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Arterial Compliance, Renal, Cardiac, Endocrine and Metabolic Disorders as a Predictors of Hypertension Syndrome

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Hypertension is a late manifestation of a syndrome consisting of dyslipidemia, insulin resistance, endocrine and renal dysfunction, obesity, left ventricular hypertrophy and diastolic dysfunction. The aim of this research is to study the arterial compliance, renal, cardiac, endocrine and metabolic disorders as predictors of hypertension syndrome. Identification and treatment of these patients before the onset of high blood pressure may provide a better opportunity for reversing the disease progress and protecting patients from developing cardiovascular and renal diseases. This study was conducted on 130 cases, 50 patients with essential hypertension, 50 normotensive offspring of the hypertensive patients and 30 healthy subjects without family history of hypertension. All the subjects had electrocardiography, doppler and echocardiography examination for the measurement of arterial compliance, left ventricular diastolic function and left ventricular systolic function. Specific laboratory tests included lipid profile, serum insulin, plasma norepinephrine, plasma renin plasma homocysteine, plasma and urinary endothelin and urinary microalbumin. The results of the present study showed significant statistical increase of total cholesterol, triglyceride, LDL-c, microalbuminuria, insulin, norepinephrin, renin and homocysteine also significant statistical increase of left ventricular mass in hypertensive and offspring groups compared to control group and significant statistical decrease of HDL-c, urinary endothelin and of left ventricular diastolic function in hypertensive and offspring groups compared to control group. There is a significant increase of plasma endothelin in hypertensive group compared to offspring and control groups, while non significant statistical increase of plasma endothelin in offspring group compared to control group. While ejection fraction was statistically decreased in hypertensive group compared to offspring and control groups and there was no difference between offspring and control group. Comparing the hypertensive and offspring groups, there is a negative correlation between arterial compliance and total cholesterol, triglyceride, LDL-c, insulin, renin, norepinephrine, microalbuminuria, homocysteine, plasma endothelin, left ventricular mass and a positive correlation with left ventricular function. There is also a positive correlation between left ventricular mass and cholesterol, triglyceride. LDL-c, insulin, renin, norepinephrine, microalbuminuria, homocysteine, plasma endothelin and negative correlation with left ventricular function. The present study suggested that many of the hypertension syndrome as lipid abnormalities, changes in renal and endocrine functions, insulin resistance and changes in the structure and function of the left ventricle and of vascular smooth muscle precede the onset of high blood pressure and impaired homocysteine metabolism may be considered as one component of the hypertension syndrome. The normotensive offspring with positive family history of hypertension have cardiovascular risk factors similar to that of the subjects with hypertension. Exercise and diet treatment are beneficial and could be the only modality for some patients, whereas early intervention with drug treatment may be necessary to the others to prevent the onset of high blood pressure.

Key words: Insulin, hypertension, cardiovascular

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INTRODUCTION

Much of the focus in the management of hypertension has centered on reducing blood pressure to the normotensive range in the hope that this will decrease the cardiovascular morbidity and mortality so commonly associated with high blood pressure. Although there is no doubt that reduction of high blood pressure is important, particularly with respect to stroke, it has not resulted in the predicted decrease in coronary artery disease in patients treated only for hypertension. One possible reason for this disappointing decrease in heart disease is that high blood pressure is a very late manifestation of a much broader syndrome of cardiovascular risk factors and physicians have focused mainly on lowering the blood pressure. These associated risk factors may be present for years before the onset of high blood pressure and may precipitate a coronary event either before or very soon after the onset of high blood pressure (Crimm *et al*., 1990; Neutel, 2001).

There are many convincing data showing that hypertension is an inherited syndrome of cardiovascular risk factors that clinically manifest at different times and occur independently of one another (Neutel and Smith, 1995). Moreover, it is possible that the patients with the hypertension syndrome will develop coronary artery disease prior to the development of high blood pressure (Neutel *et al*., 1999). When comparing cardiovascular risk factors in normotensive patients with a family history of hypertension to hypertensive patients with and without a family history of hypertension, there were no differences among the groups. All three groups, however, were significantly worse off than normotensive subjects without a family history of hypertension (Neutel, 2000; Glasser, 2001).

Studies show that adult normotensive subjects who have a family history of hypertension exhibit increased incidence of other risk factors, such as high cholesterol, left ventricular hypertrophy, reduced arterial compliance and insulin resistance. These patients with (normotensive hypertension) share many characteristics with patients with fully developed hypertension, both uncontrolled and controlled. The link between these many risk factors and high blood pressure seems to lie in endothelial cell balance. If this balance is upset, elements of the hypertension syndrome start to become manifest, often before blood pressure becomes elevated (Neutel, 2000).

Patients with family history of hypertension (hypertensive-prone patients) had abnormalities of arterial function despite the fact that they were normotensive (Taddei *et al*., 1992). This finding suggests that the abnormalities of arterial structure and function frequently associated with hypertension may precede the onset of high blood pressure (Neutel, 2001). Blood pressure, as well as blood volume hemostasis, depends to a large extent on humoral influences stemming from the renin-angiotensin axis and the sympathetic nervous system (Manica *et al*., 2006). Neutel *et al*. (1999) reported a strong and significant inverse correlation between arterial compliance and plasma levels of norepinephrine, cholesterol and insulin as well as plasma renin activity. This would suggest that these neurohormones, which are powerful growth factors, appear to play an important role in the structural and functional changes of the arteries before the onset of high blood pressure. Thus patients with hypertensive syndrome may inherit abnormalities of neurohormonal function, reduced compliance by causing smooth muscle cell hypertrophy and connective tissue deposit (Glasser, 2001). Renin-angiotensin system plays a central role in the pathogenesis of vascular hypertrophy and arterial stiffness. Angiotensin-converting enzyme inhibitors have been shown to reduce arterial stiffness to a greater degree than diuretics or beta blockers (Izzo, 2000; Abarquaz, 2001).

Left ventricular hypertrophy is a well known cardiovascular risk factor. Left ventricular mass reduction following antihypertensive treatment has also been demonstrated (Braz, 2005). In human hypertension it has been shown that there is a correlation between plasma catecholamine concentrations and left ventricular muscle mass. AngiotensinII concentrations also have been correlated to left ventricular mass (Neutel *et al*., 1999; Glasser, 2001). Left ventricular diastolic dysfunction is strongly related to left ventricular structural abnormalities such as left ventricular hypertrophy and fibrosis and is associated with a poor prognosis. Hypertension is a major underlying disease for left ventricular diastolic dysfunction, even without systolic dysfunction (Elan *et al*., 2006).

In hypertensive patients, the relationship between glucose intolerance, Left Ventricular Hypertrophy (LVH) and Left Ventricular Diastolic Function (LVDF) have been described in several reports which indicate that insulin resistance is an important factor affecting LVH and LVDF (Watanabe *et al*., 1999). Also hypertensive patients with microalbuminuria show higher prevalence of unfavorable left ventricular geometric patterns, depressed left ventricular function and early signs of extra cardiac vascular damage. These findings support the role of microalbuminuria as an indicator of subclinical cardiovascular disease and may account for the worse outcome that is usually associated with increased urinary albumin excretion in essential hypertension (Pontremoli *et al*., 1999; Wachtell *et al*., 2002).

Obesity, insulin resistance, hypertension, dyslipidemia and atherosclerosis often coexist as metabolic syndrome X. Insulin's action could lead to hypertension by stimulating sympatho-adrenal axes or by stimulating vascular smooth muscle cell hypertrophy. Insulin could also cause hypertriglyceridemia and low HDL-c through increased catecholamines (James, 2005). The hypertension and dyslipidemia together greatly increase cardiovascular risk (Reaven *et al*., 1996).

While type 1I diabetes is known to be associated with endothelial dysfunction, only recently has there been evidence that endothelial dysfunction also takes place in insulin resistance state without diabetes (Dell'Omo *et al*., 2004). One possibility could be related to angiotensin II, which shares a common signaling pathway with insulin. Defects in insulin sensitivity may interfere with insulin-stimulated endothelial vasodilatation. This may occur through defects in the phosphotidyl inositol-kinase pathway, which normally stimulates endothelial nitric oxide synthase to produce the vasodilator nitric oxide (James, 2005).

Hyperinsulinemia may affect the activity of endothelin-I (ET-I) system, since insulin has been shown to increase ET-I gene expression in cultured endothelial cells and to enhance ET-I release in both human endothelial and vascular smooth muscle cells. Also it has been demonstrated in humans that hyperinsulinemia is associated with increased plasma ET-I levels. Activation of the ET-I system in the setting of increased body mass may play a role in the development or maintenance of high blood pressure (Cardillo *et al*., 2004).

Interventions to improve insulin sensitivity and hypertension should be initiated early (Tracy *et al*., 1995). Weight loss, even in modest decrements, is effective in reducing obesity-hypertension, possibly by ameliorating several of the proposed pathophysiologic mechanisms (Thakur *et al*., 2001).

Elevated levels of homocysteine (hyperhomocysteinemia) has been implicated as an independent risk factor for cardiovascular disease. The vascular risk associated with hyperhomocysteinemia has been observed to be stronger in hypertensive individuals (Sharma *et al*., 2006) and homocysteine lowering treatment is associated with a reduction in systolic and diastolic blood pressures (Mangoni *et al*., 2002). Thus a considerable body of evidence suggests a role for plasma homocysteine in the pathogenesis of hypertension (Van Guldener *et al*., 2003). Mechanisms by which homocysteine could promote hypertension include increased arterial stiffness (Vermeulen *et al*., 2001), reduced vasodilatory capacity (Mujumdar *et al*., 2001) and insulin resistance (Van Gulender *et al*., 2003). If hyperhomocysteinemia were a risk factor for hypertension, then it would be of public health importance because elevated levels can be lowered through relatively simple nutritional measures such as increased use of folic acid supplements or fortification of foods with folic acid (Lim and Cassano, 2002; Sundstrom *et al*., 2003).

The aim of this study is to study arterial compliance, renal, cardiac, endocrinal and metabolic disorders as predictors of hypertension syndrome. Identification and treatment of these patients before the onset of high blood pressure may provide a better opportunity for reversing disease process and protecting those patients from developing cardiovascular and renal diseases.

MATERIALS AND METHODS

This study was conducted in Theodor Bilharz Research Institute over a period of two years between 2004 and 2006. This study include one hundred and thirty subjects classified into three groups:

Group 1: Fifty subjects with essential hypertension (23 males and 27 females), their age ranged from 49 to 65 years with a mean of 56.22±4.73, divided into two subgroups according to body mass index, the first subgroup (BMI<27), the second one (BMI>27).

Group II: Fifty normotensive offsprings with family history of hypertension (offsprings of group 1 subjects) (31 males and 19 females), their age ranged from 20 to 35 years with a mean of 27.9±4.66, divided into two subgroups according to body mass index, the first subgroup (BMI<27), the second one (BMI>27).

Group III: Thirty healthy normotensive subjects without family history of hypertension (13 males and 17 females), as normal control. Their age ranged from 21 to 30 years with a mean of 25.4±2.76.

Group1 and II subjects were selected from the out-patient clinic of Theodor Bilharz Research Institute Hospital and the control subjects were selected from the laboratory and medical staff.

All the subjects were subjected to history, full clinical examination including calculation of body mass index [BMI = weight/height (kg m^{-2})], electrocardiography and the following laboratory investigations:

- Urine analysis.
- Complete blood picture performed using coulter counter model T660.
- Serum creatinine, blood urea and serum uric acid done by conventional methods, using autoanalyzer (Kone lab 20).

- Serum calcium, Serum sodium and potassium done by ion selective electrode.
- Fasting and postprandial blood sugar (Tietz, 1976).

The blood pressure for all subjects was measured in sitting position and we recorded the average of two or more measurements. Hypertension was defined as a systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg. Normal blood pressure as systolic <130 mm Hg and diastolic <85 mm Hg (Neutel *et al*., 1992).

Exclusion criteria: Patients with diabetes, proteinuria, chronic renal or liver diseases, heart disease, peripheral vascular disease and secondary form of hypertension were excluded by history, clinical examination, laboratory investigations and echocardiography.

Blood sampling: After an overnight fasting blood samples were collected under aseptic condition using clear vein puncture. Fifteen milliliter of blood were drawn and distributed as follows:

- Five milliliter in a dry centrifuge tube, sera were separated for routine laboratory investigations.
- Five milliliter in a prechilled centrifuge tube containing a protein Trasylol and EDETA for determination of endothelin, renin and norepinephrin.
- Five milliliter in prechilled centrifuge tube containing 7.2 mg EDTA for determination of homocysteine and insulin.

Urine sampling: Twenty four hour urine was collected and urine sample was centrifuged. The supernatant was taken and stored frozen at -20°C, then used for determination of microalbuminuria and urinary endothelin.

Specific laboratory tests:

- Serum lipids: total cholesterol, triglycerides, HDL-c and LDL-c (enzymatic methods).
- Microalbuminuria was measured using a competitive solid phase enzyme immunoassay (ELISA). (ORG 5MA- Orgenec Diagnostika, GmbH).
- Serum insulin by a solid phase radioimmunoassay using I^{125}- labeled insulin. ((DPC Diagnostic Products Corporation).
- Plasma norepinephrine (Radioimmunoassay) (IBC Hamburg): Norepinephrine extracted by microtitrate plate is determined by radioimmunoassay, wherein I^{125} tracer noradrenalin competes for a fixed time with norepinephrine in the patient sample for sites on norepinephrine-specific antibody.
- Plasma renin concentration [Diagnostic system laboratory, Inc. (DSL-25100), Active® renin IRMA]: The procedures employs a two-site immunoradiometric assay.
- Plasma homocysteine (ELISA): Homocysteine is an enzyme immunoassay for the determination of total homocysteine in blood (Frantez *et al*., 1998).
- Plasma endothelin (EISA) (Biomedicas group Gesellschaft GmbH): The endothelin test kit is an enzyme immunoassay designed to determine endothelin directly in plasma.
- Urinary endothelin (EISA). With separation of C18 using column extraction (Peninsula laboratories Inc, San Carlos).

Doppler and echocardiography examination: All the subjects had Doppler and echocardiographic examination of the arterial compliance, left ventricular mass and function.

Statistical analysis: The following statistical tests were applied in the statistical analysis of this work:

- Arithmetic mean (x).
- Slandered deviation (SD).
- Correlation test, where
  $p>0.05$ = Not significant, $p<0.05$ = Significant, $p<0.01$ = Highly significant, $p<0.001$ = Very highly significant.

Analysis of the data was carried out using statistical computer program.

RESULTS

Clinical characteristics of the studied groups: The control and the offspring groups showed no significant difference ($p>0.05$) as regard age, BMI, systolic and diastolic blood pressure, but in the hypertensive group the mean age, systolic and diastolic blood pressure were significantly higher than in the control and offspring groups ($p<0.001$). There was no significant difference as regard BMI among the three studied groups. Fifteen patients out of the 50 hypertensive patients had ischemic heart disease but the offspring and the control groups had no ischemic heart disease (Table 1).

Biochemical parameters of studied groups: The three studied groups showed no significant difference ($p>0.05$) as regard serum creatinine, hemoglobin, serum calcium, serum sodium, serum potassium, fasting and post prandial blood sugar. Regarding blood urea and serum uric acid, they were significantly higher in offspring and hypertensive groups ($p<0.05$) than the control group (Table 2).

Table 1: Clinical characteristics of the studied groups

Characteristics	(n = 30)	Control group (n = 50)	Offspring of HTN group (n = 50)	Hypertensive group (HTN)
Sex	F	17	19	27
	M	13	31	23
Age	Range	21-30	20-35	49-65
	Mean	25.4	28.0	56.2
	±SD	2.76	4.67	4.7
BMI (%)	Range	21-30	21-30	21-30
	Mean	26.1	26.3	27.5
	±SD	3.23	2.72	2.9
SBP (mm Hg)	Range	100-130	100-135	140-170
	Mean	118.0	118.4	157.5***, ###
	±SD	6.9	8.36	7.8
DBP (mm Hg)	Range	70-80	70-80	90-110
	Mean	75.67	76.2	99.2***, ###
	±SD	4.69	4.9	6.95
Ischemic Heart Disease		-	-	15

BMI = Body mass index, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, *** p<0.001: Significant difference between HTN group and control group. ### p<0.001: Significant difference between offspring and HTN gp

Table 2: Biochemical parameters of the studied groups

Parameters		Control group (n = 30)	Offspring of HTN group (n = 50)	Hypertensive group (HTN) (n = 50)
S. creatinine	Range	0.6-1.3	0.7-1.2	1.0-1.4
(mg dL^{-1})	Mean	0.95	0.96	1.15
	±SD	0.23	0.17	0.15
Blood urea	Range	15-36	20-40	23-40
(mg d L^{-1})	Mean	28.07	30.7a	34.12**, #
	±SD	3.94	5.43	4.15
Hb	Range	12-14.9	12.1-14.8	11.1-14.5
(mg dL^{-1})	Mean	13.48	13.52	12.79
	±SD	0.96	0.88	1.11
S. Ca	Range	8.6-10.5	8.3-10.3	7.8-10.6
(mg dL^{-1})	Mean	9.47	9.36	9.17
	±SD	0.65	0.68	0.76
S. Na (mEq L^{-1})	Range	130-142	128-144	128-148
	Mean	135.87	135.34	138.3
	±SD	4.17	3.95	4.37
S. K (mEq L^{-1})	Range	3.5-5.2	3.4-5.3	3.5-5.0
	Mean	4.32	4.37	4.32
	±SD	0.61	0.59	0.37
S. uric acid	Range	3.0-6.8	4.0-7.2	5.0-8.5
(mg dL^{-1})	Mean	4.94	5.64a	6.79*,#
	±SD	1.16	0.88	0.89
F. blood sugar	Range	80-115	80-120	88-122
(mg dL^{-1})	Mean	95.23	99.96	104.12*
	±SD	10.84	11.86	9.54
P.P. blood	Range	120-155	120-150	138-150
sugar (mg dL^{-1})	Mean	136.53	138.92	140.1
	±SD	10.77	7.39	6.52

* p<0.05, ** p<0.01: Significant difference between HTN group and control group. # p<0.05: Significant difference between offspring and HTN gp

Lipid profile in the studied groups: The hypertensive and the offspring groups showed significant higher total cholesterol, triglycerides and LDL-c compared to the control group. Also the hypertensive group showed significant higher total cholesterol, triglycerides and LDL-c compared to the offspring group. As regard HDL-c, the hypertensive and the offspring groups showed significant lower HDL-c compared to the control group, also the hypertensive group showed significant lower HDL-c compared to the offspring group (Table 3).

Table 3: Lipids profile in the studied group

Lipids		Control group (n = 30)	Offspring of HTN group (n = 50)	Hypertensive group (HTN) (n = 50)
Total	Range	100-206	116-240	135-260
cholesterol	Mean	143.53	170.62@@	190.62***, #
(mg dL^{-1})	±SD	28.63	29.21	27.28
Triglycerides	Range	54-152	72-278	84-290
(mg dL^{-1})	Mean	89.13	129.36@@	141.4***, #
	±SD	26.59	47.68	49.68
HDL-c	Range	46-56	38-55	36-49
(mg dL^{-1})	Mean	50.9	46.0@	41.82**, #
	±SD	3.29	4.19	3.8
LDL-c	Range	44-133	44-175	66-196
(mg dL^{-1})	Mean	76.97	98.76@	120.48***, ##
	±SD	26.24	29.49	30.86

** p<0.01, ***p<0.001: Significant difference between HTN group and control group, # p<0.05, ##p<0.01: Significant difference between offspring and HTN gp, @p<0.05, @@ p<0.01: Significant difference between offspring and control gp

Specific biochemical parameters of studied groups: The hypertensive and the offspring groups had significant higher microalbuminuria, serum insulin, plasma norepinephrine, plasma homocysteine and plasma renin activity compared to the control group. The hypertensive group had significant higher microalbuminuria, plasma renin concentration compared to the offspring group, but there is no significant difference as regard serum insulin, plasma norepinephrine, plasma homocysteine between the hypertensive and the offspring groups. The hypertensive group had significant higher plasma endothelin compared to control group, but there was no significant difference in plasma endothelin between the hypertensive and the offspring groups and between the offspring and the control groups. As regard urinary endothelin, the hypertensive and the offspring groups had significant lower urinary endothelin compared to the control group. Also the hypertensive group had significantly lower urinary endothelin than the offspring group (Table 4).

Doppler and echocardiographic parameters of the studied groups: The hypertensive and the offspring groups had significant higher left ventricular mass, septal thickness and left ventricular posterior wall thickness compared to the control group and the hypertensive group had significant higher left ventricular mass, interventricular septum thickness, left ventricular posterior wall thickness compared to the offspring group. There was no statistical significant difference in the left ventricular diastolic diameter among the three studied groups. The hypertensive and the offspring groups had significant

Table 4: Specific biochemical parameters of the studied groups

Parameters		Control group (n = 30)	Offspring of HTN group (n = 50)	Hypertensive group (HTN) (n = 50)
Microalbumin-urea	Range	1.7-22	2.8-167	13-425
(ug mL^{-1})	Mean	8.06	63.1@@@	152.3***, ###
	±SD	5.98	37.19	114.92
Insulin	Range	3-19	5.4-58	6.8-68
(uIu mL^{-1})	Mean	9.62	17.33@@	20.82***
	±SD	4.31	11.74	12.73
Norepinephrine	Range	100-240	160-650	140-800
(pg mL^{-1})	Mean	163.67	352.2@@@	374.6***
	±SD	39.35	96.01	146.01
Homocysteine	Range	3.4-20	4.1-39	5.5-55
(µmol L^{-1})	Mean	10.79	13.94@	16.21**
	±SD	5.23	6.04	10.12
P. Endothelin	Range	0.5-2.3	0.98-3.2	0.98-4.3
(F mole mL^{-1})	Mean	1.23	1.58	1.73*
	±SD	0.419	0.47	0.525
U.Endothelin	Range	73-224	51-224	43-192
(pg/24 h)	Mean	140.77	129.92@	113.84*, #
	±SD	35.308	40.35	32.75
Plasma renin	Range	19-46	18-162	19-230
concentration	Mean	30.8	65.36@@	86.34***, ##
(pg mL^{-1})	±SD	7.03	33.87	55.0

*p<0.05, ** p<0.01, ***p<0.001: Significant difference between HTN group and control group, # p<0.05, ##p<0.01: Significant difference between offspring and HTN gp, @p<0.05, @@ p<0.01, @@@p<0.001: Significant difference between offspring and control gp

Table 5: Doppler and echocardiographic parameters of the studied groups

Parameters		Control group (n = 30)	Offspring of HTN group (n = 50)	Hypertensive group (HTN) (n = 50)
Arterial	Range	0.18-0.4	0.06-0.36	0.05-0.32
compliance (AC)	Mean	0.26	0.18@@	0.134***, #
%/10 mm Hg	±SD	0.06	0.07	0.06
Left ventricular	Range	64-136	100-240	108-340
mass (LV mass)	Mean	95.33	177.94@@	226.54***, ##
Gm	±SD	19.19	36.9	42.27
Interventricular	Range	6-10	8-13	11-16
septal thickness	Mean	7.9	11.54@	13.1**, #
(IVST) mm	±SD	1.03	1.13	1.25
Left ventricular	Range	6-11	8-13	9-16
posterior wall	Mean	8.07	11.48@	12.82**, #
thickness	±SD	1.31	1.18	1.51
(LVPWT) mm				
Left ventricular	Range	35-45	36-47	37-48
diastolic diameter	Mean	38.5	40.0	41.1
(LVDD) mm	±SD	2.6	2.4	2.1
Left ventricular	E wave	92.33±4.7	84.94±3.0@	64.2±3.1**, #
diastolic function	A wave	59.27±4.6	74.94±3.0@@	76.84±3.2**
	E/A	1.56±0.12	1.133±0.12@	0.84±0.13*, #
Left ventricular	Range	52-68	46-68	37-64
systolic function	Mean	60.0	59.0	46.9 **, ##
(EF)	±SD	4.39	4.22	5.32

E wave = Early peak diastolic filling, A wave = Late peak diastolic filling, EF = Ejection fraction, * p<0.05, ** p<0.01, ***p<0.001: Significant difference between HTN group and control group, # p<0.05, ##p<0.01: Significant difference between offspring and HTN gp, @p<0.05, @@ p<0.01: Significant difference between offspring and control gp

lower arterial compliance compared to the control group, also the hypertensive group had significant lower arterial compliance compared to the offspring group (Table 5).

As regard the left ventricular diastolic function as determined by E/A ratio where E wave is the early peak diastolic filling and A wave is the late peak diastolic filling. The hypertensive and the offspring groups had significant lower E/A ratio compared to the control group. Also the hypertensive group had significant lower E/A ratio compared to the offspring group.

The hypertensive group had significant lower ejection fraction compared to the offspring and the control groups, but there is no significant difference in ejection fraction between the offspring group and the control group.

Table 6: Comparison of different parameters between hypertensive patients with and without ischemic heart disease (IHD)

Parameters	With IHD (n = 15)	Without IHD (n = 35)
Age	59.5±4.2	54.8±4.3*
Systolic Blood Pressure	162.3±5.6	155.4±7.8*
Diastolic Blood Pressure	102.7±5.9	97.7±6.5*
Body Mass Index	26.3±3.2	26.6±2.8
Blood picture	12.4±1.1	13.0±1.1
S.Creatinin	1.2±0.2	1.2±0.2
Bl. Urea	33.5±4.9	34.4±3.9
S. uric acid	6.7±0.7	6.8±1.0
S. Ca	9.2±0.8	9.2±0.7
S. Na	140.4±4.7	137.4±3.9
S. K	4.3±0.4	4.3±0.4
F. Bl. Sugar	104.3±9.0	104.0±9.9
P.P. Bl. Sugar	139.7±7.9	140.5±6.0
Total Cholesterol	194.1±27.7	189.1±30.1*
HDL-c	42.9±2.9	41.4±4.1
LDL-c	124.0±30.0	119.0±31.5*
Triglycerides	135.3±51.0	144.0±49.6
Microalbuminurea	262.7±112.5	105.0±78.3**
Insulin	22.4±10.2	18.2±11.8*
Norepinephrine	388.7±169.4	368.6±137.1*
Homocysteine	17.5±10.6	13.9±10.0*
P. Endothelin	1.7±0.4	1.7±0.6
U. Endothelin	133.3±32.4	105.5±29.6*
Renin	91.9±66.2	84.0±50.4*
LV mass	232.2±27.9	213.3±46.3*
Arterial Compliance	0.1±0.1	0.1±0.1
Ejection Fraction	46.8±4.8	46.9±5.6
LVPWT	12.1±1.0	13.1±1.6
IVST	12.5±1.1	13.3±1.2
E/A ratio	0.82±0.12	0.86±0.12

* p<0.05, ** p<0.01

Comparison of different parameters between hypertensive patients with and without ischemic heart disease: The hypertensive patients with ischemic heart disease had a significant higher age, systolic and diastolic blood pressure, total cholesterol, LDL-c, microalbuminuria, insulin, norepinephrine, homocysteine, urinary endothelin, renin and left ventricular mass and had significant lower triglycerides concentration than hypertensive patients without ischemic heart disease. Both groups showed no significant differences concerning BMI, hemoglobin, serum creatinine, blood urea, serum uric acid, serum calcium, serum sodium, serum potassium, fasting and postprandial blood sugar, HDL-c, plasma endothelin, arterial compliance, ejection fraction, left ventricular posterior wall and interventricular septum (Table 6).

Table 7: Comparison of different parameters between patients with BMI<27 and patients with BMI ≥ 27 in offspring and hypertensive groups

	Offspring group		Hypertensive group	
Parameters	BMI<27 (n = 17)	BMI = 27 (n = 33)	BMI<27 (n = 28)	BMI = 27 (n = 22)
Insulin	12.3±10.7	22.4±12.8***	14.8±10.7	26.0±14.1**
Total cholesterol	160.2±22.4	181.2±32.6**	175.4±24.2	205.2±29.8**
Triglycerides	119.4±34.6	139.2±49.2*	122.4±41.6	160.2±45.8**
HDL-c	53.1±3.2	39.2±5.2**	44.6±2.6	38.8±3.8*
LDL-c	78.8±26.2	118.4±31.2***	102.2±28.4	138.6±32.4**
LV mass	168.0±38.2	188.0±38.2*	206.5±43.2	246.6±40.2**
E/A	1.133±0.12	1.131±0.12	0.86±0.12	0.82±0.14
Microalbuminurea	61.6±38.1	65.2±36.2	149.8±104.9	157.2±114.9
P. Endothelin	1.48±0.56	1.68±0.64	1.62±0.44	1.84±0.58
Plasma Renin Conc.	69.4±34.8	68.8±32.9	87.6±52.0	88.4±56.0
Norepinephrin	346.6±90.1	358±98.4	368.6±148.2	372.2±144.2
Homocysteine	15.8±6.2	11.8±6.0	18.2±8.2	14.2±10.2

*p<0.05, **p<0.01, ***p<0.001

Table 8: Correlation coefficient (r) between arterial compliance and different parameters in hypertensive and offspring groups

Parameters	HTN group	Offspring group
Arterial Compliance (AC)		
Cholesterol	-0.321*	-0.382*
Triglycerides	-0.362*	-0.324*
LDL-c	-0.331*	-0.311*
HDL-c	0.042	0.064
Insulin	-0.532***	-0.506***
Renin	-0.546***	-0.588***
Norepinephrine	-0.313*	-0.218*
Microalbuminuria	-0.286*	-0.306*
Homocysteine	-0.432**	-0.261*
Endothelin	-0.098	-0.211*
LV diastolic function (E/A)	0.443**	0.623***
LV mass	-0.421**	-0.402**
Ejection Fraction	0.426**	0.286*

* p<0.05, ** p<0.01, *** p<0.001

Table 9: Correlation coefficient (r) between left ventricular mass and different parameters in hypertensive and offspring groups

Parameters	HTN group	Offspring group
Left Ventricular mass (LV mass)		
Cholesterol	0.383*	0.388*
Triglycerides	0.368*	0.358*
LDL-c	0.568***	0.386*
HDL-c	-0.081	-0.098
Insulin	0.681***	0.432**
Renin	0.486**	0.521***
Norepinephrine	0.388*	0.396*
Microalbuminuria	0.482**	0.521***
Homocysteine	0.442**	0.288*
Endothelin	0.521	0.482**
LV diastolic function (E/A)	-0.348*	-0.488**
Ejection Fraction	-0.286*	-0.288*

* p<0.05, ** p<0.01, *** p<0.001

Comparison of different parameters between patients with BMI<27 and BMI>27 in offspring and the hypertensive groups: The patients with BMI>27 had significant higher plasma insulin, total cholesterol, LDL-c and left ventricular mass and significant lower HDL-c compared to patients with BMI<27 while the other parameters (endothelin, microalbuminuria, renin, norepinephrine, homocysteine and E/A ratio) showed no significant difference (Table 7).

Correlation coefficient (r) between arterial compliance and different parameters in hypertensive and offspring groups: Both groups showed significant inverse correlation between arterial compliance and total cholesterol, triglycerides, LDL-c, insulin, renin, norepinephrine, microalbuminuria, homocysteine and left ventricular mass but a positive correlation between arterial compliance and ejection fraction and left ventricular diastolic function and significant positive correlation with HDL-c (Table 8).

Correlation coefficient between left ventricular mass and different parameters in hypertensive and offspring groups: Both groups showed significant positive correlation between left ventricular mass and total cholesterol, triglycerides, LDL-c, insulin, renin, norepinephrine, microalbuminuria, homocysteine and endothelin. Both groups showed significant inverse correlation between left ventricular mass and ejection fraction and left ventricular diastolic function and significant inverse correlation with HDL-c (Table 9).

DISCUSSION

In the present study we demonstrated that total cholesterol, triglycerides and LDL-c are significantly higher in hypertensive group and offspring group compared to the control group and HDL-c is significantly lower in hypertensive and offspring groups compared to control group. These results agreed with those mentioned by Weber *et al.* (1991), Neutel *et al.* (1992), Neutel *et al.* (1999), Cobe (1998), Glasser (2001), Neutel (2001) and Joshi *et al.* (2003), who reported that lipid abnormalities in subjects with family of hypertension precede blood pressure abnormalities in patients likely to develop high blood pressure over next few years.

During the past few years, microalbuminuria has become a prognostic marker for cardiovascular and/or renal risk in diabetic and nondiabetic subjects. In essential hypertension, an increased transglomerular passage of albumin may result from several mechanisms e.g., hyper filtration, glomerular basal membrane abnormalities, endothelial dysfunction and nephrosclerosis (Redon and Pascual, 2006).

Microalbuminuria is frequently seen in patients with established essential hypertension and is a predictor of a higher risk for cardiovascular and probably renal dysfunction. This fact indicates that the detection of an

increased urinary albumin excretion could probably the best index of an increased global cardiovascular risk in a given patient. Blood pressure control is accompanied by a fall in the content of albumin in urine. Angiotensin converting enzyme inhibitors have shown a capacity to decrease urinary albumin excretion, which is independent of their ability to lower blood pressure (Rodico *et al*., 1998; Abarquez, 2001).

Multiple clinical studies demonstrated an increased relative risk of cardiovascular events in patients with insulin resistance (syndrome X). Hyperinsulinemia leads to hypertension both directly by effects on renal sodium excretion and most importantly, by sympathetic stimulation (Ruige *et al*., 1998; Raji *et al*., 2001; Imazu, 2002; Decasi and Monlar, 2003).

The sympathetic nervous system and the renin-angiotensin system are believed to play an important role in the pathogenesis of high blood pressure. Many studies suggested that activation of the neuroendocrine function may occur before the development of high blood pressure, so the hypertensive effects of these hormonal system are not entirely due to their vasoconstrictor properties but may also result from their influence on the structure and function of cardiovascular smooth muscle (Neutel *et al*., 1999; Lambert, 2000). By interrupting the influences of angiotensin II on sympathetic function, therapeutic interventions aimed at blocking the renin-angiotensin system exert favorable effects on the hemodynamic, metabolic and renal profile. This has important implications for the treatment of hypertension, congestive heart failure, renal insufficiency and metabolic syndrome (Manica *et al*., 2006).

In this study, we demonstrated that microalbuminuria, plasma insulin and plasma norepinephrine concentrations and plasma renin activity are significantly higher in hypertensive and offspring groups compared to the control group, these results are in agreement with those of Weber *et al*. (1991), Neutel *et al*. (1992), Neutel *et al*. (1993), Masuo *et al*. (1998). Glasser *et al*. (2001) and Neutel *et al*. (2001) who demonstrated that microalbuminuria, insulin, norepinephrine and plasma renin concentration were significantly higher in patients with family history of hypertension than in the normotensive without family history of hypertension. Microalbuminuria may be related to increased plasma renin activity in subjects with family history of hypertension. Increased activity of renin-angiotensin system can cause efferent arteriolar vasoconstriction, which in turn results in glomerular hypertension, hyperfiltration and increased albumin excretion (Neutel *et al*., 1999; Neutel, 2001). Insulin is a powerful growth factor that directly stimulates smooth muscle proliferation in the circulation, in addition, it plays an important role in the promoting the action of other growth factors on vascular tissue. Moreover, insulin appears to enhance formation of atherosclerotic plaque by facilitating the transport of atherogenic lipid particles into the media of the vessel wall. Increased insulin levels also appear to be associated with high blood pressure through its stimulating effect on the sympathetic nervous system and also causes reabsorption of sodium by the kidney (Williams *et al*., 1990; Gupta *et al*., 1992; Imazn, 2002).

Hyperhomocysteinemia is increasingly recognized as a risk factor for vascular disease affecting heart, brain and extremities. A considerable amount of genetic, biochemical, pathophysiological, clinical and epidemiological data suggest a causal role for hyperhomocystinemia in the development of atherosclerosis and thrombosis (Chico *et al*., 1998; Durand *et al*., 2001; Boysen *et al*., 2003). Detecting hyperhomocysteinemia in patients at high risk of CVD is of importance, because safe and effective treatment is currently available. Administration of folate, vitamin B12, vitamin B6 and betaine are very effective in reducing homocystein concentrations in plasma (Stampfer and Malinow, 1995; Desouza *et al*., 2002; Wold *et al*., 2003).

In this study we demonstrated that plasma homocystein is significantly higher in hypertensive and offspring groups compared to the control group, these results are in agreement with those of Mendis *et al*. (1999) who mentioned that patients with essential hypertension had significantly higher serum concentration of homocysteine compared to normal healthy subjects and in agreement with results of Jong *et al*. (1997) who found a high prevalence of hyperhomocysteinemia in siblings of young patients with vascular disease and hyperhomocysteinemia. Kahleova *et al*. (2002) showed that essential hypertension in adolescent is associated with decreased folate and increased homocysteine level. These data suggest that disturbed folate and homocysteine metabolism in young individuals may play a role in early stage of hypertension. Jain *et al*. (2003) showed that plasma homocysteine levels were found to be significantly higher in patients with hypertension and their normotensive siblings compared to controls without family history of hypertension. Thus plasma homocysteine may serve as a marker for the development of essential hypertension.

The endothelins (ET) are potent vasoconstrictor peptides produced in many different tissues, particularly in the endothelium of blood vessels. Endothelin-1 may play important roles in the pathophysiology of cardiovascular and renal diseases. This is recognized by the potential therapeutic use of endothelin antagonists or

endothelin converting enzyme inhibitors (Schiffrin, 1998; Iglarz and Schiffrin, 2003).

In the present study we demonstrated that plasma endothelin is significantly higher in hypertensive group compared to the control group but there is no significant difference between hypertensive group and offspring group and between the offspring group and the control group. These results are consistent with those of Leonardis *et al.* (1995) who reported that plasma endothelin was significantly higher in essential hypertension than in healthy subjects. On the other hand Davenport *et al.* (1990) and Susuki *et al.* (1990) reported that circulating plasma levels of endothelin were not increased in patients with essential hypertension. Plasma endothelin concentration in essential hypertension was found to be normal in patients with mildly elevated blood pressure (Schiffrin and Thibault, 1991), but increased in patients with moderate to severe hypertension (Kohno *et al.*, 1990; Schiffrin, 2001).

Present results showed that urinary endothelin is significantly lower in hypertensive and the offspring groups compared to the control group. These results agreed with Hoffman *et al.* (1997) who reported that the urinary endothelin was markedly decreased in essential hypertension than in healthy subjects, while Leonardis *et al.* (1995) showed that the urinary excretion of endothelin in essential hypertension was identical to that in normotensive subjects. The possible sources of urinary endothelin could be either circulating endothelin, which is filtered by the kidney or local production within the kidney. The decreased amount of urinary endothelin-1 in patients with essential hypertension represent a reduction in renal production of ET-1. This reduction in renal endothelin synthesis may be secondary to systemic hypertension with high renal perfusion pressure, similar to the pressure related renin release from juxtaglomerular apparatus. However, the possibility that the decreased renal production of ET-1 is a primary phenomenon in these patients and has an etiological role in the development of essential hypertension cannot be excluded (Abassi *et al.*, 1992).

Hypertension is characterized by structural changes in the arterial wall. Hypertrophy and hyperplasia of arterial wall is linked to increased laying down of connective tissue elements. As hypertension progresses, high systolic blood pressure produces additional structural changes in the vessel walls that results into decreased arterial compliance. As blood pressure increases, arterial distensibility depends less on the relatively extensible elastin and becomes more dependent on the more rigid collagen components. In hypertensive patients, reduced arterial compliance is not necessarily linked to rise of blood pressure and abnormalities of vascular compliance can precede rise of blood pressure. Furthermore, it has been demonstrated that reduced compliance causes an increase in blood pressure and therefore may play a role in the pathophysiology of increased blood pressure (Safar *et al.*, 1987; Weber *et al.*, 1991; Neutel *et al.*, 1999; Glasser, 2001).

In the present study, we showed that arterial compliance is significantly lower in hypertensive and offspring groups compared to the control group. These results confirm the previous results of Weber *et al.* (1991); Neutel *et al.* (1992), Neutel *et al.* (1999) and Glasser (2001) who mentioned that the abnormalities of arterial structure and function frequently associated with hypertension may precede the onset of high blood pressure.

Although sustained high blood pressure can produce secondary hypertrophy of left ventricle, there is evidence that left ventricular hypertrophy and impaired diastolic function may actually precede the onset of hypertension or develop early in its course (Drayer *et al.*, 1981; Gosse *et al.*, 1999; Glasser, 2001).

In this study, we demonstrated that the left ventricular mass, interventricular septum and left ventricular posterior wall thickness are significantly greater in hypertensive and offspring groups compared to the control group. These results are consistent with those of Weber *et al.* (1991), Neutel *et al.* (1999), Neutel (2000), Neutel (2001), Cooke *et al.* (2001) and Glasser (2001) who reported that the abnormalities of left ventricular muscle mass may occur before the development of high blood pressure. Therefore left ventricular hypertrophy is another cardiovascular risk factor that appears to be genetically determined and commonly associated with high blood pressure, but its presence is independent of and may occur before the onset of high blood pressure.

Our results showed that Left Ventricular Diastolic Function (LVDF) is significantly decreased in hypertensive and offspring groups compared to the control group. So delayed diastolic filling precede the onset of high blood pressure and with advanced stages of hypertension, this may result in congestive heart failure (Bogaty *et al.*, 2002). We also found that the ejection fraction is significantly decreased in hypertensive group compared to the offspring and the control groups but there is no difference in ejection fraction between the offspring and the control groups. These results agreed with those of Savage *et al.* (1979) and Schilleci *et al.* (2002) who mentioned that mean left ventricular ejection fraction diminished with increased severity of hypertension.

In this study, microalbuminuria, insulin, plasma renin, plasma homocysteine, total cholesterol and LDL-c are significantly higher in hypertensive patients with ischemic heart disease compared to hypertensive patients without ischemic heart disease. These results are in consistent with those of Neutel *et al.* (1999) and Imuzu (2002) who showed that increased insulin concentration were implicated in the development of coronary artery disease and patients with higher insulin levels had increased concentration of cholesterol, triglycerides and decreased HDL-c. Aronow *et al.* (1997) mentioned association between plasma renin activity and coronary heart disease through its association with left ventricular hypertrophy.

In this study, a significant higher plasma insulin, total cholesterol, triglycerides, LDL-c and left ventricular mass and significantly lower HDL-c were recorded in patients with body mass index>27 g m^{-2} than patients with body mass index<27 g m^{-2}. So obesity is associated with metabolic complications considered to be risk factor of cardiovascular disease, including insulin resistance, hyperinsulinemia, glucose intolerance, NIDDM, hypertension, changes in concentrations of plasma lipids and lipoproteins Pereira *et al.* (2002) and Rosa *et al.* (2001) showed association between obesity and increased left ventricular mass.

In the present study we showed a significant inverse correlation between arterial compliance and norepinephrine, insulin, renin, left ventricular mass, total cholesterol, triglycerides, LDL-c and microalbuminuria, but there was a positive correlation between arterial compliance and left ventricular diastolic function. These results agreed with those of Neutel *et al.* (1992), Neutel *et al.* (1999), Weber *et al.* (2000) and Neutel (2001) who mentioned that in normotensive subjects with abnormal arterial compliance have a strong and significant inverse correlation between arterial compliance and plasma levels of norepinephrine, cholesterol, triglycerides, insulin and plasma renin activity. This would suggest that these neurohormones, which are powerful growth factors, appear to play an important role in the structural and functional changes of the arteries before the onset of high blood pressure. Furthermore, it is believed that stiff vessels actually cause increase in blood pressure. Thus patients with hypertension syndrome may inherit abnormalities of neurohormonal function. By time, the growth effects of these hormones will alter vascular compliance by causing smooth muscle hypertrophy and connective tissue deposit. This activity has a dual effect. It creates an environment for development of atheromatous plaques and possibly cardiovascular disease and increases arterial stiffness, resulting in increased blood pressure (Neutel *et al.*, 1999).

CONCLUSIONS

Finally, the present study confirmed that, many of the components of the hypertension as lipid abnormalities, changes in renal and endocrine function, insulin resistance and changes in the structure and function of the left ventricle and of vascular smooth muscle in the vasculature precede the onset of high blood pressure and that impaired homocysteine metabolism may be considered as one component of the hypertension syndrome.

In terms of cardiovascular risk, the normotensive offspring with positive family history of hypertension have cardiovascular risk factors similar to that of the subjects with hypertension, the two groups are at similar risk for cardiovascular disease, the only difference being that the normotensive subjects have not yet developed high blood pressure, which seems to be a late manifestation of this disease process. Identification and treatment of these patients earlier in the disease process, before they develop high blood pressure, then we might have a bigger impact on the course of the disease and might protect them from developing high blood pressure and perhaps thereby protect them from developing cardiovascular disease.

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