Is prehypertension a risk factors for cardiovascular diseases among Iranian women?

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Background: Numerous studies have reported *prehypertension* (pre-HTN) as a risk factor for the cardiovascular diseases as hypertension (HTN). **Aim**: The present study aimed to evaluate the effects of pre-HTN on cardiovascular incidences among the females of Isfahan cohort study (ICS). **Materials and Methods:** Healthy female at baseline were followed for a median of 6.7 years. They were divided into 3 groups of normal blood pressure, pre-HTN (120/80 < BP < 139/89 mmHg) and HTN (BP > 140/90 mmHg) based on their baseline measurements. The endpoints were ischemic heart disease (IHD), stroke, CVD (combination of IHD and stroke) and mortality. **Results:** Normal BP, pre-HTN and HTN were observed in 1073 (33%), 1185 (36%), and 994 (31%) participants, respectively. One hundred and ninety-eight subjects developed CVDs and 110 died. In the HTN group, the hazard ratio [HRs (95% confidence interval)] adjusted for age and other risk factors were 3.44 (1.95-6.09) for IHD (*P* value < 0.001), 1.28 (0.59-2.77) for stroke (*P* value = 0.536) 4.89 (1.37-17.45) for CVD mortality (*P* value < 0.001) and 1.70 (0.98-2.96) for all cause mortality (*P* value = 0.060). Although, pre-HTN significantly increased the risk of IHD incidence in the crude model (HR 2.21, 95% CI 1.23-3.97) and after adjustments for age (HR 1.85, 95% CI 1.02-3.33), (*P* value < 0.001) the association did not remain statistically significant after including other risk factors in the model. **Conclusion:** Hypertension (HTN) to be a strong risk factor for CVD and IHD. However, in contrast to previous researches, pre-HTN was not found to be a risk factor for CVD, IHD or death independent to other risk factors in women.

Key words: Cardiovascular disease, cohort study, coronary artery disease, hypertension, mortality, prehypertension

INTRODUCTION

Hypertension (HTN) is a big concern in today's world. With 26% of the adult world population having HTN, a number that is predicted to be 1.56 billion by 2025,^[1] it is indicated as the fourth reason for premature death in developed countries.^[1] Hypertension (HTN) is a major cause of death, cardiovascular disease and cerebrovascular diseases.^[2] Recent studies revealed that even having a blood pressure (BP) higher than 115/75 mmHg in adults can increase CVD (cardiovascular disease) risk, i.e., a 10 mmHg increment in diastolic pressure, or a 20 mmHg in systolic pressure can double the chance of ischemic heart disease (IHD) and stroke.^[3] Thus, in 2003, Joint National Committee defined the term "prehypertension" (pre-HTN) in its seventh guideline (JNC-7) as a condition with systolic BP between 120 and 139 mmHg, or a diastolic BP

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between 80 to 89 mmHg in two measurements.^[3] Since this term was coined, people who had been considered as normotensive having BP just above the optimal level were then known as suffering pre-HTN. Based on the previous studies, HTN is more likely to occur in patients with pre-HTN^[4] and prehypertensive patients have also a higher risk of getting CVDs and being more frequently hospitalized due to these problems.^[5,6] Prospective studies have shown the BP within the normal range as a risk reducing factor for CVDs.^[7]

Iran is no exception. A meta-analysis conducted on HTN prevalence in Iran reported the average prevalence rate to be 12.5%, being more prevalent in women and lower average BP was observed in men.^[8] 52.1% of Iranian adults were reported to have pre-HTN.^[9] Since, no prospective study has been performed to examine associations between CVD incidence and different levels of BP in the country, the present study was carried out on women participating in Isfahan cohort study (ICS) to investigate the links between CVD occurrence and HTN and pre-HTN.

MATERIALS AND METHODS

This study was conducted to determine the effects of hypertension on CVD occurrence in female

Address for correspondence: Dr. Masoumeh Sadeghi, Cardiac Rehabilitation Research Center, Isfahan Cardiovascular Research Institute, Khorram Ave, Isfahan, Isfahan, Iran. PO BOX: 81465-1148, E-mail: sadeghimasoumeh@gmail.com Received: 15-10-2011; Revised: 23-08-2012; Accepted: 06-09-2012 participants of Isfahan cohort study (ICS) during a 7-year follow-up period. Isfahan cohort study (ICS) was a longitudinal 10-year study on 6,504 individuals aging over 35 years. All the studied individuals were evaluated in the first phase of Isfahan healthy heart program (IHHP) in 2001.^[10] The first phase of IHHP was a community-based cross-sectional study performed in Isfahan, Najaf Abad and Arak (all in central Iran). Multistage random sampling was used to select subjects from all rural and urban areas of the mentioned cities. In order to collect data, questioners referred to the houses of participants and filled a questionnaire including knowledge, attitude and performance toward lifestyle factors (diet, physical activity, smoking, and stress) and CVD (causes, risk factors, symptoms and complications). The questionnaire also included history of CVDs, hypertension, diabetes mellitus, and hyperlipidemia, as well as related medications. All subjects were invited to IHHP-affiliated clinics to be examined. Their blood pressure, height, weight, and hip and waist circumferences were measured at the clinics. More details were described elsewhere.^[11] Participants aging over 35 years were included in ICS and followed by biennial phone calls or visits. In 2003, 2005-2006 and 2007, 954 (14.6%), 430 (6.6%) and 286 (4.3%) individuals were lost to follow-up, respectively, mainly due to changed addresses or phone numbers.

The present study was conducted on 3,251 female ICS participants who were followed until the third phase (2007). Demographics, lifestyle-related information (physical activity and smoking), body mass index (BMI), blood pressure and history of diabetes mellitus and hypercholesterolemia were determined according to baseline data. A global dietary index (GDI) of diet quality was calculated, representing the average of the mean of twenty-nine frequency questions in seven categories. A smaller GDI indicates better behavior.^[12] Subjects were considered to be "current smokers" if they reported smoking, at least one cigarette a day during the past year. ^[13] Total daily physical activity (TDPA) was assessed in MET (metabolic equivalent) per day, by considering 3 types of physical activity: transport, leisure time and working at home.^[14] Participants were divided into three groups of normal blood pressure (NBP, BP < 120/80 mmHg), pre-HTN (120/80 < BP < 139/89 mmHg) and HTN $(BP > 140/90 \text{ mmHg}).^{[3]}$

Endpoints were IHD, stroke, CVD and all cause mortality. CVD was defined as combination of IHD and stroke. IHD included myocardial infarction, unstable angina pectoris (UAP) and sudden cardiac death. Myocardial infarction was diagnosed based on the World Health Organization (WHO) expert committee criteria. Therefore, individuals were diagnosed with acute myocardial infarction (AMI), if they had a typical chest pain for over 30 min, an ST elevation > 0.1 mV in, at least two electrocardiography leads, and increased levels of cardiac biomarkers such as creatine kinase (CK) and CK-MB. UAP was confirmed in case of typical chest discomfort which lasted for a minimum of 20 min and caused the patient to refer to a hospital within 24 h, a change in typical chest pain with a crescendo pattern resulting in a severe frank pain, or ischemia-related ST and T changes in at least two electrocardiography leads. Sudden cardiac death was defined as death within 1 h of symptoms onset, a witnessed cardiac arrest or abrupt collapse not preceded by more than 1h of symptoms. According to the definition by the WHO, stroke was considered as a rapid onset of focal neurological symptoms with a probable vascular origin during 24hrs. Subjects with IHD or stroke were regarded as CVD patients.

During the follow-up period, the records of hospitalization or death certificates were evaluated by a physician in order to provide relevant documents for panel of specialists. A verbal autopsy with a family member of the deceased patient was also conducted in case of out of hospital death. All diagnoses were approved by a panel consisting of 3 cardiologists and a neurologist.

SPSS for Windows (version 15; SPSS Inc., Chicago, IL., USA) was used for data analyses. Analysis of variance (ANOVA) and chi-square test were used to compare baseline data between the 3 groups. Follow-up period for each individual was considered from the beginning of the study until the last phone call or occurrence of any of the endpoints. Cox regression analysis was employed in order to determine the hazard ratio (HR) of HTN and pre-HTN on each endpoint, as well as 95% confidence interval (95% CI). The effects were once evaluated in a crude model. Afterwards, HR was calculated by adjusting demographics (age and education level), lifestyle (physical education and smoking), obesity, and diabetes and hypercholesterolemia.

RESULTS

This study examined the data of 3,255 women of which 1,073 (33%) had normal blood pressure, 1,185 (36%) were categorized as pre-HTN, and 997 (31%) were diagnosed with HTN at baseline. Table 1 shows demographics and risk factor profile of 3 groups. Post hoc ANOVA test confirmed significant differences in pairwise comparisons. In the normal group, the average age was significantly lower and the education level was significantly higher than the other 2 groups. CVD risk factors including low total daily physical activity (TDPA), body mass index (BMI), diabetes mellitus and hypercholesterolemia were significantly lower in those

with normal blood pressure. Although, the smoking rate in the normal group was lower than the HTN group, the difference was not significant.

The median follow-up period was 6.75 years during which 198 CVD events and 110 deaths were observed. Table 2 summarizes CVD and death incidences in each group. All incidences were lower in individuals with normal blood pressure. A total number of 35 CVD mortality cases were reported during the follow-up period with 3, 5, and 27 subjects in NBP, pre-HTN, and HTN groups, respectively.

Table 3 shows in the risk pertaining to pre-HTN and HTN for CVD events and all cause mortality based on 3 models. While HTN considerably increased CVD risk even in full adjusted model, it only increased risk of all cause mortality in the crude model. On the other hand, HTN had a significant and strong effect on CVD mortality (HR 10.08, 95% CI 3.06-33.22) in the crude model but the strength of association decreased (HR 4.89 95% CI 1.37-17.45) after adjustment for age and other risk factors.

Pre-HTN significantly increased IHD risk in the crude model and after adjustment for age. However, after including other risk factors, it was not found to have any significant effects on IHD incidence. In addition, pre-HTN did not show a significant association with stroke, CVD events and death.

DISCUSSION

There was a worsening trend of CVD risk factors from NBP group to subjects with pre-HTN and finally HTN. Smoking was an exception. The worsening pattern could be in part due to increasing pattern of age among these groups. IHD, CVD and all cause mortality incidence rates also showed an increasing pattern among NBP, pre-HTN and HTN groups, respectively. However, stroke incidence in pre-HTN group was less than both normotensives and hypertensives. Independent to age and other risk factors, HTN was found to be a strong risk factor for IHD, but the association with stroke did not remain significant after age adjustment. Pre-HTN increased IHD risk more than 2 times and the association remained significant after age adjustment, but not after considering other risk factors.

HTN has been proved as an independent risk factor for IHD and CVD.^[15-18] The 36-year follow-up period in the framingham study indicated HTN as the most important and strongest factors affecting CVD, IHD and death incidences.^[19] Lawes *et al.*, evaluated the global burden of blood pressure and reported 7.6 million premature deaths (about 13.5% of all deaths) to be caused by HTN. They also suggested 47% of IHD cases to be resulted from HTN.^[20] Likewise, previously published results of ICS revealed HTN as a leading risk factor for CVD.^[11] Similarly, the

| | NBP (%) | Pre-HTN (%) | HTN (%) | P-value |
|----------------------|-------------|-------------|-------------|---------|
| n (%) | 1073 (33%) | 1185 (36%) | 997 (31%) | |
| Age (years) | 43.3±9.07 | 49.6±10.70 | 56.6±11.36 | < 0.001 |
| Education | | | | < 0.001 |
| primary school | 791 (74%) | 948 (80%) | 877 (88%) | |
| middle school | 246 (23%) | 202 (17%) | 104 (11%) | |
| above diploma | 35 (3%) | 34 (3%) | 14 (1%) | |
| TDPA (MET-min/day) | 698.1±410.3 | 652.6±413.6 | 602.2±440.1 | < 0.001 |
| BMI (Kg/m²) | 26.6±4.54 | 27.9±4.6 | 28.6±4.7 | < 0.001 |
| Diabetes | 69 (6%) | 116 (10%) | 168 (17%) | < 0.001 |
| Hypercholesterolemia | 579 (54%) | 749 (63%) | 756 (76%) | < 0.001 |
| Current smoking | 22 (2%) | 28 (2%) | 24 (2%) | 0.832 |
| GDI | 1.01±0.24 | 0.97±0.26 | 0.89±0.28 | < 0.001 |
| Menopause | 243 (23%) | 460 (39%) | 65 (65%) | < 0.001 |

NBP=Normal blood pressure; pre-HTN=Prehypertension; HTN=Hypertension; TDPA=Total daily physical activity; BMI=Body mass index; GDI=Global dietary index

| Incidence rate | Total | NBP | Pre-HTN | HTN | P-value |
|-----------------------|-------------------|------------------|------------------|--------------------|---------|
| N | 150 | 16 | 38 | 96 | |
| IHD | 880 (750-1032) | 280 (171-457) | 619 (451-851) | 1848 (1513-2257) | < 0.001 |
| Ν | 48 | 13 | 8 | 27 | |
| Stroke | 279 (211-371) | 227 (132-392) | 129 (65-259) | 512 (351-746) | < 0.001 |
| n | 198 | 29 | 46 | 123 | |
| CVD | 1168 (1016-1343) | 509 (354-733) | 752 (563-1004) | 2395 (2007-2859) | < 0.001 |
| n All cause mortality | 110 637 (528-768) | 20 348 (225-540) | 26 420 (286-616) | 64 1200 (939-1533) | < 0.001 |

NBP=Normal blood pressure; pre-HTN=Prehypertension; HTN=Hypertension; IHD=Ischemic heart disease; CVD=Cardiovascular disease (the combination of stroke and IHD)

| | Pre-HTN | P-value | HTN | P-value |
|-----------------------|-------------------|---------|-------------------|---------|
| IHD | | | | |
| Crude model | 2.21 (1.23-3.97) | 0.008 | 6.78 (3.99-11.53) | < 0.001 |
| Age adjusted model | 1.85 (1.02-3.33) | 0.042 | 4.19 (2.40-7.32) | < 0.001 |
| Fully adjusted model* | 1.62 (0.89-2.94) | 0.115 | 3.44 (1.95-6.09) | < 0.001 |
| Stroke | | | | |
| Crude model | 0.56 (0.23-1.36) | 0.202 | 2.24 (1.15-4.33) | 0.017 |
| Age adjusted model | 0.50 (0.20-1.22) | 0.127 | 1.68 (0.81-3.46) | 0.163 |
| Fully adjusted model* | 0.43 (0.17-1.07) | 0.069 | 1.28 (0.59-2.77) | 0.536 |
| CVD | | | | |
| Crude model | 1.47 (0.92-2.34) | 0.103 | 4.82 (3.21-7.22) | < 0.001 |
| Age adjusted model | 1.24 (0.78-1.99) | 0.366 | 3.11 (2.02-4.79) | < 0.001 |
| Fully adjusted model* | 1.11 (0.68-1.79) | 0.680 | 2.57 (1.64-4.02) | < 0.001 |
| All cause mortality | | | | |
| Crude model | 1.20 (0.671-2.15) | 0.537 | 3.66 (2.21-6.07) | < 0.001 |
| Age adjusted model | 0.78 (0.43-1.42) | 0.421 | 1.34 (0.78-2.29) | 0.283 |
| Fully adjusted model* | 0.86 (0.47-1.56) | 0.618 | 1.70 (0.98-2.96) | 0.060 |

*The model was adjusted for age, diabetes, total cholesterol, body mass index, smoking and menopause; Pre-HTN: Prehypertension, HTN: Hypertension, IHD: Ischemic heart disease, CVD: Cardiovascular disease (the combination of stroke and IHD)

present study showed HTN as a strong risk factor for IHD independent of age and other risk factors among women older than 35 years of age. In the case of stroke, the significant effect turned insignificant after the adjustment for age and other risk factors. HTN was found to insignificantly increase risk of death when adjusted for age, however, including other risk factors resulted in marginal significant association. Longer periods of follow-up and thus higher numbers of events may cause trustworthy statistical significant levels in terms of stroke and all cause mortality.

Pre-HTN was also suggested as another risk factor for CVD, IHD and death. Vasan et al., in the framingham cohort study, initially classified 6,859 participants into 3 BP groups including optimal (BP < 120/80 mmHg); normal (BP 120-129/80-89 mmHg) and high normal (BP 130-139/85-89 mmHg). They reported CVD to occur in 4% of 35 to 64 year-old women with high normal BP. The rate increased to 18% in elderly women. Risk factors adjusted HR of high normal BP for CVD incidence among females was found to be 2.5 (1.6-4.1) in their study.^[6] However, we used a different blood pressure categorization, i.e., we grouped together all subjects with systolic blood pressure between 120 and 140 mmHg or diastolic blood pressure between 80 and 90 mmHg. Therefore, individuals with high normal blood pressure in the previously mentioned study had actually higher blood pressure which might have resulted in the stronger association observed.

In another cohort study, Kukubo *et al.*, followed 5,494 Japanese individuals aging 30-70 years divided subjects into 5 groups of BP. While the first group had optimal blood pressure, the fifth group had a systolic blood pressure higher than 160 mmHg or a diastolic blood pressure over 100 mmHg. The results suggested an increment in blood pressure to be associated with raised myocardial infarction and stroke occurrences. They also indicated the fifth group as having the highest HR in myocardial infarction and stroke incidences. Compared to subjects with optimal blood pressure, individuals with normal or high normal blood pressure were more than twice at risk of CVD in multivariate models.^[21] However, we only found HTN to have such an effect.

In 18-year cohort study conducted by Liska et al., on 25-74 year-old subjects from the National Health and Nutrition Examination Survey (NHANES I) also showed that an increase in blood pressure to a level higher than optimal led to an augmentation in myocardial infarction, congestive heart failure and stroke incidences. They evaluated the individuals in 3 groups similar to our study and found HR for CVD occurrence to be 1.32 (1.05-1.65) among the pre-HTN group after adjustment for other risk factors. They also divided people with pre-HTN into two groups of low pre-HTN (BP 120-129/80-84 mmHg) and high pre-HTN (BP 130-139/85-89 mmHg) and reported HTN to have a significant effect on CVD occurrence only in the latter group. The highest frequency of CVD was observed in subjects with a blood pressure of 140/90 mmHg.^[22] Dividing the individuals with pre-HTN into 2 groups could have resulted in significant relations between high normal BP and CVD or IHD in the present study.

Hsia *et al.*, followed 60,785 postmenopausal women for 7.7 years and determined pre-HTN as a risk factor for CVDs. The HR obtained in their study for all cardiovascular incidences was 1.66, with the highest HR corresponding to the relation between pre-HTN and stroke.^[23] In terms of stroke, the association was absent in current study.

However, we found pre-HTN to significantly increase IHD risk, but the relation did not remain significant after adjustment for other risk factors. Menopause may be responsible for the differences between the 2 studies.

Overall, in line with previous studies, we found HTN to be a strong risk factor for CVD and IHD. In contrast, pre-HTN was not an independent risk factor for either disease. However, lengthening follow-up period might reveal the significant effects of pre-HTN. In addition, Iranians may differ from previously studied populations in terms of racial and genetic characteristics. As numerous studies have suggested racial differences as effective on CVD and CVD-related deaths,^[24-26] future race-adjusted research may better determine the risk factors among Iranians. On the other hand, a similar study on men might result in different findings. It is an important subject for future attempt.

CONCLUSION

The present study showed HTN to be a strong risk factor for CVD and IHD. However, in contrast to previous researches, pre-HTN was not found to be a risk factor for CVD, IHD or death independent to other risk factors in women.

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