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Longitudinal Study of Blood Pressure during 8 Years; Patterns and Correlates: Yazd Healthy Heart Project

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Abstract

Introduction: Hypertension (HT) is a prevalent contributor to cardiovascular diseases. To evaluate the incidence of HT and its relationship with other cardio metabolic risk factors changes and lifestyle components, Healthy Heart Project follow up data for 8 years were analyzed.

Methods: A total of 283 unique normotensive participants of Yazd Healthy Heart Project (1169 observations) attended blood pressure longitudinal study. Multi-level model and Generalized estimation equation (GEE) model with an unstructured correlation matrix were used to analyze the longitudinal data by Stata/MP 11.2.

Results: The incidence rates of HT and prehypertension were 39.5 and 77.93 in each 1000 person-year follow-up, respectively. In addition, systolic blood pressure was significantly predicted by diastolic blood pressure (B=1.09, 95% CI=0.99-1.19, P<0.0001), uric acid (B=1.04, P=0.003), and waist circumference (B=0.131, P=0.033). Moreover, GEE model with logit link function showed that hypertension was significantly predicted by triglyceride (OR=1.003, P=0.044), cholesterol (OR=0.97, P=0.004), LDL-cholesterol (OR=1.02, P=0.003), uric acid (OR=1.19, P=0.023), body mass index (OR=1.09, P=0.028), and also significantly predicted by obesity (B=1.85, P=0.007), abdominal obesity (B=1.85, P=0.007), age (B=1.47, P=0.017), and diabetes mellitus (B=2.14, P=0.003).

Conclusion: The study results showed that the incidence rate of HT was high in Yazd and the major predictors of systolic blood pressure were abdominal obesity and diastolic blood pressure. Besides, diastolic blood pressure was significantly determined by systolic blood pressure and general obesity. Moreover, both systolic and diastolic blood pressures were independently predicted by serum uric acid level.

Keywords: Longitudinal; Hypertension; Systolic blood pressure; Diastolic blood pressure; Yazd; Predictors

Background

Hypertension is a prevalent contributor to cardiovascular diseases. It is now a major public health problem affecting 1 billion individuals worldwide [1-3].

One single blood pressure (BP) measurement has a predictive value for future blood pressures given that many individuals remain normotensive. Medical Research Council (MRC) trial showed that 12-15% of the patients with diastolic blood pressure of at least 90 mmHg developed HT within 3-5 years [4,5]. The age- and sex-adjusted incidence rate of HT varies in different populations. For instance, it has been reported as 12.75 per 1000 person-years adults in Chinese population and 25.5 per 1000 person-years among Canadians. Researchers have predicted a 24% increase in the prevalence of hypertension in developed countries from 2000-2025 [6,7].

In general, baseline age, high income levels, prehypertension, overweight, obesity, family history of hypertension, and low physical activity have been mentioned as the independent predictors of incident hypertension [7].

Investigators reported that age-related increases in BP are not exclusively increases with age rising and some other factors may be responsible [2].

Longitudinal studies can detect individual development of hypertension over time, the relationship between different variables and incident hypertension and longitudinal blood pressure changes [4].

The knowledge of blood pressure tracking may be useful for delaying age related increases in BP and development of systolic hypertension in older individuals [2]. To evaluate the pattern of blood pressure tracking and its relationship with changes in other cardio metabolic risk factors and lifestyle, we analyzed Healthy Heart Project follow-up data during 8 years.

Methods

Study sample

Phase I of Healthy Heart Project included assessment of the prevalence of cardiovascular diseases (CVD) risk factors in Yazd urban population, a city in center of Iran, in 2005.

The participants of this project were enrolled in a cohort study and underwent annual examination of CVD risk factors. Afterwards, 283 unique normotensive participants (1169 observations) attended blood pressure longitudinal study. Yet, 9 participants died from March 2005 up to October 2013 (n=7 dead due to cardiovascular causes). The study protocols for all the examinations were approved by the Institutional Review Board of Shahid Sadooghi University of Medical sciences. Besides, written informed consents were obtained from all the attendees at each examination.

Clinical assessment

Blood pressure was assessed at each examination using mercury sphygmomanometer based on the standardized protocol [8]. Accordingly, the first and five Kortokof sounds were considered as systolic and diastolic blood pressure, respectively and the means of the two measurements in each visit were recorded. In addition, pulse pressure was calculated as SBP-DPB and Mean Arterial Pressure (MAP) was calculated as DBP+(1/3 PP) or 2DBP+ABP. In case the two measurements were different by more than 20 mmHg, the third measurement was performed. Hypertension was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or taking antihy-pertensive therapy. Besides, diabetes mellitus was defined as fasting blood glucose ≥ 126 mg/dL or use of hypoglycemic medications. Moreover, hyper-cholesterolemia was defined as serum cholesterol ≥ 200 mg/dl and hyper-triglyceridemia was defined as serum triglyceride ≥ 150 mg/dl or use of lipid lowering medications.

Statistical analysis

The longitudinal design measures more than two times at multiple level: at individuals (between subject) and at different times (within subject). In this study, multilevel model was used to analyze the data. In general, multilevel models are used to evaluate the effect of clinical covariates on the pattern of blood pressure changes. Multilevel models can include and analyze maximal number of observations in a longitudinal study.

We used generalized estimation equation (GEE) model with an unstructured correlation matrix. Random intercept and random effects of age were used to reflect different starts and different slopes of each blood pressure for each participant. Then, a pre-specified model was fitted based on biologically plausible clinical and paraclinical covariate and blood pressure.

Blood pressure and its pathophysiological predictors were measured at unequal times (1, 2, 3, 4, 5, and 8 years after phase I of Yazd Healthy Heart Project). All the analyses were performed using Stata/MP, version 11.2 and 2-tailed P-value <0.05 was considered as statistically significant.

Results

The baseline and final measurements of the study sample have been shown in Tables 1 and 2. Measurements of BP and other metabolic measures were collected from a total of 1169 observations over 8 years of follow-up. The results indicated that most of the cardiometabolic factors were more prevalent at the end of the study compared to the first measurement.

	Number	Percent	S.E
Sex (male)	170	60.1	0.026

Impaired Fasting Glucose	5	1.8	0.007
Impaired glucose tolerance test	33	11.7	0.019
Diabetes mellitus	31	11	0.018
Cholesterol >240 mg/dl	42	14.8	0.021
Cholesterol >200 mg/dl	123	43.5	0.029
Triglyceride >150 mg/dl	135	47.7	0.029
Cholesterol/HDL >4	58	18.7	0.027
LDL Cholesterol >160	25	8.9	0.017
HDL Cholesterol >40 in men-LDL Cholesterol <50 in women	83	29.3	0.029
BMI >30	37	13.2	0.02
Waist >88cm in women, >102cm in men	73	25.8	0.026
25< BMI <30	116	41	0.029
Metabolic Syndrome	68	24	0.025
Hyperuricemia (75% percentile)	56	19.8	0.023
Smoking	34	12	0.019
Passive smoking	39	13.8	0.02
Typical Angina Pectoris rose score ≥ 3)	39	13.8	0.027

Table 1: The demographic and clinical characteristics of participants in baseline measurement.

Baseline characteristics based on sex						
	Last measurement			First measurement		
	P value	Women (113)	Men (170)	P value	Women (113)	Men (170)
Impaired fasting glucose	0.18	23.3	30	0.66	1.8	1.8
Impaired glucose tolerance test	0.02	7.9	1*	0.55	11.5	11.8
Diabetes mellitus	0.37	20.7	29.11	0.13	8	12.9
Cholesterol>240 mg/dl	0.33	19.3	16.1	0.53	15	14.7
Cholesterol >200 mg/dl	0.37	44.3	47.6	0.18	39.8	45.9
Triglyceride >150 mg/dl	0.31	43.2	47.6	0.2	44.3	50
Cholesterol/HDL >5	0.11	34.4	65.6	0.2	15.9	20.6
LDL-cholesterol >160 mg/dl	0.38	18.3	15.7	0.28	7.3	10
HDL Cholesterol >40 in men-LDL	0.0001	60.2	37.9	0.0001	45.6	18.8

Cholesterol <50 in women						
(BMI >30)	0.011	29.3	15.5	0.02	18.8	9.5
(Waist) >88 cm in women, >102 cm in men	0.001	69	45.3	0.001	36.3	18.8
25< BMI <30	0.42	46.7	41.1	0.1	46	37.6
Hyperuricemia (75% percentile)	0.44	27.7	2s5.8	0.39	18.6	20.6
Smoking	0.19	15.6	21.1	0.06	8	14.7
Passive smoking	NA	NA	NA	0.53	14.2	13.5
Typical Angina Pectoris rose score ≥3)	0.43	17.6	19.5	0.09	37.2	28.8

Table 2: First and final measurement of cardiometabolic factors.

Also, the results of Cochran's Q test showed that the prevalence of hypertension significantly increased during 8 years (Cochran's Q=27.67, P<0.0001).

The incidence rates of hypertension and prehypertension were 39.5 in each 1000 person-year (95% CI=31.76-47) and 77.93 in 1000 person-year (95% CI=63.43-92.43), respectively. Additionally, the mean age at onset of pre-hypertension was 50.5+2.1 in males and 50.4+2.1 in females, while that at the onset of hypertension was 55.7+1.6 in males and 55.9+1.6 in females.

The analysis of the data as a longitudinal study and the cluster data by GEE model showed that diastolic blood pressure (B=1.09, 95%CI=0.99-1.19, P<0.0001), uric acid (B=1.04, 95% CI=0.362-1.72, P=0.003), and waist circumference (B=0.131, 95% CI= 0.01-0.25, P=0.033) significantly predicted the increase in systolic blood pressure during 8 years. In addition, blood pressure changes were mostly predicted by sex, HDL cholesterol, and fasting blood glucose (P>0.05) (Table 3).

SBP	Coef.	Std. Err.	z	P>|z|	95% confidence	Interval
Sex	1.96	1.06	1.84	0.07	-0.12	4.04
Age	0.1	0.06	1.63	0.1	-0.02	0.21
Diastolic Blood Pressure	1.09	0.05	21.71	0	0.99	1.19
Fasting Blood Sugar	0.02	0.02	1.36	0.17	-0.01	0.05
Teriglyceride	0	0.01	-0.08	0.94	-0.01	0.01
Choesterol	0.01	0.01	0.7	0.49	-0.02	0.04
LDL-Cholesterol	0	0.01	-0.05	0.96	-0.01	0.01
HDL-Cholesterol	-0.06	0.04	-1.7	0.09	-0.13	0.01
Uric Acid	1.04	0.35	3	0	0.36	1.72
waist	0.13	0.06	2.14	0.03	0.01	0.25
Body Mass Index	-0.23	0.18	-1.28	0.2	-0.59	0.13
Time	-2.36	0.56	-4.18	0	-3.47	-1.25
Time*age	0.05	0.01	4.23	0	0.02	0.07
_cons	17.82	5.9	3.02	0	6.25	29.38

Table 3: Systolic blood pressure prediction by GEE population-averaged model.

Table 4 depicts the diastolic blood pressure predictors by GEE model with identity link function.

Diastolic Blood Pressure	Coef.	Std. Err.	z	P>|z|	[95% Conf.]	[Interval]
Systolic blood pressure	0.437	0.019	22.45	0	0.399	0.476
sex	-0.954	0.593	-1.61	0.107	-2.116	0.207
age	0.012	0.037	0.33	0.741	-0.061	0.085
waist	0.057	0.026	2.19	0.029	0.006	0.108
Uric Acid	-0.089	0.212	-0.42	0.676	-0.504	0.327
Teriglyceride	0.003	0.003	0.74	0.459	-0.004	0.009
LDL-cholesterol	-0.001	0.004	-0.34	0.737	-0.01	0.007
HDL-cholesterol	0.04	0.022	1.84	0.066	-0.003	0.082
Fasting blood glucose	-0.003	0.01	-0.32	0.746	-0.023	0.016
time	0.938	0.384	2.44	0.014	0.186	1.69
Time age interaction	-0.024	0.007	-3.35	0.001	-0.039	-0.01
_cons	20.932	3.414	6.13	0	14.241	27.623

Table 4: Diastolic blood pressure prediction by GEE population-averaged model.

The GEE model with logit link function revealed that hypertension was significantly predicted by triglyceride (OR=1.003, 95% CI=1.0001-1.006, P=0.044), cholesterol (OR= 0.97, 95% CI=0.96-0.99, P=0.004), LDL-cholesterol (OR=1.02, 95% CI=1.007-1.03, P=0.003), uric acid (OR=1.19, 95% CI=1.02-1.39, P=0.023), body mass index (OR=1.09, 95% CI=1.02-1.17, P=0.028), and also significantly predicted by obesity (B=1.85, 95% CI=1.18-2.88, P=0.007), abdominal obesity (B=1.85, 95% CI=1.18-2.88, P=0.007), age (B=1.47, 95% CI=1.07-2.02, P=0.017), diabetes mellitus (B=2.14, 95% CI=1.3-3.25, P=0.003) (Table 5).

Hypertension	Odds Ratio	Std. Err.	z	P>|z|	95% Conf.	Interval
sex	0.69	0.16	-1.62	0.1	0.45	1.08

Age	1.01	0.01	0.45	0.65	0.98	1.03
Fasting Blood Sugar	1	0	1.21	0.23	1	1.01
Triglyceride	1	0	2.01	0.04	1	1.01
Cholesterol	0.98	0.01	-2.87	0	0.96	0.99
LDL-Cholesterol	1.02	0.01	2.95	0	1.01	1.04
HDL-Cholesterol	1.02	0.01	1.64	0.1	1	1.03
Uric Acid	1.2	0.09	2.28	0.02	1.03	1.4
waist	1.02	0.01	1.5	0.14	0.99	1.05
Body Mass Index	1.09	0.04	2.2	0.03	1.01	1.18
Time	0.81	0.1	-1.73	0.08	0.64	1.03
Time*age	1	0	0.87	0.39	1	1.01

Table 5: Hypertension prediction by GEE population-averaged model.

Furthermore, generalized linear mixed model by Stata/MP 11.2 showed that systolic blood pressure was predicted by diastolic blood pressure (B=1.11 95% CI=1.007-1.2 P<0.0001), uric acid (B=0.88 95% CI=0.24-1.5 P<0.007), waist circumference (B=0.26 95% CI=0.13-0.38 P<0.0001), and time (B=0.31 95% CI=0.016-0.61 P=0.03) during 8 years.

Discussion

This study was a prospective analysis of Yazd Healthy Heart Project data. According to the results, the incidence rate of hypertension in our population was 39.5 in each 1000 person-year (95% CI=31.76-47) and that of prehypertension was 77.93 in 1000 person-years (95% CI=63.43-92.43). In addition, the mean age at the onset of prehypertension was 50.5 ± 2.1 in males and 50.4 ± 2.1 in females, while that at the onset of prehypertension was 55.7 ± 1.6 in males and 55.9 ± 1.6 in females. Namayandeh et al. showed that the prevalence of hypertension was 25.6% in Yazd (23.3% among females and 27.5% among males (P<0.001) [9].

World Health Organization (WHO) has predicted that the prevalence rate of hypertension will increase by 24% in developed countries from 2000-2025. Karen et al. reported that the age and sex-adjusted incidence rate of hypertension increased from 25.5 per 1000 adults in 1997 to 32.1 per 1000 in 2004, showing a relative increase of 25.7% (P<0.001) that could be attributed to obesity and sedentary lifestyle.

The age- and sex-adjusted prevalence rate of hypertension has increased by about 60.0% (from 153.1 per 1000 adults in 1995 to 244.8 per 1000 in 2005, P<0.001) [6]. Sun et al. [7] evaluated the incidence of hypertension in China. After age adjustment, the incidence rate of hypertension was 12.75 per 100 person-years (95% CI, 12.74-13.14) in males and 10.04 per 100 person-years (95% CI, 9.69-10.41) in females. In normotensives, the incidence rate of hypertension was 11.08 per 100 person-years (95% CI, 10.33-11.86) in males and 7.90 per 100 person-years (95% CI, 7.38-8.45) in females. Besides, the incidence rate of hypertension among the participants with prehypertension was 13.24 per 100 person-years (95% CI, 12.79-13.69) in males and 11.22 per 100 person-years (95% CI, 10.77-11.69) in females [7]. The present study was conducted on a subpopulation of Yazd Healthy Heart Project that

had referred in first year after the initial phase and did not have the history of hypertension. The incidence rate of hypertension in Yazd, the center of Iran, was almost 2 folds and 12% higher than that among Chinese and Canadians, respectively. This can be due to the high prevalence of metabolic risk factors, such as obesity, particularly abdominal obesity, and diabetes mellitus, in our population [10].

In the study by Framingham, 458 out of the 3329 participants (13.8%) developed hypertension at the 4th year of follow up. In addition, age- and sex-adjusted incidence rates of hypertension increased progressively from 9.8% in the lowest quartile to 15.6% in the highest quartile of serum uric acid. Besides, the progression rate of BP increased from 32.8% (lowest quartile) to 39.6% (highest quartile) [11]. This rate is equal to 34.2 per 1000 person year and is almost similar to our study findings. Unfortunately, the present study researchers could find no publications about the incidence rate of hypertension in Iran, except for a study in Isfahan that reported the incidence rate of hypertension to be 542 (22.1%) during 7 years of follow-up. That study revealed isolated systolic hypertension in 153 participants (28.2%), increase in diastolic blood pressure alone in 92 participants (17.0%), and both systolic hypertension and diastolic hypertension in 162 participants (29.9%) [12]. One other study in Isfahan reported the incidence rate of hypertension among diabetic patients to be 20.8 per 100 person-years based on 9403 person-years of follow-up (20.6 among males and 20.9 among females) [13].

The results of the current study demonstrated that diastolic blood pressure, time, waist circumstance, and uric acid significantly predicted the increase in systolic blood pressure during 8 years. Besides, sex and age predicted blood pressure changes modestly.

Furthermore, diastolic blood pressure was significantly predicted by systolic blood pressure, time, and BMI. Moreover, GEE model with logit link function showed that hypertension was positively predicted by triglyceride, LDL cholesterol, uric acid, and BMI and negatively by cholesterol.

Generalized linear mixed model by Stata/MP 11.2 showed that systolic blood pressure was predicted by diastolic blood pressure (B=1.11 95% CI=1.007-1.2 P<0.0001), uric acid (B=0.88 95% CI=0.24-1.5 P<0.007), waist circumference (B=0.26 95% CI=0.13-0.38 P<0.0001), and time (B=0.31 95% CI=0.016-0.61 P=0.03) during 8 years.

Up to now, a number of important predictors of hypertension have been identified, including overweight/obesity, excessive dietary sodium intake, low physical activity, and smoking. A longitudinal study which was conducted on 5,296 female participants between 20 and 77 years of age in Dallas showed that even normal BMI, independent of other predictors, predicted hypertension development during 30 years of follow-up. However, the results revealed no significant relationship between waist circumference and hypertension development [14].

Increase in salt reabsorption by insulin in the distal nephron and hyperinsulinemic states have been shown to be associated with increased expression of renal NaCl cotransporter (NCC) [15]. Thus, increase in waist circumference resulting from insulin resistance can be associated with hypertension because of occurrence of hypervolemia due to salt reabsorption in this state.

Nonetheless, the pathophysiological mechanism by which higher BMI increases the risk of hypertension is not completely known. Complex interactions between metabolic and neurohormonal pathways, such as insulin resistance, renin-angiotensin-aldosterone

system, and sympathetic tone, might be altered by increase in BMI. Investigators have indicated decreases in plasma renin activity and plasma aldosterone levels after weight loss, also suggesting this association [14]. High fat diet leads to blood pressure elevation and induces renal sympathetic nerve activity (RSNA). This effect is mediated by central actions of leptin. In lower scale of the hypertension, insulin has central role but independent of RSNA [16]. Furthermore, duration of overweight plays a significant role in obesity-related metabolic disorders, such as hypertension and diabetes mellitus [17,18]. In contrast, investigators have reported that there was no risk of hypertension development at a low diastolic blood pressure without weight gain. Borderline diastolic blood pressure (85-95 mmHg) and obesity increase the risk of development of hypertension especially in men with the lower socioeconomic status.

In our study, waist circumference was significantly correlated with systolic blood pressure, hypertension development, and increase in BMI, but not with diastolic blood pressure. It has been thought that in comparison to diastolic blood pressure, systolic blood pressure was more significantly correlated to abdominal fat distribution and its underlying insulin resistance mechanism [5].

The association between serum uric acid and urine pH and metabolic syndrome has been evaluated in some studies. The association of a high serum uric acid and low urine PH with metabolic syndrome and hypertension has also been reported by other studies [19,20]. Additionally, a meta-analysis on a total of 18 prospective cohort studies (55,607 participants) showed that hyperuricemia was associated with an increased risk of new onset of hypertension (adjusted risk ratio=1.41, 95% CI=1.23-1.58). These effects were significantly larger in young women [21].

The findings of the current study indicated that serum uric acid independently predicted systolic and diastolic blood pressure and hypertension development. A cross sectional study in Yazd also showed that age, total cholesterol, LDL-cholesterol, triglyceride, fasting blood glucose, impaired glucose tolerance test, body mass index, and waist circumference were significantly correlated to hypertension [9]. Some predictors of hypertension have been mentioned in various longitudinal studies. A cross sectional study in South-East Nigeria revealed that the mean total cholesterol, triglyceride, and LDL-cholesterol were significantly higher in hypertensives and the mean HDL-C was comparable (P=0.8) [22].

Also, age [1,23], systolic and diastolic blood pressure level, smoking, family history of hypertension, diabetes mellitus [2], high body mass index [1], female sex, and lack of exercise were associated with development of hypertension [23]. Other investigators have found a negative association between smoking and incident hypertension [1,2]. Smoking cigarette acutely isncreased aortic stiffness and blood pressure in male subjects [24].

Moreover, serum cotinine levels, independent from other risk factors of cardiovascular diseases, were found to be associated with systolic blood pressure and hypertension in higher passive smokers [25].

In the studies conducted in USA between 1890 and 1990, in comparison to earlier cohorts, more recent cohorts had smaller increases in systolic blood pressure and their systolic blood pressure distributions were shifted lower as the age increased. The median systolic blood pressure decreases as 1.9 mmHg in per decade translates into 11.4-13.3 mmHg over 6-7 decades [26].

In our study, time was negatively correlated to systolic blood pressure. This can be explained by the design effect. Besides, age had a positive but non significant correlation with systolic blood pressure.

Study Limitations

This study reevaluated the participants who were visited in the first year after baseline measurement. Thus, 283 participants were enrolled into this study. One of the limitations of the study was that heart rate measurement and glucose tolerance test were not performed in the first year and, consequently, we could not estimate heart rate changes and impaired glucose tolerance prediction value of hypertension.

Suggestion

The study can be followed for more years until all the participants experience outcome. Nonetheless, lifestyle is recommended to be evaluated for preventive intervention targets in future studies.

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