

Association between hypertension and insulin resistance in non-diabetic adult populations: a community-based study from the Iran

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Abstract

Background and objectives: High blood pressure increases the probability of insulin resistance and hyperinsulinemia. Also, insulin resistance can be defined as a risk factor for hypertension. The present study investigated the relationship between hypertension and insulin resistance in non-diabetic participants who were referred to Qazvin Metabolic Diseases Center.

Material and methods: In this cross sectional study, 1103 participants (111 non-diabetic with newly diagnosed hypertension and 992 normotensive subjects aged ≥ 20 years) were enrolled from September 2014 to April 2016 in Qazvin (Iran). Systolic and diastolic blood pressure, insulin resistance, waist circumference, body mass index, triglycerides, cholesterol, LDL-cholesterol, fasting blood glucose (FBG) were measured. Fasting triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C) was used as a surrogate of insulin resistance. Data were analyzed using SPSS software and $p < 0.05$ was assumed as significant level.

Results: Ten percent of all participants had hypertension. TG/HDL-C was 3.78 ± 3.28 in non-HTN and 5.76 ± 5.35 in HTN participants ($p < 0.001$). The frequency of all cardio-metabolic risk factors (except HDL cholesterol level) was higher in hypertensive group, after adjusting for age and gender ($p < 0.001$).

Conclusion: Based on these results, essential hypertension is associated with a higher prevalence of hyperinsulinemia and insulin resistance in the non-diabetic community in Iran.

Key words: hypertension; insulin resistance; non-diabetic

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Introduction

Hypertension (HTN) is one of the most important and constantly increasing global health problems [1]. Hypertension is a well-known modifiable risk factor for cardiovascular diseases, chronic renal failure, stroke, and a high morbidity rate [2]. Cardio-

vascular diseases affect more than 1 billion people worldwide. They are responsible for more than 10 million preventable deaths globally each year [3]. A linear association is between cardiovascular and cerebrovascular events with a wide spectrum of blood pressure elevation in clinical presentation severity. In subjects aged between 40 and 70 years,

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each 20-mm Hg increase in systolic or 10-mm Hg in diastolic blood pressures doubles risk of cardiovascular and cerebrovascular events [4, 5]. Around the world, it is estimated that the prevalence of hypertension will increase up to > 1.5 billion in the year 2025 [6]. Hypertension is present in more than 50% of patients with diabetes mellitus (DM) and contributes significantly to both micro and macrovascular disease in diabetic patients [7]. Similar to the prevalence of type 2 diabetes in the Middle East, HTN is rising and it is estimated to be an important public health problem in this region [8]. The common findings in hypertension are hyperinsulinemia and insulin resistance [9, 10]. It has been estimated that about half of patients with essential hypertension are insulin-resistant [11]. Insulin resistance is defined as a decrease in the physiological response to insulin and compensatory over-secretion of insulin. In this situation, the transport of glucose into the skeletal muscle and fat cells are impaired. Therefore, pure results are hyperinsulinemia and hyperglycemia [12]. Hyperinsulinemia may directly promote atherosclerosis by enhancing LDL-cholesterol accumulation in vessel walls, vascular smooth muscle migration, proliferation, augmenting connective tissue synthesis in the arterial wall, and decreasing the regression of lipid plaques [13]. There are several reports that there is a link between essential hypertension and insulin resistance; however, the underlying pathogenesis seems inherently contradictory [14]. It is important that more studies proposed for assaying the association between blood pressure elevation and other underlying pathologies [15, 16]. In the Middle East countries due to demographic transition and lifestyle westernization, the incidence of obesity and associated complications are increased [3, 17]. Similar to other countries in the world, the prevalence of hypertension and metabolic syndrome is growing in Iran, so that the prevalence of hypertension has been reported by about 20% and 23% in men and women, respectively (2004–2006). Total prevalence is about 32.5% [18, 19]. The current study was designed to evaluate the association between essential hypertension and insulin resistance among non-diabetic adult participants that are newly diagnosed as hypertensive in the Qazvin province of Iran.

Material and methods

Data sets and subjects

This cross-sectional study included 1103 volunteers (111 non-diabetic patients with newly diagnosed

hypertension and 992 normotensive individuals aged 20 years or older) who were referred to the Qazvin Metabolic Diseases Center (Iran) from September 2014 to April 2016.

All participants (526 men and 577 women) signed written informed consent before enrollment. Their responses were confidential. The ethics board of the Qazvin University of Medical Science approved the study. Participants were selected by a multistage cluster random sampling method. The inclusion criteria were newly diagnosed hypertension and normal population aged 20 years or older in the Qazvin. Exclusion criteria were: smoking, malignant or accelerated hypertension, heart failure, cardiomyopathy, peripheral vascular disease, past medical history of cardiovascular or cerebrovascular disease, or any secondary hypertension (liver and kidney diseases, hyperthyroidism, or aldosteronism, etc.).

Data collection

The demographic data, such as age, gender, prior history of treatment for diabetes, and hypertension were collected with interview sessions. The anthropometric characteristics (weight, height, waist circumference, and hip) were measured by standard methods. Bodyweight was measured to the nearest 0.1 kg with a balanced-beam scale while wearing light clothing, and height was measured with a stadiometer to the nearest 0.5 cm. Body mass index (BMI) was calculated based on the $\text{weight}/(\text{height})^2$ formula. Participants with a BMI between 25 and 29.9 kg/m^2 were considered overweight. Obesity was defined as BMI of more than 30 kg/m^2 . Waist circumference between the lowest rib and the iliac crest, at the level of the umbilicus, was measured in duplicate to the nearest millimeter using flexible tape. Waist circumference (WC) equal or more than 85cm in females and equal or more than 90 cm in males was considered central obesity. Blood pressure was measured by a calibrated sphygmomanometer. Systolic (Korotkoff phase I) and diastolic (Korotkoff phase V) blood pressure was measured twice a day on the left upper arm and the average of the two amounts was considered [20].

Biochemical measurement

Venous blood samples were collected from all participants after 12 hours of overnight fast. Blood samples were stored at 70°C. The serum was separated by centrifugation at 3000 rpm for 15 min. Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), glucose, and high-density lipoprotein (HDL-C) were measured by the calibrated automatic biochemical analyzer

(HITECH 7080, Tokyo, Japan). Enzymatic methods were applied to estimate levels of TC, LDL, glucose, and TG. Insulin levels were measured with a sensitivity of 0.25 ($\mu\text{U}/\text{mL}$) via an electrochemiluminescence immunoassay (ECLIA). The ratio of triglyceride (TG) to high-density lipoprotein (HDL-C) (TG/HDL-C) was used as a measure of insulin resistance. According to several studies' definitions, insulin-resistant (IR) was TG/HDL-C ratio greater than 3.0, and insulin-sensitive (IS) was TG/HDL-C ratio less than 2.0 [10, 21]. LDL-C was calculated using Friedwald's formula ($\text{TG} \leq 400 \text{ mg/dL}$). Diagnosis of the cardiometabolic risk factors in adults including women and men is based on revised National Cholesterol Education Program-Adult Treatment Panel III (NCEP/ATPIII) and World Health Organization (WHO) criteria. Metabolic syndrome was defined by the presence of three or more following findings: (1) abdominal obesity (WC ≥ 90 cm in men and ≥ 85 cm in women) or BMI > 30 , (2) a high triglyceride level $\geq 150 \text{ mg/dL}$ or medical therapy for hypertriglyceridemia; (3) a low HDL cholesterol level ($< 40 \text{ mg/dL}$ for men and $< 50 \text{ mg/dL}$ for women); (4) high blood pressure (systolic ≥ 130 mm Hg and diastolic ≥ 85 mm Hg or antihypertensive medical therapy; and (5) a high fasting plasma glucose concentration $\geq 100 \text{ mg/dL}$ or medical treatment for type 2 DM [21].

Statistical analysis

Chi-square and odds-ratio tests were used to compare qualitative parameters. To compare quantitative variables, we used unpaired student t test or Mann-Whitney test, as appropriate. For a comparative analysis of quantitative variables between HTN

or insulin resistance subgroups, one-way ANOVA was used. To control confounding variables such as age and gender, a partial correlation by Spearman ρ was applied to find a significant correlation between clinical and biochemical characteristics. IBM SPSS Statistics 22.0 for Windows (IBM Corp., Armonk, NY, USA) was used for all the statistical analyses, and $P < 0.05$ was assumed as significant differences.

Results

Demographical characteristic of participants

Of the total of 1103 participants, 47.7% were male and 52.3% were female. There were 10% participants with hypertension. The mean age of the subjects was 40.08 ± 10.33 years (Tab. 1).

Comparative biochemical characteristics of participants based on gender

Comparing the two sexes except for the mean cholesterol, LDL, and systolic and diastolic pressure, all of the variables had significant differences ($p < 0.00$) (Tab. 2).

Table 1. Age distribution of the study population

Age (yrs)	Male	Female	Total
20–29	78	118	17.8%
30–39	83	184	24.3%
40–49	261	218	43.6%
50–59	82	38	10.9%
60–70	23	14	7.9%

Table 2. Comparison (mean \pm SD) of the clinical and biochemical characteristics of participants based on gender

Variables	Male (n = 527)	Female (n = 572)	F	p value
WC [cm]	92.0 \pm 0.40302	87.2669 \pm 0.46560	20.086	0.000
BMI [kg/m^2]	25.1502 \pm 0.16170	26.6907 \pm 0.20338	30.332	0.000
TG [mg/dL]	166.4722 \pm 5.26090	128.7887 \pm 2.92453	26.683	0.000
TC [mg/dL]	184.3808 \pm 1.67147	182.2814 \pm 1.71750	0.034	0.381
HDL [mg/dL]	38.4333 \pm 0.37941	45.3373 \pm 0.46345	18.871	0.000
LDL [mg/dL]	109.3038 \pm 1.07617	104.9747 \pm 1.11455	0.744	0.389
FBG [mg/dL]	99.6729 \pm 1.19488	99.8213 \pm 1.33409	5.286	0.000
Insulin [mU/mL]	11.8186 \pm 0.35082	12.2111 \pm 0.29846	0.120	0.002
SBP [mg Hg]	115.4411 \pm 0.74522	109.5407 \pm 0.74548	0.064	0.800
DBP [mg Hg]	73.7500 \pm 0.50089	69.6267 \pm 0.49482	0.559	0.455

WC — waist circumference; BMI — body mass index; TG — triglycerides; TC — total cholesterol; HDL — high density lipoprotein; LDL — low density lipoprotein; FBG — fasting blood glucose; SBP — systolic blood pressure; DBP — diastolic blood pressure

Table 3. Comparison (mean \pm SD) of the clinical and biochemical characteristics in male patients with hypertension (HTN) and without hypertension (non-HTN)

Variables	Non-HTN (n = 371)	HTN (n = 153)	F	p value
WC [cm]	90.0243 \pm 0.44029	96.7763 \pm 0.76870	0.569	0.000
BMI [kg/m ²]	24.3947 \pm 0.18491	26.9652 \pm 0.28480	0.001	0.000
TG [mg/dL]	148.3433 \pm 4.73326	212.2886 \pm 13.54566	19.630	0.000
TC [mg/dL]	179.4087 \pm 1.84096	196.7477 \pm 3.74389	3.313	0.000
HDL [mg/dL]	38.9423 \pm 0.44784	36.9736 \pm 0.71659	0.008	0.019
LDL [mg/dL]	106.1420 \pm 1.21572	117.2852 \pm 2.14042	1.016	0.000
FBG [mg/dL]	96.3807 \pm 0.95700	107.5174 \pm 3.35732	13.125	0.000
Insulin [mU/mL]	11.0215 \pm 0.43861	13.8774 \pm 0.54260	1.294	0.000
SBP [mg Hg]	107.4124 \pm 0.54261	135.1765 \pm 1.10516	7.937	0.000
DBP [mg Hg]	68.6523 \pm 0.40689	86.1111 \pm 0.74798	3.219	0.000

WC — waist circumference; BMI — body mass index; TG — triglycerides; TC — total cholesterol; HDL — high density lipoprotein; LDL — low density lipoprotein; FBG — fasting blood glucose; SBP — systolic blood pressure; DBP — diastolic blood pressure

Clinical and biochemical characteristics in non-HTN and HTN individuals

In males, there were significant differences between patients with hypertension (HTN) and non-hypertensive participants in WC, BMI, lipid profiles (including: TG, TC, HDL-C, and LDL-C), fasting blood glucose (FBG), insulin level, systolic, and diastolic blood pressure ($p < 0.00$) (Tab. 3).

In women participants, there were significant differences between HTN non-HTN participants in all mentioned variables, except for total cholesterol and LDL-C ($p < 0.00$) (Tab. 4).

Clinical and biochemical characteristics in insulin-resistant and insulin-sensitive individuals

There were significant differences in insulin resistance and biochemical variables such as WC, BMI, lipid profiles, FBG (except in males), and insulin level, in both male and female groups, between insulin resistant and insulin-sensitive participants ($p < 0.000$).

Also, in both genders, the systolic (M: 116.82 ± 1 vs. 112.72 ± 1.07 mm Hg, F: 113.67 ± 1.29 vs. 107.18 ± 0.91 mm Hg) and diastolic (M: 74.49 ± 0.57 vs. 72.19 ± 0.72 mm Hg, F: 72.51 ± 0.86 vs.

68.1 ± 0.6 mm Hg) blood pressure were significantly higher in insulin-resistant patient than in insulin-sensitive participants ($p < 0.00$) (Tab. 5, 6).

Cardio-metabolic factors in HTN vs. non-HTN participants

The mean of TG/HDL as an index of insulin resistance or sensitivity was 3.97 ± 3.59 among all of the participants. This index was different between HTN and non-HTN participants. TG/HDL-C was 3.78 ± 3.28 in non-HTN and 5.76 ± 5.35 in HTN participants ($p < 0.001$). Overall, the correlation between HTN and cardio-metabolic factors in both genders was considerable; the frequency of all cardiometabolic risk factors (except HDL and TC level) was higher after adjusting for age and gender in the hypertensive group (Tab. 5, 6).

Discussion

The prevalence of high blood pressure is increasing rapidly across the world, especially in developing countries like Iran. This epidemiological transmission in developing countries leads to an alarming increase in non-transmitted diseases, especially diabetes

Table 4. Comparison (mean \pm SD) of the clinical and biochemical characteristics in female patients with hypertension (HTN) and without hypertension (non-HTN)

Variables	Non-HTN (n = 474)	HTN (n = 102)	F	p value
WC [cm]	86.1540 \pm 0.50098	92.4455 \pm 1.09729	0.131	0.000
BMI [kg/m ²]	26.1891 \pm .22249	29.0764 \pm 0.43878	0.398	0.000
TG [mg/dL]	123.1947 \pm 3.11338	155.2434 \pm 7.54399	3.147	0.000
TC [mg/dL]	181.5674 \pm 1.81223	185.5929 \pm 4.32648	0.750	0.325
HDL [mg/dL]	45.8158 \pm 0.50983	43.0636 \pm 1.10976	0.539	0.026
LDL [mg/dL]	104.2556 \pm 1.21746	108.5172 \pm 2.78362	0.321	0.163
FBG [mg/dL]	98.2074 \pm 1.38064	107.5455 \pm 3.91051	8.005	0.026
Insulin [mU/mL]	11.7356 \pm 0.32458	14.5660 \pm 0.71456	0.086	0.000
SBP [mg Hg]	103.6498 \pm 0.54905	137.1569 \pm 1.47046	2.263	0.000
DBP [mg Hg]	65.9599 \pm 0.37506	86.6667 \pm 1.14756	10.517	0.000

WC — waist circumference; BMI — body mass index; TG — triglycerides; TC — total cholesterol; HDL — high density lipoprotein; LDL — low density lipoprotein; FBG — fasting blood glucose; SBP — systolic blood pressure; DBP — diastolic blood pressure

Table 5. Comparison (mean \pm SD) of the clinical and biochemical characteristics in insulin-resistant and insulin-sensitive male individuals

Variables	TG/HDL \leq 3 (n = 199)	TG/HDL $>$ 3 (n = 321)	F	p value
WC [cm]	89.2778 \pm 0.67473	93.6688 \pm 0.48313	2.956	0.000
BMI [kg/m ²]	23.9278 \pm 0.27410	25.8763 \pm 0.18906	6.456	0.000
TG [mg/dL]	90.9196 \pm 1.57376	208.9938 \pm 6.05391	106.618	0.000
TC [mg/dL]	171.3769 \pm 2.30311	191.4966 \pm 2.08855	3.041	0.000
HDL [mg/dL]	44.6157 \pm 0.56950	34.6006 \pm 0.36586	9.608	0.000
LDL [mg/dL]	103.1734 \pm 1.65782	113.3184 \pm 1.35321	0.000	0.000
FBG [mg/dL]	97.3714 \pm 1.22056	100.9121 \pm 1.77307	3.712	0.149
Insulin [mU/mL]	10.5172 \pm 0.41689	12.6000 \pm 0.50266	1.868	0.004
SBP [mg Hg]	112.7259 \pm 1.07529	116.8281 \pm 1.00013	3.934	0.005
DBP [mg Hg]	72.1939 \pm 0.72891	74.4984 \pm 0.67097	9.250	0.026

WC — waist circumference; BMI — body mass index; TG — triglycerides; TC — total cholesterol; HDL — high density lipoprotein; LDL — low density lipoprotein; FBG — fasting blood glucose; SBP — systolic blood pressure; DBP — diastolic blood pressure

Table 6. Comparison (mean \pm SD) of the clinical and biochemical characteristics in insulin-resistant and insulin-sensitive female individuals

Variables	TG/HDL \leq 3 (n = 346)	TG/HDL $>$ 3 (n = 211)	F	p value
WC [cm]	84.6908 \pm 0.59562	91.5308 \pm 0.68886	4.350	0.000
BMI [kg/m ²]	25.8013 \pm 0.27636	28.0422 \pm 0.27304	14.230	0.000
TG [mg/dL]	89.2075 \pm 1.33481	193.8820 \pm 4.76650	154.072	0.000
TC [mg/dL]	172.8957 \pm 1.79029	197.7166 \pm 3.01460	7.352	0.000
HDL [mg/dL]	49.9438 \pm 0.52805	37.7616 \pm 0.55819	7.823	0.000
LDL [mg/dL]	98.4184 \pm 1.22199	115.7569 \pm 1.94344	7.135	0.000
FBG [mg/dL]	94.8075 \pm 1.06864	108.0668 \pm 2.97811	41.222	0.000
Insulin [mU/mL]	11.3238 \pm 0.38298	13.6519 \pm 0.45993	0.585	0.000
SBP [mg Hg]	107.1821 \pm 0.91860	113.6730 \pm 1.29037	2.319	0.000
DBP [mg Hg]	68.1014 \pm 0.60911	72.5118 \pm 0.86324	3.906	0.000

WC — waist circumference; BMI — body mass index; TG — triglycerides; TC — total cholesterol; HDL — high density lipoprotein; LDL — low density lipoprotein; FBG — fasting blood glucose; SBP — systolic blood pressure; DBP — diastolic blood pressure

and high blood pressure [23]. The prevalence of both systolic and diastolic hypertension in our community-based study was about 10% of the total population, with no significant difference between men and women. Various studies have been carried out on the prevalence of HTN in different parts of Iran, which reported different rates [24]. A new systematic and meta-analytical review (based on studies published in national and international journals between 2004 and 2018) stated that the overall prevalence of HTN in Iranian society was 25% and the prevalence of HTN in older adults was 42% higher than other age groups [25]. The outcome of another cross-sectional study, which was conducted among 2,107 Iranian adult residents of Isfahan, has shown that the overall prevalence of HTN was 17.3% (18.9 and 15.5% in men and women) [26]. The highest prevalence of HTN was found to be 46.0% among adults in Africa, in contrast to 35.0% among American adults [27] and roughly 23.0% among Canadian adults [28]. In this study, the prevalence of HTN was lower than in similar studies [25–28]. The reason might be that normal population participated in our study, according to their reference to the center, because of the prevalence of HTN can be affected by demographic factors, such as age, race, gender and socioeconomic status, and type of study (cross-sectional or cohort study) [29]. In this study, the relationship between hypertension and insulin resistance was examined. The results showed that the mean of TG/HDL as an index of insulin-resistant was significantly different between untreated essential hypertensive and normotensive participants. This finding is consistent with most studies, which referred to the concurrence of hypertension and insulin resistance [9, 10]. These two variables are the components of metabolic syndrome and often coexist [30]. It's estimated that about 50% of patients with essential hypertension have been suffering from insulin-resistant or hyperinsulinemia, and glucose intolerance. Also, up to 80% of patients with type 2 diabetes were hypertensive [11, 30]. Clinical studies have shown a strong association between essential hypertension and insulin resistance/compensatory hyperinsulinemia. It should be noted the causal nature of them were not completely explained [16]. Some researchers suggest that insulin resistance and hyperinsulinemia are related to hypertension [22], while others do not support this theory [15]. High blood pressure and insulin resistance have important roles in the increase in cardiovascular diseases, cardiovascular (CVD) morbidity, and mortality rates [31]. Accordingly, the reduced risk of cardiovascular diseases is dependent on early detection and treatment of high blood pres-

sure, correction of blood glucose level, and associated metabolism [32].

In this study, the WC, BMI, FBG, lipid profile, and fasting serum insulin levels were significantly higher in individuals with high blood pressure than in both normotensive and insulin-sensitive populations. This finding has been confirmed by similar studies [32]. Also, Garcia and its co-workers found abnormal glucose metabolism in hypertensive cases [29]. These risk factors induce and aggravate HTN and insulin resistance. In this regard, many studies have found the prevalence of metabolic syndrome to be higher in individuals with HTN than in the general population [33]. Additionally, the prevalence of HTN was higher in the insulin resistance patients. One of the reasons for this finding is that changes take place in the vascular walls associated with higher levels of plasma lipids that can accelerate arteriosclerosis and hypertension [13, 34]. So, insulin resistance has been proposed as the main underlying cause of cardiometabolic syndrome [9, 10]. Kim and et al. showed that four major risk factors for cardiovascular disease in non-diabetic Korean elderly individuals were glucose tolerance impairment, dyslipidemia, hypertension, and obesity [35]. Insulin resistance is also associated with high blood pressure in obese subjects. There are still some questions that remain unanswered whether high blood pressure alone was due to insulin resistance or not. Interestingly, sodium is a link between hypertension and insulin resistance. Some studies suggest that a high-salt diet impairs insulin sensitivity in hypertensive patients [36]. Insulin hypersecretion increases the reabsorption of sodium by activating the sympathetic system and alters blood pressure [37]. Of course, other mechanisms may include chronic inflammation and oxidative stress [32]. There are some degrees of chronic inflammation in obese people [37]. Also, excess nutrient intake can induce oxidative stress in the adipose tissue which is manifested by more secretion of inflammatory cytokine [38]. Furthermore, the coexistence of insulin resistance and hypertension prompt premature atherosclerosis [39]. It should be noted that all participants with high blood pressure and insulin resistance had a significantly higher waist and wrist diameters than normal individuals. It has been proven that normal blood pressure is controlled by substances that regulate vascular tone. Therefore, overweight, which often is associated with hyperinsulinemia, stimulates endothelin 1 (ET-1) production. It eventually causes an arterial disturbance. In normal physiological conditions, NO inhibits the ET-1 activity. Thus, the loss of endothelial-derived NO may increase the production of ET-1, which is important in the pathophysiology of hypertension [40].

Conclusions

The results of this study emphasize the positive correlation between hypertension and insulin resistance. Despite the latest progress in preventing non-communicable diseases, the prevalence of HTN in the world, especially in developing countries, is expanding.

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Conflict of interest

Nothing to declare — the authors declare that they have no conflict of interests.

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