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Study of the Relation between Il-6, Insulin Resistance, and Blood Pressure in Essential Hypertensive Patients

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ABSTRACT

Background: One of the most important cardiovascular risk factors is essential hypertension, a disease that affects a large percentage of the population.

Objective: The purpose of this study was to establish a probable relationship between IL-6 levels and both insulin resistance and essential hypertension.

Methods: This is a case-control study. Ninety participants were involved: sixty essential hypertensive patients and thirty healthy control who were matched for age and gender. The fasting and two-hour postprandial plasma glucose, serum fasting insulin, HOMA-IR, and serum IL6 levels of all patients and control group were all examined.

Results: In comparison to the control group, fasting insulin and the HOMA-IR values in the hypertension group were considerably higher. The median level of IL-6 in the hypertensive group (5.85 pg /ml) was substantially greater than in the control group (1.49 pg /ml). Overall fasting insulin, fasting blood glucose, and HOMA-IR showed positive correlation with IL-6, which is an indicator of insulin resistance.

Conclusion: Screening of IL-6 may be an indicator of insulin resistance in hypertensive patient. Further research into the processes underlying these connections is required.

Keywords: Blood pressure, IL-6, Insulin resistance.

INTRODUCTION

Hypertension affects more than a billion people worldwide, with up to 45 percent of the adult population suffering. Up to 60% of those over the age of 60 are affected by Alzheimer's disease [(1)].

Approximately 1.5 billion people are expected to have hypertension in the next decade, based on recent predictions. It is true that insulin is a major anabolic hormone in the management of glucose, lipid homeostasis, and energy storage because of its metabolic influence on insulin-responsive tissues. Glycogen storage in liver and skeletal muscles is promoted by insulin. However, at high levels of insulin resistance, it is impossible for insulin-responsive tissues to perform their normal anabolic metabolic functions [(2)].

Interleukin 6 (IL-6) has a dual role as an autocrine and/or paracrine cytokine that influences adipocyte activity [(3)]. It also has been related to metabolic illnesses such as multiple sclerosis (MS) and type 2 diabetes through accumulated evidence. It has been proved that people with diabetes or obesity, especially those with multiple sclerosis (MS)-like symptoms, have elevated levels of IL-6 in their adipose tissues**.** When IL-6 level was increased in MS, it had a direct effect on insulin resistance, increased glucose synthesis in the liver along with an inhibitor of insulin-mediated glucose uptake in muscle, as well as the facilitation of hypertension [(4)]. Many studies have linked elevated levels of IL-6 and tumor necrosis factor alpha (TNF-α) in the bloodstream to the development of high blood pressure in otherwise healthy individuals. Plasma levels of IL-6 and TNF-α in hypertensive individuals were revealed to be associated with coronary endothelial dysfunction [(5)].

Our study aimed to explore the relationship between IL-6, insulin resistance, and blood pressure in an essential hypertensive patient.

SUBJECTS AND METHODS

This is a cross section hospital-based study at internal medicine outpatient clinics in Benha University Hospital from January to July 2020. We recruited 60 patients who had been diagnosed with essential hypertension according to European Society of Hypertension/European Society of Cardiology guidelines (ESH/ESC) [(6)]. The patients were receiving antihypertensive medications regularly. In term of control group, we collected 30 healthy individuals who were similar in age and gender. Patients with one or more of the following were excluded; obesity, smoking, pre-diabetes, diabetes, infections, (acute or chronic), inflammation (acute or chronic), autoimmune disorders, cancer, and chronic liver illnesses. In addition, patients receiving somatostatin analogues, hormonal contraceptives, corticosteroids, or lipid lowering agent were excluded from the research. Demographic and anthropometric data were collected, as well as information on the history of hypertension and its duration.

Laboratory data:

Fasting plasma glucose (FPG) , 2 hours postprandial plasma glucose (2h PPG) levels, fasting insulin, total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), triglycerides (TGs), and kidney function tests were measured at the Clinical Pathology Department, Benha University Hospital, according to the laboratory's standard procedures. For detection of

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IL-6 level in the blood, a sample of whole blood was collected in tubes containing separating gel for analysis. When the centrifugation process was complete, the serum was collected and kept at -80°C. IL-6 was quantified using An Enzyme Linked Immunosorbent Assay (ELISA). HOMA-IR was calculated according to the formula: fasting insulin (micro/L) × fasting glucose (mg/dl) /405, which normally range from 0.5-1.4. If someone sensitivity to insulin is less than 1.0, he is doing well. At or above 1.9, insulin resistance was beginning to develop. Insulin resistance is seen when the value rises over 2.9 [7].

Ethical consideration:

This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans and has been approved by Benha University's Ethics Committee, Egypt (MS; 20-6-2020). All patients provided an informed written consent before enrollment.

Statistical analysis

The collected data were statistically analyzed using Statistical Package for the Social Sciences (SPSS) (version 24). The normality of distribution for the analyzed variables were tested using Shapiro-Wilk's test. Quantitative data were collected and summarized in terms of mean ± standard deviation (SD), median, interquartile range, and range and were compared by student t-test when normally distributed and by Mann-Whitney U test when abnormally distributed. Qualitative data were presented as number and percentage and were compared by Chi-square (χ^2) test. The level of significance in this study was ($p \leq 0.05$). While $p \leq 0.001$ was considered highly statistically significant.

RESULTS

There was a statistically significant difference in body mass index (BMI) between group A and B (table 1).

Table (1): Demographic characteristics between the studied groups

			Group A (Hypertensive group)	Group B (Control group)	Test value	P-value
			n = 60	n = 30		
Age (years)	Mean± SD		42.12± 10.40	38.83± 16.01	T=1.012	0.313
	Median (IQR)		40 (30 - 48)	45 (24 - 50)		
	Range		26.0- 67.0	19.0- 64.0		
Gender	Male	N	24	17	X^2= 2.24	0.134
		%	40.0%	56.7%		
	Female	N	36	13		
		%	60.0%	43.3%		
BMI (Kg/ m^2)	Mean± SD		24.31± 1.87	22.43± 1.54	U= 384.5	<0.001
	Median (IQR)		24.2 (22.80 - 25.25)	22.5 (22.08 - 23.70)		
	Range		20.80 - 28.70	19.50 - 24.50		

SD= standard deviation, IQR= Interquartile range, BMI= Body mass index

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly different between the two groups (Table 2).

Table (2): Blood pressure distribution between the study groups

Blood pressure / Group		Group A (n=60)	Group B (n=30)	Test	P-value
SBP (mm/Hg)	Mean± SD	137.50± 11.06	113.17± 8.25	U= 69.0	<0.001
	Median (IQR)	137 (130.0 - 145.0)	115 (105.0 - 120.0)		
DBP (mm/Hg)	Mean± SD	87.17± 10.50	70.33± 6.42	U= 158.5	<0.001
	Median (IQR)	87 (80.0 - 95.0)	72.5 (65.0 - 75.0)		

SBP =systolic blood pressure, DBP =diastolic blood pressure.

In table 3, fasting insulin, FPG, HOMA-IR, serum cholesterol, HDL-C, urea, and creatinine levels were substantially different between the two groups.

Table (3): Laboratory characteristics of the study groups

	Group A (n=60)			Group B (n=30)			Test	P-value
	Mean	SD	Median	Mean	SD	Median		
FPG (mg/dl)	96.35	5.64	96.50	88.93	3.87	89.00	264.0	<0.001
2hPPG (mg/dl)	128.38	6.13	127.00	127.17	4.87	126.00	795.0	0.366
F. insulin (Iu/ml)	13.60	1.86	13.80	7.76	1.29	7.90	0.0	<0.001
HOMA-IR	3.17	0.56	3.21	1.69	0.32	1.75	0.0	<0.001
Cholesterol (mg/dl)	163.25	20.26	170.00	149.50	13.73	152.50	463.5	<0.001
Triglycerides (mg/dl)	115.83	19.64	125.00	113.23	14.58	111.50	845.5	0.640
LDL-C (mg/dl)	109.47	17.09	112.00	106.63	11.94	105.00	739.0	0.168
HDL-C (mg/dl)	49.78	7.87	49.00	54.63	7.77	54.00	601.5	0.010
UREA (mg/dl)	25.93	5.24	25.00	21.77	4.62	22.00	499.5	<0.001
S. creatinine (mg/dl)	0.95	0.17	0.90	0.80	0.14	0.75	450.0	<0.001
eGFR (ml/minute/1.73m^2)	101.82	7.58	100.00	105.40	11.19	101.00	715.5	0.114
Alb/Cr Ratio (mg/mg)	0.32	0.12	0.31	0.44	0.58	0.30	899.0	0.993

IL-6 level in the hypertension group was significantly higher than its level in the control group (Table 4).

Table (4): Level of IL-6 in the study group

		Group A (n=60)	Group B (n=30)	Test	P-value
IL-6 (pg/ml)	Mean± SD	5.99± 0.84	1.35± 0.38	U= 465.0	<0.001
	Median (IQR)	5.85 (5.35 - 6.54)	1.49 (0.95 - 1.65)		

Table 5 revealed a significant positive correlation between IL-6 with fasting insulin, HOMA-IR, and FPG.

Table (5): Correlation between IL-6 and glycemic parameters

Parameters	IL-6	
	Hypertensive group (group A) (n=60)	
	r	p
fasting insulin (mU/ L)	0.626	<0.001
HOMA-IR	0.680	<0.001
FBG (mg⁄dl)	0.347	0.007
PPBG (mg⁄dl)	0.175	0.181

DISCUSSION

The subject of the great deal of the research is to find out and demonstrate the correlation between IL-6 levels, insulin resistance, and high blood pressure in essential hypertensive patients. In the current study, age and gender were not statistically significantly different between hypertensive and control group. Moreover, patients with hypertension had significantly higher cholesterol levels than those without. On comparison between hypertensive and control subjects, HDL-C levels were significantly higher in the control subjects. Both groups did not vary substantially in postprandial blood glucose, triglyceride, LDL, eGFR, or the albumin/creatinine ratio. **Sesso *et al.*** found that HDL-C was significantly higher in women who acquired hypertension during follow-up, although total and LDL cholesterol did not vary significantly[8]. Furthermore, **Bautista *et al.*** stated that plasma glycaemia, cholesterol, and triglycerides were all significantly higher in hypertensives than in the general population [9].

Our study revealed a significant higher systolic and diastolic blood pressure in the hypertensive patients. One study identified a statistically significant difference in the frequency of high blood pressure between non-Hispanic whites, African Americans, and Hispanics [10]. Similarly, **Ferrannini *et al.*** found this to be the case [11]. There is definite links between essential hypertension and multiple risk factors, including poor nutrition and physical inactivity as well as hereditary factors. Hypertension is more likely to occur if certain risk factors are present, obesity is one of them [12]. High blood pressure may be caused by inactivity that is successfully controlled through regular physical activity [13].

Our study declared that BMI was significantly higher in hypertensive patients, in addition there was a significant insulin resistance noticed in the hypertensive patients (higher fasting insulin and HOMA-IR). Insulin is a potent anabolic hormone that regulates glucose, lipid homeostasis, and energy storage resulting in glycogen and triglyceride storage in the liver and skeletal muscles as well as deposition of fatty acids in adipose tissue. However, the anabolic metabolic advantages of the insulin-sensitive tissues are inhibited by insulin resistance [2]. Insulin also increases sodium reabsorption in the kidneys and sympathetic nerve activity. Insulin's effects on inflammation may be pro- or anti-inflammatory, depending on the situations. Insulin increases the production of endothelial nitric oxide (NO), which has a calming and anti-inflammatory influence on the blood vessels [14].

On the contrary, low-grade inflammation, hypertension, and metabolic syndrome may result if safe lipid storage in adipose tissue is exceeded. It has been shown that obesity-induced inflammation is related to an increase in adipose tissue macrophage (ATM) invasion. There may be a link between excess nutrients in the obese fat environment and the activation of pro-inflammatory macrophages and the phenotypic switch from resident macrophages to pro-inflammatory macrophages. White adipose tissue (WAT) inflammation that finally extends to other parts of the body is an emerging feature of ATM infiltration connected to obesity. Extra WAT produces inflammatory adipokines, such as TNF-α, monocyte attractant protein 1 (MAP1), and interleukin 6 [15]. Insulin resistance is related to a varied range of complications, including obesity, cardiovascular disease, nonalcoholic fat liver disease, metabolic syndrome, and polycystic ovarian syndrome (PCOS) [16]. In the present study, insulin resistance as well as fast plasma glucose level were positively correlated with IL-6 levels. But postprandial blood glucose was not significantly correlated with IL-6. It was consistent with one study revealing elevated levels of IL-6 as marker of insulin resistance [10]. The insulin sensitivity index was highly linked to circulating IL-6 levels [17,18]. Obese Kuwaiti adolescents were found to have high levels of IL-6 as inflammatory and insulin resistance markers [19]. In both animals and humans, the metabolic importance of IL-6 has been widely examined. Obese people have higher levels of IL-6 in their adipose tissue and bloodstream that is reduced after weight reduction. Increased amounts of IL-6 were found in the subcutaneous fat of the abdomen. IL-6 concentrations in the portal vein, which drains visceral fat, were about 50% higher than those in arterial blood. Insulin resistance was associated with both plasma IL-6 levels and adipose tissue IL-6 secretion. TNF production and plasma IL-6 levels were connected to insulin resistance [20].

In our study, IL-6 levels were considerably greater in hypertensive group than the control group (mean ± SD = 5.99 ± 0.84 pg/ml and 1.35±0.38 pg/ml, respectively). Raised inflammatory biomarkers such as CRP and IL-6 were shown to be associated with high blood pressure in an observational and epidemiological research [21]. Cellular activities ranging from inflammation to tissue injury and regeneration are all affected by cytokines. They encourage the recruitment and activation of immune cells and are vital in the development of arthrosclerosis [22]. In hypertensive patients, the inflammatory state is fueled by the interaction of immunological and endothelial cells. IL-6, IL-12, IL-18, and IL-17 cytokines, which are directly linked to cardiovascular disease (CVD), must be tightly managed in order to avoid CVDs and hypertensive end-organ damage such as heart valve remodeling and involvement of the kidney and brain [23]. IL-6 may influence vascular inflammation and stiffness, as well as endothelial dysfunction, in the genesis of hypertension. In addition, it enhances the production of fibrinogen and prevents the breakdown of arterial wall collagen [24].

CONCLUSION

IL-6 is related to insulin resistance in hypertensive patients. It could be related to the development of future metabolic syndrome that is commonly seen in hypertensive patients. Inflammation plays a significant role in the development and maintenance of hypertension as well as the eventual end-organ damage that results from it.

Limitation of the study:

A bigger placebo-controlled study will be necessary to investigate the link between IL-6, insulin resistance, and hypertension. Additionally, a mechanistic investigation may be required.

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