Hyperinsulinemic response to oral glucose in obese patients with essential hypertension

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Abstract

Background and objectives: Hypertension is a common health problem. The prevalence of hypertension increases progressively with increasing Body Mass Index. The aim of this study is to investigate changes in blood pressure (BP), plasma glucose (PG) and insulin level after ingestion of oral glucose; and to assess the relation between insulin level and BP in obese and non-obese normo-tensive and hypertensive subjects.

Materials and Methods: Seventy five g glucose dissolved in 250 ml of water was given orally to 20 fasting newly diagnosed untreated patients with essential hypertension and 15 normo-tenisve control subjects matched for age, gender and Body Mass Index (BMI). Smokers and subjects with diabetes, hyperlipidemia, cardiac or renal disease or those taking medications were excluded. Subjects were monitored for 2 hours. Half hourly BP, PG and insulin were measured.

Results: Subjects were classified into obese (BMI≥ 30 Kg/m2) (11 patients, 8 normo-tensives) and nonobese (BMI< 30 Kg/m2) (9 patients, 7 normo-tensives). In obese hypertensive patients, insulin showed significant positive correlation with: systolic BP (SBP) (P=.04), diastolic BP (DBP) (P=.04) and mean BP (MBP) (P=.03). Obese hypertensive patients showed a significantly higher insulin response to oral glucose than obese normo-tensive subjects (P=.02).

In obese and non-obese hypertensive patients glucose intake was associated with significant drop in DBP ((P≤ .005), (P< .05)) and MBP ((P< .005), (P< .05)) respectively.

Conclusions: In obese hypertensive patients, the hyperinsulinemic response to oral glucose and the positive correlation of insulin with BP suggest that insulin may be involved in development of essential hypertension especially in obese patients.

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Introduction

More than 25% of the world adult population has hypertension [(1)]. Prevalence of hypertension increases progressively with increasing BMI [(2)]. The exact mechanisms for the development of essential hypertension are not known. Now it is generally accepted that genetic and environmental factors contribute equally to development of hypertension [(3)]. Among the environmental factors, dietary factors seem to have a prominent role in blood pressure (BP) homeostasis. Each meal initiates a series of integrated physiological events, which facilitate digestion and absorption of nutrients. It is also associated with haemodynamic, hormonal and electrolyte changes that can affect the BP in hypertensive and normo-tensive subjects.

There is some controversy about the hemodynamic responses to oral ingestion of glucose in normo-tensive and hypertensive subjects. A significant increase in BP following glucose intake was

reported in normo-tensive subjects[4,5] and in hyper-insulinemic, but not in normo-insulinemic hypertensive patients [5]. It is not known whether the effect of glucose on elevation of BP is higher in hypertensive subjects or in subjects with normal BP [6]. Some studies reported a significant decrease in BP after ingestion of glucose load in hypertensive patients [7-9]. It was suggested that insulin may not be directly involved in the pathogenesis of postprandial hypotension[9]. Postprandial hyperinsuliemia has been found in patients with mild essential hypertension[10].

The aim of this study is to compare changes in BP, plasma glucose (PG) and insulin levels after ingestion of an oral glucose load and to assess the relation between insulin level and BP in obese and non-obese normo-tensive and hypertensive subjects. This study may contribute to the understanding of the pathophysiology of essential hypertension taking into consideration the BMI of the patients and controls. Results of this study may throw new light on the rationale of dietary management of patients with essential hypertension regarding sugar intake.

Methods:

This is a short-term experimental study including 20 newly diagnosed untreated adult patients with essential hypertension, and 15 normo-tensive control subjects matched for age, gender, and BMI. Sample size was calculated using the formula for experimental study with serial samples:

$n=1+2C(s/d)^2$, Equation2
(SnedecorandCochran1989) [11]

Subjects with BP $\geq$ 140/90 were considered as hypertensive patients [12]. Blood pressure was measured using mercury sphygmomanometer (Kawamoto, Japan), according to the standardized methodology [12].

Hypertensive patients were recruited from primary health care centers. After screening visits to identify and select newly diagnosed cases of essential hypertension, patients signed an informed consent form approved by the Ethical Committee of Faculty of medicine, University of Khartoum and filled a questionnaire including: personal data and medical history. Complete physical examination and electrocardiogram (ECG) were done to the patients and control subjects. Known hypertensive patients, smokers, alcoholics, and subjects with hyperlipidemia, diabetes mellitus or with random blood glucose more than 200 mg/dl were excluded. Patients with mandatory reason for immediate initiation of treatment e. g. very high blood pressure, target organ damage, were also excluded. Weight in (Kg) and height in meters (M) were measured using standardized scale (Seca, Germany). The BMI in kg/m^2 was calculated as a ratio between body weight (kg) and squared height (m^2). Random blood glucose, urea, creatinine, lipid profile (Biosystem, Spain) were measured by spectrophotometer for each subject to exclude any abnormality.

Patients were advised to continue their normal dietary habits and not to restrict their usual carbohydrates intake. On the day of the experiment the selected subjects fasted overnight (8- 10 hrs). Water was allowed, and they attended at the laboratory in the early morning. After resting for 15 minutes, a base line fasting BP and blood sample were taken. Then each subject took 75gm glucose solution dissolved in 250 ml of water to be consumed in not more than 5 minutes. Each subject was monitored for 2 hours. Half hourly BP measurements and venous blood samples were taken to measure plasma glucose using glucose oxidase method (Biosystem, Spain) by spectrophotometer and serum insulin by quantitative immunoassay test kits (Immunospec, USA) using ELISA (Enzyme Linked Immunosorbent Assay) technique.

All BP measurements were done in the sitting position by the same investigator in a quiet office with comfortable room temperature. A larger cuff was used for measurement of BP in obese patients. SBP was taken as the point of onset of the auscultated pulsation (phase 1), and DBP was the point before the disappearance of the sounds (phase 5). Three readings were taken by the same investigator at intervals of at least 1 minute, and the

average of those readings was used for statistical analysis. If there is >5 mm Hg difference between readings, an additional reading was obtained, and then the average of all the readings was used[13].

Results obtained were saved and analyzed using the Statistical Package Program for Social sciences (SPSS) version 17. Descriptive statistics were done for all variables. The relation between BP, plasma glucose and serum insulin was tested with Pearson correlation. Comparison of the above variables between hypertensive and control subjects was done with independent student *t*-test. To determine changes in BP, plasma glucose and insulin following intake of glucose paired samples T- test was done.

Results:

This study included 20 patients with essential hypertension: 11 were obese (BMI≥ 30Kg/m^2) and 9 were non-obese patients (BMI< 30Kg/m^2) [14]. The normo-tensive control group included 15 subjects matched for age, gender and BMI; 8 were obese and 7 were non-obese subjects.

To assess BP responses to oral glucose, comparison of each of the 4- half- hourly samples with the baseline BP (fasting BP at 0 minute) was done using paired sample T- test in obese and non-obese hypertensive patients and normo-tensive control subjects (table 1).

Table: Changes in plasma glucose, serum insulin& blood pressure after intake of oral glucose

Variable	Time min.	Nonobese patients Mean± S.E (n=9)	Paired T-test P value	Obese patients Mean± S.E (n=11)	Paired T-test P value
Systolic Blood Pressure (SBP)	0	153.0 ±5.2		149.9± 4.6	
	30	150.95 ±5.2	.47	146.6± 4.6	.209
	60	149. 85 ±5.2	.27	146.3± 4.6	.247
	90	150.75 ±5.2	.49	145.4± 4.6	.179
	120	148.55.2±	.18	144.5± 4.6	.147
Diastolic Blood Pressure (DBP)	0	100.7± 5.7		98.7 ±5.0	
	30	95.2± 5.7	.009*	92.4 ±5.0	.003*
	60	94.3 ±5.7	.009*	92.5± 5.0	.004*
	90	94.9± 5.7	.03*	92.5± 5.0	.005*
	120	95.9± 5.7	.03*	92.4± 5.0	.002*
Mean Blood Pressure (MBP)	0	118.1 ±5.4		115.9 ±4.8	
	30	114.1 ±5.4	.08	110.5 ±4.8	.008*
	60	112.7± 5.4	.03*	110.4 ±4.8	.02*
	90	113.3 ±5.4	.09	110.0 ±4.8	.01*
	120	113.3 ±5.4	.06	110.0 ±4.8	.009*

*P is significant at <0.05

Following the intake of oral glucose load, the DBP decreased significantly in both obese (P≤ .005) and non-obese hypertensive patients (P< .05) at 30 minutes and continued throughout the 2 hour period of follow up (table 1). SBP did not show significant changes in any of the hypertensive groups. In non-obese hypertensive patients, a significant drop in MBP occurred only at 60 minutes (P= .03). In obese patients Mean BP also dropped significantly by about 5 mmHg throughout the period of follow up (P< .05) (table 1).

At baseline fasting, insulin was significantly higher in obese hypertensive subjects than obese normo-tensive control subjects (P=.02) with no significant difference in fasting blood glucose. After intake of glucose, the plasma glucose and serum insulin increased significantly in all groups. However, the mean of insulin levels in response to oral glucose intake in obese hypertensive patients was significantly higher than obese normo-tensive subjects (P=.02), despite no significant differences in plasma glucose between hypertensive and normo-tensive subjects (figures 1 & 2). Obese hypertensive patients showed a significantly higher insulin glucose ratio (0.55) compared to obese normo-tensive subjects (0.35) (P=0.009) (table 2). However, there was insignificant statistical difference in insulin glucose ratio in non-obese hypertensive patients and their matched normo-tensive control subjects (P=0.08).

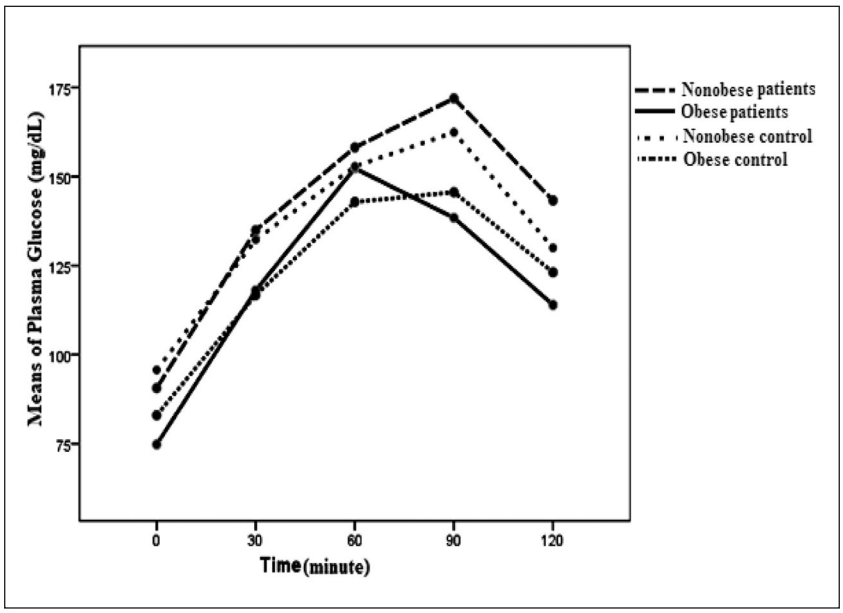

Figure 1. Plasma glucose in obese and non-obese hypertensive and normo-tensive subjects after oral glucose

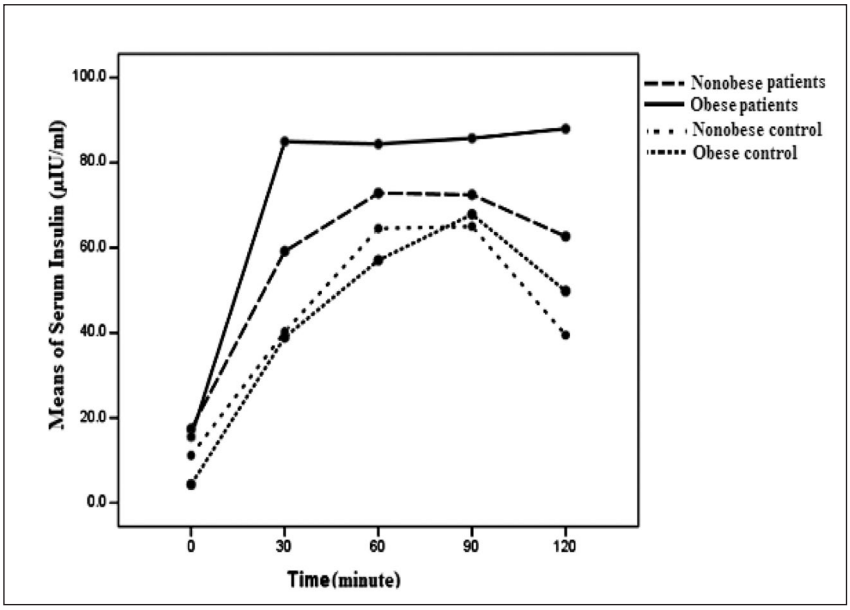

Figure 2. Serum insulin in obese and non-obese hypertensive and normo-tensive subjects after oral glucose

Table 2. Means of the variables for hypertensive patients and control subjects.

Variables (mean± SE)	Obese Patients	Obese Control	Nonobese Patients	Nonobese Control
BMI (Kg/m2)	33.4±0.4	35.6±0.9	25.3±0.3	25.4±0.3
MBP (mmHg)	113±2.2	91.5±1.1	111.9±1.5	91.8±1.4
Blood Glucose (mg/dL)	126.7±4.8	131.1±4.8	129.7±6.2	125.7±5.8
Serum Insulin (µIU/ml)	71.7±7.8	48.8±4.2	54.2±5.8	41.8±4.1
Insulin/Glucose ratio	0.55	0.35	0.40	0.32

* The means for MBP, blood glucose and serum insulin were calculated from the 5 half hourly samples for patients and control subjects.

In obese hypertensive patients insulin levels showed significant positive correlation with: SBP (P=.04), DBP (P=.04) and MBP (P=.03). This association was insignificant in normo-tensive subjects and non-obese hypertensive patients.

Discussion:

BP response to oral glucose load:

In this study, we found that DBP and MBP decreased significantly in both obese and non-obese hypertensive subjects following oral glucose intake which is comparable to previous studies[7-9]. It has been reported that the SBP and DBP decreased significantly during oral glucose tolerance test (OGTT) in hypertensive patients but not in normo-tensive subjects[7]. However, in our study the change in SBP was not significant in hypertensive or normo-tensive control subjects. In normo-tensive subjects we found that the changes in SBP, DBP and MBP were not significant. Similar results were reported in lean healthy young subjects after ingestion of 60 g glucose dissolved in 500 ml of water [15]. Contradictory results were found in other studies that reported increases in SBP in normo-tensive subjects after OGTT [5] and after intake of 100 g glucose [4]. In this study, the BP did not change significantly in normo-tensive subjects. This could be explained by the counteracting effects of the increasing insulin level after glucose ingestion causing both vasodilatation and increased sympathetic discharge which resulted in increased heart rate and stroke volume [16]. It has been found that acute increases in plasma insulin within the physiological range elevated sympathetic neural outflow, produced forearm vasodilatation but did not elevate arterial pressure in normo-tensive humans [16]. Scott et al reported that physiological insulinaemia following ingestion of a carbohydrate meal in healthy subjects was associated with overriding skeletal muscle vasodilatation, despite an increase in sympathetic vasoconstrictor discharge to the same vascular bed. The vasodilatation preceded the increase in sympathetic activity, and the time of the increase in muscle sympathetic nerve activity corresponded to the return of BP towards baseline values [17]. We found that obese hypertensive patients had significantly higher insulin level than their normo-tensive control subjects. It has been shown that the vasodilatation caused by insulin occurs early compared with the sympathetic activation [17]. Our results showed that the DBP and MBP decreased significantly in both obese and non-obese hypertensive subjects following OGTT can be explained by the vasodilatory effect of the high level of insulin which may be followed later by exaggerated sympathetic discharge leading to higher BP. We suggest that the disturbance in the balance of vasodilator and vasoconstrictor action of insulin may be one of the causes of high BP in obese hypertensive patients. However, the possibility of ethnic genetic differences cannot be excluded.

Insulin & BP in hypertensive patients:

In obese hypertensive patients, we found that serum insulin had significant positive correlation with: SBP, DBP and MBP after intake of glucose. Obese hypertensive subjects also showed significantly higher fasting and post-load insulin levels and higher insulin glucose ratio compared with obese normo-tensive subjects without a significant difference in plasma glucose. Xun et al [18] reported that fasting serum insulin levels or hyperinsulinemia in young adulthood was positively associated with incidence of hypertension later in life. It was suggested that fasting insulin may help clinicians to identify those at high risk of developing hypertension. The Diabetes Prevention Program Research Group [19] found that there was a weak, but significant, association between BP and insulin, proinsulin and insulin resistance (IR) which can be largely explained by overall adiposity.

Levin et al found that high serum glucose and insulin levels were associated with increased risk of the incidence of hypertension in community-based cohort. They suggested that these associations were independent of adiposity and other established hypertension risk factors as the magnitudes of association were attenuated by 50% after adjustment for serum cystatin C concentration, urinary albumin/creatinine ratio, and arterial elasticity measured by tonometry. They suggested that hyperglycemia and hyperinsulinemia contribute to hypertension in the absence of clinical diabetes, in part by damaging the kidney and arterial wall [20]. Hyperglycemia may damage the kidney and the arterial wall through deposition of advanced

glycation end products, generation of reactive oxygen species, and activation of protein kinase C [21, 22]. Furthermore, hyperinsulinemia stimulates the sympathetic nervous system and the renin-angiotensin- aldosterone system, which may lead to kidney and vascular damage [23, 24]. Mendizapal et al have clarified the possible pathophysiology of IR and its relationship to development of hypertension [25]. A number of proposed mechanisms caused by compensatory hyperinsulinemia associated with IR have been suggested as causes of hypertension. Insulin affects the BP through its direct cardiovascular effects as well as its systemic actions affecting the sympathetic nervous system and kidneys. Insulin increases cardiac contractility [26], increases cardiac output [27], stimulates secretion of the vasoconstrictor ET-1 from vascular endothelium and stimulates vascular smooth muscle cells proliferation and pro-inflammatory activity [28-30]. IR is associated with increased systemic and vascular inflammatory responses and oxidative stress, which may contribute to vascular dysfunction [31]. Insulin also activates the sympathetic nervous system [17] and can increase blood volume by increasing renal sodium retention [32, 33].

Contradictory results were reported by Akanji et al [34] who did not find any association between insulin level and BP in hypertensive or their age- and sex-matched healthy normo-tensive subjects at any time following a standard 75 g OGTT. Savage et al [35] voiced doubt about a direct role of insulin in the short-term regulation of BP. In non-obese normo-tensive and hypertensive subjects we did not find significant association between insulin and BP. Similar results were observed by Baba et al [36] who did not find an association between hyperinsulinemia and elevated BP after OGTT in non-obese middle-aged patients with essential hypertension and their normo-tensive control subjects.

We suggest that most of the studies which failed to detect an association between insulin and BP, investigated the hypertensive and their matched normo-tensive control subjects as one group matched for age and gender and did not take BMI and obesity into consideration. In this study, obese hypertensive patients showed higher insulin levels and the insulin levels correlated directly with BP after intake of glucose. In the non-obese, whether hypertensive or not, we did not find association between insulin and BP. We suggest a link between high BP and elevated insulin. However, to determine whether it is a cause or effect will need further investigation by cohort studies. Our results confirm the old hypothesis that obesity or the metabolic syndrome, especially associated with abdominal obesity, is the link between hypertension and hyperinsulinemia.

Conclusions

The findings from the current study point to the fact that the metabolic, hormonal and BP responses to glucose are highly inter-correlated. Thus, the time and constituents of the last meal prior to BP measurement should be taken into consideration especially when diagnosing hypertension or conducting research on hypertension. The higher insulin response to oral glucose load observed in obese hypertensive patients and the associated acute significant drop that occurred in DBP suggest that the disturbed balance between vasodilator and the well-documented delayed vasoconstrictor sympathetic response caused by high insulin, may play a role in pathophysiology of hypertension especially in obese patients.

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Conflicts of interest: No Conflicts of interest in this study.

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