SERUM HIGH SENSITIVITY C - REACTIVE PROTEIN AND SYSTEMIC HYPERTENSION

Thesis submitted for partial fulfillment
of master degree in internal medicine

By
Ashraf Ahmad Ali
M.B., B.Ch.
Faculty of medicine, Alexandria University

Under supervision of

Dr.Mona Ahmad Radwan
Professor of Internal Medicine
Faculty of Medicine, Cairo University

Dr.Mona Mohamed Amin Galal
Assistant Professor of Internal Medicine
Faculty of Medicine, Cairo University

Dr.Samar Ali Marzouk
Lecturer of Medical Biochemistry
Faculty of Medicine, Cairo University

Faculty of Medicine
Cairo University
2008

Acknowledgement

First and for most thanks are due to Allah to whom any success in life is attributed.

I wish to express my deepest gratitude to Prof. Dr. .Mona Ahmad Radwan Professor of Internal Medicine, Faculty of Medicine, Cairo University, for her faithful supervision, precious help and constant guidance.

My deepest thanks to Professor Dr.Mona Mohamed Amin Galal, Assistant Professor of Internal Medicine, Faculty of Medicine, Cairo University, to the great help and valuable advice all through this work.

I would like to express my appreciation to Dr. Samar Ali Marzouk, Lecturer of Medical Biochemistry Faculty of Medicine, Cairo University, who helped me a lot to complete this work.

Finally, I wish to thank all who helped me to complete this work ,My dearest and beloved wife, my son and all my family… thanks for all .

Abstract

Serum high sensitivity C - reactive protein and systemic hypertension Inflammation has been shown to be correlate with endothelial dysfunction and relate to rennin angiotensin system. This study is a case control analytic study that was conducted in El-Kasr El-Aini Hospital in order to find out the relation between high sensitivity-CRP and hypertension, the study included 60 patients with primary hypertension and 15 normal subjects as a control group.

Exclusion criteria: Secondary hypertension. Infection, autoimmune, inflammatory disorders, malignant disease and steroid therapy. Renal or hepatic impairment.

All patients included in the study were subjected to the following:

Full history taking with special emphasis on history of hypertension, drug therapy, complications of hypertension and cardiac history ,full medical examination including blood pressure, body mass index and signs of inflammation and autoimmune disease, Laboratory investigations including: complete blood count, erythrocyte sedimentation rate by wintergreen method, Fasting and 2 hours post-prandial blood sugar level, urea, creatinine, uric acid, SGPT, SGOT, PT, Cholesterol, Triglycerides, HDL and LDL,Serum level of C-reactive protein by a high sensitivity assay method ,ECG..

KEY WORDS:

SERUM HIGH SENSITIVITY

C - REACTIVE PROTEIN

SYSTEMIC HYPERTENSION

Table of contents

Abbreviations

ACC	*American College of cardiology*
ACS	*Acute coronary syndrome*
AHA	*American Heart Association*
AI	*Angiotensin I*
AII	*Angiotensin II*
AT_1-R	*Angiotensin type -1 receptor*
C	*Complement*
CAD	*Coronary artery disease*
CO	*Cardiac output*
Crcl	*Creatinine clearance*
CRP	*C- reactive protein*
DBP	*Diastolic blood pressure*
DM	*Diabetes mellitus*
ESr	*Erythrocyte sedimentation rate*
ET-1	*Endothelin-1*
HDL	*High density lipoprotein*
HF	*Heart failure*
HMG-CoA	*3-hydroxy-3-methylglutaryl–coenzyme A*

hs-CRP	*High sensitivity C-reactive protein*
JNC	*Joint National Committee*
LVH	*Left ventricular hypertrophy*
MI	*Myocardial infraction*
NO	*Nitric oxide*
PAI-1	*Plasminogen activator inhibitor 1*
PR	*Peripheral resistance*
PRA	*Plasma rennin activity*
RAAS	*Renin – angiotensin aldosterone system*
RAS	*Renin- angiotensin system*
ROC curve	*Receiver operator characteristic curve*
ROS	*Reactive oxygen species*
Rpm	*Round per minute*
SBP	*Systolic blood pressure*
SD	*standard deviation*
sICAM-1	*Serum intercellular adhesion molecule-1*
TNFa	*Tumor necrosis factor a*
VSM	*Vascular smooth muscle*

List of tables

Tables of results

List of Figures

Figures of results

Introduction:

As one of the earliest recorded medical conditions, hypertension and its consequences contribute significantly to worldwide morbidity and mortality. In spite of its widespread prevalence and intense research into its pathophysiology, only 5% of hypertensive patients have an identifiable cause. While our understanding of the cause of hypertension is ever increasing, we now know that hypertension is the product of dynamic interaction between various diverse genetic, physiological, environmental and psychological factors. Of considerable interest is the fact that we have not yet determined the extent to which each of these factors contribute to hypertension ***(Pearce et al., 2006).***

Studies have indicated a close relationship between hypertension and inflammation, showing that tissue expression and plasma concentration of inflammatory mediators are increased in patients with essential hypertension and in experimental models of hypertension. These inflammatory mediators include C reactive protein (CRP), interleukin (IL)-6, IL-1, tumour necrosis factor- (TNF-), monocyte chemoattractant protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), and have been linked to the activation of the nuclear factor kappa B (NF-B) system. For example, in peripheral monocytes from hypertensive patients, the production of IL-1β and TNF- was significantly increased upon lipopolysaccharide stimulation ***(Vongpatanasin et al., 2007)***.

C-reactive protein (CRP) is a marker of systemic inflammation and has been postulated to increase the risk of the development of hypertension. Although a large number of studies show that higher levels of circulating CRP are related to

higher blood pressure, these associations may be noncausal. Factors that increase CRP levels (such as obesity, smoking, adverse socioeconomic circumstances, and various disease states) may themselves influence blood pressure levels. The conventional approach to this issue is to statistically adjust for such confounding factors, but this approach may be misleading given measurement error in the assessment of confounders or the presence of unmeasured confounders, both of which lead to inadequate statistical control and residual confounding. Further, because most studies of this association have been cross-sectional, reverse causality cannot be excluded ***(Susan et al., 2007)***.

Higher level of C-reactive protein may increase BP by reducing nitric oxide production in the endothelial cells, resulting in vasoconstriction and increase production of endothelin ***(Sesso et al., 2003).***

Aim of the work:

1 To measure the level of high sensitivity C-reactive protein in patients with essential hypertension and determine the correlation between high sensitivity C-reactive protein and essential hypertension.

2 To investigate the possible correlation with other parameters as patient's age, smoking, body mass index, level of both systolic and diastolic hypertension, lipid profile and blood sugar.

Hypertension

Hypertension affects approximately 50 million individuals in the United States and approximately 1 billion worldwide. As the population ages, the prevalence of hypertension will increase even further unless broad and effective preventive measures are implemented. Recent data from the Framingham Heart Study suggest that individuals who are normotensive at age 55 have a 90 percent lifetime risk for developing hypertension.(**Brain et al. 2004**)

Incidence:

The classification of adult blood pressure based on its impact on cardiovascular disease was provided by NIH in 1997 ***(Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 1997).*** In this classification, the optimal blood pressure with respect to cardiovascular risk is SBP < 120 mm Hg and DBP < 80 mm Hg. Persons with stage I (mild) hypertension have SBP 140–159 mm Hg or DBP 90–99 mm Hg based on the average of two or more readings taken at each of two or more visits after an initial screening. Persons with stage II hypertension have SBP 160–179 mm Hg or DBP 100–109 mm Hg. Persons with stage III hypertension have SBP ≥ 180 mm Hg or DBP ≥ 110 mm Hg. Based on these definitions, as many as 43 million people in the United States have hypertension or are taking antihypertensive medication, which accounts for approximately 24% of the adult population ***(Wood et al. 1998).***

Hypertension is a major health problem in Egypt with a prevalence rate of 26.3% among the adult population (> 25 years). Its prevalence increases with aging, approximately 50% of Egyptians above the age of 60 years suffer from hypertension. About seven million Egyptians had high blood pressure in the year 1993 ***(Ibrahim et al., 1995).***

Risks of hypertension include cardiovascular complications (heart failure, myocardial infarction, atrial fibrillation, aneurysms, dissection), renal (azotemia) and cerebrovascular (stroke, transient ischemic attacks "TIA", dementia), resulting in disability and premature death. These risks can be reversed by treatment and control of hypertension. Hypertension is poorly managed in Egyptians. The rates of awareness, treatment and control are low. Only 8% of hypertensive Egyptians have their blood pressure controlled ***(Ibrahim, 2003)***.

The proportion the adult population having hypertension or taking antihypertensive medication varies with (1) race, being higher in blacks (32.4%) and lower in whites (23.3%) and Mexican Americans (22.6%); (2) age, because in the industrialized countries, systolic BP continues to rise throughout life, whereas diastolic BP rises until age 55 to 60 years, and thus the greater increase in the prevalence of hypertension is mainly due to systolic hypertension; (3) geographic patterns, because hypertension is more prevalent in the southeastern United States; (4) gender, because hypertension is more prevalent in men (though menopause tends to abolish this difference); and (5) socioeconomic status, which is an indicator of lifestyle attributes and inversely related to the prevalence, morbidity and mortality rates of hypertension ***(Carretero & Oparil 2000).***

Etiology:

Essential, primary, or idiopathic hypertension is defined as high BP without secondary causes, such as renovascular disease, renal failure, pheochromocytoma, aldosteronism, or other causes of secondary hypertension or mendelian forms (monogenic). Essential hypertension accounts for 95% of all cases of hypertension. However, essential hypertension is a heterogeneous disorder, with different subjects having different causal factors that lead to high

BP. In most patients, one or several of these causes can be recognized and modified in order to reduce the future CVD risk.

Risk factors:

1. Age.
2. Obesity.
3. Insulin resistance.
4. High alcohol intake.
5. High salt intake
6. Stress.
7. Low potassium intake.
8. Low calcium intake.
9. Genetic predisposition.

The most important independent risk factors for the development of hypertension have been shown to be age (multiple regression coefficient 0.58 in men and 0.75 in women) and subscapular skinfold as a measure of obesity (multiple regression coefficient 0.28 in men and 0.37 in women) ***(Kannel 1990).***

Future hypertensives tend to evolve from the upper end of the normal blood pressure distribution. Hence, initial BP is actually the best single predictor of the future hypertension incidence. However, a fat person is at an increased risk of future hypertension regardless of his/her initial BP. Baseline BP explains no more than 20% of the hypertension-obesity-incidence relationship. Attributable risk estimates, using an obesity threshold of 1 cm

subscapular skinfold, suggest that 78% of hypertension in men, as opposed to 65% in women, is directly attributable to adiposity.

In the Framingham study ***(Ashley & Kannel 1974),*** it was estimated that each 10% weight gain is associated with a 6.5 mmHg increase in systolic BP. The mechanism by which obesity raises BP is not fully understood, but increased BMI is associated with an increase in plasma volume and cardiac output. BP in obese adolescents is sodium-sensitive, and fasting insulin is a predictor of this sensitivity ***(Rocchini et al. 1989).***

This sensitivity has been suggested to be due to the combined effect of hyperinsulinemia, hyperaldosteronism and increased activity of the sympathetic nervous system ***(Carretero & Oparil 2000).***

Other potentially modifiable risk factors that increase BP have been shown to be insulin resistance, high alcohol intake, high salt intake (in salt-sensitive patients), stress, low potassium intake and low calcium intake ***(Lifton 1996).***

Furthermore, many of these factors are additive, such as obesity and alcohol intake. The influence of genes on BP has been suggested by family studies, pedigree and twin studies. BP variability attributed to all genetic factors varies from 25% in pedigree studies to 65% in twin studies. Additionally, genetic factors also influence behavioral patterns, which might lead to BP elevation. Mutations in at least 10 genes have been shown to raise BP through a common pathway by increasing or decreasing salt and water reabsorption by the nephron ***(Lifton 1996).***