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جمهورية العراق

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The effect of metformin on the high density lipoprotein – cholesterol level and fast plasma glucose level in the type 2 Iraqi diabetic patients

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(وقل اعملوا فسيرى الله عملكم ورسوله والمومنون)

صدق الله العلي العظيم

Dedication

I dedicate this work to the lifeline and heart of the spring in this world and it is my mother and to all those who participated in this project to each of my brothers and sisters and friends and my love.

Acknowledgment

Greetings, thanks and gratitude to all my professors and members of the research committee and special thanks to Dr. Assad and the doctors who discussed my research

INTRODUCTION

The term diabetes mellitus (DM) describes metabolic disorders of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, protein and fat and metabolism resulting from defects in insulin secretion, insulin action, or both[1&2]**.** Diabetes has been classified into two types depending upon the defect leading to it. DM type 1 is caused by a cell-mediated autoimmune destruction of the β-cells of the pancreas that result in a significant decrease in the insulin secretion and thus, the insulin Dtype2 is responsible to be the cause of diabetes in 90%-95% of the affected people.

Multiple factors are included in the onset of Dtype2 which include genetic and non-genetic factors such as obesity because of high calorie intake, increasing in age, sedentary lifestyle and central adiposity. The abnormalities of serum lipoprotein are concerned with the severity of the insulin resistance in type 2 DM. A patient with type 2 DM typically has an atherogenic serum lipid profile that is characterized by abnormalities in the values of lipid profile elements[1&2].

Treatment modalities of type 2 DM involve lifestyle modification, treatment of obesity, oral hypoglycemic agents, and insulin sensitizer like metformin, big insulin that reduces insulin resistance, is still recommended first line medication especially for obese patients.. Metformin has proven to be well tolerated and highly efficacious in reducing blood glucose in insulin resistant people, an effect largely attributed to reduction in hepatic glucose output, although some studies have reported increases in peripheral glucose uptake [3&4]. Metformin is not associated with Hypoglycemia and is considered weight neutral, although some patients may lose weight.

Metformin is used as therapeutic agent of first choice for monotherapy of the typical acidosis who exhibit mild to moderate hyperglycemia. In small studies, metformin appears to exert benefit on another fundamental biological process that influence atherogenesis, such as lipid metabolism, inflammation, and vascular endothelial function. In the present work, the results demonstrated a decrement effect on FPG that lowered it to a degree near to that of normal subject values, and in contrast it made an increment in HDL-c level [3&4].

Aim of the study

1. To determine effects of metformin on FPG level in both groups: type 2 DM patients and subjects in the control group.
2. To determine effects of metformin on HDL-c in both groups: type 2 DM patients and subjects in the control group.

1.1 Definition

Diabetes is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin action, insulin secretion, or both. The chronic hyperglycemia of diabetes is associated with long-term damage and failure of different organs, especially eyes, kidneys, nerves, heart and blood vessels.

Diabetes is a chronic disease in which the body does not make or properly use insulin, a hormone that is needed to convert sugar, starches, and other food into energy by moving glucose from blood into the cells [4&5].

Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues [23&26]. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia .Symptoms of marked hyperglycemia includes polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome.

1.2Complication of Diabetes:

The long-term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, heart disease, and stroke, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcer, amputation, and feature of autonomic dysfunction, including sexual dysfunction [2&8]. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease.

1.3: Epidemiology

DM occurs throughout the world, but is more common in the developed countries, especially type 2 diabetes.

It is estimated that 366 million people had DM in 2011; have risen to 552 million. The number of people with type 2 DM is increasing in every country with 80% of people with DM living in low and middle –income countries. The incidence of type 2 DM various substantially lifestyle risk fractions DM is estimated that 439 million people would have type 2 DM by the year 2030[5&6].

1.4: Etiology and risk factors

Majority cases of diabetes fall into two broad categories, in first category, Type 1 diabetes, this form of diabetes, which accounts for only 5– 10% of those with diabetes, and the cause is absolute deficiency of insulin secretion. At increased risk of developing type I diabetes or juvenile-onset diabetes, results from a cellular-mediated autoimmune destruction of the β cell of the the pancreas [6&8].

Type 2 DM is due to primarily to lifestyle factors and genetic [6&7].A number of lifestyle factors are known to be important to the development of type 2 DM. These physical activity, sedentary lifestyle, cigarette smoking and generous consumption of alcohol[9&10]. Obesity has been found to contribute about 55% of cases of type 2 DM[9&11] .Moreover, obesity (which is independent risk factor for type 2 DM) is strongly inherited[11&13] .There are many medical condition which can potentially give rise, or exacerbate type 2 DM .These include obesity,

hypertension, elevated cholesterol (combined hyperlipidemia), and with the condition often termed metabolic syndrome (it is also known as syndrome X, Raven's syndrome) .[12&13]
Several risk factors have been associated with type 2 diabetes which include: Family history of diabetes, Increasing age, overweight, Unhealthy diet, Physical inactivity, history of gestational diabetes ,High blood pressure, Impaired glucose tolerance (IGT) and Poor nutrition during pregnancy.[14] Other includes acromegaly, Cushing's syndrome, thyrotoxicosis, pheochromocytoma, chronic pancreatitis, cancer and drugs. Additional factors found to increase the risk of type 2 DM include aging, high fat diet and a less active lifestyle[15].

1.5: Pathophysiology

Type 2 DM is characterized by insulin insensitivity as a result of insulin resistance, declining in insulin production, and eventual beta-cell failure. This leads to decrease in glucose transport into liver, muscle cells, and fat cells. There is a breakdown of fat with hyperglycemia. The involvement of impaired alpha-cell function has recently been recognized in the pathophysiology of type 2 DM [16&18]As a result of this dysfunction, glucagon and hepatic glucose level that rise during fasting are not suppressed with meal. Inadequate levels of insulin and increase insulin resistance, hyperglycemia results. Study is ongoing on the role of mitochondrial dysfunction in the development of insulin resistance and etiology of type 2 DM[17]. Also very important is adipose tissue, as endocrine organ hypothesis (secretion of various adipocytokines, i.e. leptin, TN alpha, resistin, and adiponection implicated in insulin resistance and possibly beta-cell dysfunction [18&19].
A majority of individuals suffering from type 2 DM are obese, with central visceral adipocity. Therefore, the adipose tissue plays crucial role in the pathogenesis of type 2 DM. although the predominant theory used to explain this link is the portal/visceral hypothesis giving key role in elevated non-esterified fatty acid concentration, two new emerging theories are ectopic fat storage syndrome (deposition of triglycerides in muscle, liver, pancreatic cells). These two hypothesis constitute the framework for the study of the interplay between insulin resistances and beta-cells dysfunction in type 2 DM as well as between our obesogenic and DM risk in the next decade [20].

2.1:Diagnosis of Diabetes.

World health organization (WHO) diagnostic criteria are listed in table (1.1):

Table 1.1. Major Diagnostic criteria for diabetic and prediabetic.

Measure	Prediabetic	Diabetes
Fasting plasma glucose	100-125mg/dl	≥126mg/dl
Random plasma glucose	180-199mg/dl	≥200mg/dl
Hour plasma glucose(OGTT)	140-199mg/dl	≥200mg/dl
Glycated hemoglobin	5.7-6.4 %	≥6.5%

3.1: Prevention of type 2 DM

incidence of type 2 DM with a combination of maintaince of body mass index of 25kg/m², eating high fiber and unsaturated fat and diet low in saturated and tarns-fats and glycemic index, regular exercise absence from smoking and moderate consumption of alcohol, suggesting that majority of type 2 DM can be prevented by lifestyle modification [21&22].

4.1: Treatment of type 2 DM

The primary goal of type 2 DM is to achieve and maintain good glycemic control, and to reduce the mortality and risk of microvascular and macrovascular complications. The current consensus algorithms for medical management of type 2 DM a combination of lifestyle modification and metformin as initial therapy for type 2 DM then followed by other oral hypoglycemic agents and insulin[23&24].

4.2: Non-pharmacologic therapy (Lifestyle interventions)

The major environmental factors that increase the risk of type 2 DM are over nutrition and a sedentary lifestyle, with consequent overweight and obesity[24].Not surprisingly, interventions that reverse or improve these factors have been demonstrated to have a beneficial effect on control of glycaemia in established type 2 DM. In addition to the beneficial effects of weight loss and exercise improve co-incident CVD risk factors, such as blood pressure and Atherogenic lipid profile, and ameliorate other consequences of obesity.

4.3: Pharmacological therapy

Major factor in selecting a class of drugs, or a specific medication within a class, to initiate therapy or when changing therapy, is the ambient level of glycemic control. When levels of glycaemia are high (e.g. HbA1c >8.5%), classes with greater and more rapid glucose-lowering effectiveness , or potentially earlier initiation of combination therapy, are recommended; however, patients with recent-onset diabetes often respond adequately to less intensive interventions than those with longer term disease [26].

In addition to biguanides (metformin), there are other ant diabetic agents include several groups, i.e. sulfonylurea (glitinides), thiazodindiones (glitazone) ,α-glucosidase inhibitors (acarbose), GLP-1analogues, dipeptidyl peptidase 4 inhibitors and amylin agonists (pramlintide)[27].

5.1: Drug used in present study

Metformin-hydrochloride, is the only currently available biguanide (classified as an insulin sensitizer) that has been used to treat type 2 DM for more than 40 years either alone or in combination with insulin or with one of the other oral hypoglycemic agents[28].

5.2.1: Mechanism of action s

Metformin reduces blood glucose level by inhibiting hepatic glucose output and reducing insulin resistance, particularly in liver and skeletal muscle.Plasma insulin levels are unchanged or reduced. Metformin decreases intestinal absorption of glucose, and increase insulin sensitivity by enhance

glucose uptake and utilization in peripheral tissues. In vitro and in vivo studies have demonstrated the effect of metformin on membrane-related events, including plasma membrane fluidity, plasticity of receptor and transporter; suppression of the mitochondrial respiratory chain; increased insulin-stimulated of translocation of GLUT4 transporters to the plasma membrane; and enzymatic effect on metabolic pathways, e.g. LKB1 activation of AMP-activated protein kinase–AMPK, which inhibits gluconeogenesis and lipogenesis .

5.2.2: Chemistry

The systemic (IUPAC) name of metformin is N,N- diamethylimidodicarbonimidic diamide .metformin is oral antidiabetic drug in the biguanide class . it is first- line drug of choice for the management of T2DM practically in the overweight and obese people who have normal kidney function. Metformin hydrochloride is a white, crystalline powder which is odorless or almost odorless and hygroscopic. It is a powder with melting point 218ºC-220ºC. It is highly soluble in water and slightly soluble in 95% alcohol but practically insoluble in both ether and chloroform [30].

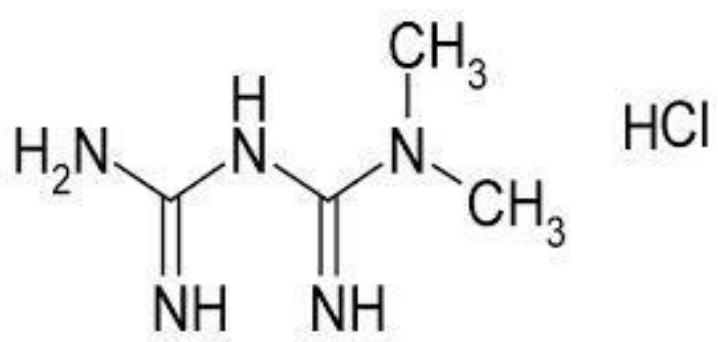

Figure (2-1): Chemical structure of metformin-hydrochloride [31]

5.3: Pharmacokinetic:

Absolute oral bioviability of metformin is 50-60%, with plasma half-life of 1. 7-4.5hours. Metformin is slowly and incompletely absorbed from the gastrointestinal tract and the absorption appears to be saturable, but it is rapidly distributed following absorption and doesn’t bind to plasma proteins. Metformin doesn’t undergo hepatic metabolism, and the major route of its elimination is renal,. However, metformin is cleared by the kidney, so metformin will increase risk of renal impairment, so

a dose of metformin should be halved with GFR 30-40ml/min and should not be used when GFR is below 30 ml/min and contraindicated in patient with hepatic impairment [33]. Metformin should be avoided in patients with chronic pulmonary diseases, sever infection alcohol abuse, history of lactic acidosis, pregnancy, or use of radiographic contrast or surgery.

5.4: Pharmacodynamics

Metformin is a first-line therapy for type 2diabetes mellitus (T2DM, formerly 'non-insulin-dependent diabetes mellitus'), as a biguanide agent, metformin lowers both basal and postprandial plasma glucose (PPG) ,Other potential effects of metformin include an increase in glucose uptake, an increase in insulin signaling, a decrease in fatty acid and triglyceride synthesis, and an increase in fatty acid β-oxidation. Metformin may also increase glucose utilization in peripheral tissues, and possibly reduce food intake and intestinal glucose absorption. As metformin does not stimulate endogenous insulin secretion, it does not cause hypoglycemia or hyperinsulinemia. It works mainly by suppressing excessive hepatic glucose production, through a reduction in gluconeogenesis .

The most come side effect of metformin is gastrointestinal disturbances, including diarrhea, nausea, vomiting, cramps and increased flatulence. Lactic acidosis is an uncommon but potentially fatal side effect. Metformin has been reported to decrease the level.

6.1: Pharmacokinetic:

Absolute oral bioviability of metformin is 50-60%, with plasma half-life of 1. 7-hours. metformin is slowly and incompletely absorbed from the gastrointestinal tract and the absorption appears to be saturable, but it is rapidly distributed following absorption and doesn't bind to plasma proteins [33&34]. Metformin doesn't undergo hepatic metabolism, and the major route of its elimination is renal. However, metformin is cleared by the kidney, so metformin will increase risk of renal impairment, so a dose of metformin should be halved with GFR 30-40ml/min and should not be used when GFR is below 30 ml/min and contraindicated in patient with hepatic impairment .Metformin should be avoided in patients with chronic pulmonary diseases, sever infection alcohol abuse, history of lactic acidosis, pregnancy, or use of radiographic contrast or surgery.

6.2: Pharmacodynamics:

Metformin is first line therapy for type 2 diabetes mellitus (T2DM, formerly ‘non- insulin dependent diabetes mellitus) as a biguanide agent, metformin lowers both basal and postprandial plasma glucose (PPG). Other potential effects of metformin include an increase in glucose uptake, an increase in insulin signaling, a decrease in fatty acid and triglyceride synthesis, and an increase in fatty acid β-oxidation. Metformin may also increase glucose utilization in peripheral tissues, and possibly reduce food intake and intestinal glucose absorption. As metformin does not stimulate endogenous insulin secretion, it does not cause hypoglycemia or hyperinsulinemia. It works mainly by suppressing excessive hepatic glucose production, through a reduction in gluconeogenesis.

6.3: Side effects:

The most come side effect of metformin is gastrointestinal disturbances, including diarrhea, nausea, vomiting, cramps and increased flatulence [(33)].Lactic acidosis is an uncommon but potentially fatal side effect .Metformin has been reported to decrease the level of thyroid stimulating hormone in people with hypothyroidism.

7.1: Lipid profile

Lipoprotein is transport vehicles in the circulation .Lipoprotein particles comprise a peripheral envelope consisting mainly of phospholipids and free cholesterol with at least one protein and a central non polar cover mostly triglycerides and esterified cholesterol .The protein particle (Apo lipoprotein) provide structure to lipoprotein activate enzyme systems and bind with all receptor .Five main types of lipoprotein particles can be recognized: chylomicron, very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), low density lipoprotein (LDL) and high density lipoprotein (HDL)[(35)].

7.2.1: High-density lipoprotein cholesterol (HDL-c)

High-density lipoprotein is one of the five major groups of lipoproteins (Chylomicron, VLDL, IDL, LDL, and HDL) that enable lipids like cholesterol and triglycerides to be transported within the water-based bloodstream .HDL particles can vary substantially in size, composition, density, and functional properties, potentially affecting their relationship to atherosclerosis[36].

7.2.2:Protective effects of HDL-c

Many studies have consistently demonstrated an inverse relationship between HDL-c levels and the risk of coronary heart disease .It appears that HDL is likely protective through multiple pathways, including both cholesterol transport and non-cholesterol-dependent mechanisms .Reverse cholesterol transport include the transfer of excess cholesterol from lipid laden macrophage (foam cells) present in peripheral tissues to the liver via HDL, with subsequent catabolism of cholesterol or excretion into bile .Which is a main reason why HDL-bound cholesterol is sometimes call "good cholesterol[35&37]. Non-cholesterol-dependent mechanisms contribute the protective effects of HDL against atherosclerosis; these involve antioxidant effects, ant-inflammatory effects, antithrombotic/profibrinolytic effects, and vasoprotective effects[36].

7.2.3 Recommended ranges of HDL-c levels

The National Cholesterol Education Program (NCEP) ([22]), provides a set of guidelines for HDL levels and risk for heart diseases

Serum HDL-C levels	interpretation
<40 for men, 50 for women	low HDL-c heightened risk for heart disease
40-50	medium HDL-c level
>60	high HDL-c level, optimal condition , protective against heart disease

8.1 Study design:

This study included 10 diabetic patients and 10 apparently healthy patients. This research was performed at Diwaniya teaching hospital and Diwaniya center for diabetic and endocrine glands.

8.2 Study Sample (patient) collection:

The study was conducted after the protocol was approved; the patients were collected from outpatient Diwaniya teaching hospital. 10 Patients
Affiliated with Type 2 DM with a mean age (45-67) years, who were taking metformin alone are enrolled in the study, all the data and history were taken according to questionnaire.

The patients are distributed randomly among group

Group 1: this group includes 10 patients (3female and 7male) with a mean age of (45-65) years and mean body mass index (29.7± 2.45Kg/m2) treated with metformin (500mg) as one pill twice to thee time daily for 1-3 years.

Group 2: this group include 10 apparently healthy patients (4 female and 6 male) as control with mean age of (45-55) years and body mass index of (27.9± 1.84 Kg/m2).

8.3 inclusion criteria:

- Uncomplicated type 2 diabetic patients**.**
- Overweight and obese patient.
- Patient aged (45-57) years old.
- Duration of Type 2 DM (1-3 years).

Metformin monotherapy for at least 1 year.

8.4:Exclusion criteria:

-Pregnancy and lactation.

- Diabetogenic medication (example: thiazide diuretic and corticosteroids).
- Chronic disease or taking other medication that interferes with pharmacokinetic of metformin.

8.5 Materials:

Drug and diagnostic kits that were used in this study are listed in Table (3.1) below along with their suppliers:

Table 3.1 Drugs and diagnostic kits used in the study.

Drug or Diagnostic kits	supplier
Metformin 500mg (Glucophage)	MERCK serono, Germany
Diagnostic kits	product ,turkey
HDL-c kit	product ,turkey
FBS kit	product ,turkey

8.6: Instruments and equipments :

Instruments that were used throughout the study listed in Table (3.2) below a long with their suppliers:

Table 3.6 Instruments used throughout the course of this study.

Instrument	Supplier
Laboratory film (Parafilm)	USA
Eppendorf tube 1.5 cc	China
Gel tube	Italy
Centrifuge	France
Elisa	Ireland
Gloves, Cotton	China

Blood Sample Collection and Handling

From each Fasting Patient (3ml) of blood was obtained by venous puncture transferred to gel tube and both are centrifuged at 3500 rpm for about 10 minutes to obtain serum, to measure FPG and HDL.

8.7: Principle of Laboratory y Investigations:

8.7.1 Measurement of FPG:

Test principle: Trinder method, Glucose was oxidized (in the presence of glucose oxidase) to gluconic acid and hydrogen peroxidase which convert phenol and 4- aminoantipyrine into red quinine which is measured at 500nm. The intensity of color of red quinine produced as directly proportional to the quantity of glucose in the sample.

Calculation:

$$\text{Concentration of standard (mg/ dl)} \times \frac{\text{A (Sample)}}{\text{A (standard)}} = \text{Glucose (mg/ dl)}$$

A= Absorbance

8.7.2 Measurement of HDL-c

Test principle: The assay is based on a modified polyvinyl sulfonic acid (PVS) and polyethylene-glycol-methyl ether (PEGME) coupled classic perception method with the improvement in using optimized quantities of PVS/ PEGME and selected detergents. LDL; VLDL by cholesterol oxidase (CHOD) and cholesterol esterase (CHER). The enzymes selectively react with HDL to produce H2O2 which is detected through a Trinder reaction.

Calculation:

$$\text{Concentration of standard (mg/ dl)} \times \frac{\text{A (Sample)}}{\text{A (standard)}} = \text{HDL-c (mg/ dl)}$$

A= Absorbance

8.8: Statistical Analysis is:

All values are expressed as mean ± standard error of the mean. Data are entered into computer system using Microsoft Office Excel 2007 software for all mathematics and statistical analysis. The means and standard errors were calculated for different variables, including age,
FPG and HDL. The student's test is used to determine the significant difference in means of each two groups. $p \leq 0.05$ was considered to be the lowest limit of significance.

9.1: RESULTS

9.1.1. Different values of plasma glucose level among Group1 (treated with metformin 500 mg twice to three time s daily) versus Group 2 (Control).

9.1 .1.1 Fastening plasma glucose (FPG):

Table 4.1 shows the mean (SD) values of FPG in Group 1(patient s) and Group 2 (control) among type 2 diabetic patients. An independent t-test was conducted to compare FPG levels in Group 1 and Group 2. There was a significant difference in the FPG levels for Group 1 (mean= 169.50, SD = 86.18 mg/ dl) and Group 2 (mean = 99.80, SD = 7.47 mg/ dl), P=0.031.These results suggest that patient s with type 2 diabetes treated with metformin, their FPG level is still higher than reference values but close to the values of the subjects in group2.

Table 4.1 Comparison of mean fasting plasma glucose (FPG) between Group 1 and Group 2

Variable	Group , Mean (SD)		p value*
	Group 1 (n = 10)	Group 2 (n = 10)	
Fasting plasma glucose (mg/dl)	169.50 (86.18)	99.80 (7.47)	0.031

Values are represented as mean ± standard deviation *p value is significant at < 0.05

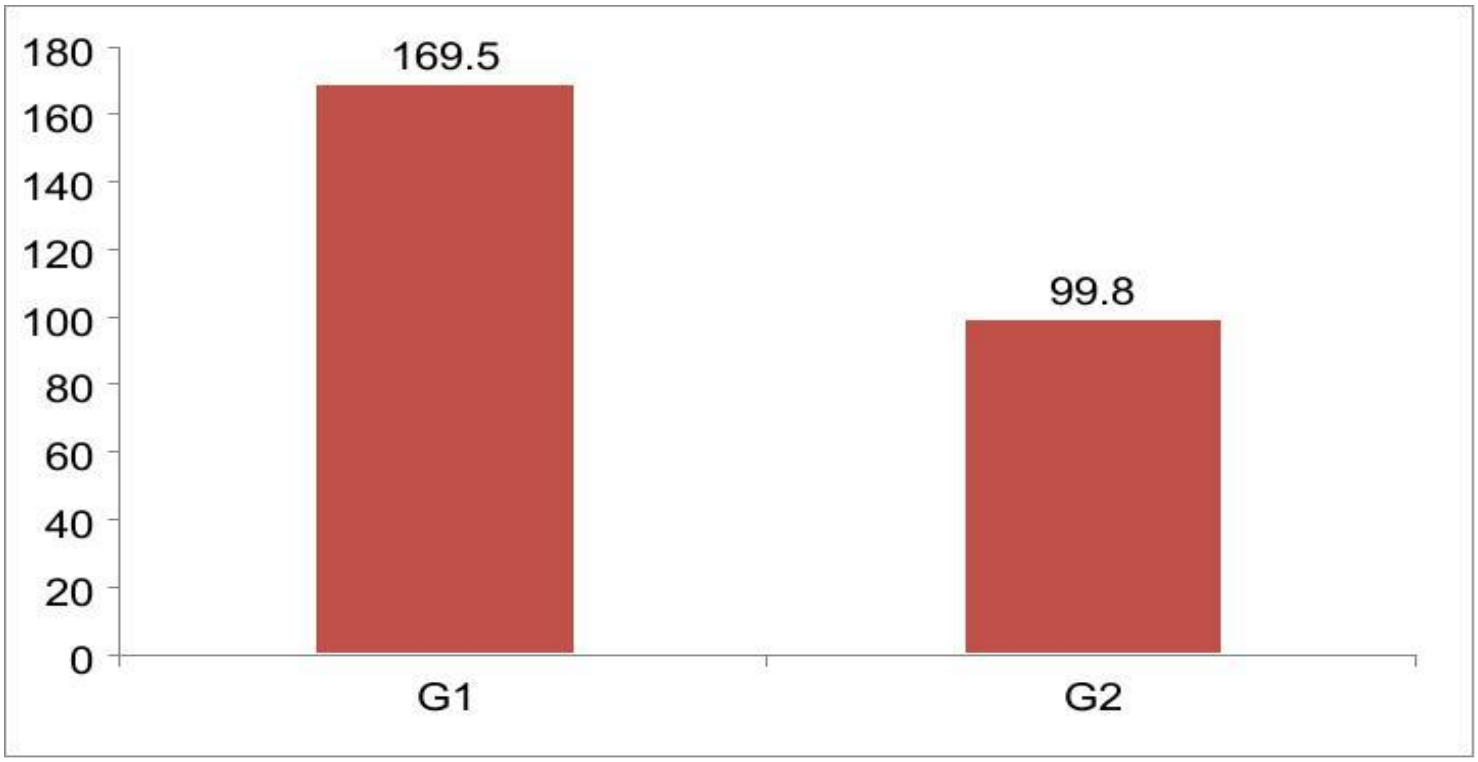

Figure e (4-1): The effect of metformin (500m g) on Fast in g plasma Glucose

10.1. Lipid profile:

10.1 .1. High Density Lipoprotein (HDL-c):

Table 4.2 shows the mean (SD) values of HDL-c in Group 1(patients) and Group 2 (control) among type 2 diabetic patients. An independent t-test was conducted to compare HDL-c levels in Group 1 and Group 2. There was a significant difference in the HDL-c levels for Group 1 (mean = 55.31, SD = 8.84 mg/ dl) and Group 2 (mean = 46.80, SD = 6.60 mg/ dl), p = 0.025.These results suggest that patients with type 2 diabetes were treated with metformin, their HDL-c levels increased significantly.

Table 4.2 Comparison of mean high density lipoprotein (HDL-c) b between Group 1 and Group 2

Variable	Group, Mean (SD)		p value*
	Group 1 (n = 10)	Group 2 (n = 10)	
High density lipoprotein (mg/dl)	55.31 (8.84)	46.80 (6.60)	0.025

Values are represented as mean± standard deviation *p value is significant at < 0.05

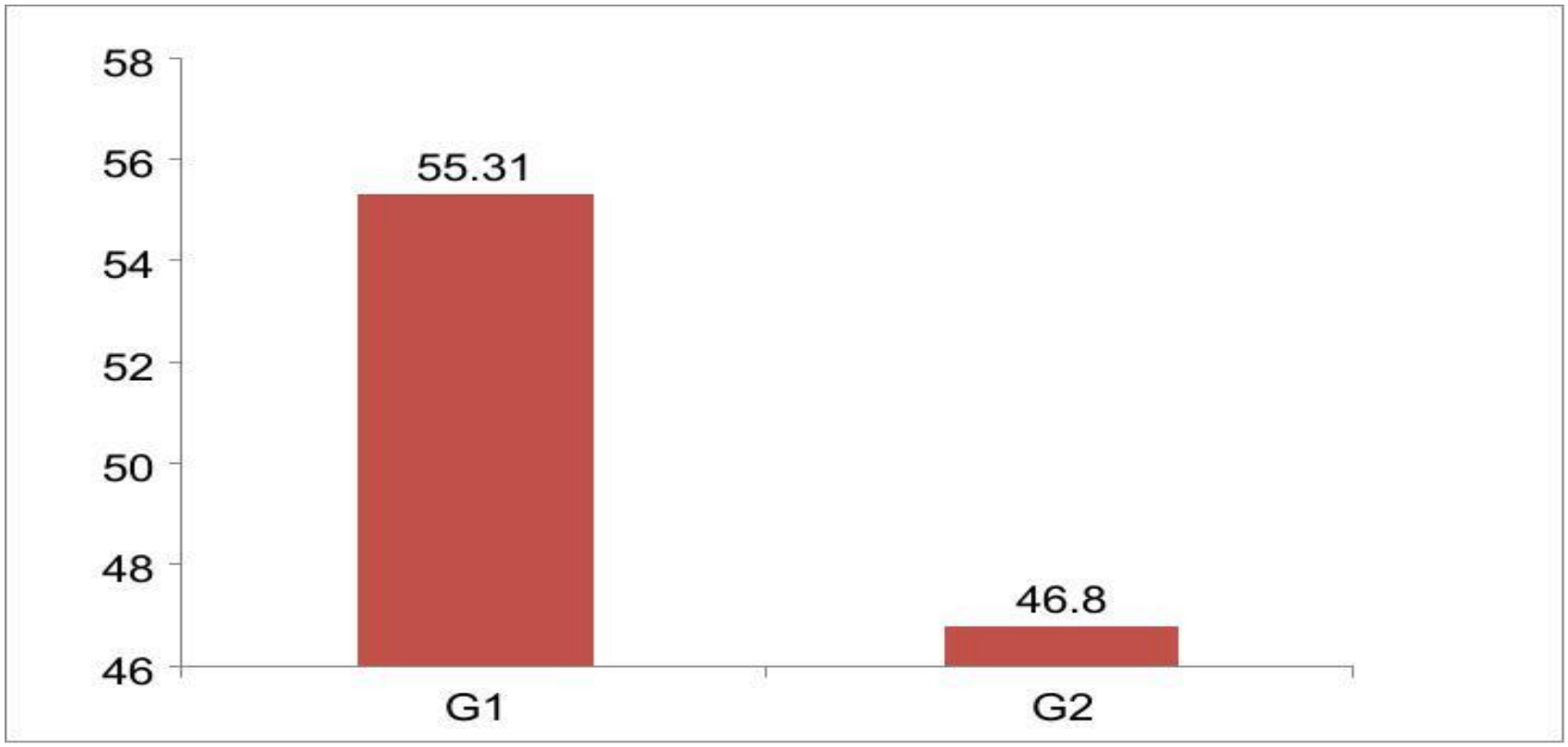

Figure (4.2): The effect of metformin (500 mg) on High density Lipoprotein.

11-1: Discussion:

Diabetic is a group of metabolic disorders characterized by hyperglycemia resulting from defect in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetic is associated with long term damage, dysfunction and failure of different organs, especially the eyes, kidneys, nerves, heart and blood vessels. The individuals with impaired glucose tolerance have hyperglycemia in spite of having highest levels of plasma insulin, indicating that they are resistant to the action of insulin. In the progression from impaired glucose tolerance to diabetes mellitus, the level of insulin declines indicating that patient s with T2DM has decreased insulin secretion. Insulin resistance and insulin deficiency are common in the average T2DM patients. Classically, type 2 diabetes occur s in the older, obese patients in the setting of strong family histories of diabetes and in association with other components of the metabolic syndrome, about 8% of the adult U.S population has diabetes, with 95% of these people having type 2 diabetes. The prevalence of diabetes increases with age, with over 25% of the elderly having type 2 diabetes. Many factor s play critical role in the incidence of this medical problem, like gender (female), age (increasing age), diet, obesity, lack of sleep, nutritional supplement received by the mother during pregnancy. But the main critical factors that play role are: lifestyle, genetic factors and other medical problems [(33)]. One of the risk factors that had been associated with disease was sudden attack of DM caused by sudden shock, horrible or bad news which could be predispose to the disease and this factor was noted in healthy

individuals. The diabetic patient had many symptoms like increase thirst, increase urination, blur red vision, fatigue, headache and some of them had other diseases like hypertension and cardiac problem. The major concern of T2DM is its increased risk (two to four fold) for CHD, manifested as angina, myocardial infarction (MI), CCF and sudden death. In addition T2DM, independent of CHD, may lead to diabetic cardiomyopathy. CHD accounts for up to two-third of deaths in T2DM. The increased risk of CHD in patients with diabetes is only partly explained by concomitant risk factor s such as hypertension, obesity, dyslipidemia, and smoking. It has been shown that hyperglycemia itself and its consequences are very important for the increased risk for CHD and related mortality.Strategy of life style interventions for non- pharmacological treatment, like diet with low calories, weight reduction and physical activity which ought to be initial therapy of newly diagnostic patients. Many of the patients will require the addition of medication over the course of t heir diabetes.

In Arab an diabetic patient with recent T2DM had shown a high level of FPG and HbA1c because not taking any type of diabetic medication,
They were only on diet and exercise regimen when patients started oral hypoglycemic drugs, they quickly responded to drug treatment and their values of FPG and HbA1c were changed to normal values within 3 months of treatment.

Metformin used as first-line pharmacological therapy in over weight patients but not preferentially in non-over weight patients .In contrast to other antidiuretic agents, metformin was an important oral antidiuretic drug that associated with reductions in body weight .Metformin provides body weight reduction for their uses as a cardio protective effects and it was consider as first drug of choice for treatment in newly diagnosed patients. The national instituted for clinical Excellent; stated that metformin was first line of hypoglycemic drug of choice in all patient s, especially t hose who were overweight.
Metformin regarded as the initial pharmacological management option from for all T2DM patients .In the United Kingdom prospective diabetes study (UKPDS) was found that metformin successfully reduced macrovascular disease endpoint in patients who were obese .Metformin demonstrated significantly reduced the risk of fatal and non-fatal Cardiovascular events in patient T2DM. In long term of DM demonstrated metformin predict good long term management that early control of glycaemia.

In the present study as shown in Table 3.1 the results indicated that FPG in patients treated with metformin 500mg twice daily is169.5± 86.17 (mean± SD) by the end of two years of treatment, a value is close to the normal level. This imparts a positive sign that metformin has a good lowering effect on plasma glucose, which could be discussed by different mechanisms of action. and stated that metformin improves fasting blood sugar by slowing down the "excessive" basal hepatic gluconeogenesis without significant changes in insulin levels that would be known to cause hypoglycemia. also confirms that metformin caused a progressive decline in fasting blood glucose from 84.9mg/ dl to 75.1mg/ dl and a reduction in fasting insulin levels from 31.3 micro U/ ml to 19.3 micro U/ ml. Albumen serum lipid is likely to contribute to the risk of CAD in diabetic patients. And determination the lipid serum level in people with diabetic patient is considered as standard of the diabetic care .

In this research as it is clear in Table 3.1 the results show the amount of HDL-C increased between control group and the end of two years Treatment with metformin was 8.51±2.3(mean± SD This imparts a Significant sign that metformin has a good elevating effect on HDL-cholesterol; hence metformin could be accounted as a cardio protective agent, large scale prospective studies have indicated that each 1 mg/ dl increase in HDL is associated with 2 to 3% decrease in the risk of CVD in men and women, respectively and improves cardiovascular system conditions against probable attacks of Myocardial infarction.

12-1: CONCLUSION:

1-Metformin had significantly lowering blood glucose effect when given to patient with essential diabetes, which could be contribute to different mechanism of action.

2-The present study demonstrated significant increase in HDL-c level in metformin treated patient.

13.1: RECOMMENDATION:

1. A study of larger sample size is required to be more Representative statically.

2-Further investigation is required to clarify the effect of metformin on other lipid profile level.

3-Study the effect of metformin in combination with other anti-Diabetic drugs like to thiazolidinedione, Dipeptidyl peptidase 4 Inhibitors and insulin

Contents

References

1- Abdulrazzaq, Y.S. (2015). Effect of small doses of metformin and glimepiride on resisten level and other biological markers in overweight and obese femal with type 2 diabetes mellitus. MCs Thesis in Clinical Pharmacy,HMU. pp. 9-32.

2- Alberti, K.G., shaw, J. (2005). The metabolic syndrome –a new worldwide definition. Lancet. 366(9391, pp. 1059-1062.

3- American diabetic association (2010). Diagnosis and classdification of Diabetes mellitus. Diabetic care. 33, pp. S62-S69.

4- Ansell, B.J., fonarow G.C., Fogelman A.M. (2006). High density lipoprotein: is it always atheroprotective ?.curr.atheroscler,rep. 8, PP, 405-411.

5- Ansell, B.J., waston, K.E., Fogelman A.M., Navab M., Fonarrow, G.C. (2005). High density lipoprotein function recent advances. J.Am.coll. cardiol. 46, pp. 1792-1798.

6- Assmann, G. Gotto A.M. , 2004 ,HDL cholesterol and protective factors in atherosclerosis . Circulation. 09, pp. III8-III14.

7- Barlow, S.E. and Expert committee (2007). Expert committee recommendation regarding the prevention , assessment and treatment of childhood ; summary report. Paediatric. 120, pp. S164-S192.

8- Bolen, S., Feldman, L., Vassy, J., Wilson, L., wiley, C., Selvin, E., et al. (2007). Systemic review : Comparative effectiveness and safety of oral medication for type 2 diabetic mellitus. Ann intern med. 47(6), pp. 386-99.

9- Dhaneshwar, S.R., Salunkhe, J.V., Bhusari, V.K. (2010). Validated HPLTC method for stimulataneous estimation of metformin hydrochloride , atorvastatin and glimepinide in bulk drug and formulation . j Anal Bioanal tech 1:09 .

10- Eisenberg, S. (1990). Metabolism of apolipoprotein and lipoproteins. Curr opinhipidol. 1, pp. 205-211.

11- Fujoka, K. (2007). Pathophysiology of type 2 Diabetes and the role of incretin hormone and beta cell dysfunctiuon. jAAPA. PP. 3-8.

12- Howland, R.D., Mycek, M.J., Harvey, R.A., Champe, P.C. (2006). Lippincott's illustrated reviews:pharmacology.3rd ed. Lippincott Williams and Wilkings. USA. pp. 289-290.

13- Hu, F.B., Manson, J.E., Stampfer, M.J., Coldize, G., Lia, s., Solomon,C.G., et al. (2001). Diet , lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med. 345(11), pp. 790-7.

14- Hundle, R.S. and Inzucchi, S.E. (2003). Metformin : new understanding, new uses. Drugs. 63, pp.1879-1894.

15- Kalender, A., Selvaraj, A., kim, S.Y., Gulati, P., Brule, S., Viollet, B., etal. (2010). Metform, independent of AMPK , inhibit mTORCI in rag GTPase-dependent manner, cell metab. 11(5), pp. 390-401.

16- Mahamood, I., Khan, M.R., Rahman, M.K., chowdhurg, M.H. (2009). A comparision of lipid profile between sedentary and non sedentary workers. T.A.J. 22:10-14.

17 - Maric, A. (2010). Metformin-more than ʻGold standardʼ in treatment of type 2 diabetes mellitus. Diabetologia croatica. pp. 39-3

18- Murray, R.K., Grauner, D.K., Rodwell, V.W. (2006). Harper's illustrated Bio chemistry. 27th ed. McGraw-hill. USA .

19- Mwyers, C.D. and Kashyap, M.L. (2004). Pharmacologic elevation of high density lipoprotein: recent insight on mechanism of action and atherosclerosis protection. Curr. Opin. Cardiol. 19, pp. 366-373

20- Natarajan, P., Raykik, K., Cannon, C.P. (2010). High density lipoprotein and coronary heart disease. J.Am.CoH cardiol., 55, pp. 1283-1299.

21- NCEP, National Cholesterol Education program. (1993). The exercise and cholesterol controversy. JAMA. 29(23):3015-3023.

22- O'Neil, M.J. (2001). Merckindex- An Encyclopedia of chemicals, Drugs, and biologicals. 13th ed. Whitehouse station:merck and Co. P. 1061.

23- Olokoba, A.B., obeteru, O.A., Olokoba, L.B. (2012). Type 2 diabetes mellitus: A review of current trends. Oman Med J. 27(4), pp. 289-273.

24- Painco, R., powell, W.H., Richer, J.C. (1993). A guide to IUPAC nomenclature of organic compounds. IUPAC/Blackwell.UK.

25- Pllan, P. (1998). Metformin and fatal lactic acidosis. Med safe. 16, pp. 22-29.

26- Powers, A.C., Fauci, A.S., Braunwauld, E., Kasper, D.L., Hauser, S.L., Longo, D.L., etal. (2008). Harrison's principles of Internal medicine. 17th ed. Newyork, McGraw-Hill, pp. 2275-2304

27- Rewers, M. and Hamman, R.F. (1995). Risk factors for non-insulin dependent diabetes. In: harrism(ed) Diabetes in America., 2nd ed.NIH publication No.95-1468.National Institute of Health. Bethesesda. pp. 179-220.

28- Ripsin, C.M., Kang, H., Urban, R.J. (2009). Management of blood Glucose in type 2 diabetes mellitus. Am fam physician. 79(1), PP. 26-36.

29- Saeed, S.D. (2010).Glibenclamide, Metformin, or their combination, for the treatment of newly diagnosed diabetic patients in hawler city. MSc Thesis in Clinical Pharmacology.HMU, pp. 10-25.

30- Saltpeter, S.R., Greyber, E., Pasternak, G.A., sulpeter, E.E. (2003). Risks of fatal and nonfatal lactic acidosis with metformin use :type 2 diabetes mellitus. Archinte. 163(21), pp. 2594-602.

31- Shah, P.K., kaul, S., Milsson, J., Cercek, B. (2001). Exploiting the vascular protective effects of high density llopoprotein and its apolipoproteins. Circulation. 104, pp. 2376-2383.
32- Shaw, J.S., Wilmot, R.L., Kilpatrick, E.S. (2007). Establishing pragmatic estimated GFR thresholds to guide metformin prescribing. Diabetic medicine. 24:1160-1163.
33- Shroff, G. (2015). Use of human embryonic stem cells in the treatment of diabetic mellitus: a case series. Diabetes mellitus. 5, pp. 313-318.
34- Smith, A.F., Beckett, G.I., Walker, S.W. (1998). lecture notes on clinical biochemistry. 6th ed. Blackwell science.UK. pp. 165-174.
35- Timerlake, K.C. (2003). Chemistry an introduction to general, organic and biochemistry . 8th ed. Benjamin C mmings. USA.
36- Vasudevan, D.M. and S.S. (2005). Text book of Biochemistry for medical students. 4th ed. Jaypee. India .

الخلاصة :

يقوم هذا البحث بعمل فحص لعدد من المرضى الموجودين داخل المستشفيات العراقية وذلك بعد اجراء الفحصوصات وتحديد النوع الثاني من داء السكري لهولاء المرضى وبعد اخذا مستويات الدم (المصل او البلازما) لكل من تحليل دم الصائم وتحليل الدهون لقياس نسبة الدهون والسكر في المرضى قبل اعطاء الدواء وبعد اعطاء الدواء لمده تتراوح 3 اشهر نقوم بحساب تحاليل الدم من جديد لكل من الدهون والسكر لهولاء المرضى فنلاحظ هنالك اختلاف في معدلات الدم من دهون وسكر وارتفاع معدل الدهون عالية الكثافية (كثر من 40 الى 55 مل /دسي لتر)وكذلك انخفاض مستوى السكر بنسب تقارب الطبيعي ومن ذلك نستنتج اهمية هذا العلاج لمرضى السكر من النوع الثاني وخاصتا ذوي السمنة منهم حيث تقل مستويات الدهون الضارة وبالتالي نقل الامراض الوعائية القلبية مستقبلاً وكذلك تقل معدلات السكر . فنصح جميع الذين يعانون من داء السكري من النوع الثاني باخذ الدواء وذلك لدوره الفعال في خفض مستويات الدهون الضاره ورفع الدهون النافعة وتقليل نسب السكر في الدم وذلك لدوره الفريد من نوعه الذي يختلف عن الانواع الاخرى كم ادوية السكر وايضا له ادور مهمه في علاج متلازمه الكياس الرحمية .