Stress as a risk factor for noncompliance with treatment regimens in patients with diabetes and hypertension

Hamidreza Roohafza(1), Ali Kabir(2), Masoumeh Sadeghi(3), Pedram Shokouh(4), Masoud Ahmadzad-Asli(5), Ali Akbar Khadem-Maboudi(6), Nizal Sarrafzadegan(7)

Abstract

BACKGROUND: We have assessed the role of stress on compliance of patients with diabetes mellitus (DM) and hypertension (HTN) with taking prescribed medications and following dietary and exercise regimens.

METHODS: A total of 9544 individuals more than 19 years of age were selected from three counties in central Iran. The presence of DM and HTN were asked from participants. We defined treatment adherence (compliance) based on agreement of individual's self-report behavior with recommendations from a physician.

RESULTS: Awareness about DM and HTN was 82.6% and 49.9%, respectively. Multivariate analysis showed that odds ratio (OR) of high to low stress level was lower than one for both “usage of medication” and “following exercise regimen” in diabetics even after adjustment for either “age and sex” or “age, sex and education”. In hypertensive patients, OR of high to low stress level was lower than one for “usage of medication” even after adjustment for either “age and sex” or “age, sex and education” and also lower than one for “following exercise regimen” only as crude index.

CONCLUSION: Cases with higher stress level had lower compliance for accepting either medication or exercise as a treatment option for their DM or HTN.

Keywords: Stress, Patient Compliance, Risk Factors, Exercise, Diabetes Mellitus, Hypertension

Date of submission: 20 Oct 2015, Date of acceptance: 12 May 2016

Introduction

The new era of disease control is obviously about chronic diseases that need long term management programs to be followed by either health systems or patients. In this dilemma, several factors play important roles to ensure effective and efficient service provision for the Management of Chronic Diseases (MCD); among them, patients’ adherence to treatment and compliance with medications are considered important factors.1,2

Adherence was defined as “the extent to which the patient follows medical instructions”3 or more extensively as “the extent to which a person’s behavior such as taking medication, following a diet, and/or following lifestyle changes, corresponds with agreed recommendations from a health care provider”.4,5 Compliance can be defined as “taking medications as prescribed”6 and has deep impact on MCD.7,8 Previous studies have reported the rate of good compliance with medication in patients with hypertension (HTN) to be between 9.6%-74%,9-12 and compliance with modifications in cardiovascular risk factors was between 39.3%-62.8%,13 and in patients with diabetes mellitus (DM) between 38%-79%.7

Many factors (including psychological factors) are proposed to affect compliance in chronic diseases such as anxiety, depression, age, race and perceived social support.14-16 The role of depression
has been studied extensively\cite{17,21} but despite the proposed role of stress and anxiety in the development and management of DM,\cite{17,22-25} little is known about the role of stress in etiology of HTN and its impact on patient's compliance with treatment. The role of anxiety and stress on factors affecting MCD especially following treatment regimens is still an issue.

The aim of this study was to assess the role of stress on the compliance of patients with DM and HTN with treatment programs such as taking prescribed medications and following dietary and exercise regimens.

### Materials and Methods

Data of this study was part of the “Isfahan Healthy Heart Program” (IHHP), a community-based program designed to prevent and control cardiovascular diseases in Iran. The main goal of IHHP was promotion of healthy nutrition and increasing physical activity and conducting stress management and tobacco control activities. The IHHP design was described in detail elsewhere.\cite{26,27}

Multistage cluster random sampling was used to stratify the study population based on living area (urban or rural) according to the national census in the last survey of the IHHP in 2007. In total, 9544 men and women over 19 years old from three counties in central Iran (Isfahan, Najafabad and Arak), were selected for this study. To achieve adequate sample size, those who declined to participate in the study were replaced by their neighbors.

The total number of participants for this study was determined according to their sex, age, and area of residence compared with the entire population. Approximately 5%-10% of households within these clusters were randomly selected for inclusion.

According to the 2006 national census, the population was 1986542 in Isfahan and 282430 in Najafabad, a county neighboring Isfahan. Arak, with a population of 615702 is located 375 km northwest of Isfahan.\cite{27,28}

Individuals who were pregnant, mental retard or physically disabled (all according to medical history by cases or their families) were excluded from the study.

After clarifying the study protocol and study process, written informed consent was obtained. Data on demographic and socioeconomic characteristics and lifestyle behaviors were recorded by a trained interviewer at baseline. We also collected some data about the presence of DM, HTN, type of medication, patient's compliance and lifestyle habits. The study protocol was reviewed and approved by the Ethics Committee of Isfahan University of Medical Sciences, Iran.

Demographic factors included age, sex, and education level (classified as 0–5 years, 6–12 years, and > 12 years).

Psychological distress was assessed by 12-item General Health Questionnaire (GHQ-12), a self-administered well established screening tool.\cite{29} This questionnaire is a consistent and reliable instrument for using in general population studies.\cite{30} The questionnaire consists of 12 items with four-point scale (less than usual, no more than usual, fairly more than usual, or much more than usual). The 0-0-1-1 method was used to score the GHQ-12 questionnaires in this study. Using this method, a participant could score between 0 and 12 points; with a score of 4 or more identified as high stress level.

After at least 12 hours fasting, all individuals were referred to the nearest health center to their home for taking a blood sample to measure their fasting blood sugar (Pars Azmon, Tehran, Iran). Before blood sampling from the veins of the antecubital region, blood pressure was measured for all participants in the sitting position twice with an interval of 5-10 minutes. Prevalence of DM and HTN, patients’ awareness of their diseases and the difference between their awareness of their disease and the actual prevalence according to physical examination and laboratory data were evaluated in this study. For calculating the exact prevalence of DM and HTN, we used either self-reports of the disease related medications or laboratory examination results since cases under treatment for these conditions (medical or non-medical) may have normal values of fasting blood glucose (FBS) or blood pressure. On the other hand, there were cases with abnormal FBS or blood pressure that were not aware of their diseases.

In this study, we defined treatment compliance based on whether patients took their medications properly and followed dietary and exercise recommendations or not. Self-reported responses to three separate questions were based on yes/no scale. “Yes” answers were considered good compliance.

The SPSS software for Windows (version 15.0, SPSS Inc., Chicago, IL, USA) was used for analyzing data. Quantitative variables were expressed as mean ± standard deviation (SD). To compare continuous variables between subjects with high and low stress level, Student’s t-test was used. Categorical variables were compared between these two groups using chi-square. Logistic regression analysis (Enter method) was used to
determine the effect of independent variables such as DM and HTN, usage of medications for these two diseases according to the physician’s advice (medical compliance), and non-medical advices such as diet and exercise (non-medical compliance) on stress level of the cases in the treatment of the DM and HTN. Age, gender and education level were considered for adjustment. Analyses of medication, diet or exercise were done in cases that were aware of their diseases. A P-value < 0.05 was considered statistically significant.

Results

Mean age of the participants was 38.7 ± 15.5 years and 4772 (50%) were male. Subjects with higher stress level were significantly older (39.5 ± 16.2 vs. 38.4 ± 15.2, P = 0.001), were more likely female (57.9% vs. 45.9%, P < 0.001) and had lower education level. The prevalence of diabetes was 404 (6.5%) and 238 (7.8%) in low and high stress individuals (P = 0.113), respectively. Also, the prevalence of hypertension was 1055 (17.1%) in low stress and 619 (19.3%) in high stress individuals (P = 0.08) (Table 1).

Table 1. Characteristics of all individual according to stress level

| Indicator               | Low stress | High stress | P     |
|-------------------------|------------|-------------|-------|
| Age (mean ± SD)         | 38.41 ± 15.19 | 39.51 ± 16.24 | 0.001 |
| Sex (Male) [n(%)]       | 3402 (54.1) | 1375 (42.1) | <0.001|
| Education (Year)        |             |             |       |
| 0-5                     | 2677 (42.6) | 1619 (49.7) |       |
| 6-12                    | 2699 (43.0) | 1278 (39.2) |       |
| > 12                    | 901 (14.4)  | 363 (11.1)  |       |
| Diabetes [n(%)]         | 404 (6.5)   | 238 (7.8)   | 0.113 |
| Hypertension [n(%)]     | 1055 (17.1) | 619 (19.3)  | 0.008 |

*Data are expressed as mean ± standard deviation (SD) for continuous variables and number (percentage) of participants for categorical variables

As table 2 shows, only 325 cases among 404 (82.6%) with low stress and 205 cases among 238 (86.1%) with high stress were aware of their DM. According to table 3, 510 (48.3%) individuals with low stress and 326 (52.7%) with high stress were aware of their HTN.

Patients with either HTN or DM in the high stress group had a significantly lower percentage of medication usage (P = 0.018 and P < 0.001, respectively) and were less likely to follow recommended exercise regimen (P = 0.039 and P = 0.032, respectively) Following dietary restrictions was not significantly different between cases with low and high stress levels (Tables 2 and 3).

Table 2. Treatment regimens of individuals who were aware of their diabetes

| Treatment | Low stress [n(%)] | High stress [n(%)] | P     |
|-----------|-------------------|--------------------|-------|
| Medication| 307 (94.6)        | 177 (86.5)         | 0.018 |
| Diet      | 222 (68.3)        | 144 (70.1)         | 0.665 |
| Exercise  | 73 (22.5)         | 36 (17.5)          | 0.039 |

Multivariate analysis showed that the odds ratio (OR) of high stress to low stress level was lower than one for both usages of medication and following exercise regimen in diabetics as crude index and even after adjustment for either age and sex or age, sex and education (Table 4). In hypertensive patients, OR of high stress to low stress level was lower than one for usage of medication as crude index and even after adjustment for either age and sex or age, sex and education and was also lower than one for following exercise regimen only as crude index (Table 4). It means lower compliance of cases with high stress level in comparison with patients with low stress level to accepting either medication or exercise as a treatment option for their DM or HTN.

Table 3. Treatment regimens of individuals who were aware of their hypertension

| Treatment | Low stress [n(%)] | High stress [n(%)] | P    |
|-----------|-------------------|--------------------|------|
| Medication| 478 (93.6)        | 279 (85.7)         | <0.001|
| Diet      | 317 (62.2)        | 213 (65.3)         | 0.088 |
| Exercise  | 130 (25.6)        | 61 (18.8)          | 0.032 |

Discussion

This study was a part of IHHP that was designed to assess the impact of community-based programs in prevention and control of cardiovascular diseases and their risk factors. Our findings showed that higher levels of stress in patients with HTN or DM had independent impact on compliance with medication and exercise, but not for dietary recommendations; the level of stress regardless of age, sex and education level had an independent effect on compliance, specially taking medication in both hypertensive and diabetic patients.

There are many sophisticated models of interaction between stress and chronic diseases such as HTN and DM, mostly emphasizing a biopsychosocial model. In this model, stress has
Table 4. Crude and adjusted odds ratio (95% confidence interval) of treatment regimens of diabetes and hypertension with stress level

| Variable                                          | Unadjusted | Adjusted (age and sex) | Adjusted (age, sex and education) |
|---------------------------------------------------|------------|------------------------|-----------------------------------|
| Prevalence of diabetes                            | 1.14 (0.97, 1.35) | 1.05 (0.88, 1.25) | 1.04 (0.88, 1.24) |
| Treatment regimens of diabetes                     |            |                        |                                   |
| Medication                                        | 0.41 (0.29, 0.87) | 0.41 (0.29, 0.88) | 0.41 (0.29, 0.90) |
| Diet                                              | 1.09 (0.74, 1.59) | 0.96 (0.65, 1.42) | 0.91 (0.61, 1.36) |
| Exercise                                          | 0.70 (0.64, 0.76) | 0.76 (0.70, 0.83) | 0.77 (0.70, 0.84) |
| Prevalence of hypertension                         | 1.16 (1.04, 1.30) | 1.09 (0.96, 1.23) | 1.09 (0.96, 1.23) |
| Treatment regimens of hypertension                 |            |                        |                                   |
| Medication                                        | 0.41 (0.35, 0.67) | 0.45 (0.37, 0.74) | 0.45 (0.37, 0.88) |
| Diet                                              | 1.10 (0.71, 1.73) | 1.12 (0.75, 1.94) | 1.13 (0.65, 1.94) |
| Exercise                                          | 0.67 (0.47, 0.97) | 0.75 (0.52, 1.09) | 0.76 (0.52, 1.11) |

biological effects such as changes in endocrine stress modulating systems including hypothalamus-pituitary-adrenal (HPA) axis. Stress has also impacts on illness behavior, on modifying risk factors and therapeutic recommendation. All of them would result in initiation and continuation of chronic diseases through a multi-factorial model.33,34 There are several reports claiming stress and other psychological factors as etiologies of DM.22,35 In our study, there was no difference in stress level between subjects with or without HTN/DM and based on our findings, we were unable to show the role of stress in the pathogenesis of HTN or DM. However, it may be involved in the management of these disorders. This contradiction could be attributed to the design of our study that only evaluated patients’ current stress level and did not consider the chronic stress state.

Interestingly, less than half of the subjects were aware of their high blood pressure; while in the case of DM about 82.6% were aware of their condition. Comparing with the previous IHHP survey that reported awareness rates of HTN and DM to be 40.3% and 54.6%, respectively,36 it seems that as the project proceeded, there was a significant increase in awareness for DM. On the other hand, awareness of HTN showed no significant change from previous phase of IHHP. This may be related to differences in subjective and cultural believes about DM and HTN as IHHP targets both conditions with similar goals,33,36 and may denote need for establishment of new strategies regarding increasing awareness of HTN. In assessment of compliance to medications, diet and exercise, we were limited to include only subjects who were aware of their disease, so we did not have access to data about possible medication/diet/exercise adherence of non-aware subjects in relation to stress level. In another IHHP report in 2007, investigators found negative impact of high stress level on diet but not on exercise and physical activity. That study enrolled all target population from the community regardless of having HTN and or DM.37 We found no relationship between stress and diet in patients with HTN and or DM, which may indicate that stress shows its effect on life style factors of chronic diseases in at risk but not diseased population. This may have implications in prevention strategies and interventions to implement programs with target to manage stress levels in at risk populations.

While there are no established etiologic pathways,16 it seems that stress and other psychological attributes play important role in compliance of patients with HTN and DM.19-21,38-40 So, they can be considered as targets for HTN and DM management and control programs.41 Addressing depression and anxiety in compliance improving programs would provide better chance to deal with management of chronic medical conditions such as DM and HTN. This effect would possibly act via several hypothetical pathways such as modification of monoamines implicated in stress and depression as well as other medical and psychological conditions that encounter disease and health, providing more adequate treatment regimens to subjects. These assumptions need to be studied deeply in further studies.

A limitation to this study is lack of information about long term stress levels in subjects and lack of differentiating stress trait and state. If such data was gathered, it might have contributed to more comprehensive understanding of the relationship between stress and HTN/DM. It is suggested to use inventories in further studies to overcome this
issue. Another limitation is that the assessment of compliance about medication was based on self-report by cases.

**Conclusion**

Management of depression and anxiety symptoms generally experienced as stress by the patient could be an efficient method in management of DM and HTN and possibly other chronic diseases. Addressing stress in clinical and community management of these chronic medical conditions would improve health status of patients via several routes such as improving compliance to medications, exercise and diet.

**Acknowledgments**

We would like to express our thanks to the Isfahan Cardiovascular Research Institute and Provincial Health Office of the Isfahan University of Medical Sciences that supported the project. The registration number of this project in this Institute was 80117.

**Conflict of Interests**

Authors have no conflict of interests.

**References**

1. World Health Organization. Noncommunicable diseases and mental health, 2008-2013 Action plan for the global strategy for the prevention and control of noncommunicable diseases. Geneva, Switzerland: WHO; 2008.
2. Talaei M, Sarrafzadegan N, Sadeghi M, Oveisgharan S, Marshall T, Thomas GN, et al. Incidence of cardiovascular diseases in an Iranian population: the Isfahan Cohort Study. Arch Iran Med 2013; 16(3): 138-44.
3. Bloom BS. Daily regimen and compliance with treatment. BMJ 2001; 323(7314): 647.
4. Burnier M, Brunner HR. Impact on clinical outcomes. Compliance in healthcare and research. Monograph series. Armonk, NY: Blackwell; 2001.
5. Sabate E. Adherence to long-term therapies: evidence for action. Geneva, Switzerland: World Health Organization; 2003.
6. Morisky DE. Adherence or compliance behavior, encyclopedia of public health [Online]. [cited 2010]; Available from: URL: http://www.encyclopedia.com/doc/1G2-340400026.html
7. Lerman I. Adherence to treatment: the key for avoiding long-term complications of diabetes. Arch Med Res 2005; 36(3): 300-6.
8. Julius RJ, Novitsky MA Jr, Dubin WR. Medication adherence: a review of the literature and implications for clinical practice. J Psychiatr Pract 2009; 15(1): 34-44.
9. Ross S, Walker A, MacLeod MJ. Patient compliance in hypertension: role of illness perceptions and treatment beliefs. J Hum Hypertens 2004; 18(9): 607-13.
10. Kabir M, Ilyasu Z, Abubakar LS, Jibril M. Compliance to medication among hypertensive patients in Murtala Mohammed Specialist Hospital, Kano, Nigeria. J Commun Med Prim Health Care 2004; 16(1): 16-20.
11. Thrall G, Lip GY, Lane D. Compliance with pharmacological therapy in hypertension: can we do better, and how? J Hum Hypertens 2004; 18(9): 595-7.
12. Tatemichi M, Hamaguchi T, Hashira M, Hayashi T, Ito M, Nakatani A, et al. Acceptability and Long-Term Compliance with Drug Treatment for Hypercholesterolemia in Japanese Male Workers: II. Long-Term Compliance with Drug Treatment. J Occup Health 2002; 44(5): 307-14.
13. Stewart A, Noakes T, Eales C, Shepard K, Becker P, Veriawa Y. Adherence to cardiovascular risk factor modification in patients with hypertension. Cardiovasc J S Afr 2005; 16(2): 102-7.
14. Gordillo V, del Amo J, Soriano V, Gonzalez-Lahoz J. Sociodemographic and psychological variables influencing adherence to antiretroviral therapy. AIDS 1999; 13(13): 1763-9.
15. Schroeder K, Fahey T, Ebrahim S, Peters TJ. Adherence to long-term therapies: recent WHO report provides some answers but poses even more questions. J Clin Epidemiol 2004; 57(1): 2-3.
16. Lehan E, McCarthy G. Medication non-adherence-exploring the conceptual mire. Int J Nurs Pract 2009; 15(1): 25-31.
17. Gonzalez JS, Delahanty LM, Safren SA, Meigs JB, Grant RW. Differentiating symptoms of depression from diabetes-specific distress: relationships with self-care in type 2 diabetes. Diabetologia 2008; 51(10): 1822-5.
18. Gonzalez JS, Peyrot M, McCar! LA, Collins EM, Serpa L, Mimiaga MJ, et al. Depression and diabetes treatment nonadherence: a meta-analysis. Diabetes Care 2008; 31(12): 2398-403.
19. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med 2000; 160(14): 2101-7.
20. Gonzalez JS, Safren SA, Cagliero E, Wexler DJ, Delahanty L, Wittenberg E, et al. Depression, self-care, and medication adherence in type 2 diabetes: relationships across the full range of symptom severity. Diabetes Care 2007; 30(9): 2222-7.
21. Nau DP, Aikens JE, Pacholski AM. Effects of gender and depression on oral medication adherence in persons with type 2 diabetes mellitus.
Gend Med 2007; 4(3): 205-13.

22. Surwit RS, Schneider MS. Role of stress in the etiology and treatment of diabetes mellitus. Psychosom Med 1993; 55(4): 380-93.

23. Fisher L, Skaff MM, Mullan JT, Arean P, Mohr D, Masharani U, et al. Clinical depression versus distress among patients with type 2 diabetes: not just a question of semantics. Diabetes Care 2007; 30(3): 542-8.

24. Thorpe JM, Kalinowski CT, Patterson ME, Sleath BL. Psychological distress as a barrier to preventive care in community-dwelling elderly in the United States. Med Care 2006; 44(2): 187-91.

25. Roohafza H, Sadeghi M, Talaei M, Pourmoghadass Z, Sarrafzadegan N. Psychological status and quality of life in relation to the metabolic syndrome: Isfahan Cohort Study. Int J Endocrinol 2012; 2012: 380902.

26. Sarrafzadegan N, Baghaei AM, Kelishadi R. First annual evaluation of Isfahan Healthy Heart Program (IHHP) [Online]. [cited 2004]; Available from: URL: http://www.ihhp.ir/ihhp/sounds/1497/First_annual_evaluation_of_IHHP.pdf

27. Sarrafzadegan N, Baghaei A, Sadri G, Kelishadi R, Malekaftenzi H, Boshtram M, et al. Isfahan healthy heart program: Evaluation of comprehensive, community-based interventions for non-communicable disease prevention. Prev Control 2006; 2(2): 73-84.

28. Sarrafzadegan N, Sadri G, Malek AH, Baghaei M, Mohammadi FN, Shahrokhkhi S, et al. Isfahan Healthy Heart Programme: a comprehensive integrated community-based programme for cardiovascular disease prevention and control. Design, methods and initial experience. Acta Cardiol 2003; 58(4): 309-20.

29. Goldberg DP, Hillier VF. A scaled version of the General Health Questionnaire. Psychol Med 1979; 9(1): 139-45.

30. Montazeri A, Harirchi AM, Shariati M, Garmaroudi G, Ebadi M, Fateh A. The 12-item General Health Questionnaire (GHQ-12): translation and validation study of the Iranian version. Health Qual Life Outcomes 2003; 1: 66.

31. Khorsavi A, Kiani Mehr G, Kelishadi R, Shirani S, Gharipour M, Tavassoli A, et al. The impact of a 6-year comprehensive community trial on the awareness, treatment and control rates of hypertension in Iran: experiences from the Isfahan healthy heart program. BMC Cardiovascular Disorders 2010; 10: 61.

32. Rabiei K, Kelishadi R, Sarrafzadegan N, Abedi HA, Alavi M, Heidari K, et al. Process evaluation of a community-based program for prevention and control of non-communicable disease in a developing country: The Isfahan Healthy Heart Program, Iran. BMC Public Health 2009; 9: 57.

33. Charney DS. Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. Am J Psychiatry 2004; 161(2): 195-216.

34. Dantzer R. Cytokine-induced sickness behavior: mechanisms and implications. Ann N Y Acad Sci 2001; 933: 222-34.

35. Talbot F, Nouwen A. A review of the relationship between depression and diabetes in adults: is there a link? Diabetes Care 2000; 23(10): 1556-62.

36. Shirani S, Kelishadi R, Sarrafzadegan N, Khorsavi A, Sadri G, Amani A, et al. Awareness, treatment and control of hypertension, dyslipidaemia and diabetes mellitus in an Iranian population: the IHHP study. East Mediterr Health J 2009; 15(6): 1455-63.

37. Roohafza H, Sadeghi M, Sarrafzadegan N, Baghaei A, Kelishadi R, Mahvash M, et al. Relation between stress and other life style factors. Stress and Health 2007; 23(1): 23-9.

38. Nabi H, Vahtera J, Singh-Manoux A, Pentti J, Oksanen T, Gimeno D, et al. Do psychological attributes matter for adherence to antihypertensive medication? The Finnish Public Sector Cohort Study. J Hypertens 2008; 26(11): 2236-43.

39. Hashmi SK, Afridi MB, Abbas K, Sajwani RA, Saleheen D, Frossard PM, et al. Factors associated with adherence to anti-hypertensive treatment in Pakistan. PLoS One 2007; 2(3): e280.

40. Luyster FS, Hughes JW, Gunstad J. Depression and anxiety symptoms are associated with reduced dietary adherence in heart failure patients treated with an implantable cardioverter defibrillator. J Cardiovasc Nurs 2009; 24(1): 10-7.

41. Bogner HR, de Vries HF. Integration of depression and hypertension treatment: a pilot, randomized controlled trial. Ann Fam Med 2008; 6(4): 295-301.

How to cite this article: Roohafza H, Kabir A, Sadeghi M, Shokouh P, Ahmadzad-Asl M, Khadem-Maboudi AA, et al. Stress as a risk factor for noncompliance with treatment regimens in patients with diabetes and hypertension. ARYA Atheroscler 2016; 12(4): 166-71.