Minestry of higher education
And scientific research

University Of Al-Qadiysiah
Collage Of Pharmacy

The Effect Of Thiazide Diuretics On Lipid Profile

A research submitted to the college of pharmacy in fulfillment of the requirements for the degree of B.Sc.

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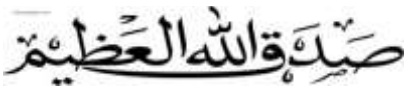
"قَالُواْ سُبْحَانَكَ لاَ عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ
الْعَلِيمُ الْحَكِيم"



سورة البقرة (32)

Dedication

This Research is dedicated to my father, who taught me that the best kind of knowledge to have is that which is learned for its own sake, It's also dedicated to my mother, who taught me that even the largest task can be accomplished if it's done one step at a time.

Thanks to Dr. Hussien Ali Sahib who has been the ideal supervisor. His sage advice, insightful criticisms, and patient encouragement aided the writing of this research in innumerable ways, I would also like to thank all of the doctors for the steadfast support for this project, A special thanks to Dr. Bassim Irheim the dean on the college.

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We would like to express our gratitude for the god of this universe who kept showing us the light till the end of the tunnel and provided us with the necessary strength to keep working till the very end of the path of this project
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Special thanks for our families the ones without them we would not be where we are, and the cause of our existence to this life and our top supporters in the long life struggle
In the end of this acknowledgement no words can express or describe our gratefulness for those who are standing in the frontal lines of battles to protect our homelands, those who are standing in front of the bullets and shields sacrificing their lives to save ours, the words "THANK YOU " are just not enough at all.

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CHAPTER ONE

Introduction

AND

Review Of Literature

1.1 Introduction:

Hypertension is a major health hazard of present day life and is a leading cause of global burden of disease. Hypertension is defined as increase in blood pressure and it is classified as primary hypertension and secondary hypertension. Both environment and genetic factors contribute to regional and racial variation in blood pressure and hypertension. [1]

Some of the known risk factors for primary hypertension like age, hereditary and gender are non-modifiable. However, majority of other risk factor like tobacco use, alcohol use, unhealthy diet, physical inactivity, overweight and obesity can effectively be prevented. [2]

Beside various risk factors there is importance of a lipid profile in hypertensive patients. The routine monitoring of lipid profile in hypertensive patients is important for coronary heart diseases and other consequences to combat morbidity and mortality. [3]

There is close association of hypertensive patient with dyslipidemia and meets measurement of blood pressure and lipid profile at regular intervals to prevent cardiovascular disease, stroke and other co morbidities. [4]

Diuretics are the drugs which block the resorption of sodium and chloride by renal tubules and increase the urinary volume. They are widely used in the treatment of hypertension. Low dose thiazide diuretics are used as first line agents alone or in combination with other antihypertensive drugs. Thiazide inhibits Na+ / Cl – pump in distal convoluted tubule and hence increased sodium excretion. [5]

Thiazide can also modify lipoprotein and glucose metabolism. [6]

Disorders of the lipid metabolism may be caused by defects in structural proteins of lipoproteins particles, in the cells receptor that recognize the various types of lipoproteins or in the enzymes that break down fats. As a result of such defects lipid may become deposited in the walls of blood vessels which can lead to atherosclerosis. [7]

Lipids are a heterogeneous group of compounds which are important dietary constituents not only because of their high energy value but also because of the fat soluble vitamins and the essential fatty acids contain in the fat of natural foods. The plasma lipid after subsequent separation of the extract into various classes of lipid shows the presence of triglycerols phospholipids, cholesterol and cholesteryl esters and in addition of existence of small fraction of free fatty acid and these free fatty acids are known to be metabolically most active of plasma lipids. In addition to free fatty acids four major groups of lipoproteins have been identified that are important physiologically and in clinical diagnosis. These are chylomicrons, VLDL, LDL and HDL. [8]

The disturbance of lipid metabolism is seen in some inherited diseases and also in patients of some kind of underline diseases. The presence of its disturbance can be detected by measuring concentration of cholesterol and triglyceride in serum. Although hyperlipidemia or hypolipidemia is the result of abnormal lipid metabolism. Hyperlipidemia is more concerned with physicians because of its close association with atherosclerosis. [9]

1.2 review of literature

1.2.1 Thiazide diuretics:

a member of a class of diuretic substances that inhibit the reabsorption of sodium chloride in the distal convoluted tubule of the kidneys: used principally to treat hypertension.
Thiazides in high dosage can increase serum low-density-lipoprotein cholesterol (LDL-C) and/or very-LDL-C and the total CI high-density lipoprotein cholesterol (HDL-C) ratio, while HDL-C is largely unchanged; triglycerides (TG) are also often elevated. Premenopausal women may be protected from this side effect. Whether diuretic induced dyslipidemia is dose-dependent and low thiazide doses (i.e. hydrochlorothiazide ^ 12-5 mg daily) are less active. [10]

Gender and the menopausal state may play a role in the interaction between diuretics and lipoproteins. In postmenopausal women, chlorthalidone administered in high dosage produced changes in serum total cholesterol and LDL-C similar to those in men; no changes were seen in premenopausal women. [11]

This points to a 'protective' influence of the premenopausal state. It seems that estrogens increase the number of hepatic LDL binding sites and stimulate the hepatic uptake of chylomicron-remnants. [12]

Combinations of a potassium-loosing diuretic (almost always a thiazide in medium dosage, for instance hydrochlorothiazide 25-50 mg. day"1) with a potassium sparing diuretic may be less prone to alter the lipoprotein metabolism than high-dose thiazides or loop-diuretics. [13] [14]

Since effects of thiazides on serum potassium, glucose and uric acid are dose-dependent, in low doses they may be also less prone to modify the lipoprotein profile [15]

Thiazide-type and loop diuretics can also impair insulin sensitivity. [16]

Changes in potassium may possibly play a role in this interaction. [17]

The latter and/or the resulting compensatory hyperinsulinemia are known to promote hypertriglyceridemia, a tendency for low HDL-C and atherogenesis [18]

1.2.2 Mechanism of actions

Antihypertensive effects:

Thiazides achieve their diuretic action by inhibition of Na^+/Cl^- cotransporter (NCC) in the renal distal convoluted tubule [19]. (The NCC facilitates the absorption of sodium from the distal tubules back to the interstitium). By decreasing sodium reabsorption, thiazide use results in an increase in fluid loss to urine, decrease extracellular fluid (ECF) and plasma volume. results in diminished venous return, increased renin release, reduced cardiac output and decreased blood pressure [20]. Within days, the reduction in cardiac output increases total peripheral resistance (TPR), which stems mostly from activation of the sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system (RAAS) [21].

during the acute thiazide treatment phase restores blood pressure to pretreatment levels. [22]

Chronically, thiazides must lower blood pressure via some other mechanism. Plasma and ECF volumes almost fully recover within 4–6 weeks of thiazide initiation, yet blood pressure reduction is maintained. [23] After chronic administration, discontinuation of thiazides results in a decrease in renin levels and rapid volume replenishment, although the rise in blood pressure is much slower [24].

Metabolic effects

Thiazides have been associated with hyperlipidemia, hyperglycemia, new-onset diabetes, hypokalemia, hyperuricemia and stimulation of the RAAS [25]. While many large randomized, prospective clinical trials show an association between thiazide use and increased blood glucose, findings are mixed regarding the association with new-onset diabetes [26]. [27]

1.2.3 therapeutic uses:

Hypertension: Clinically, the thiazides have long been the mainstay of antihypertensive medication, because they are inexpensive, convenient to administer, and well tolerated. They are effective in reducing systolic and diastolic blood pressure for extended periods in the majority of patients with mild to moderate essential hypertension. After 3 to 7 days of treatment, the blood pressure stabilizes at a lower level and can be maintained indefinitely by a daily dosage level of the drug, many patients can be continued for years on the thiazides alone [28] .

Heart failure: Thiazides can be the diuretic of choice in reducing extracellular volume in mild to moderate heart failure. If the thiazide fails, loop diuretics may be useful.

Hypercalciuria: The thiazides can be useful in treating idiopathic hypercalciuria, because they inhibit urinary Ca2+ excretion. This is particularly beneficial for patients with calcium oxalate stones in the urinary tract [28]

Diabetes insipidus: Thiazides have the unique ability to produce a hyperosmolar urine. Thiazides can substitute for antidiuretic hormone in the treatment of nephrogenic diabetes insipidus. The urine volume of such individuals may drop from 11 L/day to about 3 L/day when treated with the drug

Adverse effects:

Hypokalemia - Thiazide diuretics reduces potassium concentration in blood through two indirect mechanisms: inhibition of sodium-chloride symporter at distal convoluted tubule and stimulation of aldosterone that activates Na+/K+-ATPase at collecting duct. Inhibition of sodium-chloride symporter increases availability of sodium and chloride in urine. When the urine reaches the collecting duct, the increase in sodium and chloride availability activates Na+/K+-ATPase, which increases the absorption of sodium and excretion of potassium into the urine. Long term administration of thiazide diuretics reduces total body blood volume. This activates the renin–angiotensin system, stimulates the secretion of aldosterone, thus activating Na+/K+-ATPase, increasing excretion of potassium in urine.[19] Therefore, ACE inhibitor and thiazide combination is used to prevent hypokalemia.

Hyperglycemia

Hyperlipidemia

Hyperuricemia

Hypercalcemia

Hyponatremia

Hypomagnesemia

Hypocalciuria [29]

CHAPTER TWO

Material AND Methodology

MATERIAL AND METHOD

The present study was conducted to observe the changes in serum lipid profile, serum triglyceride, total cholesterol, HDL cholesterol, LDL-cholesterol under thiazide diuretic therapy in relation to hypertension

The study was performed in General Hospital of AL-Diwaniyah in 2018 between 27 February to 26 march

The subjects are divided into two groups.

Group A comprises of 13 healthy individuals selected randomly between age groups of 20 – 80 years including males and females.

Group B comprises of 13 hypertensive patients on diuretics therapy which were selected randomly between age groups of 20-80 years including males and females

Following investigations are carried out in all subjects:

1. Estimation of total serum cholesterol by method CHOD-PAP
2. Estimation of serum HDL-cholesterol by direct method
3. Estimation of serum triglyceride by TRINDER method
4. Estimation of serum LDL- cholesterol by DIRECT method

Collection of sample: Samples were taken after 9-12 hrs. of fasting with NO.20 needle from interior cubital vein. Haemolysed samples were discarded. Serums were separated from blood clot and above mentioned investigations were carried out on these samples.

Tests requirements:

First requirement for fasting lipid profile test is to stop eating between 9 to 12 hr, only water allow during this period, and also stable diet recommended for three weeks.

Second requirement is to stop any medication or even supplements that could affect lipid cholesterol for number of days before test.

Biological variations:

- Age: cholesterol levels increase with age.
- Sex: women have lower level than men.
- Life-style: higher in sedentary and poor diet habits.
- Smoking: cholesterol, TG, LDL higher while HDL lower in

Smoker than nonsmoker

CHAPTER THREE

RESULT

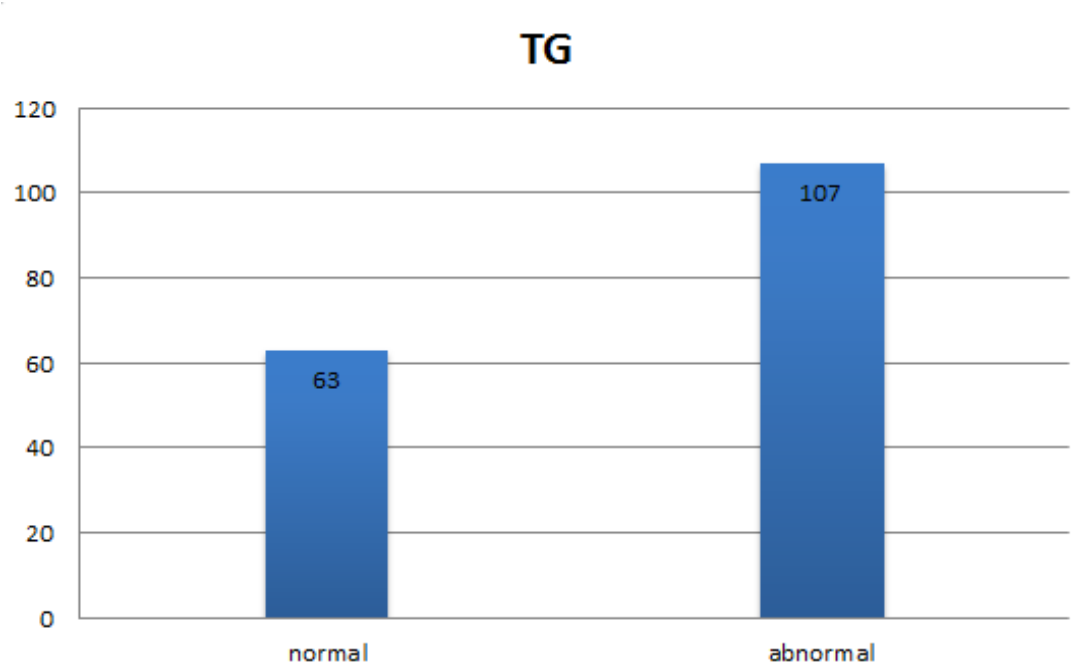

Chart 1: Comparative study of TG in healthy and diseased individuals.

The serum TG from above data in diseased individual was significantly higher 107mg as compared to healthy individual 63 mg.

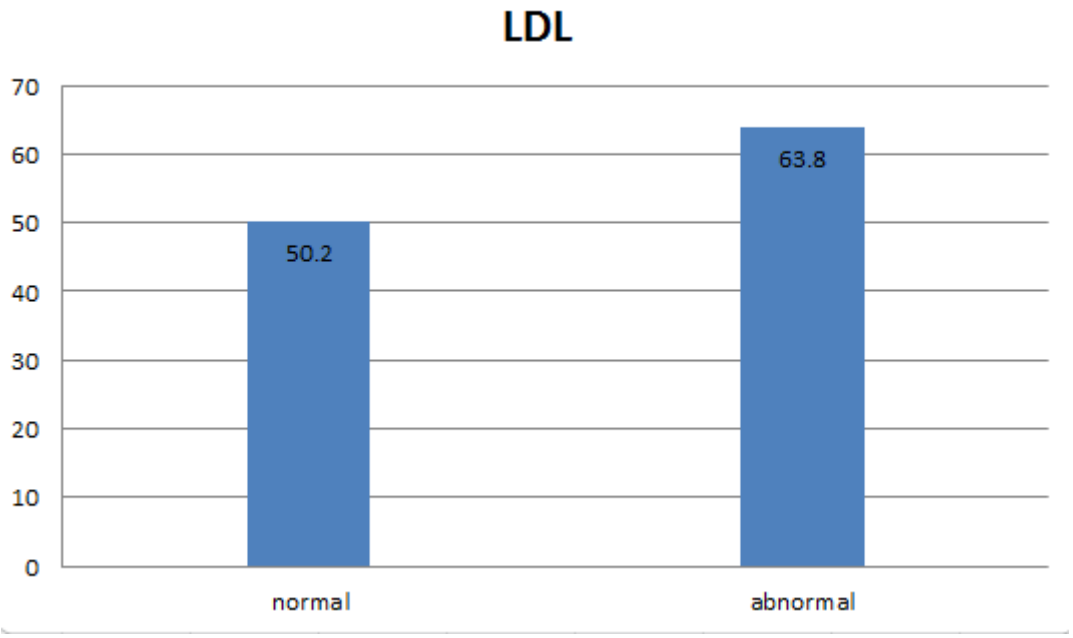

Chart 3: Comparative study of serum LDL– cholesterol in healthy and diseased individuals.

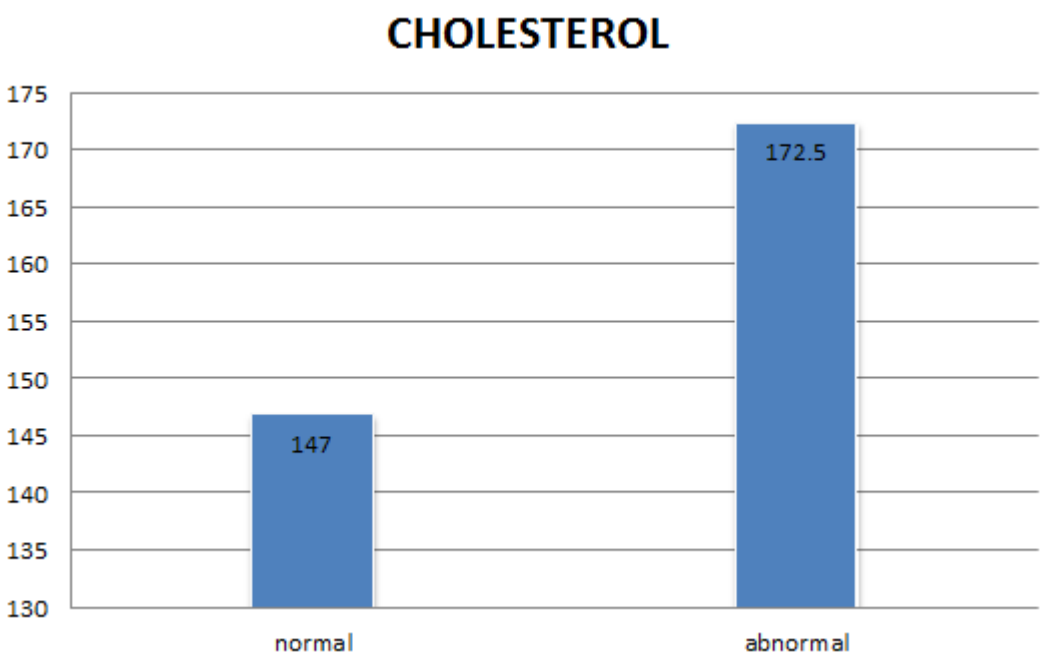

Chart 2: Comparative study of serum cholesterol in healthy and diseased individuals.

The above data shows the comparative value of serum cholesterol in the diseased individual were significantly higher as compared to healthy individuals were 147mg where as in diseased individual was 172.5 mg.

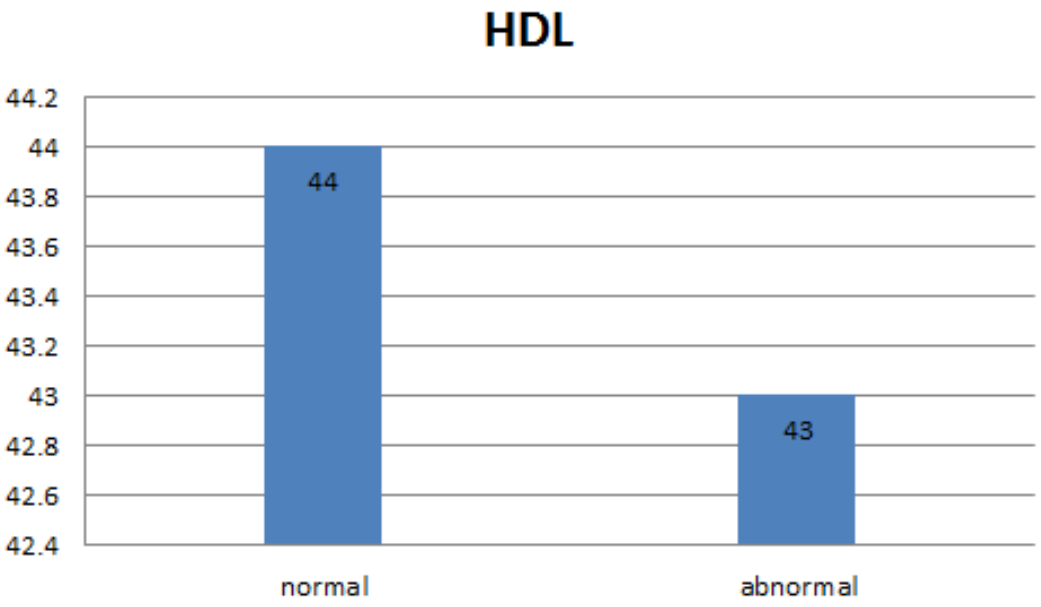

Chart 4: Comparative study of serum HDL- cholesterol in healthy and diseased individuals.

Chapter four

Discussion
Conclusion
Recommendations

4.1. Discussion:

From the data that showed in the figures we conclude increase in plasma triglyceride levels in patients taking thiazides and also increase in cholesterol.
Investigation into the alterations in plasma lipoprotein subfractions has shown that the increase in total cholesterol is associated with an increase in LDL-cholesterol levels. Changes in HDL cholesterol have been mixed, indicating that HDL-cholesterol levels are probably unaffected by the thiazide diuretics.

Unfortunately, there are several factors that affect an individual's lipid profile and because our study is based on a very short period and combine a considerable set of barrier to patient monitoring before and after thiazide diuretic administration, including resource-limitation and shortage of healthcare workers and medical infrastructures in the province, Therefore, we had a major difficulty in excluding those lipid effecting factors e.g.;(Lifestyle, Diet or other Habits) on our result, the confirmation whether the abnormality in lipid profile is due to thiazide administration or due to other factors is made by comparing the 13 patient with abnormal lipid profile who is already administering thiazide diuretic with a 13 healthy individual's that is not consuming thiazide diuretics.

From this study we found no association between single antihypertensive drug therapy and plasma lipid levels.
Plasma lipid level was mostly affected by combination drug therapies (ß-blocker and thiazide diuretics or ACEI and thiazide diuretics).

The above data showed significantly increase in triglyceride (TG) and decrease HDL – cholesterol value in patients take ß-blocker and thiazide diuretics compared to others. these

changes might to mediated through inhibition of lipoprotein lipase activity.

Also high triglyceride level or hypertriglyceridemia may be the result from high carbohydrate diet, high fat diet, obesity Sedentary lifestyle, lack of physical activity and this study was carried out in randomly patients and so it's difficult to exclude pre-existing High triglyceride level and elevated levels of triglycerides are associated with atherosclerosis even in absence of hypercholesterolemia.

the influence of antihypertensive drugs on additional cardiovascular risk factors should considered when selecting medication to reduce blood pressure. Nevertheless, before antihypertensive drug treatment is initiated, blood lipid levels should be measured to identify preexisting hyperlipidemia. Patient with elevated lipid levels, ß–blocker and diuretics may make the management of lipid disorder more difficult and for such patient it may be desirable to select alternative antihypertensive agents that will not influence the lipid profile or interfere with the therapy for hyperlipidemia.

4.2. conclusion:

The study has revealed that thiazide Diuretics causes a significant elevation of TG with generally no significant changes in TC, LDL – cholesterol, VLDL – cholesterol and HDL-cholesterol and coronary risk attributable to cholesterol and its subfractions does not seem to operate in long term thiazide treated patients.

it is important to note that observations on interactions of antihypertensive agents with lipoproteins have so far been limited largely to serum concentrations. However, lipid binding to vascular cells, the uptake, concentrations and metabolic processes in vascular cells rather than in the blood stream are decisive for atherogenesis, and effects of the different antihypertensive agents at the cellular level remain to be investigated. Therefore, possible differential indications for the various antihypertensive drugs are only beginning to emerge. Still, at this stage, it is of clinical interest that several of the generally available antihypertensive drugs seem to be metabolically 'neutral' or sometimes perhaps even potentially beneficial with regard to the lipoprotein and glucose metabolism.

4.3. Recommendation:

Knowledge the effect of thiazide diuretics on lipid metabolism is important as thiazide diuretics are most commonly used drugs for treatment of hypertension and in various other cardio vascular and renal diseases. It is pertinent that all those who deal with patients with cardiovascular and renal ailments should have in depth knowledge of effect of diuretics on lipid metabolism. clinician should also advice the patients on diuretic therapy to include some kind of physical activity to keep lipid profile within limits they should be advised for aerobic exercise by means of walking, jogging, cycling, swimming etc. or should seek advice from physiotherapist for right kind of exercises with respect to their age, heart rate, blood pressure parameters, within their specific exercise heart zone.

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