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EFFECT OF SOME ANTIHYPERTENSIVE DRUGS ON PROGRESSION AND REGRESSION OF ATHEROSCLEROSIS

Thesis

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"Pharmacology"

By

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بسم الله الرحمن الرحيم

(سنريهم آياتنا في الآفاق وفي أنفسهم حتى يتبين لهم أنه
الحق، أولم يكف بربك أنه
على كل شيء شهيد)

(سورة فصلت، الآية ٥٣)

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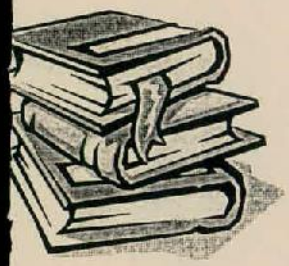
ARABIC SUMMARY

List Of Abbreviations

Apo	:	Apolipoproteins
AUC	:	Area under concentration curve
C max	:	Peak plasma concentration
FH	:	Familial hypercholesterolemia
HDL	:	High density lipoproteins
HMG–Co A	:	3-hydroxy 3-methyl glutaryl coenzyme A
HTGL	:	Hepatic triglyceride lipase
IDL	:	Intermediate density lipoproteins
LCAT	:	Lecithin cholesterol acyl transferase
LDL	:	Low density lipoproteins
LPO	:	Lipid peroxidation
MDA	:	Malondialdehyde
TGs	:	Triglycerides
VLDL	:	Very low density lipoproteins
WHHL	:	Watanabe heritable hyperlipidemic



INTRODUCTION

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ATHEROSCLEROSIS

Atherosclerosis is a response of the arterial wall to a variety of initiating agents, with multiple pathogenetic mechanisms contributing to the formation of the plaques (Bobik and Campbell, 1993).

Atherosclerotic disease affects mainly the medium sized arteries, chiefly the coronaries, carotids, cerebral and renal arteries and also the aorta particularly at its abdominal level, and the arteries of lower extremities; chiefly the iliac and femoral arteries (Badimon et al., 1993).

The lesions of atherosclerosis take different forms depending upon their anatomic site, the age, genetic constitution, physiologic status of the affected individual, and the risk factors to which each individual has been exposed (Wissler et al., 1996).

Occlusive vascular disease due to atherosclerosis and associated thromboembolic phenomena is well recognized as the major cause of mortality and morbidity in developed countries. The disease is a result of the interaction of multiple factors including a genetic predisposition. Although the process is morphologically uniform, there is the fascinating and yet unexplained predilection to affect certain anatomical regions of the arterial tree with greater frequency than others and in a given individual to affect some areas far more severely than others (Chesterman, 1987).

Atherosclerosis causes distinct clinical manifestations depending on the circulatory bed affected and the characteristics of individual lesions, which may be quite heterogeneous. Atherosclerosis of the coronary arteries commonly causes angina pectoris and myocardial infarction. Atherosclerosis of the arteries supplying nervous system frequently provokes transient cerebral ischemia and strokes. In peripheral circulation, atherosclerosis can cause intermittent claudication and gangrene. Involvement of the splanchnic circulation can cause mesenteric ischemia and bowel infarction. Atherosclerosis can affect kidney directly causing renal artery stenosis (Libby, 1998).

The normal artery structure

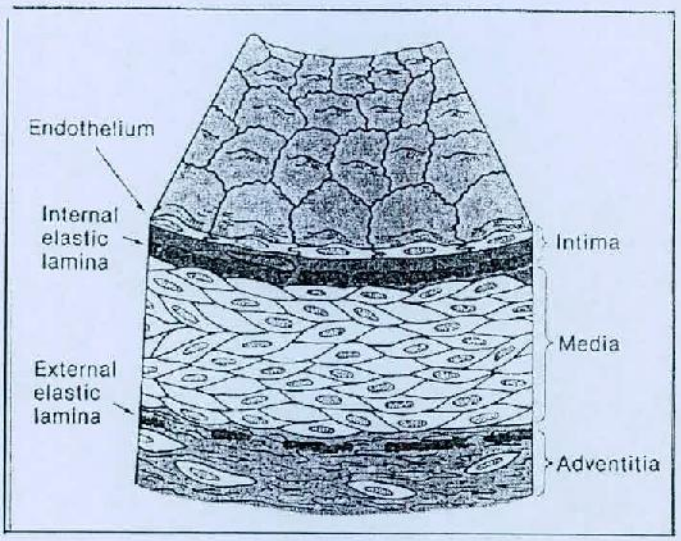

Fig. (1): The normal artery structure (Ross, R. 1992)

The normal artery (Fig. No.1) consists of an intima lined by endothelium on the inner (luminal) aspect of the vessel and bounded by the internal elastic lamina on its outer aspect. The media is bounded by the internal elastic and in well developed muscular and elastic arteries, by an external elastic lamina. This lamina consists of fenestrated sheets of elastic fibers with numerous openings. The media of muscular arteries consists of spiraling layers of smooth muscle cells attached to one another, each cell surrounded by a discontinuous basement membrane and by interspersed collagen fibrils and proteoglycan. Elastic arteries contain multiple lamellae of smooth muscle cells each equivalent to a single media in a small muscular artery, or arteriole. Each lamella is bounded by an elastic lamina on its inner and outer aspects. The adventatia is bounded by the external elastic lamina and consists of a dense collagenous structure containing numerous bundles of collagen fibrils, elastic fibers, and many fibroblasts, together with some smooth muscle cells. It is a highly vascular tissue and contains many nerve fibers as well. The adventatia provides the outer most portion of the media of large elastic arteries with much of their nutrition via vasa vasorum as well as with lymphatic channels and innervation (Ross, 1992). Abdominal aorta in

humans lacks vasa vasorum in its outer most aspects and this may be one of the reasons the abdominal aorta is particularly vulnerable to atherosclerosis.

The processes of atherosclerosis

1-The fatty streak:

The earliest lesions are commonly seen in the intima of the aorta in childhood and adolescence. The smallest that are readily visible to the naked eye appear as minute round or oval yellow spots that project slightly above the intimal surface. A number of these spots may be arranged in rows and commonly coalesce to form streaks orientated along the longitudinal axis of the aorta (Duff and Mc Millllan, 1951).

Studies using monoclonal antibodies specific for macrophages, T cells and smooth muscle cells have shown that early fatty streaks appear to consist of macrophages together with variable numbers of T lymphocytes. As the lesions expand, they contain smooth muscle cells that have migrated into the intima as well. As a consequence, these lesions become mixed macrophages – T lymphocyte - smooth muscle lesions in which both macrophages and smooth muscle are lipid laden. Each of this cell types contain deposits of cholesterol and cholesterol oleate (Wissler et al., 1996). These lipid – laden cells are called " foam cells".

The fatty streaks are of universal occurrence and distribution in children and young adults, and most either disappear or remain harmless. In certain locations (e.g. coronary arteries) and especially in the predisposed individual, these streaks may conceivably evolve into fibrous plaques (Stary, 1983).

2- The fibrous plaque

The atheroma or fibrous plaque is believed to evolve directly from the fatty streaks, although not all fatty streaks progress to plaque lesions. The fibrous plaque is grossly white in appearance and becomes elevated, so that it may protrude into the lumen of the artery .If this lesion progress sufficiently, it

can occlude the lumen and compromise the vascular supply of the involved tissue (Stary et al., 1995).

Fibrous plaque characteristically is covered by a fibrous cap. The fibrous cap of each lesion consists largely of a particular form of smooth muscle cell that is thin and pancake shaped and that is surrounded by numerous lamellae of basement membrane, proteoglycan, and large numbers of collagen fibrils. The connective tissue of the fibrous cap is exceedingly dense. Beneath the fibrous cap lies a mixture of smooth muscle cells, macrophages, and numerous lymphocytes. In this highly cellular portion of the fibrous plaque there are also large amounts of connective tissue. Beneath the cell – rich region, there is often a zone of necrotic tissue and debris, which may contain cholesterol crystals, and regions of calcification as well as numerous enlarged foam cells (Ross, 1992).

T- lymphocytes have been observed in all phases of atherogenesis in human and non-human primates (Emeson and Robertson, 1988). Their involvement in the lesions of atherosclerosis supports the notion that these lesions may develop, at least in part, as a result of an immune or possibly autoimmune response. Experimentally induced autoimmunity has been shown to induce rampant proliferative lesions of atherosclerosis in rabbits (Minick and Murphy, 1973). The nature of antigen (s) that may play a role in common atherosclerosis is unknown. However, interactions between T – lymphocytes and activated macrophages, both of which are prominent in the lesions, suggest that antigen presentation and the release of cytokines and growth factors between the activated macrophages and T cells may be important in this process (Hasson et al., 1989).

There is a lesion that generally accepted as a precursor of the fibrous plaque. This is known as fibromuscloelastic intermediate lesion of the intima, which consists of proliferated smooth muscle cells surrounded by connective tissue and contains little to no lipid (Wissler et al., 1996).