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RESEARCH TITLE

Plasma Uric Acid Concentration in Type 2 Diabetes Mellitus and Hypertension in Gezira State - Sudan

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Abstract

There is a global rise in the incidence of T2DM, and the Sudan is not an exception; as part of the various studies being made to combat this devastating disease; a study was conducted in Al Daraga Health Center, Wad Medeni, Gezira state with a main aim of finding any association between uric acid level, T2DM and hypertension. This study was conducted by recruiting 196 participants, of whom 46 were hypertensive type 2 diabetic, 49 type 2 diabetic non- hypertensive, 51 hypertensive non-diabetic, and 50 apparently healthy subjects (non- hypertensive non-diabetic) as a control group; all in the age range between 40 and 65 years. Four ml of venous blood were collected from each participant after overnight fasting. Measurements of plasma concentrations of uric acid, glucose, urea, creatinine, total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and triglycerides were conducted. Analysis was performed using standard methods. Questionnaires were filled to collect personnel, medical as well as anthropometric data of the participants. The one way analysis of variance (ANOVA) made showed that the highest uric acid level was in hypertensive (5.52 ± 0.16), followed by hypertensive diabetic (4.81± 0.19); compared with that of diabetic (4.41±0.15) and control group (4.81±0.14); this differences were statistically significant (p< 0.001). Hypertensive diabetic, diabetic, and hypertensive patients were found to have high level of TC, TG, LDLC and LDLC/HDLC compared to the control group and all the differences were statistically significant (p <0.001, 0.004, 0.001 and <0.001 respectively). Moreover, these groups were found to have lower HDLC compared with the control group and the difference was statistically significant (p= 0.02). As the uric acid level is found to be higher in hypertensive and hypertensive diabetic compared to the diabetic patients, it can be concluded that, elevated uric acid level has an association with hypertension. As increased TC/HDLC, TG/HDLC, and HDLC/LDLC ratios were found in all patient groups, which is an indication of cardiovascular risk. All the diabetic and hypertensive should maintain their uric acid and lipid profile levels in the normal range by undertaking dietary and medical interventions.

عنوان البحث

تركيز حمض اليوريك في بلازما الدم لدى مرضى السكري من النوع الثاني ومرضى فرط ضغط الدم بولاية الجزيرة – السودان

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المستخلص

هناك إرتفاع عالمي في حدوث داء السكري من النوع الثاني وكذلك في السودان ؛ كجزء من الدراسات التي تبذل لمكافحة هذا المرض المدمر. أجريت هذه الدراسة في ولاية الجزيرة في منطقة ود مدني مركز صحي الدرجة. الهدف الأساسي من الدراسة استقصاء وجود إرتباط بين مستوى حمض اليوريك وداء السكري من النوع الثاني وفرط ضغط الدم. وقد شملت هذه الدراسة 196 مشاركاً، منهم 46 مصابين بداء السكري من النوع الثاني وفرط ضغط الدم ، 49 مصابين بداء السكري من النوع الثاني فقط ، 51 مصابين بفرط ضغط الدم فقط، 50 شخص أصحاء (المجموعة الضابطة) تتراوح أعمارهم بين 40 و 65 عاماً. تم جمع أربعة مل من الدم الوريدي من كل مشارك في الصباح الباكر بعد الصيام ليلاً لمدة 12 ساعة. وأجريت قياسات تركيز كلٍ من الآتي في بلازما الدم: حمض اليوريك، و الجلوكوز، واليوريا، والكرياتينين ، والكولسترول الكلى والبروتين الدهني عالي الكثافة للكلسترول و البروتين الدهني منخفض الكثافة للكولسترول والجلسريدات الثلاثية .وقد تم تحليل العينات بإستخدام الطرق القياسية. تم إستخدام إستبيان منظم لجمع بيانات الأفراد المشاركين. أظهر تحليل التباين في إتجاه واحد أن مستوى حمض اليوريك كان أعلى بدلالة إحصائية ($p< 0.001$) في مرضى فرط ضغط الدم (5.52 ± 0.16) ، يليه مرضى السكري وفرط ضغط الدم (4.81 ± 0.19) مقارنة مع مرضى السكري (4.41 ± 0.15) و المجموعة الضابطة (4.81 ± 0.14). مرضى السكري وفرط ضغط الدم ومرضى فرط ضغط الدم لديهم تركيز عالي ذو دلالة إحصائية من الكوليسترول الكلي و الجلسريدات الثلاثية والبروتين الدهني عالي الكثافة للكلسترول ونسبة البروتين الدهني عالي الكثافة للكلسترول الى البروتين الدهني منخفض الكثافة للكلسترول مقارنة مع المجموعة الضابطة ($p <0.001,0.004,0.001$ و <0.001) على التوالي , وإنخفاض ذو دلالة احصائية في البروتين الدهني منخفض الكثافة للكلسترول ($p= 0.02$)، وتخلص الدراسة إلى أن ارتفاع مستوى حمض اليوريك يرتبط مع فرط ضغط الدم .كما أن نسبة الكلسترول الكلي إلى البروتين الدهني منخفض الكثافة للكلسترول ونسبة الجلسريدات الثلاثية إلى البروتين الدهني عالي الكثافة للكلسترول ونسبة البروتين الدهني منخفض الكثافة للكلسترول إلى البروتين الدهني عالي الكثافة للكلسترول هي مؤشر للإصابة بأمراض القلب والأوعية الدموية . لذلك يجب علي جميع مرضى السكري من النوع الثاني ومرضى فرط ضغط الدم المحافظة على مستوى حمض اليوريك والدهون في المعدل الطبيعي عن طريق إجراء التدخلات الغذائية والطبية.

CHAPTER ONE

Introduction and Literature Review

Diabetes Mellitus

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood glucose. Hyperglycemia, or raised blood glucose, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels (WHO, 2014).

347 million people worldwide have diabetes, and it is expected to be the 7th leading cause of death in 2030 worldwide. More than 80% of people with diabetes live in low and middle income countries (WHO, 2014).

In Sudan diabetes mellitus is currently emerging as an important health problem, especially in urban areas. The actual prevalence of diabetes is unknown although a prevalence of 3.4% had been reported. Diabetes is the commonest cause of hospital admission and morbidity due to a non-communicable disease 7 and 10% respectively (Ahmed and Ahmed, 2001).

Classification of Diabetes Mellitus

Diabetes mellitus is classified into 3 types: type 1 diabetes, insulin-dependent diabetes mellitus (IDDM); type 2 diabetes, non-insulin dependent diabetes mellitus (NIDDM); and gestational diabetes mellitus (GDM) (Bishop *et al.*, 2010)

Type 1 diabetes is characterized by inappropriate hyperglycemia primarily a result of pancreatic islet cell destruction and a tendency to ketoacidosis. Type 1 diabetes mellitus is a result of cellular-mediated autoimmune destruction of the beta cells of the pancreas, causing an absolute deficiency of insulin secretion. It constitutes only 10% to 20% of all cases of diabetes and commonly occurs in childhood and adolescence. In type 1, there is an absence of insulin with an excess of glucagon. This permits gluconeogenesis and lipolysis to occur. This disease is usually initiated by an environmental factor or infection (usually a virus) in individuals with a genetic predisposition and causes the immune destruction of the cells of the pancreas and, therefore, a decreased production of insulin (Bishop *et al.*, 2010).

Type 2 diabetes mellitus is characterized by hyperglycemia as a result of an individual's resistance to insulin with an insulin secretary defect. This resistance results in a relative, not an absolute, insulin deficiency. Most patients in this type are obese or have an increased percentage of body fat distribution in the abdominal region. This type of diabetes often goes undiagnosed for many years and is associated with a strong genetic predisposition, with patients at increased risk with an increase in age, obesity, and lack of physical exercise. Characteristics of type 2 diabetes mellitus usually include adult onset of the disease and milder symptoms than in type 1, with ketoacidosis seldom occurring (Burits *et al.*, 2008). However, these patients are more likely to go into a hyperosmolar coma and are at an increased risk of developing macrovascular and microvascular complications (Stratton *et al.*, 2000). Type 2 diabetes mellitus is characterized differently due to variation in the degree of insulin resistance, sensitivity, and secretion (Burits *et al.*, 2008).

The characteristic symptoms of diabetes mellitus are excessive urine production (polyuria), due to high blood glucose levels; excessive thirst and increased fluid intake (polydipsia), attempting to compensate for increased urination; blurred vision, due to high blood glucose effects on the eye's optics; unexplained weight loss and lethargy. These symptoms are likely to be less apparent if the blood glucose is only mildly elevated (Bishop *et al.*, 2010).

Criteria for the Diagnosis of Diabetes Mellitus

The three confirmatory criteria for the diagnosis of diabetes mellitus recommended by the WHO are:

- Symptoms of diabetes plus a random plasma glucose level of >11.1 mmol/L, 200 mg/dL.
- A fasting plasma glucose level of >7.0 mmol/L126 mg/dL.
- An oral glucose tolerance test (OGTT) with a 2-hour post load (75-g glucose load) level of >11.1 mmol/L 200 mg/dL.

Each of which must be confirmed on a subsequent day by any one of the three methods. The preferred test for diagnosing diabetes is measurement of the fasting plasma glucose level (WHO, 2014).

Complications of Diabetes Mellitus

Patients with long-standing diabetes are at risk of developing a variety of complications of the disorder:

- Microvascular/neuropathic which include: retinopathy, cataract (impaired vision), nephropathy (renal failure), peripheral neuropathy (sensory loss, Pain, motor weakness), autonomic neuropathy (gastrointestinal problems, postural hypotension), Foot disease (ulceration, arthropathy).
- Macrovascular (Burits *et al.*, 2008).

Management for type 2 diabetes

Diet and lifestyle changes are the key to successful treatment of type 2 diabetes and the other three main options are oral hypoglycemic agents e.g. metformin, a sulfonylurea or a thiazolidinedione (Kumar and Clark, 2012).

Hypertension

High blood pressure or hypertension is the constant pumping of blood through blood vessels with excessive force. Globally, nearly one billion people have high blood pressure; of these, two-thirds are in developing countries. Hypertension is one of the most important causes of premature death worldwide and the problem is growing; in 2025, an estimated 1.56 billion adults will be living with hypertension (WHO, 2013).

Normal adult blood pressure is defined as a blood pressure of 120 mm Hg when the heart beats (systolic) and a blood pressure of 80 mm Hg when the heart relaxes (diastolic). When systolic blood pressure is equal to or above 140 mm Hg and/or a diastolic blood pressure equal to or above 90 mm Hg the blood pressure is considered to be high (WHO, 2013). Hypertension was directly responsible for 7.5 million deaths in 2004 almost 13% of all global deaths. In nearly all high income countries, widespread diagnosis and treatment with low cost medication have led to a dramatic drop in mean blood pressure across populations and this has contributed to a reduction in deaths from heart disease. In 1980, almost 40% of adults in the European Region and 31% of adults in the Region of the Americas had high blood pressure. By 2008, this had dropped to below 30% and 23% respectively. In contrast, in the African region, more than (40% and up to 50%) of adults in many countries are estimated to have high blood pressure and this proportion is increasing. Many people with high blood pressure in developing countries remain undiagnosed, and so miss out on treatment that could significantly reduce their risk of death and disability from heart disease and stroke (WHO, 2013). According to a recent WHO report including statistics gathered from 194 countries, the percentage of men and women with raised blood pressure and blood glucose level is increasing alarmingly. Therefore adequate treatment of diabetes, as well as blood pressure control is vital and this can be achieved through introduction of different lifestyle changes such as smoking cessation and maintaining a healthy body weight (WHO, 2013).

Hypertension causes symptoms such as headache, shortness of breath, dizziness, chest pain, palpitations of the heart and nose bleeds. However, most people with hypertension have no symptoms at all (Fauci *et al.*, 2008).

The higher the blood pressure, the higher the risk of damage to the heart and blood vessels in major organs such as the brain and kidneys (Kumar and Clark, 2012). If left uncontrolled, hypertension can lead to a heart attack, an enlargement of the heart and eventually heart failure. Blood vessels may develop bulges (aneurysms) and weak spots that make them more likely to clog and burst (Kumar and Clark, 2012) .

The pressure in the blood vessels can cause blood to leak out into the brain and cause a stroke. Hypertension can also lead to kidney failure, blindness, and cognitive impairment. The health consequences of hypertension can be compounded by other factors that increase the odds of heart attack, stroke and kidney failure. These factors include tobacco use, unhealthy diet, harmful use of alcohol, lack of physical activity, and exposure to persistent stress, obesity, high cholesterol as well as diabetes mellitus (WHO, 2013).

People with high blood pressure who also have high blood sugar or elevated blood cholesterol face even higher risk of heart attacks and stroke. Therefore it is important that regular checks for blood glucose, blood cholesterol and urine albumin in hypertensive individuals take place (Clearinghouse, 2013)..

The coexistence of diabetes and hypertension acts as a multiplier of cardiovascular risk (Mourad and Le Jeune, 2008). Therefore, identifying early predictors for the development of diabetes in hypertensive patients could be useful for devising more effective strategies to reduce cardiovascular risk.

Treatment of hypertension (Kumar and Clark, 2012)

- Alpha-blockers (doxazosin, indoramin, phenoxybenzamine and phentolamin).
- Angiotensin-converting enzyme inhibitors (enalapril, lisinopril, perindopril and eamipril).
- Angiotensin II receptor blockers (losartan, candesartan, valsartan, olmesartan and telmisartan).
- Beta-blockers (atenolol, bisoprolol , carvedilol and labetalol).
- Calcium channel blockers (a mlodipine ,nifedipine ,diltiazem and verapamil).
- Diuretics (bendroflumethiazide and chlortalidone).
- Renin inhibitors (aliskiren).

Hypertension and diabetes are closely linked and one cannot be properly managed without attention to the other. Patients with hypertension and especially those with type 2 diabetes or metabolic syndrome should use lipid-lowering agents (Mancia *et al.*, 2013).

Hyperuricemia

Uric acid (UA) is formed from purine nucleosides, produced by the breakdown of nucleic acids, and in humans is the end-product of purine catabolism. The daily synthesis rate is estimated to be about 1.8 mmol, with a total body pool of approximately 7.2 mmol. Approximately 70% of uric acid is excreted by the kidneys, and the rest by the gut (Murray *et al.*, 2009).

Many factors contribute to hyperuricemia including genetics, insulin resistance, hypertension, renal insufficiency, obesity, diet, use of diuretics, and consumption of alcoholic beverages (Burits *et al.*, 2008).

Hyperuricemia has been classified into three functional types (Yamamoto, 2008):

(I) Increased production of uric acid:

- Hypoxanthine guanine phosphoribosyl transferase (HPRT) deficiency (due to HPRT gene abnormality).
- Excessive consumption of purine rich diet.
- Cytolysis induced by chemotherapy of blood neoplasm.

(II) Decreased excretion of uric acid:

- Familial juvenile hyperuricemia nephropathy (due to uromodulin gene abnormality).
- Abrupt body weight loss (due to low calorie diet).

(III) Mixed type:

- Glucose 6-phosphatase deficiency (due to glucose 6- phosphatase gene abnormality).
- Excessive consumption of alcohol beverages.

Recent studies provide both a pathogenetic and epidemiological rationale for a role of serum uric acid (SUA) in the development of diabetes (Kodama *et al.*, 2009). A prospective follow-up study showed that high serum uric acid is associated with higher risk of type 2 diabetes, independent of obesity, dyslipidemia, and hypertension (Dehghan *et al.*, 2008). A modest positive association between concentrations of uric acid and incidence of type 2 diabetes mellitus has been observed in a Chinese cohort (Chien *et al.*, 2008). Another study demonstrated that serum uric acid values may be useful as predictors of DM2 in adults who are glucose intolerant (Kramer *et al.*, 2009). Serum concentration of uric acid showed a positive relationship with the total phase of insulin secretion, even in states prior to hyperuricemia, uric acid can play an important role in the function of the beta cell in patients with DM2 (Robles-Cervantes *et al.*, 2011). Higher serum uric acid levels were inversely associated with diabetes mellitus in US adults (Bandaru and Shankar, 2011).

It is widely accepted that raised serum uric acid levels often co-present with obesity, hypertension and hyperlipidemia (Kawamoto *et al.*, 2006). Increased uric acid level has been shown to be associated with cardiovascular disease (Sundstrom *et al.*, 2005), and chronic kidney disease (Chonchol *et al.*, 2007). An epidemiological study showed that an elevated level of uric acid is a risk factor for peripheral arterial disease (Shankar *et al.*, 2006). Hyperuricemia is associated with an increased risk for incidence of hypertension (Shankar *et al.*, 2006), this was independent of traditional hypertension risk factors and more pronounced in younger individuals and women (Grayson *et al.*, 2011).

Hyperuricemia is an independent risk factor for kidney dysfunction in patients with diabetes mellitus. It is suggested that increased serum level of uric acid is an injurious factor for kidneys, as it was shown that hyperuricemia induce endothelial dysfunction, glomerular hypertension, and renal hypertrophy, decrease renal perfusion via stimulation of the afferent arteriolar vascular smooth muscle cell proliferation (Fukui *et al.*, 2008).

It has been documented in hypertensive normal glucose tolerant subjects, that UA is strongly associated with 1-h post-load glucose, similarly to what is observed in impaired glucose tolerant and diabetic patients (Perticone *et al.*, 2012).

Justification of the study

Serum uric acid has been shown to be associated with diabetes mellitus, hypertension cardiovascular diseases, and chronic kidney diseases (Sundstrom *et al.*, 2005;Grayson *et al.*, 2011;Chonchol *et al.*, 2007). However, few studies have examined serum uric acid in diabetic hypertensive patients and their findings are not consistent. Therefore, the aim of this study was to assess the plasma uric acid levels in diabetic and hypertensive Sudanese patients. Revealing the nature of this association could help in using uric acid among selected biochemical parameters as markers for diabetes-hypertension associated complications.

Study Objectives

General Objective

The objective of this study was to examine plasma uric acid concentration in type 2 diabetes mellitus and hypertension in Sudanese patients attending Al Daraga Health Centre in Wad Medani, Gezira state, Sudan.

Specific objectives

1. To measure fasting plasma concentration of:
    - Glucose.
    - Uric acid.
    - Urea.
    - Creatinine.
    - Triglycerides (TG).
    - Total cholesterol (TC).
    - High density lipoprotein cholesterol (HDL-C).
    - Low density lipoprotein cholesterol (LDL-C).
2. To test presence of albumin in a fresh urine samples.
3. To measure systolic and diastolic blood pressure of the study subjects.
4. To compare measured parameters of the cases and control groups.
5. To test presence of any correlation between measured parameters.

CHAPTER TWO

Subjects, Materials and Methods

Study Design, Area and Subjects

Study Design: This was a cross-sectional case-control study.

Study Area: The study was carried-out at Al Daraga Health Centre in Wad Medani, Gezira state, Sudan.

Study Subjects: This study recruited a total of 196 participants (age range between 40 and 65 years) classified in 4 groups: 46 patients with diabetes and hypertension, 49 patients with diabetes, 51 patients with hypertension, and 50 healthy individuals

Inclusion Criteria: type 2 diabetic Sudanese patients with or without hypertension.

Exclusion Criteria: Patients with gout, kidney diseases, liver diseases, or any current infection or disease were excluded.

Materials and Methods

Collection of Blood Samples

Four ml of venous blood were collected from each participant after an overnight fasting. It was put in a tube containing lithium heparin as an anticoagulant, after centrifugation plasma was separated and used for the measurement of uric acid(UA), fasting plasma glucose(FPG), urea(Ur), creatinine(Cr), total cholesterol(TC), high-density lipoproteins cholesterol(HDL-C) ,low density lipoproteins cholesterol(LDL-C) and triglycerides(TG).

Collection of urine samples

Morning urine samples were collected into sterile clean dry containers. The samples were analyzed immediately for presence of albumin.

Anthropometric Measurements

The weight in kilogram (kg) and height in meter (m) of each participant were measured. Then the body mass index (BMI) was calculated applying the formula:

BMI = weight (kg) / height (m^2)

Reference ranges for BMI and corresponding descriptions of groups are shown in table 2-1.

Table 2-1: Reference ranges for BMI

Range	Group
19.95 < BMI ≤ 25	Normal
25< BMI ≤ 29	Over weight
BMI ≥ 30	Obese

(Champe and Harvey, 2005). *Lippincott's illustrated reviews: biochemistry*. pp:347.

Biochemical Measurements

The biochemical analyses were carried-out using A15, a random access analyzer (code 83105) manufactured by Biosystems company (Biosystems, Barcelona, Spain). All reagents were purchased from Biosystems.

The biochemical parameters measured in this study included:-

Fasting plasma glucose

Method: Glucose oxidase / peroxidase (code 12503).

Principle of the method: Glucose in the sample is metabolized, by means of the coupled reactions described below; giving a colored complex that can be measured by spectrophotometry (Bishop *et al.*, 2010).

$$\text{Glucose} + \tfrac{1}{2}\,O + H_2O \xrightarrow{\text{glucose oxidase}} \text{gluconate} + H_2O_2$$

$$2H_2O_2 + \text{4-aminoantipyrine} + \text{phenol} \xrightarrow{\text{peroxidase}} \text{quinoneimine} + 4H_2O$$

Uric acid

Method: uricase / peroxidase (code 12521).

Principle of the method: Uric acid in the sample produces, by means of the coupled reactions described below, a colored complex that can be measured by spectrophotometry (Bishop *et al.*, 2010).

$$\text{Uric acid} + O_2 \xrightarrow{\text{uricase}} \text{allantoin} + CO_2 + H_2O_2$$

$$2H_2O_2 + \text{4-aminoantipyrine} + \text{dichlorophenolsulfonate (DCFS)} \xrightarrow{\text{peroxidase}} \text{quinoneimine} + 4H_2O$$

Total cholesterol (TC)

Method: Cholesterol oxidase / peroxidase (code 12505).

Principle of the method: Free and esterified cholesterol in the sample metabolized by means of the couple reactions described below, giving a colored complex that can be measured by spectrophotometry (Bishop *et al.*, 2010) .

$$\text{Cholesterol ester} + H_2O \xrightarrow{\text{cholesterol esterase}} \text{cholesterol} + \text{fatty acid}$$

$$\text{Cholesterol} + \frac{1}{2} O_2 + H_2O \xrightarrow{\text{cholesterol oxidase}} \text{cholestenone} + H_2O_2$$

$$2H_2O_2 + \text{4-aminoantipyrine} + \text{phenol} \xrightarrow{\text{peroxidase}} \text{quinoneimine} + 4H_2O$$

High density lipoproteins cholesterol (HDL-C)

Method: Cholesterol HDL-Direct (code 12557).

Principle of the method: The cholesterol from high density lipoprotein is broken down by the cholesterol oxidase in an enzymatic accelerated non-color forming reaction. The detergent present in reagent B, solublizes cholesterol from high density lipoproteins in the sample. The HDL cholesterol is then measured spectrophotometrically by means of the reactions described below (Bishop *et al.*, 2010).

$$\text{Cholesterol ester} + H_2O \xrightarrow{\text{cholesterol esterase}} \text{cholesterol} + \text{fatty acid}$$

$$\text{Cholesterol} + \frac{1}{2} O_2 + H_2O \xrightarrow{\text{cholesterol oxidase}} \text{cholestenone} + H_2O_2$$

$$2H_2O_2 + \text{4-aminoantipyrine} + \text{N, N-bis (4-sulfobutyl)-m-toluidine (DSBmT)} \xrightarrow{\text{peroxidase}} \text{quinoneimine} + 4H_2O$$

Low density lipoproteins cholesterol (LDL-C)

Method: Cholesterol LDL-Direct (code 12585).

Principle of the method: The cholesterol from low density lipoprotein is broken down by the cholesterol oxidase in an enzymatic accelerated non-color forming reaction. The detergent present in reagent B, solublizes cholesterol from low density lipoproteins in the sample. The LDL cholesterol is then measured spectrophotometrically by means of the coupled reactions described below(Bishop *et al.*, 2010).

$$\text{Cholesterol ester} + H_2O \xrightarrow{\text{cholesterol esterase}} \text{cholesterol} + \text{fatty acid}$$

$$\text{Cholesterol} + \frac{1}{2} O_2 + H_2O \xrightarrow{\text{cholesterol oxidase}} \text{cholestenone} + H_2O_2$$

$$2H_2O_2 + \text{4-aminoantipyrine} + \text{DSBmT} \xrightarrow{\text{peroxidase}} \text{quinoneimine} + 4H_2O$$

Triglycerides (TG)

Method: Glycerol phosphate oxidase / peroxidase (code 12528).

Principle of the method: Triglycerides in the sample produce, by means of the reactions described below, a colored complex that can be measured by spectrophotometry (Bishop *et al.*, 2010).

$$\text{Triglycerides} + H_2O \xrightarrow{\text{lipase}} \text{glycerol} + \text{fatty acid}$$

$$\text{Glycerol} + \text{ATP} \xrightarrow{\text{glycerol kinase}} \text{glycerol-3-P} + \text{ADP}$$

$$\text{Glycerol-3-P} + O_2 \xrightarrow{\text{G-3-P-oxidase}} \text{dihydroxyacetone-P} + H_2O_2$$

$$2\ H_2O_2 + \text{4-aminoantipyrine} + \text{4-chlorophenol} \xrightarrow{\text{peroxidase}} \text{quinoneimine} + 4H_2O$$

Urea/BUN - UV

Method: Urease / glutamate dehydrogenase (code 12516).

Principle of the method: Urea in the sample consumes, by means of the coupled reactions described below, NAD^+ that can be measured by spectrophotometry (Bishop *et al.*, 2010).

$$\text{urea} + H_2O \xrightarrow{\text{urease}} 2NH_4^+ + CO_2$$

$$\text{NH4} + \text{NADH} + H_+ + \text{2- Oxoglutarate} \xrightarrow{\text{glutamate deshydrogenase}} \text{glutamate} + NAD^+ + H_2O$$

Creatinine

Method: Alkaline picrate (code 12502).

Principle of the method: Creatinine in the sample reacts with picrate in alkaline medium forming a colored complex. The complex formation rate is measured in a short period to avoid interferences (Bishop *et al.*, 2010).

Urine albumin analysis:

Method: Urine reagent strips (ingredient: tetrabromophenol blue).

The test method consists of immersing the test strip completely in a well-mixed urine sample for a short period of time. The strip is then removed from the container and left to stand for 1 to 2 minutes. Finally the color appeared was compared against the chromatic scale provided by the manufacturer.

Principle of the method: based on the fact that proteins alter the color of some pH indicators even though the pH of the media remains constant. This occurs because proteins (and particularly albumin) acquire hydrogen ions at the expense of the indicator as the protein's amino groups are highly efficient acceptors of H^+ ions (Bishop *et al.*, 2010).

References ranges for the different biochemical parameters are shown in table 2-2.

Table 2-2: References Ranges for Different Biochemical Parameters

Parameter	References range
Fasting Plasma Glucose (FBG)	75 - 110 mg/dL
Plasma Urea	15 - 43 mg/dL
Plasma creatinine	Male 0.6 - 1.2 ng/mL Female 0.5 - 0.9 ng/mL
Plasma uric acid	Male 3.1–7.0 mg/dL Female 2.5–5.6 mg/dL
TC	< 200 mg/dl
HDL-C	40 – 60 mg/dl
LDL-C	< 100 mg/dl
TG	30 – 200 mg/dl

(Fauci, 2008). *Harrison's Principles of Internal Medicine* (17th ed). Appendix.

Statistical Analysis

Statistical analysis was carried-out using statistical package for social sciences (SPSS version 16, Chicago, IL, USA). Continuous data were expressed as mean ± SEM. Differences in means of continuous variables between the patient groups and control group were compared using the one way analysis of variance (ANOVA). Pearson's correlation was used to analyze the correlation between continuous variables. p values ≤ 0.05 were considered to be statistically significant.

CHAPTER THREE

Results

Characteristics of the study groups

196 participants were included in this study (46 hypertensive type 2 diabetic, 49 type 2 diabetic non- hypertensive, 51 hypertensive non-diabetic, and 50 healthy non-hypertensive non-diabetic subjects as a control group). Age ranged between 40 and 65 years. Demographic and anthropometric characteristics of the study groups are shown blow (Table 3-1).

Table 3-1: Demographic and anthropometric characteristics of the study groups

Parameter	Hypertensive diabetic	Diabetic	Hypertensive	Control
Number	46	49	51	50
Male: Female	14:32	21:28	15:36	20:30
weight (kg)	74.98 ±1.82	72.00 ±2.08	70.25 ±2.22	67.74 ±1.75
BMI (Kg/m^2)	31.22 ±0.89	30.54 ±0.92	28.50 ±0.86	27.89 ±0.77
Waist: Hip ratio	1.05±0.03	0.98±0.02	0.89±0.02	0.86±0.2

Data are expressed as mean ± SEM.

Comparison of the measured biochemical parameters between study groups

The one way analysis of variance (ANOVA) performed to compare the mean concentrations between the measured biochemical parameters in the four groups (table 3-2), showed that the highest mean level of uric acid was found in hypertensive patients (5.52 ± 0.16 mg/dl), followed by hypertensive diabetic patients (4.81± 0.19 mg/dl). The diabetic group had the lowest mean level (4.41±0.15 mg/dl). These differences were statistically significant ($p< 0.001$).

Hypertensive group showed the highest level of plasma creatinine (0.95±0.03 mg/dl) compared to the other groups; the overall difference between the groups was significant ($p=0.014$).

Hypertensive diabetic, diabetic, and hypertensive patients had elevated mean levels of TC, TG, LDLC and LDLC/HDLC compared with the control group and all the differences were statistically significant ($p<0.001$, $p=0.004$, $p=0.001$ and $p<0.001$) respectively. Furthermore, these groups were found to have lower HDLC mean concentration compared with the control group and the difference was statistically significant (p=0.02). Figures 3-1 to 3-6 show comparison of means for the measured biochemical parameters in the different study groups.

Comparison of blood pressure between study groups

Hypertensive diabetic and hypertensive groups showed higher levels of systolic blood pressure (SBP) 135.87±2.25 mmHg and 129.22±1.53 mmHg respectively, compared to the diabetic and control groups (120.41±1.46 mmHg and 120.6±0.60 mmHg respectively). Hypertensive diabetic and hypertensive groups showed higher levels of diasystolic blood pressure (DBP) (83.48±1.17 mmHg and 82.16±048 mmHg respectively) , compared to the diabetic and control groups (77.96±1.13mmHg and 80.8±0.48mmHg respectively). The differences between the groups were statistically significant (p< 0.001).

Table 3-2: Comparison of means of the biochemical parameters in the study groups

Parameter	**Hypertensive diabetic** (N = 46)	**Diabetic** (N= 49)	**Hypertensive** (N = 51)	**Control** (N = 50)	**P value** (2-tailed)
FPG (mg/dl)	174.93±10.96	186.37±11.17	97.55±2.52	96.12±2.22	**< 0.001**
Plasma uric acid (mg/dl)	4.81±0.19	4.41±0.15	5.52±0.16	4.81±0.14	**< 0.001**
Plasma creatinine (mg/dl)	0.82±0.04	0.82±0.03	0.95±0.03	0.89±0.03	**0.014**
Plasma Urea (mg/dl)	28.63±1.37	28.22±1.17	30.29±1.10	29.2±1.08	0.62
TC (mg/dl)	184.63±6.06	175.51±5.68	189.71±5.94	153.46±3.69	**< 0.001**
TG (mg/dl)	170.41±12.97	141.71±12.54	164.94±10.58	117.80±8.50	**0.004**
LDLC (mg/dl)	96.22±5.49	83.45±5.92	75.78±5.26	67.32±3.32	**0.001**
HDLC (mg/dl)	39.35±1.14	39.63±1.35	43.47±1.95	44.72±1.25	**0.02**
LDLC/HDLC	2.48±0.14	2.15±0.156	1.77±0.10	1.57±0.09	**< 0.001**

Data are expressed as mean ± SEM; N, number

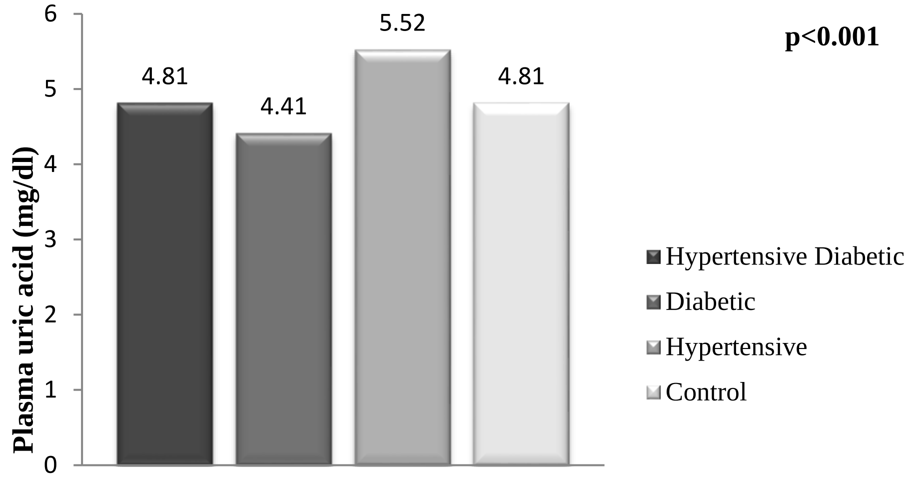

Figure 3-1: Plasma uric acid mean concentration in the study groups

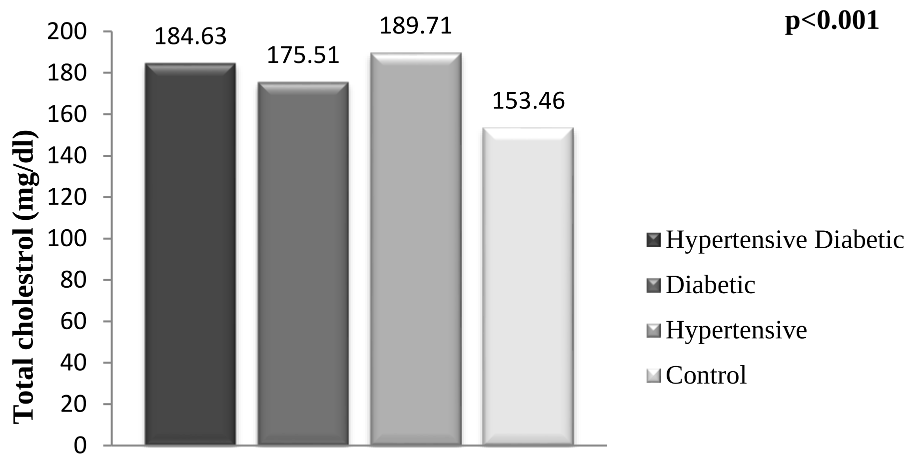

Figure 3-2: Plasma total cholestrol mean concentrations in the study groups

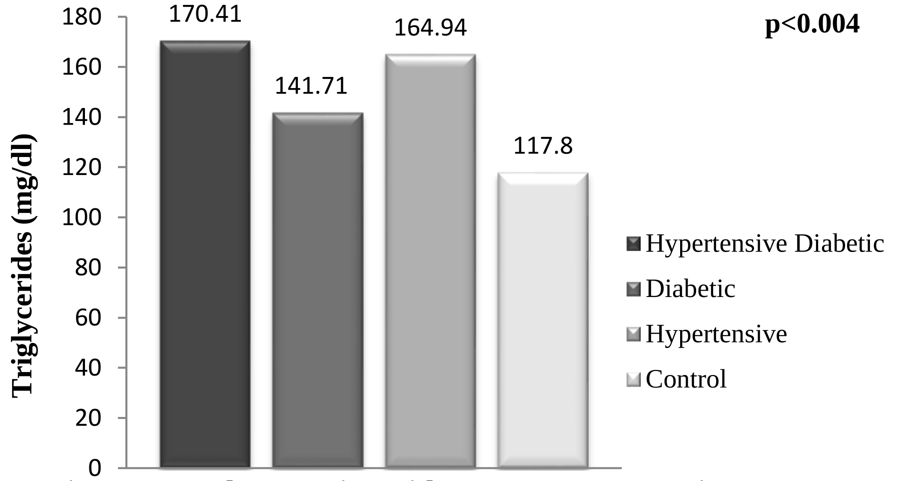

Figure 3-3: Plasma trigycrides mean concentrations in the study groups

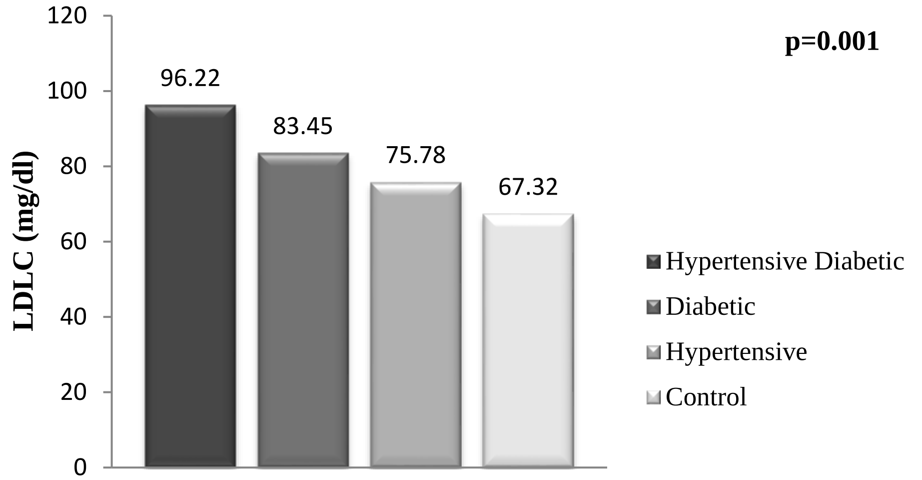

Figure 3-4: Plasma LDLC mean concentrations in the study groups

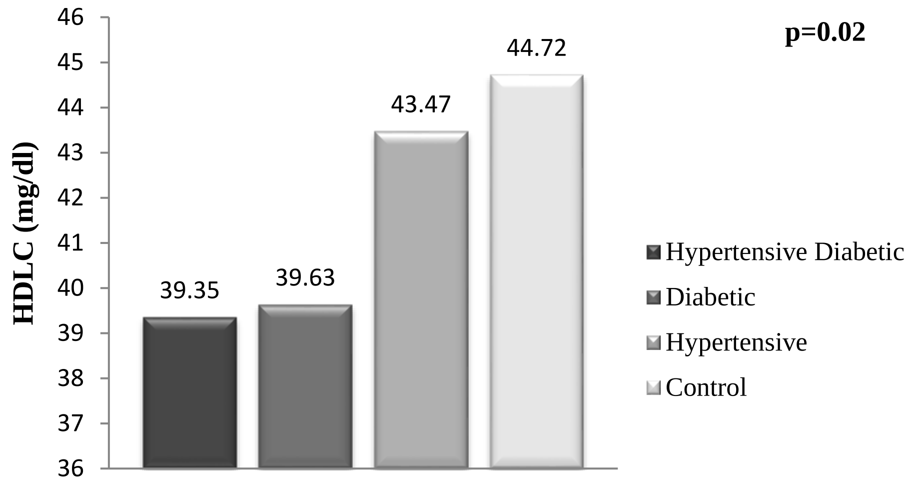

Figure 3-5: Plasma HDLC mean concentrations in the study groups

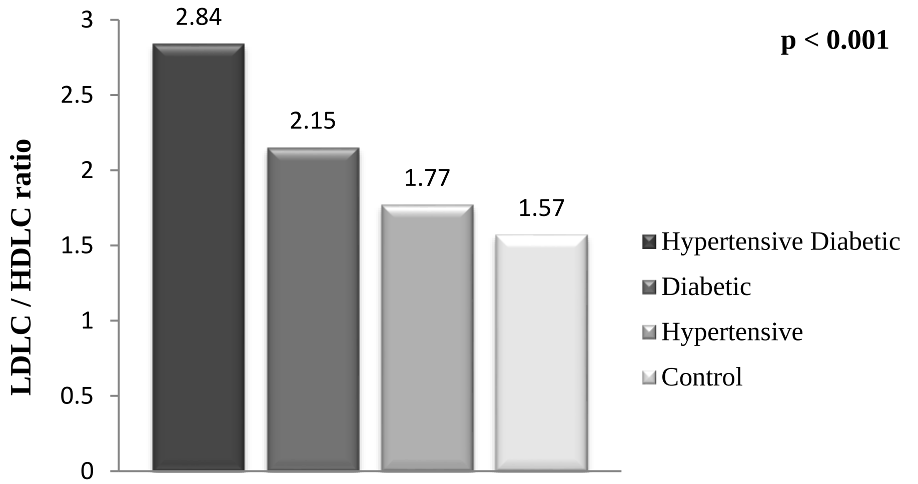

Figure 3-6: LDLC to HDLC ratio in the study groups

Correlation analysis

Plasma uric acid showed a weak positive significant correlation with plasma creatinine, plasma urea , total cholesterol and Triglycerides (r= 0.257, 0.302, 0.246 and 0.251 respectively), all with p< 0.001.

Body mass index showed a weak negative significant correlation with duration of diabetes (r= - 0.24, p< 0.019); plasma creatinine (r= - 0.160, p= 0.025); Plasma urea (r= - 0.172, p= 0.016) and HDLC (r= -0.135, p =0.016). BMI had a weak positive significant correlation with LDLC/HDLC (r= 0.211, p=0.003).

Duration of diabetes showed moderate positive significant correlation with plasma creatinine (r= 0.477, p< 0.001) as well as plasma urea (r= 0.387, p< 0.001).

Fasting plasma glucose showed a weak negative significant correlation with plasma uric acid and plasma creatinine (r= - 0.295, p< 0.001; r= - 0.248, p< 0.001 respectively); and a weak positive significant correlation with LDLC (r= 0.186, p 0.009) and LDLC/HDLC (r= 0.240, p= 0.001).

Plasma creatinine showed a strong positive significant correlation with plasma urea (r= 0.667, p< 0.001), and very weak positive significant correlation with total cholesterol (r= 0.06, p= 0.04).

Plasma urea showed a weak positive significant correlation with total cholesterol (r= 0.153, p= 0.032).

Total cholesterol showed moderate positive significant correlation with triglycerides, LDLC, HDLC and LDLC/ HDLC ratio (r= 0.421, 0.612, 0.338; 0.388, respectively) with p< 0.001.

Triglycerides showed moderate positive significant correlation with, LDLC and LDLC/ HDLC ratio with r= 0.432 and 0.440 respectively) and p< 0.001.

LDLC showed a weak positive significant correlation with HDLC (r= 0.236, p 0.001), and a strong positive significant correlation with LDLC/ HDLC ratio (r= 0.849, p < 0.001). HDLC showed a weak negative significant correlation with, LDLC/ HDLC ratio (r= -0.268, p< 0.001). Correlation analysis is presented in table 3-3.

Table 3-3: Correlation analysis of different parameters in the study group

Parameter		BMI	DOD	FPG	PUA	PCr	PUr	TC	TG	LDLC	HDLC	LDLC / HDLC
BMI	r	1	- 0.24	0.103	- 0.082	- 0.160	- 0.172	0.031	0.059	0.129	- 0.135	0.211
	p		**0.019**	0.152	0.254	**0.025**	**0.016**	0.664	0.413	0.072	*0.058*	**0.003**
DOD	r		1	0.055	0.111	0.477	0.387	0.007	- 0.056	0.001	- 0.158	0.099
	p			0.595	0.284	**<0.001**	**<0.001**	0.944	0.587	0.993	0.126	0.339
FPG	r			1	- 0.295	- 0.248	- 0.112	0.034	0.129	0.186	- 0.125	0.240
	p				**<0.001**	**<0.001**	0.118	0.633	0.072	**0.009**	0.081	**0.001**
PUA	r				1	0.257	0.302	0.246	0.251	0.135	0.041	0.122
	p					**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.06	0.571	0.088
PCr	r					1	0.667	0.06	- 0.034	0.015	0.017	0.021
	p						**<0.001**	**0.0403**	0.639	0.832	0.817	0.774
PUr	r						1	0.153	0.006	0.097	0.058	0.054
	P							**0.032**	0.931	0.175	0.422	0.451
TC	r							1	0.421	0.612	0.338	0.388
	p								**<0.001**	**<0.001**	**<0.001**	**<0.001**
TG	r								1	0.432	0.015	0.440
	P									**<0.001**	0.833	**<0.001**
LDL C	r									1	0.236	0.849
	P										**0.001**	**<0.001**
HDL C	r										1	-0.268
	P											**<0.001**
LDL C/ HDL C	r											1
	P											

Frequency distribution of normal and abnormal levels of the biochemical parameters in the study groups

The frequency of patients with increased plasma uric acid concentration was higher in the hypertensive and hypertensive diabetic groups (43.6% and 25.6% respectively).

There was significant increase in plasma level of creatinine in hypertensive patient (48.6%) compared to other groups (p 0.002). There was also significant increase in total cholesterol in patient groups compared to the control group (p<0.001). There was no significant difference in triglycerides.

There was a significant increase in LDLC in patient groups compared to control (p<0.001) and significant decrease in HDLC in patient groups compared to control (p<0.001).

For cardiovascular disease risk (according to the classification *by the American Heart Association*), all patient groups showed significant increase in the risk compared with control, as shown by TC/HDLC, and TG/HDLC ratios which are statistically significant with p<0.001 and p0.003 respectively. Specifically hypertensive diabetic and diabetic groups showed significant increase in the risk, as the HDLC/LDLC ratio was found to be statistically significantly different (p=0.002) compared to the control group (table 3-4 and figure 3-7).

The analysis of urine albumin revealed absence of urinary albumin in all patients and controls.

Table 3-4: Frequency distribution of normal and abnormal Levels of biochemical parameters in the study groups

Parameter \ Group		Hypertensive diabetic	Diabetic	Hypertensive	control	Total	P value
PUA	Decreased	2(50%)	2(50%)	0(0%)	0(0%)	4	**0.02**
	Normal	34(22%)	43(28%)	34(22%)	42(27%)	153	
	increased	10(25.6%)	4(10.3%)	17(43.6%)	8(20.5%)	39	
PCr	Decreased	0(0%)	1(100%)	0(0%)	0(0%)	1	**0.002**
	Normal	44(27.5%)	44(27.5%)	34(21.2%)	38(23.8%	160	

					)		
	increased	2(5.7%)	4(11.4%)	17(48.6%)	12(34.3%)	35	
PUr	**Normal**	45(23.9%)	46(24.5%)	49(26.1%)	48(25.5%)	188	0.81
	increased	1(12.5%)	3(37.5%)	2(25%)	2(25%)	8	
TC	**Normal**	28(19.4%)	36(25%)	31(21.5%)	49(34%)	144	**<0.001**
	Increased	18(34.6%)	13(25%)	20(38.5%)	1(1.9%)	52	
TG	**Normal**	35(21.3%)	42(25.6%)	40(24.4%)	47(28.7%)	164	0.07
	increased	11(34.4%)	7(21.9%)	11(34.4%)	3(9.4%)	32	
LDL C	**Normal**	26(17.7%)	36(24.5%)	38(25.9%)	47(32%)	147	**<0.001**
	increased	20(40.8%)	13(26.5%)	13(26.5%)	3(6.1%)	49	
HDL C	**decreased**	25(29.1%)	22(25.6%)	23(26.7%)	16(18.6%)	86	**<0.001**
	normal	20(20.2%)	27(27.3%)	19(19.2%)	33(33.3%)	99	
	Increased	1(9.1%)	0(0%)	9(81.8%)	1(9.1%)	11	

HDL C/ LDL C	**High risk**	12(44.4%)	10(37%)	3(11.1%)	2(7.4%)	27	**0.002**
	Low risk	34(20.1%)	39(23.1%)	48(28.4%)	48(28.4%)	169	
TC/H DLC	**High risk**	21(35.6%)	18(30.5%)	16(27.1%)	4(6.8%)	59	**<0.001**
	Low risk	25(18.2%)	31(22.6%)	35(25.5%)	46(33.6)%	137	
TG/H DLC	**High risk**	19(31.7%)	17(28.3%)	19(31.7%)	5(8.3%)	60	**0.003**
	Low risk	27(19.9%)	32(23.5%)	32(23.5%)	45(33.1%)	136	

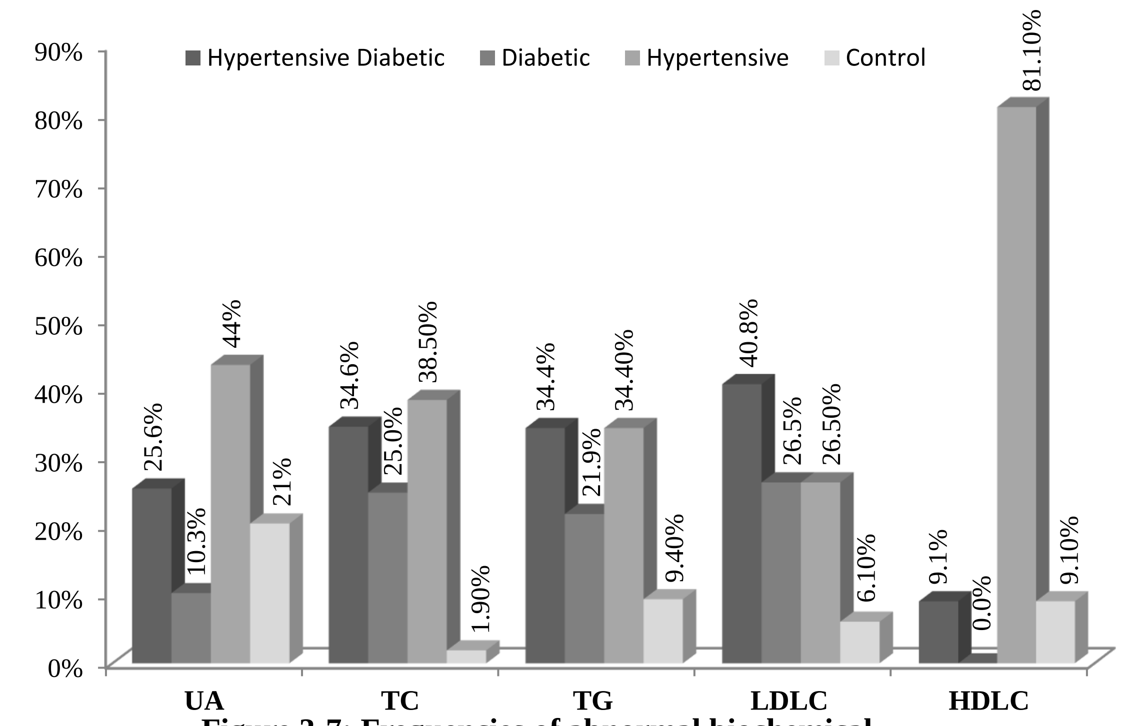

Figure 3-7: Frequencies of abnormal biochemical values in the study groups

CHAPTER FOUR

Discussion

Hypertensive diabetic and diabetic groups were found to have higher weight, BMI, and Waist: Hip ratio compared to the hypertensive and control groups. These results are in accordance with the results by Schienkiewitz and his group which had clearly pointed out that obesity and increased body weight are among the most important risk factors for type 2 diabetes (Schienkiewitz *et al.*, 2006).

In this study hypertensive and hypertensive diabetic groups were found to have higher levels of uric acid compared to the diabetic and control groups ($p < 0.001$); this finding is in agreement with Voelkel and his collegues who reported an elevation of serum uric acid levels in patients with hypertension (Voelkel *et al.*, 2000).

In the line with the current finding, Rao *et al.* showed that serum uric acid level was decreased in diabetics compared to controls (Rao *et al.*, 2012). Another study which was conducted on US adults showed that higher serum uric acid levels is inversely associated with diabetes mellitus (Bandaru and Shankar, 2011). A reasonable mechanism for the observed results of decreased uric acid in diabetes mellitus may be related to the inhibition of uric acid reabsorption in the proximal tubule by high glucose levels in diabetic individuals (Kumar and Clark, 2012).

In the current study, hypertensive diabetic, diabetic, and hypertensive patients were found to have high level of TC, TG, LDL and LDLC/HDLC compared to the control group and all the differences were statistically significant. In addition, these groups had lower HDLC values compared to the control group. This finding is partly in line with Suryawanshi *et al* who found elevated mean values of cholesterol, triglyceride, LDL-C and decreased HDL-C in diabetic cases compared to healthy controls (Suryawanshi *et al.*, 2006). However, our finding disagrees with Habib *et al* who showed no significant difference in the levels of cholesterol, TG and LDL-C between diabetic and control groups (Habib *et al.*, 2006).

In this study all groups showed significant increase in the risk of cardiovascular disease compared to control. This finding agrees with the Framingham study who reported that a tremendous increase in CVD in the past 50 years in USA was attributed to DM (Fox *et al.*, 2007).

In our study plasma cholesterol level is increased in all patients' groups, particularly in the hypertensive diabetic and diabetic, compared with the control group; some of the possible reasons of such higher concentration of serum cholesterol in diabetes may be attributed to decreased muscular exercise or inhibition of cholesterol catabolism (Awobajo *et al.*, 2013).

In general the high level of cholesterol, triglyceride, LDLC and low HDL were observed on the hypertensive diabetic, diabetic and hypertensive groups. These findings are plausible because diabetes is one of the complex diseases which cause metabolic disorders in general, particularly that of lipids (Kumar and Clark, 2012) .

Assessing the risk of cardiovascular diseases based on the American heart association guidelines, all the patient groups in this study showed significant increase in the risk of cardiovascular diseases compared with control (Guidelines, 2014).

CHAPTER FIVE

Conclusions and Recommendations

Conclusions

- The highest levels of uric acid were found in hypertensive patients, followed by hypertensive diabetic. Therefore, increased uric acid concentration seems to be associated with hypertension.
- Diabetic, hypertensive diabetic, and hypertensive patients had increased level of plasma TC, TG, LDLC and LDLC/HDLC but decreased level of HDLC compared to the control group.
- Duration of diabetes showed moderate positive significant correlation with plasma urea and creatinine.
- Fasting plasma glucose level showed a weak negative significant correlation with plasma uric acid and creatinine.
- All patient groups showed significant increase in the cardiovascular risk compared to the control group, this is evident from the elevated value of TC/HDLC, TG/HDLC, found in all of them and the highest value of LDLC/HDLC was obtained in the hypertensive diabetic and diabetic groups in particular.

Recommendations

As evident in this study, elevated level of uric acid was found to have association with hypertension. Therefore - as elevated uric acid level is one of suggested to be a precipitating risk factor for the onset of hypertension, which in turn is the prime cause of cardiovascular complication- every individual specifically diabetic and hypertensive subjects should take all cautious measures so as to keep their uric acid level within the normal range. This can be achieved by carrying out various interventions such as:

- Avoid foods which are very rich in purine like meats, beans, chick, peas… etc.
- Adopt healthy life style i.e. regular exercise and reduce calorie-intake so as to decrease the risk for cardiovascular disease.
- Undergo a regular checkup on their uric acid level and lipid profile.

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