

The Relationship Between Parathyroid Hormone, Insulin Resistance and Blood Pressure in Newly Diagnosed Hypertensive Patients with Various Levels of Kidney Function

Değişik Seviyelerde Böbrek Fonksiyonu Olan Yeni Tanı Almış Hipertansif Hastalarda Paratiroid Hormon, İnsülin Direnci ve Kan Basıncı Arasındaki İlişki

ABSTRACT

OBJECTIVE: There are scarce data regarding the relationship between insulin resistance, parathyroid hormone (PTH) and blood pressure (BP) in the literature. This study is aimed to investigate the interrelationships between BPs, insulin resistance and PTH levels in never treated newly diagnosed essential hypertensive patients.

MATERIAL and METHODS: All patients underwent history taking, physical examination, BP measurement, 12 lead electrocardiographic evaluations, routine urine analysis, biochemical analysis and 24-hour urine collection to measure protein excretion and creatinine clearance. Insulin resistance was calculated by homeostasis model assessment (HOMA) index.

RESULTS: In total 92 patients were included. Spearman correlation analysis revealed that systolic BP was correlated with diastolic BP (rho: 0.337, p: 0.001), with age (rho: 0.214, p: 0.041) with body mass index (rho: 0.325, p: 0.004), with blood urea nitrogen (rho: 0.262, p: 0.012), with HOMA-INDEX (rho: 0.273, p: 0.009) and with insulin levels (rho: 0.262, p: 0.012). There was no correlation between PTH and systolic BP. Spearman correlation analysis revealed that diastolic BP was correlated with fasting blood glucose (rho: 0.220, p: 0.035), and PTH levels (rho: 0.235, p: 0.024).

CONCLUSION: In conclusion, we suggest that although PTH and HOMA-INDEX are related with BPs, discrepancy exists regarding systolic and diastolic BPs.

KEY WORDS: Blood pressure, Hypertension, Insulin, Insulin resistance, Parathyroid hormone

ÖZ

AMAÇ: Literatürde insülin direnci, paratiroid hormonu (PTH) ve kan basıncı arasındaki ilişkiyi araştıran az sayıda yayın vardır. Bu çalışmada yeni tanı almış ve ilaç kullanmayan esansiyel hipertansif hastalarda kan basıncı, insülin direnci ve PTH arasındaki ilişkinin araştırması amaçlandı.

GEREÇ ve YÖNTEMLER: Bütün hastaların tıbbi öyküleri alındı, fizik muayeneleri yapıldı, kan basınçları ölçüldü, elektrokardiyografileri çekildi, rutin idrar incelemeleri, biyokimyasal analizleri yapıldı. 24 saatlik idrar toplatılarak protein atılımı ve kreatinin klirensi hesaplandı. İnsülin direnci homeostasis model assessment (HOMA) indeksi ile hesaplandı.

BULGULAR: Toplamda 92 hasta çalışmaya alındı. Sperman korelasyon analizinde sistolik kan basıncı diyastolik kan basıncı ile (rho: 0.337, p: 0.001), yaş ile (rho: 0.214, p: 0.041), vücut kitle indeksi ile BMI (rho: 0,325, p: 0,004), kan üre nitrojeni ile (rho: 0,262, p: 0,012), HOMA indeksi ile (rho: 0,273, p: 0,009) ve insülin seviyeleri ile ilişkili bulundu (rho: 0,262, p: 0,012). Sistolik kan basıncı ile PTH arasında herhangi bir korelasyon bulunamadı. Sperman korelasyon analizinde diyastolik kan basıncı açlık kan şekeri (rho: 0.220, p: 0.035) ve PTH seviyeleri (rho: 0.235, p: 0.024) ile ilişkili bulundu.

SONUÇ: Her ne kadar PTH ve HOMA-indeksi kan basıncı ile ilişkili olsa da bu ilişki, sistolik ve diyastolik kan basıncı açısından farklılık göstermektedir.

ANAHTAR SÖZCÜKLER: Kan basıncı, Hipertansiyon, İnsülin, İnsülin direnci, Paratiroid hormon

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INTRODUCTION

It is well known that insulin resistance is highly prevalent in essential hypertensive patients and related with cardiovascular morbidity (1,2). Recent evidence also suggests that serum parathyroid hormone (PTH) levels were related with increased blood pressure (BP) (3-5). Apart from increased BP, PTH levels were shown to be associated with insulin resistance (6,7). Although the aforementioned knowledge exists, scarce data are present regarding the relationship between PTH, insulin resistance, and hypertension in the literature. Thus the current study aimed to analyze the relationship between PTH, BPs and insulin resistance in never treated essential hypertensive patients with various levels of kidney function.

MATERIALS and METHODS

The current study was conducted in the outpatient nephrology unit in a secondary state Hospital between August 2010 and January 2012. The study was in accordance with the declaration of Helsinki and local ethical approval and informed consent was obtained before enrolment. The study population consisted of patients with newly diagnosed hypertensive that was hitherto treated. All patients underwent the following procedures: history taking, physical examination, 12 lead electrocardiographic evaluation, routine urine analysis, fasting blood samples for biochemical analysis (including measurement of insulin, PTH and thyroid function tests), 24-hour urine collection to measure urinary protein excretion and creatinine clearance. An information leaflet along with a urine container was given to all subjects and they also received a verbal explanation about how to collect a proper 24-hour urine sample. After excluding the first morning urine sample of the collection day, urine was collected over 24 h, which included the first urine sample of the next morning. During the sampling period, subjects were instructed to keep urine samples in a dark and cool place. At the end of the collection period, the urine containers were taken to the laboratory within 2-4 h. Since erroneous estimations of salt intake may occur according to problems in collecting 24-h urine samples participants with urinary creatinine out of reference levels (reference intervals for 24-hour urinary creatinine were accepted as 10.7 – 26.0 g/kg for women and 12.1 – 28.9 g/kg for men) were excluded (8). Patients with diabetes mellitus, coronary artery disease, heart failure, rhythm problems, nephrotic syndrome, urinary tract infection were excluded. None of the patients reported any alcohol intake. Insulin resistance was calculated by homeostasis model assessment (HOMA-INDEX) by the following formula:

(HOMA-INDEX): [fasting plasma glucose (in millimoles per liter) × fasting serum insulin (in microunits per milliliter)]/22.5

Blood Pressure Measurement

Seated clinic BP was measured manually with a mercury column sphygmomanometer and an appropriate size cuff after 5

minutes of rest according to AHA guidelines. Hypertension was defined as systolic blood pressure between ≥ 140 mmHg and/or Diastolic BP ≥ 90 mmHg (9).

Laboratory Analysis

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

Statistics

Statistical analysis was performed using SPSS 15.0 (SPSS Inc, Evanston, Illinois, USA). Results were considered statistically significant if two-tailed P value was less than 0.05. Data was checked for normality. Data was shown as mean \pm standard deviation. For correlations of normally and non-normally distributed parameters Pearson's correlation coefficient r and Spearman's correlation coefficient ρ was used respectively. The Kruskal Wallis Test was used for the comparison of PTH and HOMA-INDEX among 3 groups (isolated systolic hypertension, isolated diastolic hypertension and both systolic and diastolic hypertension).

RESULTS

Initially 128 patients were enrolled. Two patient with coronary artery disease, 1 patients with heart failure, 3 patients with diabetes, 2 patients with nephrotic syndrome, 2 patients with atrial fibrillation, 4 patients with urinary tract infection, 5 patients with sub-clinic and overt hypothyroidism, 3 patients

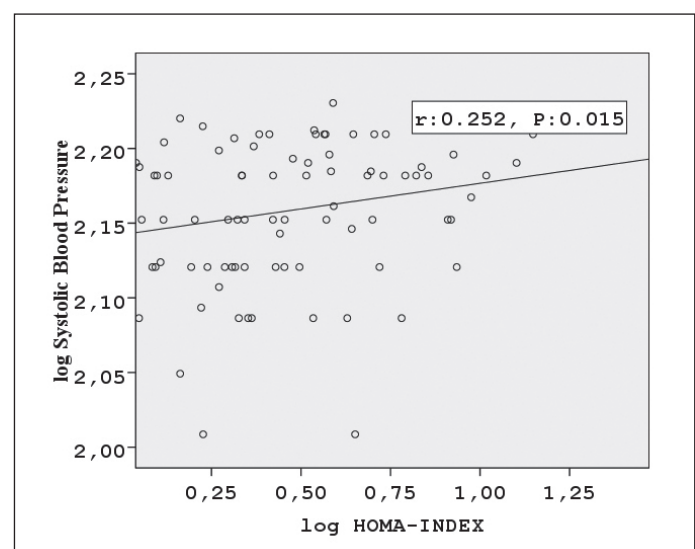


Figure 1: The scatter plot graphic between logarithmically converted systolic blood pressure with logarithmically converted HOMA-INDEX

Table I: The demographic and laboratory parameters of the 92 essential hypertensi ve patients.

Age (years) * (Range)	51.8±13.7 (26-69)
Gender (male/female)	38/54
Body Mass Index (kg/m ²) *(Range)	29.5±6.8 (19.2-40.3)
Smoker/non smoker (N:)	11/81
Systolic Blood Pressure (mmHg) * (Range)	144.4±15.0 (123-170)
Diastolic Blood Pressure (mmHg) *(Range)	92.3±12.5 (76-109)
Serum glucose (mmol/L) (mean±SD) *(Range)	5.69±0.71 (3.44-6.94)
Blood Urea Nitrogen (mmol/L) *(Range)	5.39±8.9 (3.7-34.9)
Creatinine (μmol/L) *(Range)	73.2±43.3 (55.6-233.4)
Hemoglobin (g/L) *(Range)	130.9±17.1 (10.9-17.5)
Sodium (mmol/L) *(Range)	139.3±3.5 (130.1-149.4)
Potassium (mmol/L) *(Range)	4.63±0.52 (3.41-6.17)
Calcium (mmol/L)* (Range)	2.37±0.17 (1.69-2.69)
Phosphorus (mmol/L)* (Range)	1.22±0.20 (0.77-1.84)
Albumin (g/L) *(Range)	42.5±4.4 (32.6-51.3)
Total cholesterol (mmol/L) *(Range)	4.86±1.14 (2.28-8.74)
LDL-C (mmol/L)* (Range)	2.96±0.96 (0.78-6.03)
HDL-C (mmol/L) *(Range)	1.16±0.43 (0.57-1.88)
Triglyceride (mmol/L) *(Range)	1.77±0.82 (0.58-3.84)
Uric Acid (μmol/L) *(Range)	364.6±132.6 (154.6-880.3)
Thyroid Stimulating Hormone (mU/L) *(Range)	2.30±1.40 (0.55-5.96)
FT3 (pg/ml) *(Range)	3.19±0.55 (1.87-4.48)
FT4 (ng/dl) *(Range)	1.28±0.20 (0.52-1.79)
Insulin (μU/mL) *(Range)	14.1±11.9 (3.81-48.5)
Para Thyroid Hormone (pg/mL) (Range)	47.6±32.6 (6.85-143.6)
HOMA-INDEXT (Range)	3.62±3.19 (0.43-17.7)
Creatinine clearance (ml/min)/1.73m ² *(Range)	78.2±37.1(32.1-153.5)
24-hour urinary protein excretion (mg/day) *(Range)	242.3±404.9 (7.6-1765.2)

*: Mean±Standard Deviation; **LDL-C**; Low-density lipoprotein cholesterol, **HDL-C**; low-density lipoprotein cholesterol.

FT3: Free triiodothyronine, **FT4**: Free thyroxine.

with subclinical hyperthyroidism, 1 patient with renal artery stenosis, 5 patients who did not want to participate and 8 patients with incomplete 24-hour urine calculation were excluded from the study. The final patient population consisted of never treated 92 newly diagnosed hypertensive patients. The demographic and laboratory parameters of the patients were shown in Table I.

Spearman correlation analysis revealed that systolic BP was correlated with diastolic BP (rho: 0.337, p: 0.001), age (rho: 0.214, p: 0.041) BMI (rho: 0.325, p: 0.004), blood urea nitrogen

(rho: 0.262, p: 0.012), HOMA-INDEXT (rho: 0.273, p: 0.009) and insulin levels (rho: 0.262, p: 0.012). There was also a positive correlation between logarithmically converted systolic BP with logarithmically converted HOMA-INDEXT (r: 0.252, P: 0.015) (Figure 1). There was no correlation between PTH and systolic BP. Spearman correlation analysis revealed that diastolic BP was correlated with fasting blood glucose (rho: 0.220, p: 0.035), and PTH levels (rho: 0.235, p: 0.024). There was no correlation between diastolic BP with HOMA-INDEXT. Additionally PTH levels were correlated with calcium (rho: -0.234, p: 0.028),

creatinine clearance (ρ : -0.519, $p < 0.0001$), blood urea nitrogen (ρ : 0.403, $p < 0.0001$), creatinine (ρ : 0.513, $p < 0.0001$). Of note there was no correlation between PTH and HOMA-INDEX (ρ : -0.038, P : 0.723). There were also no correlations between calcium, phosphorus and BP levels in our sample. Lastly, we divided patients into 3 groups namely:

- i) Isolated systolic hypertension (defined as: SBP \geq 140 mmHg whereas DBP $<$ 90 mmHg)
- ii) Isolated diastolic hypertension (defined as: DBP \geq 90 mmHg whereas SBP $<$ 140 mmHg)
- iii) Both systolic and diastolic hypertension (defined as: DBP \geq 90 mmHg and SBP \geq 140 mmHg). There were 25 patients with isolated systolic hypertension, 27 patients with isolated diastolic hypertension, and 40 patients with both systolic and diastolic hypertension. Comparison of PTH and HOMA-INDEX among these 3 groups showed no statistical difference with respect to PTH (P : 0.289), and HOMA-INDEX (P : 0.242).

DISCUSSION

In the current study we demonstrated that insulin resistance as evaluated with HOMA-INDEX was associated with systolic BP but not with diastolic BP. On the other hand, serum PTH levels was associated with diastolic BP but not with systolic BP.

Regarding the insulin resistance and BPs; different mechanisms play a role in the development of hypertension. Firstly insulin may cause hypertension by increasing sympathoadrenal activity and sustained activation of the sympathetic nervous system may be involved in the development of hypertension in patients with insulin resistance (10-12). Secondly, insulin resistance may be associated with endothelial dysfunction. Defective insulin-mediated and endothelium-dependent vasodilatation in insulin-resistant states may result in hypertension (13). Thus our findings were in accord with the previous findings.

Another finding of the current study was the association between PTH levels and diastolic BP. Previously it has been shown that primary hyperparathyroidism has been associated with hypertension (14-16). Multiple factors contribute to parathyroid hypertension including augmentation of renin angiotensin system (14,17), upregulation of the sympathetic nervous system (18), alteration of arterial tone due to impaired endothelial vasodilatory function (19) inducing renal damage and renal calculi (20). Lastly, increased serum calcium was thought to be responsible for increased HT in hyperparathyroidism. Hulter et al. administered supra physiological doses of human 1,34-PTH for 12 days to healthy subjects. The infusion of 1,34-PTH induced hypercalcemia and in parallel a significant increase in blood pressure. Both hypercalcemia and hypertension normalized after the infusion was stopped (21). However, in another study dose of PTH was chosen that induced only a minor increase in ionized calcium concentration within the normal

range; nevertheless a significant increase in blood pressure was seen (3). Of note in the current study we did not show any association between calcium, systolic BP and diastolic BP.

We did not demonstrate any association between PTH levels and insulin resistance in the present study. In the literature there are contrasting findings about this issue. While some studies showed association (6,22); others did not show any relationship (23). Besides some studies have shown that the insulin resistance was not changed in patients before and after parathyroidectomy (24,25). We do not know the causes of these discrete findings but patient characteristics, co-morbidities and study design may be responsible

One of the interesting finding is HOMA-INDEX is only correlated with systolic BP, where as PTH levels were only correlated with diastolic BP. We cannot make any speculations about this situation. However the literature contains studies in which the discrepancy between systolic and diastolic BP was observed. Adler et al. (26) found an association between systolic BP and microvascular and macrovascular complications in type 2 diabetic patients. In another study, 24-h average systolic BP or pulse pressure values were second only to age in their correlation with carotid artery wall status; whereas 24-h average diastolic BP had no effect (27). The discrepancy between systolic and diastolic BPs regarding insulin resistance and PTH levels must be evaluated by further studies.

This study has limitations. The standard methods for quantifying insulin sensitivity are hyperinsulinemic euglycemic glucose clamp and the intravenous glucose tolerance test [28]. As these methods are impractical in clinical practice and are difficult to perform in epidemiological research, we instead used the HOMA index for the assessment of insulin sensitivity. Second our data based on a single measurement, rather than serial measurements, must be interpreted cautiously. Thirdly since the study has cross sectional design cause and effect relationship cannot be suggested. Thirdly, our study sample was relatively small; still, we believe that because our study group was composed of special patients that included both newly diagnosed hypertensive patients without previous known cardiovascular diseases and who were not receiving any antihypertensive drugs; thus the effects of cardiovascular comorbidity and medication were potentially ruled out.

In conclusion, we suggest that although PTH and HOMA-INDEX are related with BPs, discrepancy exists regarding systolic and diastolic BPs. More studies are needed to highlight underlying mechanisms regarding PTH, insulin resistance, systolic and diastolic BPs.

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