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Impaired Fibrinolysis: Another Risk for Hypertensives

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Abstract

The study comprised 30 hypertensive normoglycemic female patients subdivided into 2 groups according to body mass index (BMI). Group I, 15 hypertensive obese females with a BMI above 30 kg/m^2. Group III, 15 non obese hypertensive females with a BMI below 30 Kg/m^2. The groups were compared to 10 normotensive control subjects. They were subjected to detailed history taking and full clinical examination. Some anthropometric measures including weights and BMI were taken. Finally they were subjected to laboratory investigations including determination of serum cholesterol, triglycerides and plasma plasminogen activator inhibitor -1. Our results concluded a statistically significant elevation of serum cholesterol, triglycerides and plasminogen activator inhibitor -1, in both the obese and non obese hypertensiye female patients in comparison to the normal control subjects. Also, there was positive correlation coefficient between PAI-1, cholesterol and TG in both obese and non obese patients. We suggest that, control of elevated cholesterol, triglycerides, PAI through a diet regimen or otherwise is as important as the control of elevated blood pressure itself.

Introduction

IT is now established that hypertension is an important risk factor for the development of coronary heart disease (CHD). It is thought that a certain blood lipid concentration is necessary for hypertension to become an atherogenic factor of clinical importance [1]. Indeed, a combined reduction of blood pressure and serum cholesterol level was necessary to achieve a reduction in the incidence of cardiovascular disease in the Gothenburg study of hypertensive patients [2].

Tissue plasminogen activator (*t*-PA) and plasminogen activator inhibitor (PAI-1) are now considered to be key components of the fibrinolytic system.

Release of tissue plasminogen activator (*t*.PA) from the vessel wall and the plasma concentration of plasminogen activator inhibitor-1 (PAI-1) are 2 important factors in the regulation of in vivo fibrinolytic function. An impaired function in patients with

thrombotic disease, either due to decrease in release of *t*. PA from the vessel wall endothelial cells, or more commonly to increased *p* sma PAI-1 levels or a combination of both [3]. It seems probable that, by virtue of their predictive value for myocardial infarction and for cardiovascular death [4], they may prove valuable as new cardiovascular risk factors.

The mechanisms whereby *t*-PA and PAI-1 changes produce, a hypofibrinolytic state are still unclear, but it has been suggested that several of the well-established risk factors for myocardial infarction such as smoking [5] hypertriglyceridaemia [6]. High waist/hip ratio [7] are associated with a decrease in fibrinolytic activity.

Our goal was to evaluate tissue plasminogen activator-1 as well as some other risk factors as serum cholesterol and triglycerides in hypertensive females (obese and non obese).

Material and Methods

This study comprised 30 hypertensive normoglycemic female patients, their age ranged from 30-50 years, with a mean age of 41.5+5.8 years, in comparison to 10 normotensive female subjects aged from 30-50 years with a mean of 41.3+4.6 years.

The studied hypertensive female subjects were grouped into 2 groups according to their BMI.

Group I: The obese hypertensive group: Which comprised 15 patients, with BMI above 30 Kg/m^2, their BMW ranged from (31.2-45.8) Kg/m^2 with a mean value of 37.7+4.9 Kg/m^2.

Group II: The non doese hypertensive group: with BMI below 30 Kg/m^2 which comprised 15 patients- their BMI ranged from 19.5-25.2 Kg/m^2 with a mean value of 22-1.9 kg/m^2.

Group III: 10 normotensive control group: their BMI ranged from 20.3-27 Kg/m^2 with a mean value of 23.5+1.8 Kg/m^2. All studied cases were subjected to:

1- Full Clinical Evaluation:

Including history taking, stressing on duration of hypertension and drugs used for its control or otherwise. Those on drugs affecting haemostatic system e.g. oral contraceptives or antirheumatics were excluded.

2- Full Clinical Examination:

Weight and height were measured to determine body mass index (BMI) which was calculated as weight in Kg divided by height in m^2 [8].

Hypertension was defined as systolic blood pressure above 160 mmHg and/or diastolic blood pressure above 95 mmHg on at least two separate occasions. The systolic level was determined by the first appearance of sounds and the diastolic level by muffing of sounds [9].

3- Laboratory Investigations:

All cases were subjected to the following:

- Serum cholesterol, using the enzymatic colorimetric test according to Richmond [10].
- Serum triglycerides, using the enzymatic colorimetric test with lipid clearing factor according to koditschek and Umbreit [11].
- Plasminogen activator inhibitor (PAI).

The samples were taken at early morning from 8 a.m. to 9 a.m. selected from patients admitted to the internal medicine de-

partment of kasr El-Eini Hospital, Cairo University.

Determination of the PAI capacity in human plasma was done according to Pralong et al. [12] using the chromotimer machine.

Results

The results of the present work are shown in tables 1 &2 and Figs. 1-4.

Table (1): Serum Cholesterol (mg/dl), Serum Triglycerides (mg/dl) and Serum PAI (u/ml) Levels of the Three Studied Groups.

Serum cholesterol	Obese hypertensive female (No. = 15)	Non obese hypertensive female (No. = 15)	Control subjects No. = 10
Rage	200-325	190-360	75-212
Mean	289	276	155.7
S.D.	30.5	48.5	54.1
Serum triglycerides	Obese hypertensive females(No. = 15)	Non obese hypertensive female (No. = 15)	control subjects No. = 10
Range	180-310	150-340	83-201
Mean	260.7	245	129.6
S.D.	34.1	52.2	43.6
SerumPAI	Obese hypertensive females (No. = 15)	Non obese hypertensive female (no. = 15)	control subjects No. = 10
Range	2.43-8.74	1.54-8.52	0.84-3.63
Mean	5.4	5.3	2.00
S.D.	1.4	2.1	0.80

Table (2): Correlation PAI with Cholesterol and Triglycerides in the Three Studied Groups.

Correlation of PAI with	Cholesterol			T.G.		
	r	*p*	Significane	*r*	*p*	Significane
1- The obese group	0.74	0.0001	H.S.	0.74	0.0001	H.S.
2- The non obese group	0.70	0.001	H.S.	0.66	0.001	H.S.
3- The control group	0.59		NS	0.34		NS

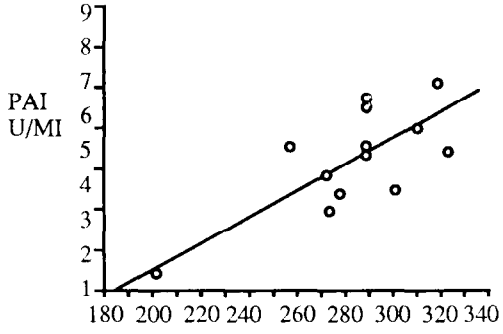

Fig. (1): Correlation coefficient between PAI and cholesterol in the obese grou.
p r = 0.74 p = 0.0001.

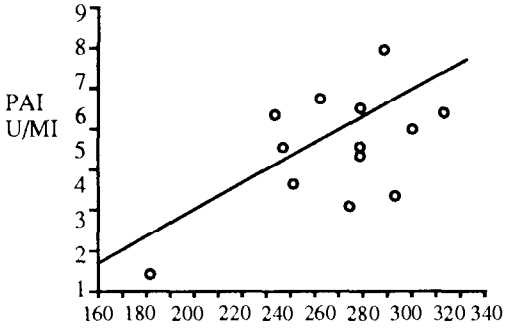

Fig. (2): Correlation coefficient between PAI and T.G. in the obese grou.
p r = 0.74 p = 0.0001.

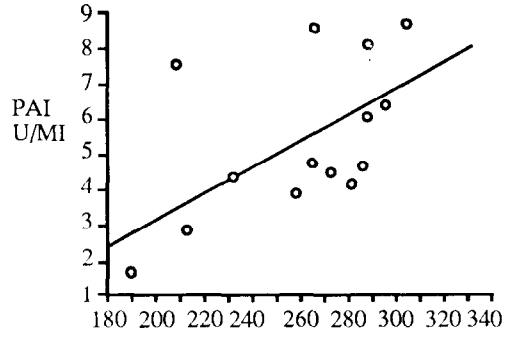

Fig. (3): Correlation coefficient between PAI and cholesterol in non obese group.
p r = 0.70 p = 0.0001.

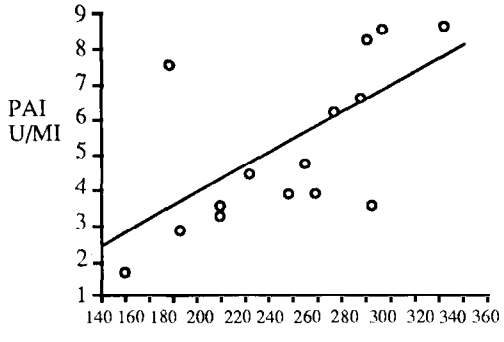

Fig. (4): Correlation coefficient between PAI and non obese group.
p r = 0.66 p = 0.0001.

Discussion

It is now established that hypertension is an important risk factor for the development of coronary heart disease (CHD). But it has been extremely difficult of demonstrate a preventive effect of traditional antihypertensive therapy to reduce the occurrence of myocardial infarction or angina, [13]. It is thought that a certain blood lipid concentration is necessary for hypertension to become an atherogenic factor of clinical importance [1]. Indeed, a combined reduction of blood pressure and serum cholesterol levels was necessary to achieve a reduction in the incidence of cardiovascular disease [2].

The fibrinolytic capacity of human blood is the result of a balance between plasminogen activators and inhibitors. Tissue type plasminogen activator (t -PA) constitutes one physiologically important pathway of plasminogen activation. An in-

hibitor of plasminogen activator (PAI-1) has been described [14]. It inactivates the tissue plasminogen activator very rapidly preventing the transformation of plasminogen into plasmin. Its synthesis by endothelial cells, hepatocytes and fibroblasts is enhanced under conditions such as local hemostasis and in the presence of endotoxine or cytokines [15].

Tissue plasminogen activator and plasminogen activator inhibitor PAI-1) are considered to be the key components of the fibrinolytic system. It seems probable that, by virtue of their predictive value of myocardial infarction and/or cardiovascular death, they may prove valuable as new cardiovscular risk factors [4].

Our results concluded a statitically significant increased level of serum cholesterol, triglycerides and PAI in obese as well as non obese hypertensive females when compared to normal control subjects.

Serum cholesterol levels show statistically significant elevation in both the obese and non obese hypertensive females when compared to normal control subjects ($p1$ = 0.0001, p 2=0.0001) but the difference between the obese and non obese groups was insignificant.

Serum triglycerides level was found to be statistically elevated in both the obese and non obese hypertensive females when compared to normal control subjects ($p1$ = 0.0001, p 2=0.0001). But the difference between two groups was insignificant.

Our study showed an elevated level of PAI-I in both the obese as well as the non obese group. As its mean value in the obese group was 5.4+1.4 μ/ml in the non obese group was 5.3+2.1 μ/ml and in the control group it was 2.0+0.8 μml. Serum PAI in both the obese and non obese group showed highly significant elevation when compared to control group as (p) value in both groups was (0.0001). The comparison between the obese and non obese groups was found to be statistically insignificant. Francis and his colleagues [15] showed that hypertension combined with elevated cholesterol and T.G. level is a cardiovascular risk factor. As it is linked to a decreased fibrinolytic capacity. PAI and t-PA are synthesized in the vascular endothelium and the hypofibrinolysis may therefore indicate endothelial dysfunction as a common denominator is the promotion of cardiovascular complication of hypertension in combination with hyperlipidaemia and perhaps, even in pathogenesis of atherosclerosis.

Wallace and his colleagues [16] concluded that the pathogenicity of hypertension is due to other metabolic disorders as elevated cholesterol, triglycerides, insulin levels and insulin resistance. Smith and his colleagues [17] showed that hyperinsulinaemia associated with hypertension leads to metabolic disturbance as elevated cholesterol and triglycerides levels. Furthermore, insulin has been shown to produce significant increase in plasma norepinephrin level which could further contributed to an elevated blood pressure.

Recent evidence suggest that insulin is an important regulator of PAI-I in man [18].

Alessi and co-workers in 1988 [19] concluded that, hyperinsulinaemia in hypertensive patients leads to elevated level of PAI in those patients as insulin stimulates the synthesis of PAI-I by human hepatocyte in vitro.

Also Landin his colleagues [18] studied some metabolic disorders in mild hypertension even in the absence of obesity and concluded a higher glucose and insulin lev-

el, insulin resistance, higher cholesterol and triglycerides levels as well as elevated fibrinogen and PAI-I.

On the other hand Peiser and his colleagues in 1990 [20] found tthat increased plasma PAI-I capacity found in arteriosclertic patients is a relatively non specific phenomenon associated with arterial vessel disease.

Our results showed also a positive correlation coefficient between PAI in both the obese and non obese hypertensive females and serum cholesterol and triglycerides levels (p =0.0001) (Figs. 1-4).

This is in agreement with Hamsten and colleagues [4] who showed that hypertriglyceridaemia may be associated with an increased tendency to thrombosis as a result of impaired fibrinolytic capacity. Also AZnar his colleagues [21] showed that, there is a link between the elevated level of PAI-1 and two primary factors, hypertension and hypertriglyceridaemia in the development of thrombosis.

Simpson and his colleagues [22] suggested that hypertriglyceridaemia and hypercholesterolaemia lead to hypercogulability in hypertensive patient.

Furthermore, Sundell and his colleagues in 1989 [6] showed that patients with hypertension and elevated cholesterol level had a reduction in the fidrinolytic system activity as a result of high PAI-1 level.

Our results also confirmed those of Jansson and co-workers in 1991 [23] who showed that serum cholesterol and triglycerides levels were independently significantly associated with PAI-1.

On the contrary Landin and colleagues [18] found that both serum triglycerides and cholesterol levels were not significantly correlated with plasma PAI-1 level. From the previous data, hypertension is aassociated with other metabolic risk factors as impaired fibrinolytic system as a result of elevated level of PAI-1, elevated cholesterol and triglycerides levels. These disturbances are likely to be important for the thrombotic process in an atherosclerotic plaque and it may be even more important to treat them than the elevated blood pressure. The incidence of the thrombotic disorders can be limited by diet intervention programme cauaing a reduction in the patients mean plasma triglycerides level, reduction in triglycerides level caused a significant increase in fibrinolyic activity [22].

So we come to the conclusion that the pathogenicity of hypertension is attributed to many associated risk factors of which hypofibrinolysis is evident. The three studied risks are independently significantly correlated. The insignificant role of obesity in our results since there had been no significant difference between the obese and the nonobese females studied regarding cholesterol, T.G. and PAT.1 suggests that hypertension through a vascular endothelial factor or through an associated hyperinsulinaemia is the leading cause.

We suggest that Control of elevated cholesterol, triglycerides and PAI through diet regimen or otherwise is as important as the control of blood pressure itself.

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