Obesity, hypertension and atherosclerosis

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Reprinted from INTERNATIONAL ANGIOLOGY

Vol. 12 - No. 4 - pp. 326-330 (December 1993)

EDIZIONI MINERVA MEDICA - TORINO

Hypertension and obesity are associated with an increased risk of clinical cardiovascular complications due to atherosclerosis. Moreover has been reported that hypertension may predispose to atheroma development. In the present review some common aspects to hypertension and atherosclerosis including smooth muscle cell proliferation, endothelial damage and intervention of growth factors have been analyzed. Additional data have to be provided to explain if the connections between hypertension and atherosclerosis could be considered two effects with one unknown cause. In addition some aspects related to obesity and atherosclerosis have been dissected. In particular we have reported our results indicating that young obese subjects without risk factors for cardiovascular disease have already several markers of cardiovascular damage i.e. atherogenetic lipid pattern, pro-thrombotic and hypofibrinolitic pattern without sign of coagulation and/or platelet in vivo activation, increased plasma endothelin and catecholamine values, rised fasting and after OGTT insulin levels. In view of this more extensively data have to be necessary to support the opinion that obesity and atherosclerosis could be two associated conditions evolving during the time to develop cardiovascular disease or events.
[Int Angiol 1993; 12:326-330].

Key words: **Obesity - Hypertension - Atherosclerosis.**

Atheroma as expressed by deaths from myocardial infarction or cerebrovascular events is the major killer in industrialized nations. The major risk factors involved have been reviewed by some Authors [1 2] and include age, diabetes, family history for the development of cardiovascular diseases, diets leading to high serum cholesterol levels, smoking, hypertension, lack of physical exercise, obesity, psychosocial factors (stress) and increased levels of factor VII and fibrinogen [3].

Paper presented at the 2nd International Joint Workshop on Atherosclerosis, Peripheral Arterial Disease, New Trends in Cardiovascular Therapy (Monte-Carlo, January 28-30, 1993).

Much has been written about the development of atheroma and the many and varied factors which are likely to be involved.[4 5] It is our contention that two important factors involved in the development of atheroma and cardiovascular damage are hypertension and obesity.

The following review will discuss the connections between hypertension and overweight with some aspects of atherosclerosis.

Hypertension and atherosclerosis

Epidemiological aspects

Hypertension is perhaps the most important risk factor underlying cardiovascular morbidity and mortality in industrialized countries. Several epidemiological data show a steady increase in risk with increasing elevations of both systolic and diastolic blood pressure.[6 7] Hypertension is a major factor underlying the 500,000 strokes and the 175,000 deaths from strokes that occur annually in the USA; it is also a significant contributing factor in the 1,500,000 heart attacks and 567,000 fatal heart attacks each year.[8]

Data from the Framingham Study [9] show that hypertensive subjects experienced a seven-fold greater incidence of stroke, a five fold increase in congestive heart failure and a three-fold rise in coronary heart disease as well as a doubling of peripheral arteriosclerosis when compared with normotensive individuals. A continuous exponential increase in risk is present over the whole range of blood pressure.[9]

Although epidemiological data have demonstrated conclusively that hepertension is a major determinant of cardiovascular complications, its effect on the atherosclerotic process is less clear.

The international atherosclerosis project involving 14 countries and 23,000 autopsied cases perhaps provides the best data on the extent and severity of arterial lesions.[10] This showed:

1) the mean extent of fatty streak and raised lesions in the coronary arteries and aorta of hypertensives was significantly greater than in controls;

2) fibrous plaques and advanced lesions with calcification were more frequently seen in hypertensives than normotensives and this has been confirmed by Matova [11] and by Kagan.[12]

Reviews on the influence of hypertension [13] and antihypertensive drugs in atherogenesis [14] conclude that hypertension and other haemodynamic factors appear to have a major influence on the development of atherosclerotic disease.

In addition it could be that the development of atheroma in mild hypertensives without any ischemic heart disease is minimal over the 4-5 years' duration of the prospective studies. This is supported by the fact that in the majority of patients the rate of progression of atherosclerosis is moderate, taking at least 5-8 years to develop.[15]

In contrast patients with more severe hypertension with or without ischemic heart disease, are likely to be higher risk cases and therefore stand to benefit more from antihypertensive treatment.[16]

The inherent difficulties in reversing atherosclerosis were recently reviewed, when it was concluded that the treatment of hypertension and other risk factors should be instituted as early as possible, before severe and organ disease has developed.[17]

Developmental origins of hypertension and atherosclerosis

An increasing interest has been developed on the cellular alterations observed in experimental hypertension involving growth factors that could be responsible of some aspects common to hypertension and atherosclerosis. [18]

A recent question has been postulated by Bondjers: [19] hypertension and atheroslerosis: cause and effect, or two effects with one unknown cause?

This question is very exciting but to date it is no possible to give a certain response.

In view of this it has been already suggested that hypertension and atherosclerosis are associated with increases in the vascular smooth muscle cells mass. The increase in peripheral vascular resistance, leading to an elevation of blood pressure, may reflect an increase in the mass of the wall of resistance vessels.[20]

Hypertension could, therefore, be considered as a disease of abnormal growth of the arterial media. An important role has been recently attributed to insuline resistance, to hyperadrenergic activity and to angiotensin II.[21-23]

Atherosclerosis, on the other hand, is expressed as an increase in the mass of the arterial intima.[19]

The changes that initiate atherogenesis are still unknown, despite the following two hypotheses have been accepted:

1) lipid filtration hypothesis;

2) response to injury hypothesis.

Another hypothesis recently suggests that the atherosclerotic plaque represents a monoclonal cell proliferation reminiscent of a tumorlike formation.[19]

Since the distribution of fatty streaks does not coincide with fibrous plaque and later stages in the development of atherosclerosis, additional changes in the smooth muscle population must be necessary for an atherosclerotic plaque to develop. This represents a common point between hypertension and atherosclerosis.

The possibility that trophic changes in SMC in hypertension, as well as atherosclerosis, might reflect more generalized alterations in cell physiology has to be further demonstrated. In addition generalized, possibly genetically determined, changes in cellular reactivity to adrenergic stimuli and growth factors may be implicated.

If so, atherosclerosis and hypertension might perhaps be regarded as two independent expression of the same cellular defect.[19]

Another aspect has to be considered and regards the alterations in endothelial structure. It is known that endothelial integrity is decreased and endothelial cell turnover is increased during atherosclerotic process. Some evidences indicate an involving of endothelial structure dur-

ing hypertension and it by the evaluation of ET-1 that has been found increased in hypertensive subjects in comparison with normotensives.[22 24 25]

In conclusion our knowledge of the relation between hypertension and atherosclerosis has been already limited.

The pattern that is emerging from the recent data is complex and related to origin of atherosclerosis and hypertension, control of endothelial cell growth, development of distinct smooth muscle linkages and genetic control of growth factors.

Obesity and atherosclerosis

Obesity is without any doubt an important risk factor for cardiovascular disease, especially when there is an abdominal fat distribution, for the frequent association with hypertension, hyperlipidemia and diabetes mellitus. Although several indications suggest an independent role of obesity to promote cardiovascular diseases, however it has not been accepted by all the Authors.[22]

In view of this, recent results by a follow-up of the Harvard Growth Study (1922-1935) indicate that the risk of morbidity from coronary heart disease and atherosclerosis was increased among men and women who had been overweight in adolescence.[26]

These Authors affirme that overweight in adolescence predicted a broad range of adverse health effects that were independent of adult weight after 55 years of follow-up.

In addition the effect of overweight in adolescence on adult mortality has been demonstrated to reflect the central deposition of fat that occurs in adolescence.[27 28]

These considerations induce to think the existence of an early connection between obesity and atherosclerosis and its clinical manifestations. Few data are to date available on the relation between obesity and atherosclerosis and its markers.

Personal data

So our research was carried out to identify pathophysiological connections which could concretely point out that obesity alone can be considered an atherogenic condition, able to develop autonomously during the time, ischemic and atherotrombotic events.

In view of this we have recognized and studied in the last years young obese subjects without major risk factors for cardiovascular diseases i.e. hypertension, diabetes, lipid abnormalities and smoke. In all these subjects the known atherosclerotic markers and a complete noninvasive examination of left ventricular funcion and structure both at rest and after exercise have been well determined. We found that young obese subjects differ from the young lean subjects for the following characteristics:

1. *Atherogenetic lipid pattern*: higher plasmatic levels of Apo-B and a reduction of HDL cholesterol levels (Table I).

TABLE I.—*Metabolic measurements in young lean and obese subjects.*

Parameters	Lean	Obese
Total number	10	25
Gender (M/F)	10/10	12/13
Age (yrs)	38.5±7.8	38.7±5.2
BMI (W/H^2)	23±1	37.5±3*
WHR	0.80±0.04	0.94±0.07*
Total Chol. (mg/dl)	178±14	185±16
Triglycerides (mg/dl)	128±29	160±43
HDL-C (mg/dl)	43.3±2.1	34±6.1**
ApoA1 (mg/dl)	139.5±12	128.7±15.2
ApoB (mg/dl)	106.4±13.5	140.2±25.3**
LDL (mg/dl)	109.2±10.2	119.7±14.1
Lp(a)	7.3±9.3	14.7±19.3
Fasting glucose (mg/dl)	89±2.9	92±4
Fasting insuline (μU/ml)	9.1±2.5	12.8±3.5

*$p<0.01$; **$p<0.05$.

TABLE II.—*Coagulation and fibrinolytic measurements in young lean and obese subjects.*

Parameters	Lean	Obese
Total number	20	25
Factors VII (%)	80.5±12.2	106.3±14.5*
Fibrinogen (mg/dl)	346.5±68.1	50.6±71.3*
Plasminogen (mg/dl)	8.8±0.8	11.1±1.5*
PAI (U/ml)	1.4±0.4	5±1.9*
t-PA baseline (ng/ml)	4.7±0.6	6.4±1.4
t-PA stasis (ng/ml)	24.5±4	16.2±2.9*

*$p<0.05$.

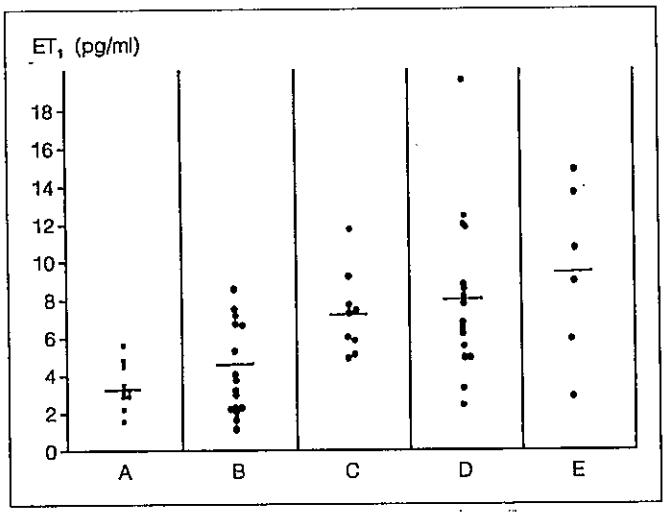

Fig. 1.—Plasma endothelin levels in lean (A), obese without risk factors for cardiovascular disease (B), diabetic obese (C), obese with multiple risk factors for cardiovascular disease (D) and in obese hypertensive subjects (E). ET_1 = Endothelin.

TABLE III.—*Acute myocardial infarction prevalence related to BMI class.*

Parameters	BMI <25	BMI 25-30	BMI >30
N. (%)	282 (44.5)	271 (42.8)	80 (12.6)
Males (%)	207 (41.5)	230 (46.1)	62 (12.4)
Females (%)	75 (56)	41 (30.6)	18 (13.4)

2. *Pro-thrombotic and hypo-fibrinolitic pattern*: higher plasmatic levels of factor VII, fibrinogen, PAI and t-PA (Table II).

Moreover we found in the young obese without major risk factors for cardiovascular disease higher plasmatic levels of plasma endothelin (Fig. 1) and no sign of coagulation and/or platelet "in vivo" activation. In addition higher fasting and after OGTT insulin levels and plasma catecholamine values have been found in young obese subjects than in lean controls.

In the end we also carried out a retrospective study on the prevalence of acute myocardial infarction (AMI) in the obese subjects. In this study a high frequence of overweight and overt obesity among subjects with a myocardial infarction has been recognized and these classes of patients are struck down by AMI more frequently than the lean ones in younger age (Table III). Moreover in the obeses the infarction is more frequently localized in multiple sites, at least in males under 65 years.

We have noticed various significant correlations between the different parameters examined i.e. t-PA, Lp(a), ANF, Aldosterone, left ventricle internal diameters and resting ejection fraction, change in ejection fraction response to exercise, left ventricular mass with duration of obesity.

In view of this duration of obesity, which is generally associated to a high degree of obesity could be considered one of the principal determinants of cardiovascular events, particularly in subjects with upper-body obesity.

Conclusion

There appears to be a strong interrelationship between hypertension, obesity, cardiac damage and the atheromatous process.

Evidence is available indicating that several alterations could be common between hypertension and atherosclerosis including alterations in endothelium structure, hypertrophy in smooth muscle cells and intervention of growth factors. These abnormalities seem to be genetically controlled.

Additional data have to be provided to explain if the connections recently reported between hypertension and atherosclerosis could be considered as a common pathophysiological view.

The role of obesity as risk factors for atherosclerotic events is emerging and some evidences indicate the early detection of atherosclerotic markers in young obese subjects. The relevant role of obesity during adolescence on the future cardiovascular events further supports the hypotized connection between the two conditions.

Even in this issue additional and more extensively data have to be provided to support the opinion that obesity and atherosclerosis could be two associated conditions evolving during the time to develop cardiovascular diseases or events.

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