STUDIES ON THE INTER-RELATIONSHIP BETWEEN LIPID METABOLISM, HYPERTENSION AND BLOOD COAGULATION

THESIS

Submitted for the Degree of Ph D

(Physiology)

By

SALAH ABD-EL-MEGID ABU-SHANAB

M. B. B. Ch., M. Sc. (Physiology)

Supervised By

Prof. Dr. Omar Ahmed Zaki
Professor of Physiology
Department

Prof. Dr. Ahmed Kamel
Professor of Physiology
Department

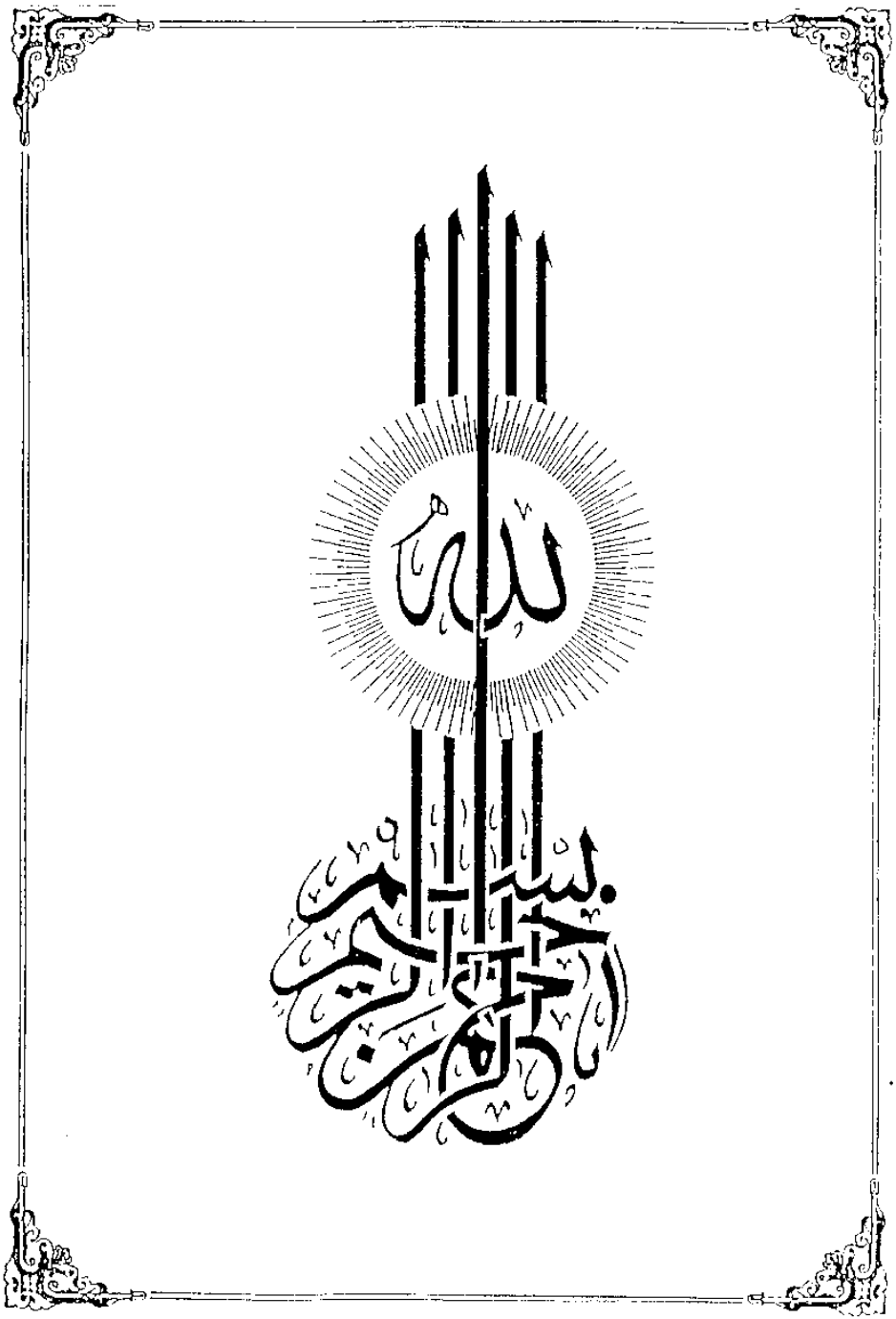
Prof. Dr. Mahmoud Hamdi Abdel
Professor of Physiology Department

Faculty of Medicine
Ain Shams University

1985

Finally I would like to thank all my colleagues in Physiology Department, Ain-Shams University for their encouragement.

.....



C O N T E N T S

Volume I

Page

S E C T I O N I

* Introduction
* Aim of work
* Review of literature

I N T R O D U C T I O N

Lipids have long been known to exert important effect on blood coagulation, its procoagulant effect was recognized by many workers (*Macfarlane et al.,1941 ; Duncan and Waldron, 1949; Robinson and Poole, 1956; Shore and Alpers, 1963; Hoak,1963; Kerr et al., 1965*). A work done in our Department in 1979 studied the relationship between plasma lipids and blood coagulation. It was concluded that lipids play a definite role in the process of blood coagulation, which would be specifically ascribed to phospholipids and/or free fatty acids, being anionic surface active agents. A further work is needed to provide the exact mechanism by which lipids affect blood coagulation.

Also the relations between hormones, lipid metabolism and blood coagulation were investigated by previous workers however, the results of these investigations are contradictary. The abnormality in lipid metabolism is diabetes mellitus was attributed to the abnormality in lipoprotein metabolism (*Garcia et al., 1974*). Several studies have suggested that a deficient removal of circulating triglyceride plays an important role in the pathgenesis of diabetic hyperlipemia in man (*Reaven et al.,1975*). Also the increased thrombotic tendency in diabetes was stated to result from a

probably inhibition of the fibrinolytic system (*Almer and Pandolfi, 1976*). On the other hand, the mechanisms of insulin action on triglyceride levels have not been defined (*Jones and Ronald, 1965*). In addition the release of endogenous inslin was suppressed by an intravenous infusion of adrenaline (*Havel, 1969*). Previous reports suggests that there is rise in free fatty acids concentration following S.C. injection of epinephrine in normal subjects although this response is diminished with increasing the weight (*Glemon et al., 1965*)

ACTH or cortisone in man can be followed by thromboembolic complications (*Cosgriff, 1951*). Although others deng this (Russek et al., 1954), although it can increase the cholesterolemia (*Cosgriff, 1951*), and induce changes in the fibrinolytic system (*Kwaan and McFadzean, 1956*).

Thyroid hormones have a definite hypolipidemic effect, but its effect on blood clotting and fibrinolytic system need further studies to explain it.

Sex hormones are well known for its procoagulant effect, also has a definite hyperlipidemic effect.

It was observed that there are changes in blood coagulation and lipid metbaolism in hypertension. Vascular lesions

develop during the course of hypertension and are the major cause of morbidity and mortality from this disease (*Stamler et al.,1972*). Abnormality in lipid metabolism was detected and recognized in spontaneously hypertensive rats (SHR) such abnormality include lowering of plasma cholesterol and increase in plasma triglyceride and free fatty acid levels. Although, the pathological implication of this in hypertension and related vascular lesions is not yet clear (*Iritani,1977*). Also hypertension changes the kinetics of plasma triglycerides with increased need for unsaturated fatty acids (*Michaailov,1977*). In addition hypertensive patients with or without protodiabetes mellitus (PD) exhibited a significant insulin enhancement. Simultaneously with the endogenous insulin peak the contents of free fatty acids decreased. Such condition may be potential indications of premature arteriosclerotic states at the early stage of essential hypertension (*Baumann,1977*).

It was concluded that hypertensive sclerotic male subjects presented a higher thrombogenic risk than the female subjects. Hypertension had an aggravating influence on the thrombophilia in both groups, indicated by an increase in the plasma fibrinogen concentration (*D'Eredita et al., 1976*).

AIM OF WORK

The aim of the present work is to study the effect of hypertension on blood coagulation and lipid metabolism. On the other hand, stuyding the blood coagulability as well as the changes in blood lipids and blood pressure following administration of some hormones (adrenaline,sex hormones, DOCA, thyroxine and insulin) and some endocrinal disorders. Also studying the blood coagulability following the *in vivo and in vitro* addition of different lipid fractions (free fatty acids, phospholipids and cholesterol). These may help to throw more light on the inter-relations between hypertension, blood coagulation, hormones and lipid metabolism and to elucidate and provide the possible mechanism (s) involved.

PART (I)

HYPERTENSION

H Y P E R T E N S I O N

Despite the annual publication of nearly 80,000 original research articles and abstracts related to hypertension and the accumulated work of over 100 years of investigation, the aetiology in nearly 90% of all hypertensive patients is unclear and the associated disorder is termed essential hypertension. Although the origins of this condition remains undefined significant progress has been made in understanding the basic physiologic mechanisms that control arterial blood pressure and the manner in which these mechanisms are altered during the develcpment of hypertension.

Present understanding of physiology of arterial pressure regulation indicates that renal-body fluid volume system determines the level at which the mean pressure resides over long periods of time(*Guyton,et al.,1972; Guyton,et al.;1974*).

Relationships between blood volume, size and compliance of the entire vascular system and intrinsic regulation of tissues blood flow determine the sequence of observed changes in cardiac and total peripheral resistance (*Byrom,1954; Guyton,et al.,1954; Landau and Davis,1957; Hutchins,1972*).

It is worth stressing that the high pressure in "hypertension" is confined to the systemic arteries and arterioles. The pressure in all other vessels is usually normal (*Roddis and Wallace, 1975*).

High blood pressure appears to be linked with civilisation (*Harris,1927; Donnison,1929; Fishberg,1939*).

For those interested in the subject of hypertension there are a number of reviews that could be consulted (*Tobian,1960; Guyton et al.,1970; Guyton et al.,1974; Swales,1979; Muirhead,1980; Swales,1981*).

EXPERIMENTAL HYPERTENSION

Animal models have always been the favourite tools in the hands of research workers to investigate medical problems. The pathogenesis and management investigations of hypertension owe a great deal of their progress to the work on animals made experimentally hypertensive. There are several methods to induce hypertension in animals. These include:

1. Salt-induced hypertension:

It is obtained by loading genetically liable rats with salts for one year (*Meneely et al.,1953*). *Kolesty (1959)*; *Kolesty and Goodsitt (1960)* found that combination of severe reduction of renal mass and administration of 1% saline increase the incidence of hypertension.

2. DOCA- induced hypertension:

The correlation between adrenal steroids and hypertension was forst demonstrated for the steroid desoxy corticosterone (DOCA) by *Kuhlmann et al. (1939)*. Subsequently, *Selye et al.(1943)* pointed out that an experimental animal could be sensitised to the hypertensive action of this compound if the renal mass was reduced, if the kidneys were