blood pressure	0.023	0.889
Creatinine clearance	0.406	0.012
24-h urinary protein excretion	0.053	0.774
Insulin	−0.430	0.007
Cortisol	−0.531	0.098
Thyroid stimulating hormone	0.173	0.397
FT3	0.369	0.099
FT4	−0.048	0.799

FT3: Free triiodothyronine; FT4: Free thyroxine

Discussion

In the current study, to the best of our knowledge, we firstly evaluated the relationship between 24-h urinary Na excretion with insulin, cortisol and thyroid function tests in newly diagnosed essential hypertensive patients who were hitherto treated. Although all these hormones have been shown to be antinatriuretic, we demonstrated that only insulin levels had an independent relationship with 24-h urinary Na excretion.

It is well-known that GCs, whether endogenous, as in Cushing syndrome, or exogenous, through pharmacologic provision, induce hypertension.[9] Traditionally, GC have commonly been believed to increase BP by the activation of the mineralocorticoid receptor in the kidney.[15,16] Surprisingly in the current study, we found no relationship between urinary Na excretion and cortisol levels. We do not know exactly the cause of our findings; however, it was recently speculated that hypertension caused by GCs was not due to the excess reabsorption of Na and water but due to actions on smooth muscle.[9] Clinical experience demonstrates that the hypertension induced by steroids occurs much too rapidly to be accounted for solely, if at all, by increased renal Na reabsorption and excess renal salt reabsorption does not seem to be required for GC to induce hypertension.[17,18] In addition, there were also conflict results in the literature regarding the relationship between urinary free cortisol and hypertension. While some studies have demonstrated that urinary free cortisol were related with hypertension,[19,20] others did not demonstrate these relationships.[21] These points argue convincingly that GC have a wide range of hemodynamic effects distinct from their presumed

activation of renal mineralocorticoid receptor, thus increasing the understanding of the role of GC in the regulation of BP is of interest.[9] Thus, due to above-mentioned issues we might not find any relationship between cortisol levels and 24-h urinary Na excertion.

Insulin has been shown to increase Na reabsorption by the kidney as well as reduced Na excretion independently of blood glucose levels, filtered load of glucose, glomerular filtration rate, renal blood flow, and plasma aldosterone levels.[22] Insulin, when provided in the perfusion bath for isolated, perfused tubule studies, has been shown to increase Na reabsorption in the proximal tubule[23] and the thick ascending limb.[24,25] Another study had also demonstrated that insulin infusion increased activity of distal renal tubular Na transport pathways including Na-Cl cotransporter and epithelial Na channel possibly through trafficking into the apical membrane.[7] Thus, all these previous findings were in accord with our findings, which demonstrated that insulin levels were independently associated with 24-h urinar Na excretion.

It was shown that hypothyroid rats show defect in tubular Na reabsorbtion.[11,26] The mechanism underlying this defect remains undefined, being variously attributed to relative deficiency of adrenocortical hormones and defective distal Na reabsorption.[27] Thyroid hormones have also a significant role in controlling kidney growth and function. The hormones are important regulators of renal plasma flow, glomerular filtration rate, concentration and dilution of urine, oxygen consumption, and the reabsorption of phosphate, calcium and Na. Thyroid hormones stimulate Na^+, K^+-ATPase activity and changes in renal Na^+, K^+-ATPase activity closely parallels alterations in net transport of Na. It has also been proposed that thyroid hormones augment renal Na^+, K^+-ATPase activity by an adaptive mechanism responding to changing resorptive Na loads. Both mechanisms, the induction of Na pump elements and the adaptive response to increased filtered Na, could operate together in mediating the action of thyroid hormones on Na reabsorption. Despite all these considerations we found no relationship between thyroid hormones and 24-h Na excretion in the current study. We do not have full explanation for our findings, but speculations can be made. Firstly, we measured the levels of hormones for only once and temporal relationships cannot be speculated. Secondly, we do not specifically include hypothyroid patients, but we treat FT3, FT4, and TSH as continuous variables in our analysis.

This study has limitations that deserve mention. Firstly, since our study is cross-sectional, cause and effect relationship cannot be suggested. Secondly, since daily variability can be observed in urinary Na excretion of individuals and the collection of urine samples and hormones were performed for only once temporal relationships cannot be suggested. Thirdly, our study sample is relatively small. Still, we believe that because our study group was composed of special patients that included newly diagnosed essential hypertensive patients who were not receiving any antihypertensive medication such as diuretics the effects of medication were potentially ruled out.

Conclusion

We found that insulin but not cortical and thyroid hormone levels were independently related with 24-h urinary Na excretion in newly diagnosed essential hypertensive patients.

Acknowledgment

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Conflict of Interests

Authors have no conflict of interests.

References

1. Arici M, Turgan C, Altun B, Sindel S, Erbay B, Derici U, et al. Hypertension incidence in Turkey (HinT): a population-based study. J Hypertens 2010; 28(2): 240-4.
2. Erdem Y, Arici M, Altun B, Turgan C, Sindel S, Erbay B, et al. The relationship between hypertension and salt intake in Turkish population: SALTURK study. Blood Press 2010; 19(5): 313-8.
3. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003; 289(19): 2560-72.
4. Mancia G, de Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007; 25(6): 1105-87.
5. Jin Y, Kuznetsova T, Maillard M, Richart T, Thijs L, Bochud M, et al. Independent relations of left ventricular structure with the 24-hour urinary

excretion of sodium and aldosterone. Hypertension 2009; 54(3): 489-95.
6. Kawasaki T, Itoh K, Uezono K, Sasaki H. A simple method for estimating 24 h urinary sodium and potassium excretion from second morning voiding urine specimen in adults. Clin Exp Pharmacol Physiol 1993; 20(1): 7-14.
7. Song J, Hu X, Riazi S, Tiwari S, Wade JB, Ecelbarger CA. Regulation of blood pressure, the epithelial sodium channel (ENaC), and other key renal sodium transporters by chronic insulin infusion in rats. Am J Physiol Renal Physiol 2006; 290(5): F1055-F1064.
8. Tiwari S, Nordquist L, Halagappa VK, Ecelbarger CA. Trafficking of ENaC subunits in response to acute insulin in mouse kidney. Am J Physiol Renal Physiol 2007; 293(1): F178-F185.
9. Goodwin JE, Zhang J, Geller DS. A critical role for vascular smooth muscle in acute glucocorticoid-induced hypertension. J Am Soc Nephrol 2008; 19(7): 1291-9.
10. Emmanouel DS, Lindheimer MD, Katz AI. Mechanism of impaired water excretion in the hypothyroid rat. J Clin Invest 1974; 54(4): 926-34.
11. Michael UF, Barenberg RL, Chavez R, Vaamonde CA, Papper S. Renal handling of sodium and water in the hypothyroid rat. Clearance and micropuncture studies. J Clin Invest 1972; 51(6): 1405-12.
12. Kinsella J, Sacktor B. Thyroid hormones increase Na+-H+ exchange activity in renal brush border membranes. Proc Natl Acad Sci U S A 1985; 82(11): 3606-10.
13. Junge W, Wilke B, Halabi A, Klein G. Determination of reference intervals for serum creatinine, creatinine excretion and creatinine clearance with an enzymatic and a modified Jaffe method. Clin Chim Acta 2004; 344(1-2): 137-48.
14. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003; 42(6): 1206-52.
15. Whitworth JA, Coghlan JP, Denton DA, Graham WF, Humphery TJ, Scoggins BA. Comparison of the effects of 'glucocorticoid' and 'mineralocortocoid' infusions on blood pressure in sheep. Clin Exp Hypertens 1979; 1(5): 649-63.
16. Mantero F, Boscaro M. Glucocorticoid-dependent hypertension. J Steroid Biochem Mol Biol 1992; 43(5): 409-13.
17. Mangos GJ, Whitworth JA, Williamson PM, Kelly JJ. Glucocorticoids and the kidney. Nephrology (Carlton) 2003; 8(6): 267-73.
18. Wallwork CJ, Parks DA, Schmid-Schonbein GW. Xanthine oxidase activity in the dexamethasone-induced hypertensive rat. Microvasc Res 2003; 66(1): 30-7.
19. Chamarthi B, Kolatkar NS, Hunt SC, Williams JS, Seely EW, Brown NJ, et al. Urinary free cortisol: an intermediate phenotype and a potential genetic marker for a salt-resistant subset of essential hypertension. J Clin Endocrinol Metab 2007; 92(4): 1340-6.
20. Litchfield WR, Hunt SC, Jeunemaitre X, Fisher ND, Hopkins PN, Williams RR, et al. Increased urinary free cortisol: a potential intermediate phenotype of essential hypertension. Hypertension 1998; 31(2): 569-74.
21. Krall P, Carvajal C, Ortiz E, Munoz C, Garrido JL, Mosso L, et al. Urinary free cortisol is not a biochemical marker of hypertension. Am J Hypertens 2007; 20(4): 459-65.
22. DeFronzo RA, Cooke CR, Andres R, Faloona GR, Davis PJ. The effect of insulin on renal handling of sodium, potassium, calcium, and phosphate in man. J Clin Invest 1975; 55(4): 845-55.
23. Baum M. Insulin stimulates volume absorption in the rabbit proximal convoluted tubule. J Clin Invest 1987; 79(4): 1104-9.
24. Gupta AK, Clark RV, Kirchner KA. Effects of insulin on renal sodium excretion. Hypertension 1992; 19(1 Suppl): I78-I82.
25. Mandon B, Siga E, Chabardes D, Firsov D, Roinel N, De RC. Insulin stimulates Na+, Cl-, Ca2+, and Mg2+ transports in TAL of mouse nephron: cross-potentiation with AVP. Am J Physiol 1993; 265(3 Pt 2): F361-F369.
26. Holmes EW, Discala VA. Studies on the exaggerated natriuretic response to a saline infusion in the hypothyroid rat. J Clin Invest 1970; 49(6): 1224-36.
27. Discala VA, Kinney MJ. Effects of myxedema on the renal diluting and concentrating mechanism. Am J Med 1971; 50(3): 325-35.

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Is responsiveness to weight loss diets affected by family history of diabetes?

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Original Article

Abstract

BACKGROUND: Obesity is associated with many metabolic and chronic diseases, such as diabetes and cardiovascular disease. Family history of diabetes (FHD) is also an important risk factor for type 2 diabetes. Furthermore, the presence of FHD and obesity has a synergic effect on risk of diabetes incidence. The aim of this study was to determine whether FHD influence the weight loss induced by weight loss diet.

METHODS: This study was an intervention between individuals with or without FHD. Seventy-eight positive FHD and 74 negative FHD individuals were participated in this study. Two groups were matched for age, gender, and body mass index (BMI). In the present study, expert interviewers collected socio-demographic data and prescribed dietary recommendations in a face-to-face method.

RESULTS: Dietary intervention significantly reduces the body weight and BMI in both groups, but these reductions were not different between negative and positive FHD groups. This study could not find any significant association between FHD and responsiveness to weight loss diets ($\beta = -0.058$; 95% confidence interval, −1.618 to 0.832; $P = 0.526$).

CONCLUSION: Individuals with FHD have higher risk for obesity and chronic diseases, but in the current study there was no difference in responsiveness to weight loss in individuals with a positive family history and those without a family history.

Keywords: Body Weight, Body Mass Index, Weight Loss Diet, Family History of Diabetes

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Introduction

Obesity has considered as one of the serious health problem.[1] During the previous decades, incidence of obesity has increased even faster,[2,3] so that in 21st century, obesity is become one of the most important health problem.[4] Obesity in Iran has also increased during a 14-year period, in order that the prevalence of obesity increased 5.8% and 17.4% in men and women, respectively, which become 10.5% in men and 17.4% in women.[5] Obesity is associated with many metabolic and chronic diseases, such as diabetes, cardiovascular disease, arthritis, respiratory diseases and some cancers.[6] In the pathogenesis of glucose intolerance and metabolic diseases, the effects of obesity have been documented.[7] In another investigation, insulin sensitivity is negatively associated with body mass index (BMI).[7] It has been shown that obesity is the main potentially risk factor for type 2 diabetes.[8] Moreover, in some experimental and cohort studies, weight gain is positively related with risk of diabetes mellitus.[9-11]

Diabetes as a major risk for mortality and morbidity has great direct and indirect costs.[12] Family history of diabetes (FHD) is an important risk factor for type 2 diabetes. In some prospective studies, higher risk for type 2 diabetes was positively associated with FHD.[13,14] Based on case definition and study design, FHD has 2-6 times higher risk for type 2 diabetes.[15] Moreover, in a cross-sectional study, individuals with positive FHD had higher adiposity than individuals without a family history.[16] Furthermore, the presence of FHD and obesity has a synergic effect at risk of diabetes incidence.[17] There are evidences that show lifestyle interventions such as dietary changes, physical activity, and weight loss in overweight people is associated with enhanced insulin-glucose homoeostasis and could decrease the type 2 diabetes risk.[18,19] Moreover, in

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subjects with type 2 diabetes, weight loss has positive effects on glycemic control, insulin sensitivity, and diabetes complications.[20]

During previous decades, Iran like other developing countries has faced with swift changes in many phases such as urbanization, lifestyle and dietary habits, and as a result, obesity and diabetes has become more critical health problem. FHD could be an important target group for lifestyle modification, which we expect to improve health outcome and postpone disease arrival. A randomized clinical trial on impair glucose tolerance patients confirmed that weight loss, fat intake reduction and physical activity could decrease the type 2 diabetes by 58%.[18] Genetic or behavioral factors have effects on glycemic control in FHD. For instance, people who have parental history of diabetes may have higher insulin resistance and poorer glycemic control because of their genetic factors, which could lead to obesity and influence the pathogenesis of their disease. To the best of our knowledge, there is no study that considers whether FHD has any effect on weight loss mediation. Doing this study may improve our understanding of the known genetic differences for weight loss intervention. We conducted a study to determine this effect and find out if FHD influence the weight loss diet.

Materials and Methods

Study population

We conducted an intervention study involving overweight or obese Iranian adults (BMI > 25) without diabetes who were participating in the weight loss program in Salamat Clinic in 2009. Based on convenience non-random sampling procedure, 78 people with positive FHD and 74 negative FHD participants were participated in this study. Participants with at least one first-degree relative with diabetes were considered positive family history. First-degree relatives could be father, mother, sibling or child. Controls were obese people without FHD. People who had missing socio-demographic, family history or dietary variable data were excluded from the study. Two groups were matched for age, gender and BMI. From each participant a written informed consent was obtained.

Assessment of variables

Socio-demographic date such as age, gender, education, and FHD were self-reported. Assessment of weight and height was completed while participants were barefoot and wearing light clothes. Subjects' weights were measured using a digital scale to the nearest 0.1 kg and heights were measured by a wall fixed measuring tape to the nearest 0.1 cm. As a measure of obesity, BMI was calculated as weight (kg) divided by height square (m^2). Measurement of waist circumference (WC) was done horizontally between lowest rib margin and the iliac crest by a measuring tape and for the hip circumference at the widest point. Waist to hip ratio was calculated as WC divided by hip circumference. Dietary intake was assessed with a single 24 h dietary recall to evaluate subjects' food habits. Participants' data were assessed at baseline and 6 months after the dietary interventions.

Dietary intervention

All patients were treated based on the usual dietary programs. For each subject, energy requirement was calculated by Harris and Benedict equation.[21] For weight loss diet, energy intake was reduced by 500 kcal in all people. All diets and foods were self-selected based on habits and preferences. We asked the participant to reduce fat intake by 30% of their total energy intake. For every subject weekly individual meetings were arranged to assure compliance to the arranged diet, and discuss success strategies and correct the diet if necessary.

Statistical methods

For all statistical analyses in this study, we used SPSS for windows (version 15, SPSS Inc., Chicago, IL, USA). Test of normality with Kolmogorov-Smirnov test showed that the data were normally distributed. To compare means of continues variables between positive and negative FHD groups, we applied Student's t-test and for categorical variables chi-square test was used. Linear regression was used to discover the associations between positive FHD and weight and BMI.

Results

The characteristics of total study population and separated by FHD are provided in table 1. There was no significant difference between individuals with negative FHD and those with a positive history in age, sex, weight, BMI, and WC at the baseline point. Based on the results of table 2 which shows the effect of weight loss diet on body weight in people with positive FHD and participants with negative FHD, dietary intervention significantly reduces the body weight and BMI in both groups, but these reductions were not different between negative and positive FHD groups ($P = 0.526$ and $P = 0.413$ for weight and BMI, respectively). Table 3 shows the simple linear regression between FHD and the effect of dietary weight loss. In this study, we failed to find any significant association between FHD and responsiveness to weight loss diets.

Table 1. Characteristics of study participants based on family history of diabetes*

Baseline characteristic	Total	Negative FHD	Positive FHD	P
Age (year)	36.62 ± 14.13	37.90 ± 15.44	34.64 ± 11.70	0.189
Weight (kg)	80.42 ± 16.65	78.93 ± 16.45	82.71 ± 16.88	0.223
BMI (kg/m^2)	30.34 ± 5.56	29.61 ± 5.46	31.40 ± 5.59	0.089
Waist circumference (cm)	88.97 ± 12.69	87.38 ± 14.00	90.75 ± 10.92	0.217
Waist to hip ratio	0.82 ± 0.07	0.82 ± 0.07	0.83 ± 0.07	0.918
Sex (female) (%)	77.9	70.3	89.6	0.120

* Data are means ± standard error unless indicated; FHD: Family history of diabetes; BMI: Body mass index

Table 2. Comparing the effect of dietary intervention on body weight and body mass index in individuals with and without family history of diabetes

	Positive FHD				Negative FHD				P**
	Beginning	End	Differences	P*	Beginning	End	Differences	P*	
Weight (kg)	82.71 ± 16.88	81.28 ± 16.43	1.43 ± 4.59	0.036	78.93 ± 16.45	77.11 ± 15.29	1.82 ± 2.18	P < 0.001	0.526
BMI (kg/m^2)	31.40 ± 5.59	30.86 ± 5.36	0.53 ± 1.71	0.038	29.61 ± 5.46	28.89 ± 5.09	0.73 ± 0.76	P < 0.001	0.413

* P compares the effect of diet in each group; ** P compares the differences between positive FHD group and negative FHD group; FHD: Family history of diabetes; BMI: Body mass index

Table 3. Simple linear regression between family history of diabetes and dietary weight loss effect

	β	95% CI	R^2	P
Weight	−0.058	−1.618 to 0.832	0.003	0.526
BMI	−0.077	−0.656 to 0.271	0.006	0.413

CI: Confidence interval; BMI: Body mass index

Discussion

In this study, the influence of FHD on weight loss in responses to diet induced weight loss was examined. We found a significant decrease in body weight after dietary intervention in both groups; however, we failed to find any significant difference in weight loss between individuals with positive FHD and those with negative FHD.

It has been well-known that FHD is correlated with higher risk of developing diseases.[15] It has also been found that parental history of diabetes is associated with insulin resistance, and high fasting insulin levels.[22] Body weight, BMI, glucose, triglyceride, and low-density lipoprotein cholesterol are positively related with higher insulin levels;[23] however, in the present study, there was no difference in body weight and BMI in individuals with or without FHD. Obesity and FHD simultaneously could greatly increase the risk of chronic diseases,[17] conversely, lowering body weight could decline the risk of diabetes, so weight loss is an excellent treatment for obese patients with FHD. Although FHD could be a significant risk factor for obesity[24] in our study, it had no effect on weight loss as compared with normal individuals, which is particularly in line with previous studies that during weight loss intervention type 2 diabetic patients lose weight as much as diabetic individuals.[25] FHD may affect glycemic control through behavioral or genetic mechanism. They may have poorer glycemic control because of their genetic risk factors, and on the other hand, they may have enhanced health behavior or knowledge of disease risk factors or they may have received more encouragement to lose weight that could lead to better glycemic control.[26] Individuals with a positive FHD engaged in health protective activities such as weight control behaviors more than individuals without FHD.[27] Since, many of them consider themselves to be at higher risk, they may engage in these behaviors.

Several limitations deserved comment in this study. First of all, in this study, we used convenient sampling and we could not generalize it to our population. Second, self-report was the most important method to obtain the information, which may cause bias in measurement. Third, it is estimated that between 33% and 50% of people with diabetes has not been recognized[28] so people may not know about the diabetes status of all of their family members which may lead to misclassification. Finally, we were unable to discriminate between type 1 diabetes and type 2 diabetes and so we were unable evaluating its effect on their family members.

Conclusion

Although individuals with FHD have higher risk for obesity and chronic diseases, in the current study, there was no difference in responsiveness to weight loss in individuals with a positive family history and those without a family history. Further investigations with higher sample size and longer period of intervention are necessary to confirm this relationship.

Conflict of Interests

Authors have no conflict of interests.

References

1. Malekzadeh R, Mohamadnejad M, Merat Sh, Pourshams A, Etemadi A. Obesity pandemic: an iranian perspective. Arch Iranian Med 2005; 8(1): 1-7.
2. Sturm R. Increases in clinically severe obesity in the United States, 1986-2000. Arch Intern Med 2003; 163(18): 2146-8.
3. Sturm R. Increases in morbid obesity in the USA: 2000-2005. Public Health 2007; 121(7): 492-6.
4. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. JAMA 2010; 303(3): 235-41.
5. Ayatollahi SM, Ghoreshizadeh Z. Prevalence of obesity and overweight among adults in Iran. Obes Rev 2010; 11(5): 335-7.
6. O'Kane JW, Teitz CC, Fontana SM, Lind BK. Prevalence of obesity in adult population of former college rowers. J Am Board Fam Pract 2002; 15(6): 451-6.
7. Caprio S. Insulin resistance in childhood obesity. J Pediatr Endocrinol Metab 2002; 15(Suppl 1): 487-92.
8. Pinkney J. Prevention and cure of type 2 diabetes. BMJ 2002; 325(7358): 232-3.
9. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med 1995; 122(7): 481-6.
10. Ford ES, Williamson DF, Liu S. Weight change and diabetes incidence: findings from a national cohort of US adults. Am J Epidemiol 1997; 146(3): 214-22.
11. Resnick HE, Valsania P, Halter JB, Lin X. Relation of weight gain and weight loss on subsequent diabetes risk in overweight adults. J Epidemiol Community Health 2000; 54(8): 596-602.
12. Brancati FL, Kao WH, Folsom AR, Watson RL, Szklo M. Incident type 2 diabetes mellitus in African American and white adults: the Atherosclerosis Risk in Communities Study. JAMA 2000; 283(17): 2253-9.
13. Wilson PW, Meigs JB, Sullivan L, Fox CS, Nathan DM, D'Agostino RB, Sr. Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. Arch Intern Med 2007; 167(10): 1068-74.
14. Magliano DJ, Barr EL, Zimmet PZ, Cameron AJ, Dunstan DW, Colagiuri S, et al. Glucose indices, health behaviors, and incidence of diabetes in Australia: the Australian Diabetes, Obesity and Lifestyle Study. Diabetes Care 2008; 31(2): 267-72.
15. Harrison TA, Hindorff LA, Kim H, Wines RC, Bowen DJ, McGrath BB, et al. Family history of diabetes as a potential public health tool. Am J Prev Med 2003; 24(2): 152-9.
16. van Dam RM, Boer JM, Feskens EJ, Seidell JC. Parental history of diabetes modifies the association between abdominal adiposity and hyperglycemia. Diabetes Care 2001; 24(8): 1454-9.
17. Morris RD, Rimm DL, Hartz AJ, Kalkhoff RK, Rimm AA. Obesity and heredity in the etiology of non-insulin-dependent diabetes mellitus in 32,662 adult white women. Am J Epidemiol 1989; 130(1): 112-21.
18. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001; 344(18): 1343-50.
19. Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care 2004; 27(1): 155-61.
20. Henry RR, Wiest-Kent TA, Scheaffer L, Kolterman OG, Olefsky JM. Metabolic consequences of very-low-calorie diet therapy in obese non-insulin-dependent diabetic and nondiabetic subjects. Diabetes 1986; 35(2): 155-64.
21. Harris JA, Benedict FG. A biometric study of basal metabolism in man. Washington, DC: Carnegie Institution of Washington; 1919. p. 279.
22. Gonzalez-Ortiz M, Martinez-Abundis E, Cardona-Munoz EG, Lifshitz A, Quinones-Galvan A. Metabolic profile and insulin sensitivity in healthy young Mexicans with a strong family history of non-insulin-dependent diabetes mellitus in the paternal branch. Arch Med Res 1997; 28(3): 421-4.
23. Zamora-Gonzalez J, Yamamoto-Kimura L, Lerman-Garber I, Cardoso-Saldana G, Fajardo-Gutierrez A, Posadas-Romero C. Clustering of metabolic disorders and hyperinsulinemia in Mexico City. Int J Obes Relat Metab Disord 1996; 20(4): 311-8.
24. van der Sande MA, Walraven GE, Milligan PJ, Banya WA, Ceesay SM, Nyan OA, et al. Family history: an opportunity for early interventions and improved control of hypertension, obesity and diabetes. Bull World Health Organ 2001; 79(4): 321-8.
25. Guare JC, Wing RR, Grant A. Comparison of obese NIDDM and nondiabetic women: short- and long-term weight loss. Obes Res 1995; 3(4): 329-35.
26. Gong L, Kao WH, Brancati FL, Batts-Turner M, Gary TL. Association between parental history of type 2 diabetes and glycemic control in urban African Americans. Diabetes Care 2008; 31(9): 1773-6.
27. Baptiste-Roberts K, Gary TL, Beckles GL, Gregg EW, Owens M, Porterfield D, et al. Family history

of diabetes, awareness of risk factors, and health behaviors among African Americans. Am J Public Health 2007; 97(5): 907-12.

28. Harris MI. Undiagnosed NIDDM: clinical and public health issues. Diabetes Care 1993; 16(4): 642-52.

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The association of genetic variations with sensitivity of blood pressure to dietary salt: A narrative literature review

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Review Article

Abstract

Salt sensitivity of blood pressure (BP) is an independent risk factor for cardiovascular morbidity. Up to 50% of patients with essential hypertension are salt-sensitive, as manifested by a rise in BP with salt intake. Several genetic variations have been identified as being associated with salt sensitivity. The present study aimed to review the evidence on the effect of gene polymorphisms on the salt sensitivity of BP. We searched in PubMed website from 1990 to 2011, with the use of following keywords: "hypertension, dietary salt, polymorphisms, and blood pressure". The effect of sodium intake on BP differed by genotype at the genes of the renin-angiotensin system, aldosterone synthase, cytochrome p450 3A, epithelial sodium channel genes, genes of sympathetic nervous system, β-3 subunit of G-protein, alpha-adducin, endothelial nitric oxide synthase, Kallikrein-Kinin system. These approaches suggest that these polymorphisms may be potentially useful genetic markers of BP response to dietary salt. There is evidence that genetic predisposition modulates the BP response to diet. Therefore, diet and nutrition can mitigate or enhance the effects of genetic predisposition. Increasing our knowledge of this relationship can lead to individualized treatment and increased understanding of hypertension.

Keywords: Hypertension, Genetics, Diet Therapy

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Introduction

Hypertension is a major worldwide risk factor for cardiovascular diseases (CVDs) such as heart attack, congestion, heart failure, stroke, and peripheral vascular disease.[1] The prevalence of hypertension has dramatically increased in recent years.[2] Essential hypertension is a complex disease that characterized by chronically elevation in blood pressure (BP) with no specific underlying medical or biological cause.[3] As that shown in the previous studies in the field of similar problems such as hyperlipidemia and other CVDs,[4] hypertension is a complex trait resulting from interaction of multiple genetic factors and lifestyle exposures including: dietary salt intake, alcohol consumption, and body weight.[5] The heritability of hypertension is often reported in the range of 30-60%.[6]

Requirements and tolerable upper limits of nutrients could be different in different people.[7] Several studies of nutritional genomics have shown that some of the gene variations could influence the level of nutrients requirements.[8] On the other hand, intake of some nutrients could alter the gene expression and protein synthesis.[9]

High dietary sodium intake is the most prevalent risk factor in modern societies. Although many studies found that high dietary salt intake is associated with hypertension, but BP responses to high and low salt intake may be influenced by various genetic factors[10] and some studies have suggested that dietary sodium restriction may not be beneficial to everyone. Salt restriction has been reported to decrease cognitive function in salt sensitive and salt resistant population;[11] thus, there is a need to recognize the genetics determinants of salt sensitivity that increase our understanding of the mechanism underlying hypertension and finally distinguish salt sensitive from salt resistant subjects.

Salt sensitivity of BP is defined by the observed changes of arterial pressure as daily salt intake is changed.[12] Most studies searching for genetics causes of essential hypertension have been observed association between candidate genes with salt sensitive hypertension. These genes including:

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renin-angiotensin converting enzyme (ACE) gene, angiotensinogen (AGT) gene, angiotensin II type 1 receptor, epithelial sodium channel (ENaC) genes, 11-beta hydroxy steroid dehydrogenase (11-BHSD) genes, sympathetic alpha receptor gene, beta receptor gene, endothelial nitric oxide synthase gene, adducin gene, and others.[13]

This narrative literature review outlines some of genes associated with salt sensitive hypertension; emphases on genetic variations related to salt sensitivity in individuals and highlight the recent finding on the genetic basis of salt sensitive hypertension.

Genes of Renin-Angiotensin System (RAS)

The renin-angiotensin system (RAS) is the most important regulation of homeostatic system that controls body fluid volume, electrolyte balance, and BP.[14]

Components of RAS were studied as candidate genes for salt sensitive hypertension. The most studies have examined several loci within this system: the ACE gene, the AGT gene, and the angiotensin type 1 receptor gene.

ACE Gene

Many studies have examined the association between ACE and salt sensitivity.[15-17]Meneton et al. found that the prevalence of salt sensitivity hypertension in II phenotype and ID phenotype is significantly higher than DD phenotype.[15] Zhang et al. found that ACE I/D had been significant association with salt sensitivity hypertension.[17]

However, reports of the association between ACE genotype and salt sensitivity hypertension were inconsistent. Strazzullo et al. in a meta-analysis of 145 case–control studies observed that DD homozygote and ID heterozygote had increased CVD, but not for hypertension in contrast with II homozygote.[18]

AGT Gene

Norat et al. found that molecular variants in the AGT gene including M235T, T174M, and mutation in the promoter region that involve in the insertion of adenine instead of guanine (G-6A) had been a positive association with salt sensitivity hypertension[19] that was in line with results of two previous studies.[20,21] Schorr et al. found that the presence of the AA (or TT) genotype in the promoter region is associated with salt-sensitive BP.[21] Also, Hunt et al. found an association between AGT-GG linkages with AGT M235T with a decrease in BP after a decrease in sodium intake.[22] Beeks et al. concluded that patients who are homozygous for M allele had lower BP after mild salt restriction compare with TT and MT genotype.[23]

Svetkey et al. found that BP response to the dietary approaches to stop hypertension (DASH) diet is higher in the genotype of G-6A AGT SNP than GG genotype.[24]

Angiotensin Type 1 Receptor

Anginotensin II regulates vascular contracting, BP and sodium reabsorbing by kidney through binding with angiotensin II receptor.[25] Two subtype of gene variations of angiotensin II type 1 receptor, 1A ($AT_{1A}R$) and 1B ($AT_{1B}R$), may effect on BP.[26]

Moreover, Gu et al. found an association between rs4524238 alleles G/A and A/A with salt sensitivity hypertension.[27]

Aldestron Synthase

Aldestron secretes by the adrenal gland and has been important in the regulation of water electrolyte balance.[28] This hormone synthesize by the aldosterone synthase enzyme, which is encoded by the CYP11B2 gene.[29] Many studies reported that CYP11B2 polymorphisms, especially −344C/T are associated with salt sensitivity hypertension.[30-32] However, in two studies CYP11B2 T344C polymorphism was not associated with hypertension.[18,23]

11BHSD2 Gene

Mineralocorticoid activity may be increased with decreased activity of 11BHSD2, which inactivates 11-hydroxy steroids in the kidney, thereby protecting the nonselective mineralocorticoid receptor from occupation by glucocorticoids.[33] Smolenicka et al. found that Mutations in the 11BHSD2 gene may lead to a rare form of salt sensitive hypertension.[34] Alikhani-Koupaei et al. identified polymorphism G534A in exon 3 of this gene could increase susceptibility to salt sensitive hypertension.[35]

Cytochrome p450 3A (Cyp3A)

Cytochrome p450 3A (Cyp3A) is a subfamily of cytochrome P (CYP) 450. This group of cytochromes are involved in the metabolism of drugs (e.g., anti-hypertensive drugs) and endogenous substrate such as steroids. These

metabolites effect on renal sodium transport.[36] Components of Cyp3A subfamily are located on chromosome 7q22. These genes include Cyp3A4, Cyp3A5, Cyp3A7, and Cyp3A43 (cyt3). Cyp3A5 is of particular interest because it is expressed in the kidney; Cyp3A5*1 expresses the wild-type protein while the Cyp3A5*3 allele (A6986G, rs776746) reduces Cyp3A5 protein expression. In a Japanese population, Zhang et al. found that BP was associated with the level of salt intake in Cyp3A5*3/*3, but not CYP3A5*1/*1.[37]

ENaC Genes

ENac has major roles in Na^+ reabsorption in the distal tubule, regulation of extracellular fluid volume and BP.[18] Lifton et al. found that T594M mutation of the β-subunit in black people is associated with a greater chance of hypertension compared with individuals without this mutation.[38]

On the other hand, neural precursor cell expressed developmentally downregulated 4-like (NEDD4L) is an ubiquitin ligase, express in the distal nephron and regulates the expression of the epithelial Na^+ channel.[39] Some studies reported association between variation in NEDD4Land salt sensitive hypertension.[39,40] Dahlberg et al. found that a common polymorphism located in intron 2 (rs4149601, A/G) of the NEDD4L gene was found to be associated with salt sensitive hypertension.[39]

Manunta et al. found a combination of two common single nucleotide polymorphisms (rs4149601 and rs2288774) located in the NEDD4L gene is associated with salt sensitive hypertension and suggested that carriers of NEDD4L rs4149601 G-allele have higher ENaC expression compared with carriers of A-allele.[40]

Genes of Sympathetic Nervous System

The sympathetic nervous system is a primary regulator of acute change in BP and increased sympathetic function has reported in salt sensitive hypertension.[41]

Weber et al. found that salt-sensitive men have increased noradrenergic receptor sensitivity and circulating cortisol levels.[42]

The genes encoding for β_2-adrenergic receptor (ADRβ2) is located on chromosome 10qr and encoded 477 amino acids. Eisenach et al. found that an amino terminal variant in the β_2-adreno receptor that encodes glycin instead of argennin (Arg16gly) has been associated with salt sensitive hypertension.[43] Pojoga et al. found a Similar association between this polymorphism and BP in normotensive people.[44] Svetkey et al. reported that dietary Na^+ restriction blunted the increased NO-mediated β_2-ADR responsiveness in Gly16 homozygotes observed in a previous study after normal dietary Na^+ intake and demonstrated that β_2-ADR downregulation might serve to explain the decreased β_2-adreno receptor expression on the fibroblasts of salt sensitive individuals compare with salt resistant and normotensive people.[45]

Another study has been found that the β_2-ADR C79G and β_2-ADR A46G SNPs were associated with salt sensitive hypertension. Pojoga et al. have reported that greater risk of salt sensitive hypertension is associated with an allele of A46G and the C allele of C79G.[44] They compared the dietary change (from low- to high-sodium balance) in mean arterial pressure (MAP) among the 171 hypertensive subjects. Although baseline (low-sodium) BP was similar among genotype groups, MAP differed significantly by genotype, the 46AA and 79CC homozygotes demonstrated the greatest MAP.

β-3 Subunit of G-Protein

The β-adrenoreceptor-G-protein system is essential for function of adenylyl cyclase.[46] Bagos et al. have been reported that polymorphism C825T in exon 19 is associated with salt sensitive hypertension.[47] The T allele of this polymorphism is associated with higher risk of salt sensitive hypertension. Siffert et al. found that carriers of TT homozygotes and TC heterozygotes have a higher risk of hypertension compare with CC homozygotes.[48]

Alpha-Adducin

Adducins are a cytoskeletal protein that may regulate the membrane organization of spectrin-actin.[49] Manunta et al. found that a mutation (Gly460Trp) in human's α-adducin was reported to be associated with salt sensitive hypertension.[40] Manunta et al. found the association between Gly460Trp allele and hypertension in some population.[50] Wang et al. in a recent meta-analysis involving 454 salt sensitive and 366 non-salt sensitive participants concluded that the association between ADD1 Gly460Trp and salt sensitivity is statistically significant in Asian, but not Caucasian populations; the difference may be related to the greater frequency of ADD1 Gly460Trp in Asians than in Caucasians.[51] Wang et al. found that the interaction among ADD1 Gly460Trp, ACE DD, and CYP11B2 −344CC may contribute to the BP response to dietary salt.[52]

Endothelial Nitric Oxide Synthase

Nitric oxide (NO) is a vasodilator that produced from l-arginine by NO synthase. Harsha et al. reported the association between Glu298Asp variant with hypertension.[53] Miyaki et al. found that two polymorphisms of NO synthase, T786C and G894T have been associated with essential hypertension.[54] Dengel et al. found an association between T786C polymorphism and salt sensitive hypertension.[55]

Kallikrein-Kinin System

This system has important roles in the kidney to increase renal blood flow.[56] Chao et al. found that the Q121E SNP of kallikrein gene was reported to be associated with hypertension.[57] Cervenka et al. found that deletion of the bradykininB_2 receptor gene in mice produces salt-sensitive hypertension.[58]

Conclusion

There is evidence that genetic predisposition modulates the BP response to diet. On the other hand, diet and nutrition can mitigate or enhance the effects of genetic predisposition. Increasing our knowledge of this relationship can lead to physiologically individualized treatment and increased understanding of Pathophysiology. Major focuses in clinical research are to develop personalized treatment strategies that are preemptive and to allow persons to be proactive. While we await new studies that allow us to tailor such interventions and treatments, we must not lose sight of the wealth of information already accumulated on the effects of lifestyle modifications on BP. Reduced sodium intake, the DASH diet, weight loss, and exercise have substantial effects in almost all subgroups of the population and should continue to be widely and broadly promoted.

Conflict of Interests

Authors have no conflict of interests.

References

1. Hickler RB. "Hypertensive emergency": a useful diagnostic category. Am J Public Health 1988; 78(6): 623-4.
2. Burt VL, Cutler JA, Higgins M, Horan MJ, Labarthe D, Whelton P, et al. Trends in the prevalence, awareness, treatment, and control of hypertension in the adult US population. Data from the health examination surveys, 1960 to 1991. Hypertension 1995; 26(1): 60-9.
3. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Hypertension 2008; 51(6): 1403-19.
4. Doaee S, Gholamalizadeh M. Polymorphism of A I, A IV and E apolipoprotein genes and effect of fat intake on HDL levels. Genetics in the 3rd Millennium 2011; 9(1): 2323-8.
5. Knight BS, Sunn N, Pennell CE, Adamson SL, Lye SJ. Developmental regulation of cardiovascular function is dependent on both genotype and environment. Am J Physiol Heart Circ Physiol 2009; 297(6): H2234-H2241.
6. Hedayati SS, Elsayed EF, Reilly RF. Non-pharmacological aspects of blood pressure management: what are the data? Kidney Int 2011; 79(10): 1061-70.
7. Safavi SM, Doaei S, Gholamalizadeh M. Unsaid of nutrition and genetics. The World of Nutrition Journal 2007; 6(60): 22-3. [In Persian].
8. Doaei S, Gholamalizadeh M. The association between dietary fat with gene polymorphisms. Proceedings of the 11th Iranian Nutrition Congress; 2010 Nov 1-4; Shiraz, Iran; 2010. [In Persian].
9. Doaei S, Gholamalizadeh M, Akbari M, Safavi SM. Nutritional genomics: a window to the future. 1st ed. Qom, Iran: Andishe Mandegar Publication; 2011. p. 5-9. [In Persian].
10. He FJ, MacGregor GA. How far should salt intake be reduced? Hypertension 2003; 42(6): 1093-9.
11. Cohen HW, Alderman MH. Sodium, blood pressure, and cardiovascular disease. Curr Opin Cardiol 2007; 22(4): 306-10.
12. Cowley AW. Genetic and nongenetic determinants of salt sensitivity and blood pressure. Am J Clin Nutr 1997; 65(2 Suppl): 587S-93S.
13. Doaei S, Gholamalizadeh M. The association of genetic variations with sensitivity of blood pressure to dietary salt. Proceedings of the 1st International Congress on Prevention, Diagnosis & Management of Hypertension in Iran; 2011 Sep 27-29; Isfahan-Iran; 2011. [In Persian].
14. Poch E, Gonzalez D, Giner V, Bragulat E, Coca A, de La SA. Molecular basis of salt sensitivity in human hypertension. Evaluation of renin-angiotensin-aldosterone system gene polymorphisms. Hypertension 2001; 38(5): 1204-9.
15. Meneton P, Jeunemaitre X, de Wardener HE, MacGregor GA. Links between dietary salt intake, renal salt handling, blood pressure, and cardiovascular diseases. Physiol Rev 2005; 85(2): 679-715.
16. Caprioli J, Mele C, Mossali C, Gallizioli L, Giacchetti G, Noris M, et al. Polymorphisms of

EDNRB, ATG, and ACE genes in salt-sensitive hypertension. Can J Physiol Pharmacol 2008; 86(8): 505-10.
17. Zhang L, Miyaki K, Araki J, Song Y, Kimura T, Omae K, et al. Interaction of angiotensin I-converting enzyme insertion-deletion polymorphism and daily salt intake influences hypertension in Japanese men. Hypertens Res 2006; 29(10): 751-8.
18. Strazzullo P, Galletti F. Genetics of salt-sensitive hypertension. Curr Hypertens Rep 2007; 9(1): 25-32.
19. Norat T, Bowman R, Luben R, Welch A, Khaw KT, Wareham N, et al. Blood pressure and interactions between the angiotensin polymorphism AGT M235T and sodium intake: a cross-sectional population study. Am J Clin Nutr 2008; 88(2): 392-7.
20. Jeunemaitre X, Soubrier F, Kotelevtsev YV, Lifton RP, Williams CS, Charru A, et al. Molecular basis of human hypertension: role of angiotensinogen. Cell 1992; 71(1): 169-80.
21. Schorr U, Blaschke K, Beige J, Distler A, Sharma AM. Angiotensinogen M235T variant and salt sensitivity in young normotensive Caucasians. J Hypertens 1999; 17(4): 475-9.
22. Hunt SC, Cook NR, Oberman A, Cutler JA, Hennekens CH, Allender PS, et al. Angiotensinogen genotype, sodium reduction, weight loss, and prevention of hypertension: trials of hypertension prevention phase II. Hypertension 1998; 32(3): 393-401.
23. Beeks E, Kessels AG, Kroon AA, van der Klauw MM, de Leeuw PW. Genetic predisposition to salt-sensitivity: a systematic review. J Hypertens 2004; 22(7): 1243-9.
24. Svetkey LP, Harris EL, Martin E, Vollmer WM, Meltesen GT, Ricchiuti V, et al. Modulation of the BP response to diet by genes in the renin-angiotensin system and the adrenergic nervous system. Am J Hypertens 2011; 24(2): 209-17.
25. Kobori H, Nangaku M, Navar LG, Nishiyama A. The intrarenal renin-angiotensin system: from physiology to the pathobiology of hypertension and kidney disease. Pharmacol Rev 2007; 59(3): 251-87.
26. Crowley SD, Gurley SB, Herrera MJ, Ruiz P, Griffiths R, Kumar AP, et al. Angiotensin II causes hypertension and cardiac hypertrophy through its receptors in the kidney. Proc Natl Acad Sci U S A 2006; 103(47): 17985-90.
27. Gu D, Kelly TN, Hixson JE, Chen J, Liu D, Chen JC, et al. Genetic variants in the renin-angiotensin-aldosterone system and salt sensitivity of blood pressure. J Hypertens 2010; 28(6): 1210-20.
28. Pinto V, Pinho MJ, Hopfer U, Jose PA, Soares-da-Silva P. Oxidative stress and the genomic regulation of aldosterone-stimulated NHE1 activity in SHR renal proximal tubular cells. Mol Cell Biochem 2008; 310(1-2): 191-201.
29. White PC, Rainey WE. Editorial: polymorphisms in CYP11B genes and 11-hydroxylase activity. J Clin Endocrinol Metab 2005; 90(2): 1252-5.
30. Brand E, Chatelain N, Mulatero P, Fery I, Curnow K, Jeunemaitre X, et al. Structural analysis and evaluation of the aldosterone synthase gene in hypertension. Hypertension 1998; 32(2): 198-204.
31. Matsubara M, Sato T, Nishimura T, Suzuki M, Kikuya M, Metoki H, et al. CYP11B2 polymorphisms and home blood pressure in a population-based cohort in Japanese: the Ohasama study. Hypertens Res 2004; 27(1): 1-6.
32. Tang W, Wu H, Zhou X, Cheng B, Dong Y, He L, et al. Association of the C-344T polymorphism of CYP11B2 gene with essential hypertension in Hani and Yi minorities of China. Clin Chim Acta 2006; 364(1-2): 222-5.
33. White PC, Mune T, Agarwal AK. 11 beta-Hydroxysteroid dehydrogenase and the syndrome of apparent mineralocorticoid excess. Endocr Rev 1997; 18(1): 135-56.
34. Smolenicka Z, Bach E, Schaer A, Liechti-Gallati S, Frey BM, Frey FJ, et al. A new polymorphic restriction site in the human 11 beta-hydroxysteroid dehydrogenase type 2 gene. J Clin Endocrinol Metab 1998; 83(5): 1814-7.
35. Alikhani-Koupaei R, Fouladkou F, Fustier P, Cenni B, Sharma AM, Deter HC, et al. Identification of polymorphisms in the human 11beta-hydroxysteroid dehydrogenase type 2 gene promoter: functional characterization and relevance for salt sensitivity. FASEB J 2007; 21(13): 3618-28.
36. Thompson EE, Kuttab-Boulos H, Witonsky D, Yang L, Roe BA, Di RA. CYP3A variation and the evolution of salt-sensitivity variants. Am J Hum Genet 2004; 75(6): 1059-69.
37. Zhang L, Miyaki K, Wang W, Muramatsu M. CYP3A5 polymorphism and sensitivity of blood pressure to dietary salt in Japanese men. J Hum Hypertens 2010; 24(5): 345-50.
38. Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. Cell 2001; 104(4): 545-56.
39. Dahlberg J, Nilsson LO, von Wowern F, Melander O. Polymorphism in NEDD4L is associated with increased salt sensitivity, reduced levels of P-renin and increased levels of Nt-proANP. PLoS One 2007; 2(5): e432.
40. Manunta P, Lavery G, Lanzani C, Braund PS, Simonini M, Bodycote C, et al. Physiological interaction between alpha-adducin and WNK1-NEDD4L pathways on sodium-related blood pressure regulation. Hypertension 2008; 52(2): 366-72.
41. Yatabe MS, Yatabe J, Yoneda M, Watanabe T, Otsuki M, Felder RA, et al. Salt sensitivity is associated with insulin resistance, sympathetic over activity, and

decreased suppression of circulating renin activity in lean patients with essential hypertension. Am J Clin Nutr 2010; 92(1): 77-82.
42. Weber CS, Thayer JF, Rudat M, Sharma AM, Perschel FH, Buchholz K, et al. Salt-sensitive men show reduced heart rate variability, lower norepinephrine and enhanced cortisol during mental stress. J Hum Hypertens 2008; 22(6): 423-31.
43. Eisenach JH, Schroeder DR, Pike TL, Johnson CP, Schrage WG, Snyder EM, et al. Dietary sodium restriction and beta2-adrenergic receptor polymorphism modulate cardiovascular function in humans. J Physiol 2006; 574(Pt 3): 955-65.
44. Pojoga L, Kolatkar NS, Williams JS, Perlstein TS, Jeunemaitre X, Brown NJ, et al. Beta-2 adrenergic receptor diplotype defines a subset of salt-sensitive hypertension. Hypertension 2006; 48(5): 892-900.
45. Svetkey LP, Timmons PZ, Emovon O, Anderson NB, Preis L, Chen YT. Association of hypertension with beta2- and alpha2c10-adrenergic receptor genotype. Hypertension 1996; 27(6): 1210-5.
46. Martin DN, Andreu EP, Ramirez LR, Garcia-Junco PS, Vallejo M, I, Santos RA, et al. G-protein beta-3 subunit gene C825 T polymorphism: influence on plasma sodium and potassium concentrations in essential hypertensive patients. Life Sci 2005; 77(23): 2879-86.
47. Bagos PG, Elefsinioti AL, Nikolopoulos GK, Hamodrakas SJ. The GNB3 C825T polymorphism and essential hypertension: a meta-analysis of 34 studies including 14,094 cases and 17,760 controls. J Hypertens 2007; 25(3): 487-500.
48. Siffert W, Rosskopf D, Siffert G, Busch S, Moritz A, Erbel R, et al. Association of a human G-protein beta3 subunit variant with hypertension. Nat Genet 1998; 18(1): 45-8.
49. Nishi A, Eklof AC, Bertorello AM, Aperia A. Dopamine regulation of renal Na+, K(+)- ATPase activity is lacking in Dahl salt-sensitive rats. Hypertension 1993; 21(6 Pt 1): 767-71.
50. Manunta P, Cusi D, Barlassina C, Righetti M, Lanzani C, D'Amico M, et al. Alpha-adducin polymorphisms and renal sodium handling in essential hypertensive patients. Kidney Int 1998; 53(6): 1471-8.
51. Wang R, Zhong B, Liu Y, Wang C. Association between alpha-adducin gene polymorphism (Gly460Trp) and genetic predisposition to salt sensitivity: a meta-analysis. J Appl Genet 2010; 51(1): 87-94.
52. Wang JG, Liu L, Zagato L, Xie J, Fagard R, Jin K, et al. Blood pressure in relation to three candidate genes in a Chinese population. J Hypertens 2004; 22(5): 937-44.
53. Harsha DW, Sacks FM, Obarzanek E, Svetkey LP, Lin PH, Bray GA, et al. Effect of dietary sodium intake on blood lipids: results from the DASH-sodium trial. Hypertension 2004; 43(2): 393-8.
54. Miyaki K, Tohyama S, Murata M, Kikuchi H, Takei I, Watanabe K, et al. Salt intake affects the relation between hypertension and the T-786C polymorphism in the endothelial nitric oxide synthase gene. Am J Hypertens 2005; 18(12 Pt 1): 1556-62.
55. Dengel DR, Brown MD, Ferrell RE, Reynolds TH, Supiano MA. A preliminary study on T-786C endothelial nitric oxide synthase gene and renal hemodynamic and blood pressure responses to dietary sodium. Physiol Res 2007; 56(4): 393-401.
56. Bellini C, Ferri C, Piccoli A, Carlomagno A, Di FL, Bonavita MS, et al. The influence of salt sensitivity on the blood pressure response to exogenous kallikrein in essential hypertensive patients. Nephron 1993; 65(1): 28-35.
57. Chao J, Zhang JJ, Lin KF, Chao L. Human kallikrein gene delivery attenuates hypertension, cardiac hypertrophy, and renal injury in Dahl salt-sensitive rats. Hum Gene Ther 1998; 9(1): 21-31.
58. Cervenka L, Harrison-Bernard LM, Dipp S, Primrose G, Imig JD, El-Dahr SS. Early onset salt-sensitive hypertension in bradykininB (2) receptor null mice. Hypertension 1999; 34(2): 176-80.

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Tachycardia-induced cardiomyopathy

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Case Report

Abstract

BACKGROUND: Tachycardia-induced cardiomyopathy (TIC) is a rare cause of dilated cardiomyopathy (DCMP). The diagnosis can be missed because tachycardia is a common symptom in DCMP.

CASE REPORT: We reviewed a case 5-year-old with palpitation and dyspnea with symptoms and signs of heart failure that diagnosed as DCMP initially. Then, in the evaluation for cause of tachycardia, atrial tachycardia was detected. Hence, treatment with flecainide was started and after 3 months, left ventricular (LV) systolic function and symptoms of the patient was relieved.

CONCLUSION: TIC should be suspected in all patients with unexplained LV dysfunctions in the setting of a persistent tachyarrhythmia.

Keywords: Dilated Cardiomyopathy, Heart Failure, Tachyarrhythmia

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Introduction

Tachycardia-induced cardiomyopathy (TIC) is a form of dilated cardiomyopathy (DCMP) caused by supraventricular and ventricular tachyarrhythmias. The diagnosis requires a high index of suspicion, as the culprit tachyarrhythmia may not always be apparent. We report a case of TIC referred to our center with palpitation and dyspnea for more evaluations.

TIC is a form of DCMP and heart failure that is caused by persistent or frequent paroxysmal supraventricular or ventricular tachyarrhythmias.[1] The clinical manifestations of TIC are associated with ventricular systolic dysfunction. Regardless of etiology, persistent tachycardia predisposes patients to develop ventricular dilatation and left ventricular (LV) dysfunction.[2] On the other hand, TIC is generally reversible once the underlying arrhythmia is controlled.[3] It is therefore important to make diagnosis early and treat the tachycardia responsible for the condition promptly. A common clinical problem is determining if the tachycardia is the primary cause of the cardiomyopathy or it is a consequence of a cardiomyopathy of different etiology, which makes the diagnosis difficult.[4]

Case Report

In March 2012, a 5-year-old boy with palpitation and dyspnea was referred to our center for more evaluations. His symptoms began after an upper respiratory infection 3 months before admission. The patients had received antibiotic, but his symptoms continued and progressed. In initial physical examination, he was not cyanotic but was fairly pale. He had tachycardia (heart rate = 170) and respiratory distress too. In cardiac examination S1 and S2 were normal; a grade II-III/VI systolic murmur in lower sternal border was auscultated. The lungs were clear. In abdominal exam, abdomen was soft with no guarding and tenderness. There is no hepatomegaly and no splenomegaly. His laboratory data includes: white blood cells = 4500/ml; creatine phosphokinase = 88 µ/l; hemoglobin = 11/9 g/l; lactate dehydrogenase = 578 µ/l; platelet = 254,000/µl; Ca = 10/4 mg/dl; Mg = 2/5 mg/dl; erythrocyte sedimentation rate was within normal range. C-reactive protein was negative. Electrolytes were within normal values.

Chest X-ray revealed a cardiomegaly with normal pulmonary blood flow. Electrocardiogram showed atrial tachycardia, normal axis, normal QRS, and QT interval duration. Transthoracic

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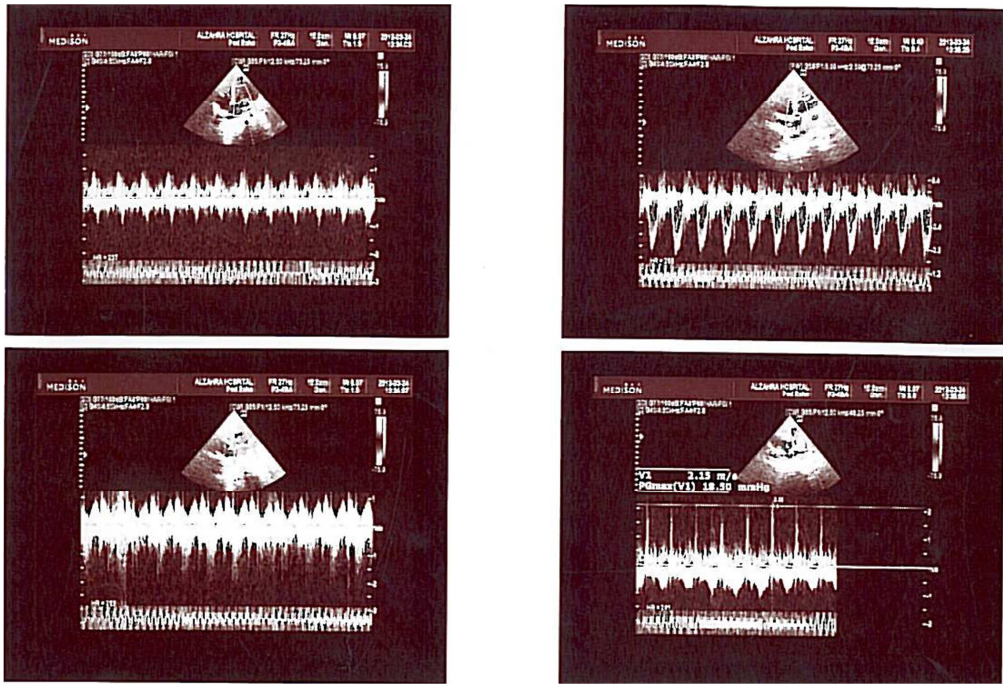

Figure 1. Panel representative trans thoracic echocardiography (TTE) shortly after admission

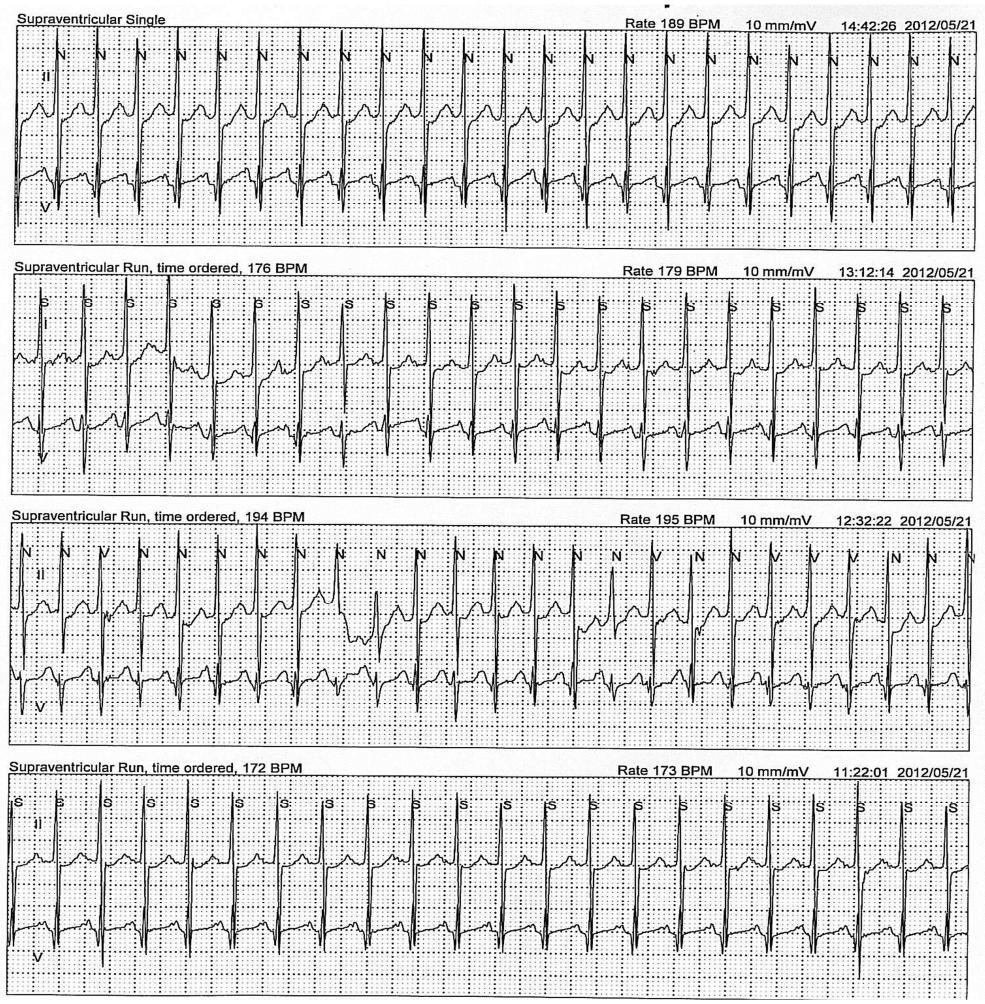

Figure 2. Holter monitoring shows atrial tachycardia (heart rate = 189 beat/min)

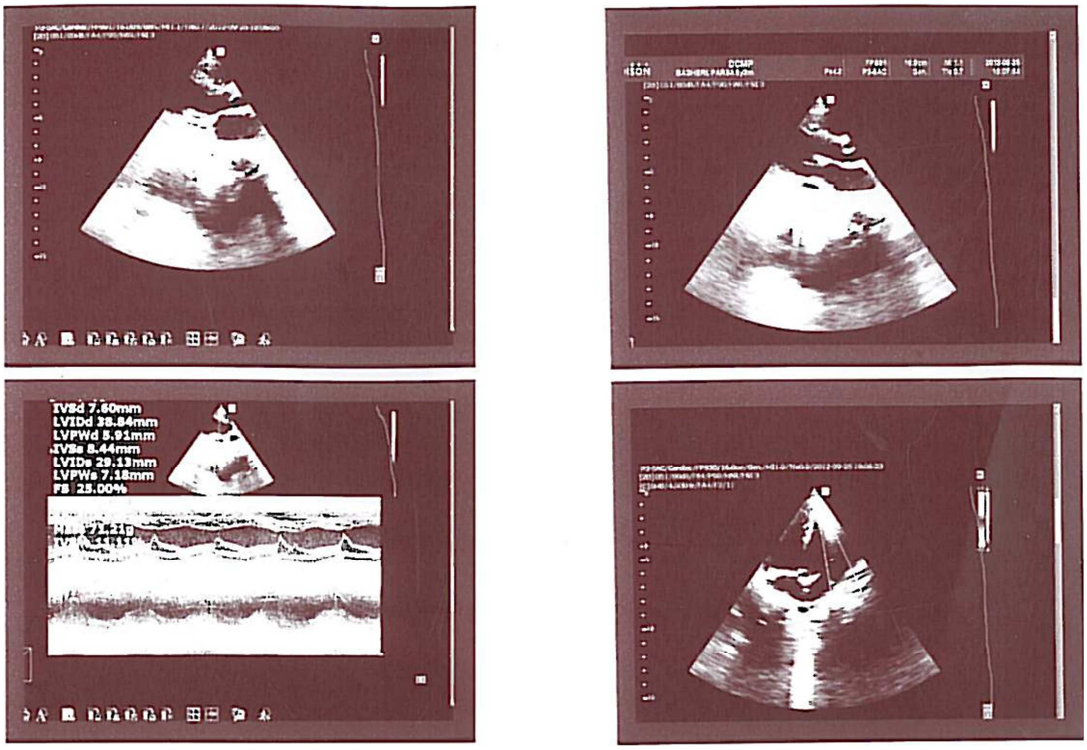

Figure 3. Trans thoracic echocardiography (TTE) obtained 3 month after flecainide therapy. Note the significant improvement in systolic function

echocardiography demonstrated DCMP, dilated left atrium and LV, markedly reduced LV ejection fraction (LVEF) at 22-30% (Figure 1). There was no family history of cardiac disease or sudden death.

He had no remarkable response to conventional treatment (digoxin, captopril, and L-carnitin) for DCMP. Tachycardia was referred to congestive heart failure. So, carvedilol was added to previous treatment for 1 month, but it was not effective. For more evaluation of tachycardia Holter monitoring was performed, and atrial tachycardia with mean heart rate of 189 beat/min was detected (Figure 2). After that, he was treated with flecainide. After 3 months, treatment with flecainide, his signs and symptoms improved and ejection fraction increased (LVEF = 57%) (Figure 3). With this treatment, no side-effects was occurred.

Discussion

TIC is an under diagnosed reversible form of DCMP.[5,6] TIC greatly depends on the ventricular rate. The patients with higher ventricular rate develop cardiomyopathy earlier.[7,8] The time to onset of LV dysfunction also depends on the duration and type of the tachycardia and any underlying structural cardiac disease.[9] Controlling the heart rate can result in significant improvement or even normalization of systolic function. Generally, the restoration of systolic function was obtained within about 4 weeks after controlling the tachycardia.[10] It is of paramount importance to recognize the condition as soon as possible and manage underlying tachyarrhythmia in order to restore systolic function.

Conclusion

The huge useful effect of heart rate control on cardiac function is clearly demonstrated in our patient. Since diagnosis may be difficult and some patients are misdiagnosed as idiopathic cardiomyopathy, TIC should be suspected in all patients with unexplained LV dysfunctions in the setting of a persistent tachyarrhythmia.

Conflict of Interests

Authors have no conflict of interests.

References

1. Umana E, Solares CA, Alpert MA. Tachycardia-induced cardiomyopathy. Am J Med 2003; 114(1): 51-5.
2. De Giovanni JV, Dindar A, Griffith MJ, Edgar RA, Silove ED, Stumper O, et al. Recovery pattern of left ventricular dysfunction following radiofrequency ablation of incessant supraventricular tachycardia in infants and children. Heart 1998; 79(6): 588-92.

3. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med 2000; 342(15): 1077-84.
4. Redfield MM, Kay GN, Jenkins LS, Mianulli M, Jensen DN, Ellenbogen KA. Tachycardia-related cardiomyopathy: a common cause of ventricular dysfunction in patients with atrial fibrillation referred for atrioventricular ablation. Mayo Clin Proc 2000; 75(8): 790-5.
5. Grimm W, Menz V, Hoffmann J, Maisch B. Reversal of tachycardia induced cardiomyopathy following ablation of repetitive monomorphic right ventricular outflow tract tachycardia. Pacing Clin Electrophysiol 2001; 24(2): 166-71.
6. Wu EB, Chia HM, Gill JS. Reversible cardiomyopathy after radiofrequency ablation of lateral free-wall pathway-mediated incessant supraventricular tachycardia. Pacing Clin Electrophysiol 2000; 23(8): 1308-10.
7. Shinbane JS, Wood MA, Jensen DN, Ellenbogen KA, Fitzpatrick AP, Scheinman MM. Tachycardia-induced cardiomyopathy: a review of animal models and clinical studies. J Am Coll Cardiol 1997; 29(4): 709-15.
8. Quiniou G, Chevalier JM, Barbou F, Bire F, Clementy J. Tachycardia-induced cardiomyopathy, unusual and reversible cause of left ventricular dysfunction: report of 9 cases. Ann Cardiol Angeiol (Paris) 2000; 49(5): 301-8.
9. Fenelon G, Wijns W, Andries E, Brugada P. Tachycardiomyopathy: mechanisms and clinical implications. Pacing Clin Electrophysiol 1996; 19(1): 95-106.
10. Khan MN, Jais P, Cummings J, Di Biase L, Sanders P, Martin DO, et al. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. N Engl J Med 2008; 359(17): 1778-85.

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