Republic of Iraq
Ministry of Higher Education and Scientific Research
University of Al-Qadisiyah
College of Medicine
Department of Community and Family medicine

Hyperglycemia Induced by Statin in Patients Using Statin Therapy

A Thesis

Submitted to The council of the College of Medicine/ University of Al-Qadisiyah
In Partial Fulfillment for the Degree of Higher Diploma **Equivalent to Master Degree** in Family Medicine

By

Noor Khalid Mohamed

M.B.Ch.B

Supervised by

Assistant Professor

Dr. Hassan Raji Jallab

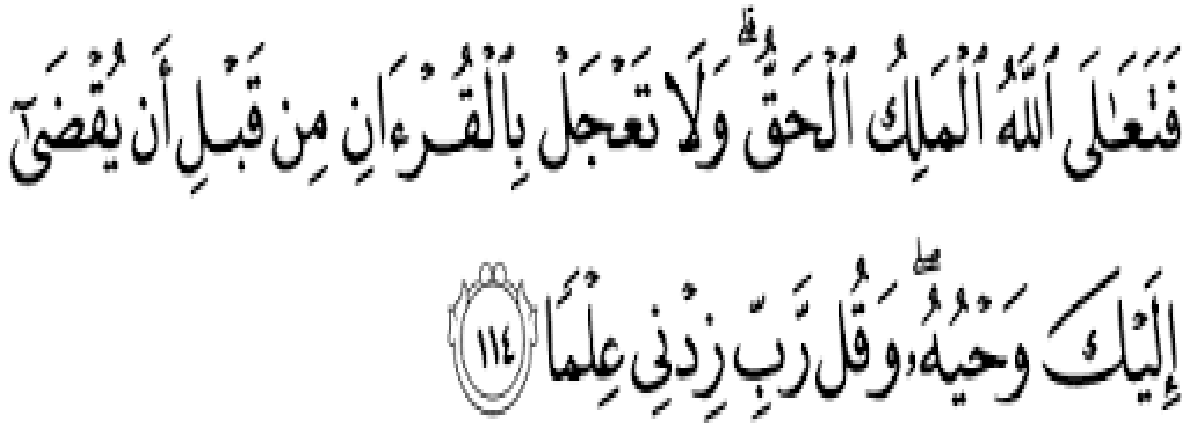
H.D.S.M(ph.D.)

Department of Community and Family medicine
University of Al-Qadisiyah

College of Medicine

2018 A.D. 1440 A.H.

بسم الله الرحمن الرحيم



صدق الله العلي العظيم

من سورة طه الاية (114)

We, the examining committee, certify that this thesis entitled **"Hyperglycemia Induced by Statin in Patients Using Statin Therapy"** was prepared by "**Noor Khalid Mohamed**" and have examined the student in its content and that in our opinion it is accepted as a thesis for the degree of Higher Diploma in Family Medicine.

Signature
Professor
Dr. Hasan Alwan Baiee
chairman
Date: / /2018
22/10

Signature
Assistant Professor
Dr. Radhi F. Shlash
Member
Date: 22/10/2018

Signature
Assistant Professor
Dr. Sinaa Abdulamir kadhim
member
Date: 22/10/2018

Signature
Assistant Professor
Dr. Hassan Raji Jallab
Member/superviser
Date: 22/10/2018

Approved for the faculty Committee of Graduated Studies

Signature
Professor
Dr. Aqeel Raheem Al-Barqa'awee
Dean college of Medicine / University of Al-Qadissiyah
Date: 22/10/2018

Supervisor's certification

I certify that this thesis entitled "**Hyperglycemia Induced by Statin in Patients Using Statin Therapy**" was prepared by student "**Noor Khalid Mohamed**" under my supervision at the college of Medicine, University of Al-Qadisiyah as a partial fulfillment of the requirements for the Degree of Higher Diploma in Family Medicine.

Signature
Assistant Professor
Dr. Hassan Raji Jallab
Department of Community and Family medicine
University of Al-Qadisiyah
College of medicine
Date 22/7/2018

In view of the available recommendations, we forward this thesis for debate by the examining committee.

Signature
Lecturer
Dr. Ali Abdul-Hussein Mousa
Head of Department of Community and Family medicine
F.I.C.M.S.
University of Al-Qadisiyah
College of medicine
Date 22/7/2018

Dedication

To

Patients who unfortunately suffered from Diabetes mellitus and especially those participated in this study

To *My Teachers, my Husband,my family, my friends and anyone who helped me*

I dedicate this plain effort

Research Student
Noor 2018

Acknowledgements

First of all I would like to express my deep thanks to **Allah** for his great support, blessing, mercy and passion.

I would like to express my great appreciation and thanks to Al-Qadisiyah University/ Faculty of Medicine including the **Dean** , Vice Dean for postgraduate studies and scientific affairs and all staff members for their great support and encouragement and being extremely helpful in accomplishing the current work.

It is of great interest to express a special kind of thanks and appreciations to Assistant Professor **Dr. Hassan Raji Jallab** for his supervision and great support and help to accomplish the theoretical and the practical aspects concerning the present study.

Deep appreciations and thanks are to be expressed to all staff members of health institutes in Al-Dewaniyah Province including primary and secondary health centers.

I would like to express my deep thanks to **Lecturer Dr. Thair Wali Ali** for his help in statistical analysis and presentation of collected data related to the current study.

Never to forget all who participate by their encouragement, support, assistance and advice in order to accomplish the current work in its final appearance.

Abstract

Background

Dyslipidemia is a major risk factor involved in the pathogenesis of atherosclerosis and associated cardiovascular complications and strokes. Control of dyslipidemia resulted in significant reduction in morbidity and mortality related to cardiovascular ischemic events and hence the use of statin as a primary mode in controlling dylipidemia became a usual trend in the practice of medicine. Because of the rarity of Iraqi published articles dealing with the relationship between the use of statin and hyperglycemia, the present study was designed to investigate the association between the use of statin therapy and the development of hyperglycemia or diabetes among Iraqi patients taking statin therapy for the control of dyslipidemia.

Aim of the study

To identify the association between statin use, in terms of the specific drug used, duration of therapy and dose of treatment, and the development of hyperglycemia and or frank diabetes in a cohort of Iraqi patients on variable statin drugs.

Patients and methods

The study was designed to be a cross sectional study involving a cohort of 220 Iraqi patients on statin therapy for controlling dyslipidemia. Patients were selected in a systemic random way from the population of patients already visiting Al- Diwaniyah Teaching Hospital and the primary health care centres. Any patient who was already diagnosed by a specialist to diabetes mellitus before starting statin therapy was excluded from this study. The study was carried out at Al-

Diwaniyah Teaching Hospital, Al-Forat and Al-Talea primary health care centres. The beginning of data collection was dated on the 20th March 2018 and ended on the 10th June 2018.

Results

1)Diabetes mellitus had developed in 45 out of 220 patients which account for (20.5%).

2) Body mass index, duration of statin use, and dose of statin showed significant association with diabetes mellitus(p value`<0.05), whereas, none of the other variables had significant effect on prevalence rate of diabetes mellitus(p value>0.05).

Conclusion

Statin therapy responsible for at least in part for the development of hyperglycemia and or frank diabetes among the study group.

List of contents

List of tables

List of figures

List of abbreviation

ADA	American Diabetes Academy
AHA	American Heart Association (AHA)
ATP	adults treatment panel (ATP)
BMI	Body mass index
CVA	Cerebrovascular accidents
CVD	Cardiovascular disease
DM	Diabetes mellitus
HRs	Hazard ratios
FBS	Fasting blood sugar
FDA	drug and food administration (FDA)
GTPase	Guanosin tri-phosphatase
GTT	Glucose tolerance test

HBa1c	Hemoglobin
HDLs	high density lipoproteins (HDLs)
HMG coA	The 3_hydroxy 3_methyl glutaryl Co enzyme A
IDLs	Intermediate low density lipoproteins (IDLs),
JUPITER	Justification for the Use of statin in primary prevention ; An Intervention Trial evaluating Rousvastatin
LDLs	low density lipoproteins (LDLs)
NCEP	National Cholesterol Education Program (NCEP)
NHANES	National Health And Nutritional Examination survey
PROSPER	the prospective study of pravastatin in the elderly at risk (PROSPER)
RCTs	Randomized controlled trials
RBS	Random blood sugar
VLDLs	very low density lipoproteins (VLDLs),

Chapter one

Introduction

اكتب المعادلة هنا.

Chapter one

Introduction

Diabetes mellitus comprises a group of heterogeneous disorders that share in common the criteria of chronic hyperglycemia [(1)]. It is one of the most commonly encountered health problems in primary health centers [(2)]. Diabetes mellitus may be of type 1 or type 2 [(3)]. Type 1 diabetes mellitus is characterized by profound deficiency of insulin due to autoimmune destruction of Langerhans islets that contain, in addition to other endocrine cells, the cells responsible for synthesis and secretion of insulin, namely beta cells[(4)].In small proportion of patients with type 1 diabetes, the destruction of beta cells is of unknown etiology and hence considered idiopathic [(4-6)]. The most common form of diabetes mellitus is type 2 that is characterized by resistance to insulin action in addition to some deficiency of endogenous insulin[(7)]. Type 2 diabetes usually encountered at an age that is older than type 1, hereditary factors plays more significant role in type 1 diabetes and those patients usually benefit from oral hypoglycemic agents at least early in the disease [(7)]; however, patients with type 1 diabetes may ultimately need insulin at later stages of disease because of more profound deficiency of insulin with time and hence older designation insulin dependent and non-insulin dependent diabetes became obsolete [(8)]. Other forms of diabetes include secondary to endocrine abnormalities or certain drugs, monogenic forms of diabetes mellitus and gestational diabetes [(1)].

The long term complications of diabetes mellitus that are related to macrovascular and microvascular events accompanying hyperglycemia are the main health concerns for both patients and health care workers [(9, 10)].

Atherosclerosis is accelerated and is more severe in patients with diabetes and its related complications such as ischemic heart disease, stroke and poor circulation to extremities, are more frequent and more severe in diabetic patients [11-13]. Efforts to control dyslipidemia in patients with ischemic heart disease, stroke patients and patients with disturbed lipid profile are core in medical practice and the use of statins becomes increasingly frequent in medical practice aiming at prevention of dyslipidemia related complications. Recent controversial studies raised the issue of hyperglycemia among patients on statin therapy [14-17]; however, little has been found in Iraqi published papers concerning this association. This controversy and the poverty of Iraqi literatures dealing with this subject justified the conductance of the current study.

1.2 Aim of the study

To identify the association between statin use, in terms of the specific drug used, duration of therapy and dose of treatment, and the development of hyperglycemia and or frank diabetes in a cohort of Iraqi patients on variable statin drugs.

Chapter Two

Literature Review

Chapter two

Literature review

2.1 Abnormal lipid profile

Hyperlipidemia is abnormally elevated levels of any or all lipoproteins in the blood. It is the most common form of dyslipidemia, while dyslipidemia refers to abnormal concentration of lipid or lipoproteins in the blood either high or low (an elevated total or low density lipoprotein cholesterol levels, triglyceride levels or low levels of high density lipoprotein cholesterol). dyslipidemia is a strong and well documented risk factor for cardiovascular disease and strokes [(18)]. Plasma lipoprotein levels are major modifiable risk factors for cardiovascular disease. Increased levels of atherogenic lipoproteins (especially LDL, but also IDL, and possibaly chylomicron remnants) contribute to the development of atherosclerosis [(19)] . The plasma lipoproteins are divided into five major classes based on their relative density: chylomicrons, very low density lipoproteins (VLDLs), Intermediate low density lipoproteins (IDLs), low density lipoproteins (LDLs) and high density lipoproteins (HDLs). Each lipoprotein class comprises a family of particles that vary in density, size and protein compositions [(20)]. Cholesterol is a waxy fat particle made by the liver. It is essential for healthy cell membranes; brain functioning, hormone production and vitamin storage. While lipoprotein transport cholesterol through the blood to the cells, cholesterol becomes a problem when too much LDL is produced or ingested through unhealthy food [(21)]. HDL cholesterol is involved in reversed cholesterol transport so, excess cholesterol is eliminated from the body via the liver which secrete it in the bile or convert it to bile salts, While triglyceride present in the blood to enable the bidirectional transference of adipose

fat and blood glucose from the liver, and it is the main constituent of body fats in humans [22]. Hyperlipidemia may basically be classified into: familial (also called primary) or acquired (also called secondary) when resulting from underlying disorder that leads to alterations in the plasma lipid, it may be idiopathic [23] .There is absolutely no doubt that higher levels of cholesterol (particularly LDL or bad cholesterol) are associated with high risk of vascular events including heart attacks, stroke, blocked arteries in the legs and the need for bypass surgery and stenting[23] . Elevated blood cholesterol level leads to deposition of (LDL) so called (bad cholesterol) in the arterial walls leading to atherosclerosis, left untreated, eventually will leads to heart attacks due to coronary heart disease or stroke[23] . Therefore, the United State Preventive Services Task Forces (USPSTF) recommended screening with non fasting total cholesterol and HDL levels for the following groups [24] :-

- All men over age 35 (A recommendation).
- Men age 20 to 35 year with one or more risk factor for atherosclerotic cardiovascular disease (B recommendation)
- Women more than 45 year with one or more risk factor for atherosclerotic CVD (A recommendation).
- Women age 20 to 45 year with one or more risk factor for atherosclerotic CVD.(B recommendation).

2.2 Dietary therapy for management of hyperlipidemia

A healthy diet can improve lipids and reduce the risk of developing atherosclerotic CVD. Healthy diet guidelines according to American Heart Association (AHA) include [25] :

- Eat mostly plant based food.
- Eat 9 to 10 servings of fruits and vegetables daily.

- Choose whole grain and high fiber diet
- Add monounsaturated fats to your diet.
- Eat fish once or twice a week.
- Limit saturated and transfat.
- Add water soluble fiber in the diet.

According to meta analysis of randomized control trials Low fat diet had the most favorable effects on total cholesterol and LDL cholesterol levels, whereas low carbohydrate diets had the most favorable effects on triglyceride and HDL cholesterol levels [26] .

2.3 Lipid lowering agents (Statins)

The 3_hydroxy 3_methyl glutaryl Co enzyme A (HMG Co A) reductase inhibitors inhibit rate limiting steps of conversion of HMG Co A to mevalonate and thus limit cholesterol synthesis [27] . Statins lower serum LDL and triglyceride, rise HDL cholesterol and improve surrogate markers for cardiovascular event, most importantly statin reduce the risk for major cardiovascular events. Patient with greatest absolute risk of cardiovascular disease will derive the greatest benefit from the treatment(28). Statin therapy reduces the risk of death from any cause by 9% per 1 mmol \ L reduction in LDL cholesterol [28] . The National Cholesterol Education Program (NCEP) through the adults treatment panel (ATP) has recommended reducing LDL cholesterol as the primary goal and supports the use of statin as initial [29] . The preventive effect of statin on coronary events is not only associated with the cholesterol lowering effect but also various effect on vascular wall which include improvement of endothelial function, anti oxidation and anti inflammatory activity, also inhibit cholesterol synthesis in the liver ,of

significance, because most circulating cholesterol came from internal manufacture rather than the diet[30] . It increases LDL receptor expression increasing its uptake and consequently, decreasing plasma LDL concentration. The role of statin has been widespread as on inflammatory marker (c-reactive protein CPR, interleukin6,adhesion molecule) and nitric oxide [30] . It improves endothelial function and prevents blood clot formation through inhibiting the specific prenylated protein. It also reduces the release of C-reactive protein, adhesion molecule as well as modulating T-cell activity, and has extensive immune modulating properties that operate independently of lipid lowering. The therapeutic benefit of treatment of statin includes plaque stabilization, improvement of coronary endothelial function, inhibition of platelet thrombotic formation and anti inflammatory activity [31] .

2.3.1 Specific statins drugs

There are seven different statin drugs available for prescription and these are:

2.3.1.1 Atorvastatin

It is synthetic, it lowers LDL level as well as triglyceride level. It is estimated that 21% of statins prescribed in U.S is Atorvastatin. It is available as 10, 20, 40 and 80mg tablet. Its main side effects are muscle pain, weakness, tenderness, increased liver enzyme, diarrhea, sore throat and stuffy nose, and interaction with grape fruit and alcohol [32] .

2.3.1.2 Lovastatin

It is strong statin and is naturally occurring in some food like oyster mushrooms and red yeast rice. It causes little side effects than other statin group, the main side effects are muscle pain, weakness, infection, indigestion, diarrhoea, and rarely hepatotoxicity [33] .

2.3.1.3 Simvastatin

It's made from fungus Aspergillus tesseus. It is used along with excessive diet and weight loss to treat dyslipidemia and decrease risk of heart failure. Its main side effects are muscle breakedown, liver problem, and increase blood sugar. Others include joint pain, memory loss, rhabdomyolysis, and allergic reaction. The usual dose ranges from 10 to 80 mg [34] .

2.3.1.4 Rousvastatin

At 2013 it was the fourth highest- selling drug in U.S. The effect of it on LDL cholesterol is dose- related, and it modestly increases HDL level as compared with other statins according to a meta-analysis study. Its main side effects are indigestion, depression, joint pain and rarely allergy, hoarseness and numbness. Its available doses are (5, 10, 20 and 40) mg [34] .

2.3.1.5 Fluvastation

It is used for treatment of hypercholesterolemia and mixed dyslipidemia. It is available as (20, 40 and 80) mg capsule [34] .

2.3.1.6 Pravastatin

It reduces circulating cholesterol and LDL a major reduction in triglyceride and increase HDL, available as (20, 40 and 80) mg. It is well tolerated and displays few non cardiovascular abnormalities in patients undergone a double- bind randomized-trials using the 40 mg [35] .

2.3.1.7 Pitvastatin

It is taken off the market in 2001 because it`s serious side effects [36] .

2.3.2 Statin and diabetes

Diabetes mellitus is a clinical syndrome characterized by hyperglycemia due to absolute or relative deficiency of insulin. As of 2015, An estimated 415 milion people has diabetes worldwide. With type 2 diabetes making up about 90% of the cases [37] .

2.3.2.1 Diagnosis of diabetes mellitus

Diabetes is confirmed by either: plasma glucose in random sample more than or equal to 11.1 mmol\l (200mg\dl), or Fasting blood glucose more than or equal to 7.0 mmol\l (126 mg\dl).

While pre diabetes is classified as:

1) Impaired fasting glucose: FBG more than or equal to 6.0 mmol\l (108mg\dl) and less than 7.0 mmol\l (126mg\dl).

2) Impaired glucose tolerance: FBG less than 7.0 mmol\l (126mg\dl) and 2 hours after 75 g oral glucose 7.0- 11.1 mmol\l (140- 200) mg\dl.

The classic symptoms of diabetes include:- weight loss, poly urea, polydipsia, polyphagia, Which develop more slowly. Added to that, blurred vision, headache, fatigue, slow healing of wounds, and itching [37] .

2.3.2.2 Classification of diabetes mellitus

For detailed etiologic classification see table 2.1

1) Type 1 DM

It is caused by pancreatic beta cell destruction, usually immune- mediated, mostly, associated with either HLA DR3 or HLA DR4. Occur at any age but most commonly in children and young adults. The presentation is mostly with polyurea, polydypsia and weight loss, also ketonemia and keton urea [38] .

2) Type 2 DM

In this type cells become more resistant to action of insulin, and the pancreas is unable to make enough insulin to overcome this resistance , instead of moving into the cell, sugars builds up in the blood stream. The four major determinants are increasing age, obesity, ethnicity, and family history. Type 2 diabetes mellitus is associated with central obesity, hypertension, hypertriglyceridemia, decrease HDL cholesterol and increase in pro inflammatory markers, this group of conditions called (metabolic syndrome) [37] . A new study on 2018 cassify diabetes in adulthood into five distinct categories in which type 1 diabetes and a late- onset autoimmune form of diabetes can be grouped together as one form, dubbed sever autoimmune diabetes . However, the researchers state that would generally have

been called type 2 diabetes encompasses two categories, two of which are sever form of the disease [39] .

The treatment goal for adults with diabetes includes;-

1) Hb A 1c less than 7.0 %.

2) pre prandial capillary plasma glucose (80_ 130)mg\dl.

3)Post prandial capillary plasma glucose less than 180 mg\dl.

4) Blood pressure less than 140\80 mm hg.

.. lipids;-

5) Low density lipoprotein less than 2.6 mmol\l (100 mg\dl).

6) High density lipoprotein more than 1 mmol\l (40 mg\dl) in men . and more than 1.3 mmol\l (50 mg\dl) in women.

7) Triglyceride less than 1.7 mmol\l (150 mg\dl) [40] .

Diet and exercise therapy are expected to improve glycemic and lipid metabolism (grade A consensus). In patients in whom the lipid control goals cannot be achieved after improvement in life style and glycemic control, drug therapy should be considered. HMG Co A reductase inhibitors or statins are drug

for the first choice for elevated LDL cholesterol.(grade A consensus) [40] . Cardiovascular disease is the most prevalent complication of diabetes. I it is estimated that 77% of hospitalization in the U. S for chronic complication of diabetes is due to cardiovascular disease. Multiple factors contribute to the accelerated atherosclerosis in diabetes. Researchers have discovered how diabetes by driving inflammation and slowing blood flow dramatically accelerate atherosclerosis according to the Journal circulation research on March 14 edition. Numerous metabolic abnormalities associated with type 2 diabetes increase the risk of atherosclerotic cardiovascular disease among those are advanced glycation end products. In addition, as a part of the insulin resistance syndrome reffered to as syndrome X or (metabolic syndrome) [41] . Dyslipidemia should be aggressively treated in patient with diabetes , Its resolution leads to a decrease in the incidence of cardiovascular disease [40] . According to the American Heart Association (AHA) and The American Diabetes Academy (ADA) for prevention of cardiovascular disease in type 2 diabetes state that;-

Most individuals with type 2 diabetes have diabetic dyslipidemia: Elevated triglyceride, decrease HDL, elevated, borderline,normal LDL- c. LDL- c is the primary target of lipid lowering therapy. LDL-c reduction with statin reduce the risk of major cardiovascular events in individuals with or without diabetes. Every 39mg\dl (1mmo\l) LDl- c reduction equates to a proportional 21% reduction in major cardiovascular events.

LDL- c treatment

- life style changes are the foundation.
- Individuals aged 40- 45 years with diabetes and LDL –c 70- 189 mg\dl require moderate intensity ststin.

- Individuals aged 40- 75 years wih diabetes and more than 7.5% atherosclerotic cardiovascular disease risk require high intensity statin.
- Individuals aged less than 40 or more than 75 years with diabetes require evaluation of the benefits for statin therapy.

The treatment goals for treatment of diabetic according to the American Diabetic Association are [42]

- Lower LDL-c to less than 100 mg\dl or in patients more than 40 yr of age `30% if total cholesterol equal or more than 135 mg\dl regardless of the baseline LDL.
- Lower triglyceride to less than 150 mg\dl
- Rise HDL-c to more than 40mg\dl for men; more than 50 mg\dl for women.

The recommendation according to (ADA):

- Lifestyle modification to improve lipid profile if LDL-c equal or more than 100 mg\dl.
- Reduction of saturated fat and cholesterol intake, weight loss, exercise, smoking cessation. goals with life style modification).
- Aggressive statin therapy to lower LDL-c and reduce cardiovascular events. Combination therapy with statin and fibrates or niacin to achieve lipid targets. Although, outcome studies for event reduction and safety are not available.

2.4 Statin and risk of hyperglycemia

Statin are the most commonly prescribed cardiovascular drugs worldwide. Although , safe and generally well tolerated , a new data suggested that statins are associated with an increase risk of new onset diabetes, these recent concern have prompted the U.S drug and food administration (FDA) to add these to statin safety label about the increased the risk of hyperglycemia [(43)] . In 2010, a clinical trial meta- analysis reported that statin therapy overall was associated with slightly increased risk of new- onset diabetes. Although, a small risk, but, could potentially result in a significant number of additional cases of diabetes per year [(44)] . In 2011 a new study shows the association between atorvastatin and new- onset diabetes , There`s sufficient evidence to support the risk of new- onset diabetes and atorvastatin use , however, the risk appear to be mainly in patient already at increased risk of diabetes [(45)] . The recent data, from prospective and retrospective trials and meta- analysis suggested an increased incidence of new- onset diabetes with statin, The incidence is not negligible for specific patient such as women, elderly, those with family history of type 2 diabetes and Asian ethnicity. Overall, compared with non- taking statin , their use was associated with a 36% increase in the risk of developing type 2 diabetes This published on Tuesday 24 October 2017. Another meta- analysis of Randomized controlled trials by sattar et al showed that statin therapy was associated with 9% increased risk of incident diabetes, After a period of four years involve 255 patient, There is one extra case of diabetes mellitus. And this study also suggests that rousvastatins were statistically significant in favour of high diabetes risk. And there is a stronger effect with more potent statin or with greater lowering of LDl-c. A new meta- analysis includes 6 statin trials with 57,593 participants, reports a small increase risk of diabetes with no evidence of heterogencity across trials. Another study of post menopausal women using data from women health initiative, report that statin was associated with increased risk of diabetes in those group. But, the effect is unrelated to the

type or potency of statin [46] . Intensive – dose statin therapy was associated with increased risk of new- onset diabetes compared with moderate- dose statin. Statin therapy appear to increase the risk of type 2 diabetes even after adjustment of the confounding factors. And the effect is considered that its class- medication effect [47] . Atorvastain and simvastatin are associated with increased risk of diabetes as compared to pravastatin [48] . Justification for the Use of statin in Primary Prevention ; An Intervention Trial Evaluating Rousvastatin (JUPITER), using Rousvastatin 20 mg\dl , this trial reported a 26% higher incidence of diabetes in the follow up of less than two years. This study also showed as compared to placebo statin group was associated with a higher risk of physician reported new- onset diabetes and the risk was higher in women compared with men [49] . In the prospective study of pravastatin in the elderly at risk (PROSPER). There was a 32% higher incidence of diabetes with pravastatin therapy. Those in high dose of statin are more prone to suffer dangerous spikes in blood sugar levels. Studies show those prescribed statin are less likely to develop heart disease but, it is appears to make them more vulnerable to type 2 diabetes. While statin provide clear benefits in term of cardiovascular prevention, those effect may be offset by increased risk of diabetes over time and should be monitored [50] .

There is sufficient evidence to support the association between the statin use and the risk of new onset diabetes, however, the risk may be mainly in patients already at increased risk of diabetes mellitus, and these factors may include:

- History of hypertension.
- Raised triglycerides
- Raised body mass index at baseline.

And the key factor for determining the increased risk of diabetes is raised fasting blood glucose. There is limited data to support the increased risk with

intensive dose of Atorvastatin and Simvastatin therapy [51] . This study also shows the dose- dependent association between statin therapy and the risk of incident diabetes, It revealed that intensive- dose statin therapy was associated with a high incidence of new- onset diabetes ,though, it decrease cardiovascular risk as well [51] . A few studies show the association between statin use and the increased level of HB A 1C [52] . In a study regarding the comparison between pravastatin and Atorvastain , Although the use of 80 mg atorvastatin and 40 mg pravastatin were both associated with a small increased level of hemoglobin A1c (HbA1c) (0.37% for atorvastatin and 0.18% for pravastatin) , but, atorvastain was significantly increased risk of developing HB A 1c more than 6% compared with pravastatin [53] . In two Japanese studies involving non- diabetic patients, atorvastatin, but, not pravastatin was associated with an increase Hb A 1C levels [54, 55] . According to meta- analysis study of randomized controlled- trials regarding the lipid- lowering with statin , the treatment was associated with a small increase , approximately, 10%-12% in the risk of developing diabetes compared with placebo. Authors did not find any apparent difference lipophilic and hydrophilic statin in association with diabetes risk [56] . Atorvastatin has been associated with increased risk of diabetes in the Anglo Scandinavian Cardiac Outcomes trials [57] . Another study involving participants with type 2 diabetes and the results show impaired glucose metabolism in some of these cases, [58] . In prospective non randomized study demonstrated an increased insulin resistance in patients with coronary bypass graft – surgery [59] . However, The potential increased risk of diabetes should always be weighed against any benefits of statin which include reduced risk of heart attacks and stroke in certain groups of people. For individual patient , A modest increase in the diabetes risk needs to be balanced against the consistent and highly significant reduction in heart attacks,stroke and cardiovascular deaths associated with statin treatment [59] . One of the met- analysis comparing high dose- statin

therapy with moderate- dose found that the high- dose is associated with improve cardiovascular outcomes, though, at the same time , there was a 12% increased risk of new- onset diabetes mellitus [58] . And this study reported that there is controversy about the treatment with moderate dose statin therapy in patients not attaining a target lipid profile [58] . As compared to the other cardiovascular medication , like thiazide diuretics, and beta- blockers , statin are three times less likely to cause diabetes. The use of statin therapy in patient with risk factor like;- older age, increase weight, and higher blood sugar levels before the use of statin, can unmask diabetes mellitus in those individuals. The rate of reduction of cardiovascular events outbalanced the risk of incident diabetes even in patients at higher risk for developing diabetes[59] .

2.5 The mechanism of diabetogenic effect s of statin

The precise mechanism underlying the diabetogenic effect is still unclear , It is still not known whether the chemical or biological differences of statin are responsible for the diabetogenic effect [51] . Statin have been thought to affect glucose metabolism and insulin sensitivity and it may adversely affect glycemic control through the loss of adeponectin`s proposed protective and anti-angiogenic properties. Another mechanisms explaining the possible effect of statin on hyperglycemia are that statin by inhibiting phosphorylation interfere with the signal transduction pathway of insulin, interfere with the action of GTPase, and inhibit insulin secretion by inhibiting the differentiation of beta cell of pancreas. Statins thought to induce insulin resistance through inhibition of isoprenoid synthesis which is an intermediate product in cholesterol formation, because,theses effects could be reversed by mevalonate, the isoprenoid precursor, the inhibition of isoprenoids pathway may produce dowenregulation of GLUT4 receptors on adipocyte cells. All these can lead to decrease glucose uptake or glucose intolerance [60, 61] . Statin cause overproduction of nitric oxide so, that causes beta

cell apoptosis [62] . A lipophilic statin (Atorvastatin) decrease glucose uptake by beta- cell of pancreas in hypercholesterolemic patients and induce cytotoxicity [63] . A lipophilic simvastatin inhibited glucose – induced insulin secretion through dependently, inhibit the first phase signaling of(CA+2) in rats islet beta cells, and it is thought that will decreases insulin secretion through the blocking L-type Ca +2 channels in the beta cells [64] . The decrease in the glucose uptake was dose-dependent regarding all three concentration (1, 10, 100) nm for atorvastatin, pravastatin and pitvastatin. Furthermore, atorvastatin thought to be associated with elevated HB A1c levels [55] . In a small study of 28 patients with poly cystic ovarian syndrome ,those patient was treated with atorvastatin 20 mg for 6 month , it reported that there is decrease in insulin sensitivity despite, adcrease in a C-reactive protein (CPR); the inflammatory marker [65] . One of the effects of statin on pancreatic beta –cell function is that statin, by increasing influx of cholesterol through the inhibition of HMG CoA, can inhibit the ubiquinone (coQ 10) synthesis , leads to mitochondrial oxidative stress and beta-cell death [66] . Despite, the proven anti inflammatory effect of statin, a recent hypothesis reports that under certain conditions, statin may activate the inflammosome NLRP3 from macrophages leading to insulin resistance mediated by interleukin-1B [67] . In the presence of obesity, this may provide the endotoxin lipopolysaccharide that may mediate the pro- inflammatory effect of statin by activation of these inflammosome [68] . In a cross- sectional study of 27,000 adults followed for 10 years shown that their fat and total calorie intake and weight gained over time compare with those not taking statin [69] . Finally, a randomized controlled trials reported that there is a genetic polymorphism associated with reduced activity of HMG CoA reductase , so, a significant weight gain and insulin resistance occur in those patient. There is still no clear mechanism for the increased risk for diabetes, and all patients prescribing statin should be informed about of their risk for developing diabetes in

the future. This advice will help them to alleviate their diabetes risk, and further reduce their cardiovascular disease risk [70] .

2.6 Benefit versus risk of statins

Cardiovascular disease is a major cause of mortality and one of the most common cause of morbidity in the world. Because of the importance of low density lipoprotein cholesterol as a modifiable risk factor, several guidelines have recommended the achievement of LDL goals in patients with different cardiovascular risk profiles. Statins have been demonstrated to be beneficial in secondary prevention of cardiovascular events and primary prevention in high_ risk patients. Few drugs have, had such a dramatic effect upon health outcomes. Over four years of statin use, a 1 mmol\l (39mg\dl) reduction in LDL cholesterol reduce mortality by 9% in those with diabetes and 13% in those without, and even greater benefits occur over long- term use [71] . Although diabetes mellitus is a serious disease, risk and benefits must be considered at the same time. It is clear that statin prevent heart disease in patients with high risk or established cardiovascular disease, but, the use of statins for primary prevention (in patient with low risk of cardiovascular disease) is less certain, although, large study reports the use of statin may benefits low – risk population, but , the risk of statin-induced diabetes is important and unknown in this population. If diet and life style changes cannot achieve LDL goals, statin therapy should be considered [72] . Anothor study have reported increased diabetic risk over a longer duration [73] . And long- standing diabetes has been shown to increase risk of coronary heart disease [74] . One meta-analysis study compare between high and moderate- dose statin therapy found that there is improvement in cardiovascular outcome in patient with moderate- dose statin, although, at the same time, there was a12% increase in

risk of developing new- onset diabetes mellitus. So, there is controversy about the treating patients not reaching target lipid profile on moderate- dose of statin. The benefit of statin therapy decrease by increasing age and the increasing age increase the risk of diabetes as well [75] . Modest increase in blood glucose levels by statin is not an issue of concern if they decrease morbidity and mortality due to microvascular and macrovascular complications [76] . In patients with cardiovascular risk factor, the benefit of statin overcome the risk of diabetes [77] . Thus, it is now clear that statin therapy should not be withheld in patients at high risk factor for cardiovascular disease for the relatively minor propability of progression to diabetes, and in the presence of risk factors for diabetes , the modest diabetogenic effect of statin therapy may lead to progression from prediabetes to diabetes. The potential modest increase in diabetes risk needs to be balanced against the highly significant reduction in myocardial infarction, stroke, and cardiovascular death associated with statin treatment. Therefore, ,although, the risk of diabetes mellitus is higher in patients receiving statin, statin ultimately benefits cardiac health in patient with established heart disease or in those at a risk for heart disease. And there is a constant but weak association between statin therapy and new- onset- diabetes and worsening of diabetes mellitus [78] . So, new guidelines have paved the way for greater attention for the initiation of statin therapy in high risk individuals (prior cardiovascular disease) as with cardiovascular disease associated with multiple risk factors. Higher dose has the greater risk but the decrease in cardiovascular disease outweighs the risk of developing diabetes, so, physicians should be cautious about the development of diabetes in patients with intensive statin therapy, and statin therapy should be used cautiously in patient with low cardiovascular risk factors and routine monitoring of fasting blood sugar levels should be done [78] .

Chapter Three

Patients and Methods

Chapter three

Patients and Methods

3.1 Study Design

The study was designed to be a cross sectional study involving a cohort of Iraqi patients on statin therapy for controlling dyslipidemia. No limitation for gender was proposed; however, patients were chosen to be 20 years or older.

3.2 Sample selection

A 220 Patients were randomly included in this study from the population of patients already visiting Al-Diwaniyah Teaching Hospital and the primary health care centres .

3.3 Patients

At the end of the period designated for data collection, 220 patients were involved in the present study. Those patients were seeking medical advice at Al-Diwaniyah Teaching Hospital and the primary health centers and already taking statin to control dyslipidemia.

3.3.1 Inclusion criteria

Any patient 20 years old or older, from any gender visiting Al-Diwaniyah Teaching Hospital and the primary health centers and already taking statin therapy was included in the current study.

3.3.2 Exclusion criteria

Any patient who was already diagnosed by a specialist to be diabetic or prediabetic before starting statin therapy, and those with chronic use of steroid was excluded from this study.

3.4 Location of the study

The study was carried out at Al-Diwaniyah Teaching Hospital, Al-Forat and Al-Talea primary health care centers. Working days were 5 days per week, starting from 9:00 AM. and ending at 1:00 PM. An average of 3 cases per day was selected to be interviewed and examined.

3.5 Duration of the study

The beginning of data collection was started from the 20th March 2018 and ended on the 10th June 2018. A total of 83 days were the length of the period required to collect data from participants.

3.6 Ethical consideration

The study was approved by the Committee of Ethical Approval at College of Medicine / University of Al-Qadisiyah. Verbal consent was considered when patients were selected to be enrolled in the present study.

3.7 Pilot study

A pilot study for two weeks was conducted in order to know the exact period required to collect information from each individual, in addition to explore the barriers that may be faced during sample and data collection. This pilot study was carried out from 23th of February 2018 to 8th of March 2018.

3.8 Method

The questionnaire includes the following:

- Sociodemographic characteristics of patients: Age, gender, residency, level of education, marital status, smoking, alcohol intake and body mass index (BMI)measurement.
- Information regarding statin therapy such as, duration of intake, dose, specific drug and time intake of drug.
- Information regarding, blood sugar checking, family history of diabetes, last blood sugar reading, personal history of ischemic heart disease or stroke and family history of chronic medical illness.
- Measurements of fasting and random blood sugar were done single handedly for all patients by the researcher.
- The questionnaire form is shown in appendix I.

3.9 Statistical analysis

Data were collected, summarized, analyzed and presented using two software programs; these were the Statistical package for social sciences (SPSS) version 23 and Microsoft Office excel 2013. Numeric variables were presented as mean, standard deviation (SD) and range, whereas, categorical variables were expressed as number and percentage. Prevalence rate of diabetes mellitus was expressed as percentage. Association between categorical variables was assessed using either Chi-Square test or Yates correction for continuity when more than 20% of cells have expected counts less than 5. The level of significance was considered at $P \leq 0.05$

Chapter Four

Results

Chapter Four

Results

4.1 Sociodemographic characteristics of the study sample

Characteristics of patients enrolled in the present study are shown in table 4.1. The study included 220 patients, 149 (67.7 %) males and 69 (31.4 %) females. Their mean age was 60.63±6.67 years and the range was from 45 to 73 years. The male to female ratio was (2.1:1). Majority of patients were from urban areas, 171 (77.7%) versus 49 (22.3%) patients from rural areas. According to educational level, 111 (50.5%), 20 (9.1%), 52 (23.6%) and 37 (16.8%) patients were illiterate, with unfinished primary education, primary and secondary or higher education, respectively. All patients were married. One hundred thirty (59.1%) patients were smokers and 90 (40.9%) patients were non-smokers. Forty (18.2%) patients were alcoholic. Mean body mass index (BMI) and standard deviation (SD) were 25.74 ±3.21 kg/m^2 and it ranged from 21-39 kg/m^2, 110 (50%) were of normal weight, 81 (36.8%) were overweight and 29 (13.2%) were obese. Only 16 (7.3%) patients admitted to practice exercise.

Table 4.1: General characteristics of the study sample

Characteristic	*n*	%
Number of cases	220	100.0
Residency		
Urban	171	77.7
Rural	49	22.3
Age		
Mean ±SD	60.63±6.67	
Range (Min.-Max.)	45-73	
40-59 years	64	29.1

≥ 60	156	70.9
Gender		
Male	150	68.2
Female	70	31.8
Education		
Illiterate	111	50.5
Primary (not finished)	20	9.1
Primary	52	23.6
Secondary or higher	37	16.8
Marrital status		
Married	220	100.0
Nor married	0	0.0
Smoking		
Smokers	130	59.1
≥20 per day	122	55.5
<20 per day	8	3.6
Non-smokers	90	40.9
Alcohol consumption		
Yes	40	18.2
No	180	81.8
BMI		
Normal	110	50
Over weight	81	36.8
Obese	29	13.2
Mean ±SD	25.74 ±3.21	
Range (Min.-Max.)	21-39	
Exercise		
Yes	16	7.3
Daily	1	0.5
More three hour / week	15	6.8
No	204	92.7

4.2. Data concerning diabetes mellitus

Data relating to diabetes mellitus is shown in table 4.2. Family history of diabetes was seen in 84 (38.2%) of patients. Relative who had diabetes was father, mother, sister or brother in 40 (18.2%), 20 (9.1%), 12 (5.5%) patients respectively.

Out of 220 patients, 212 (96.4%) admitted to check blood glucose level and accordingly the results were as following: 200 (90.9%) had blood sugar level of ≤110 mg/dl and 12 (5.5%) had blood sugar level of 151-200 mg/dl. Recent measurement of fasting blood sugar was obtained and accordingly 45 (20.5%) had FBS in the diabetic range (≥ 126 mg/dl). In addition, random blood sugar was also assessed for all patients and accordingly, 41 (18.6%) had RBS within the diabetic range (> 200 mg/dl). 57(25.9%) were in prediabetic state(impaired glucose tolerance). Hence, if FBS measurements were taken into consideration, prevalence of diabetes in those patients taking statin therapy will be 20.5%.

Table 4.2: Frequency distribution of the study sample regarding diabetes mellitus

Characteristic	*n*	%
Family history of diabetes		
Positive	84	38.2
Negative	136	61.8
diabetic Relative		
Father	40	18.2
Mother	20	9.1
Brother or sister	12	5.5
RBS checking		
Last RBS		
Yes	212	96.4
≤110 mg/dl	200	90.9
111-150 mg/dl	0	0
151-200 mg/dl	12	5.5
No	8	3.6
Recent FBS		
≤125 mg/dl	175	79.5
≥126 /dl	45	20.5
Recent RBS		
≤ 140 mg/dl	122	55.5
141-200 mg/dl	57	25.9
> 200 mg/dl	41	18.6

4.3 chronic cardiovascular disorder and family history

Out of 220 patients 163 (74.1%) had hypertension. Patients with ischemic heart disease account for 171 (77.7%), of those 58 (26%) had angina, 105 (47.7%) had myocardial infarction. 125(58.8%) had a family history of chronic medical illnesses, of those 16(7.3%) had a family history of sudden death, 60(27.3%) had a family history of myocardial infarction, 29(13.2%) heart failure and 20 (9.1%) stroke, with 95 (43.2%) had no family history.

Table 4.3: Frequency distribution of the characteristics of chronic cardiovascular disorder

Characteristic	*n*	%
Hypertension		
Yes	163	74.1
No	57	25.9
Ischemic heart disease		
Yes	171	77.7
Angina	58	26.4
Myocardial infarction	105	47.7
Other	8	3.6
No	49	22.3
Family history		
Positive	125	56.8
Sudden death	16	7.3
Myocardial infarction	60	27.3

Heart failure	29	13.2
Stroke	20	9.1
Negative	95	43.2

4.4 Lipid lowering agents

Out of 220 patients, 131 (59.5%) used to check serum lipid profile, whereas, the remaining 89 (40.5%) have been not interested in measuring serum lipid profile for routine follow up. According to the duration of statin use, eight (3.6%) patients were on statin for one month or less, 16 (7.3%) patients used statin for up to 6 months, whereas 196 (89.1%) patients used to take statin for one year or more. According to specific drug used, 195 (88.6%) patients used atorvastatin, 20(9.1%) patients used simvastatin , five (2.3%) patients used rosuvastatin and no patients used fluvastatin. According to the dose of treatment, majority of patients were using 20 milligram daily, those patients accounted for 134 out of 220 (60.9%). Eighty two (37.3%) were using 40 mg daily and only four (1.8%) were using 10 mg daily. Most patients (98.2%) taught to take the drug at night whereas, 1.8% used to take the drug at daytime. One hundred twenty six out 220 (57.3%) developed side effects these side effects where in the form of arthralgia (12.7%), myalgia (42.7%) and hematuria (1.8%), as outlined in table 4.4.

Table 4.4: Distribution of the study sample according to their lipid assessment and statin use

Characteristics	***n***	**%**
Serum lipid assessment		
Yes	131	59.5
No	89	40.5
Duration of statin use		

One month or less	8	3.6
UP to 6 months	16	7.3
One year or more	196	89.1
Drug used		
Atrovastatin	195	88.6
Simvastatin	20	9.1
Rosuvastatin	5	2.3
Fluvastatin	0	0
Dose		
10 mg	4	1.8
20 mg	134	60.9
40 mg	82	37.3
80 mg	0	0.0
Time of statin intake		
Night	216	98.2
Day	4	1.8
Adverse effects		
Present	126	57.3
Arthlagia	28	12.7
Myalgia	94	42.7
Hematuria	4	1.8
No adverse effects	94	42.7

4.5 Follow up investigations

Patients who have performed renal function test, liver function test and regular ECG study represented 20.5 %, 7.7 % and 50 % of entire sample included in the current study, as shown in table 4.5.

Table 4.5: Frequency distribution of sample according to their performance of follow up investigation

Investigation	*n*	%
Renal function test	45	20.5
Liver Function test	17	7.7
ECG	110	50.0
Total	172	78.2
No investigation	48	21.8

4.6 Prevalence rate of diabetes mellitus

Patients on statin fulfilling criteria for diagnosis of diabetes, random blood sugar of > 200 mg/ dl and / or fasting blood sugar of > 125 mg/dl, accounted for 45 out of 220 patients (20.5%), as shown in figure 4.1.

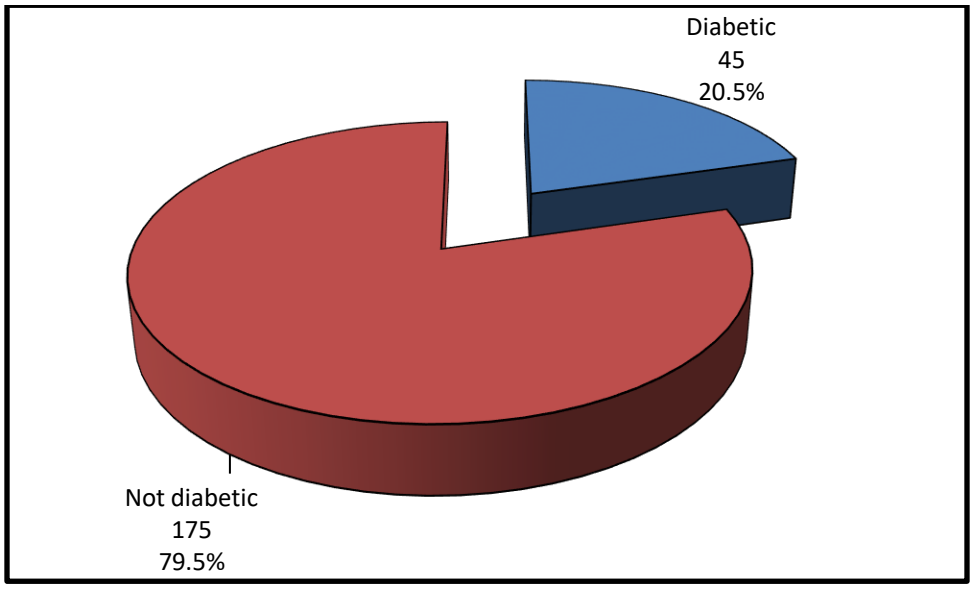


Figure 4.1: Pie-chart showing the rate of diabetic patients among those who used statin treatment

Table 4.6 showed the association between diabetes mellitus and possible risk factors. BMI, duration of statin use and dose of statin showed significant association with diabetes mellitus, whereas, none of other variables had significant effect on prevalence rate of diabetes mellitus.

Table 4-6: Association between diabetes mellitus and characteristics of study sample

Characteristic		Diabetic *n* = 45	Not diabetic *n* =175	Total	*P*	Significance
Residency	Urban	37	134	171	0.416	not significant
	Rural	8	41	49		
Age	<60	11	53	64	0.442	not significant
	≥60	34	122	156		
Gender	Male	31	119	150	0.909	not significant
	Female	14	56	70		
Education	Illiterate	23	88	111	0.606	not significant
	Primary (not finished)	5	15	20		
	Primary	9	43	52		
	Secondary or higher	8	29	37		
Economical status	Low	7	31	38	0.886	not significant
	Intermediate	33	128	161		
	Good	5	16	21		
Smoking	Smoker	24	106	130	0.378	not significant
	Non-smoker	21	69	90		
Ethanol	Alcoholic	7	33	40	0.609	not significant
	Not alcoholic	38	142	180		
BMI	Normal	10	100	110	<0.001	Highly significant
	Over weight	15	66	81		
	Obese	20	9	29		
Family history of DM	Positive	18	66	84	0.778	not significant
	Negative	27	109	136		
Duration of statin	One month or less	0	8	8	0.007	Highly significant
	UP to 6 months	0	16	16		
	One year or more	45	151	196		
Statin drug	Atrovastatin	40	155	195	0.051	not significant
	Simvastatin	4	16	20		
	Rosuvastatin	1	4	5		
Dose	10 mg	0	4	4	<0.001	Significant

20 mg	14	120	134
40 mg	31	51	82

Chapter Five

Discussion

Chapter Five

Discussion

5.1 Overview

Persuasive data from many randomized controlled trials and large, long-term observational studies indicate a modestly increased risk for the emergence of new diabetes after statin initiation [104] . Several meta-analyses of many statin trials as well as longitudinal population-based studies suggest that the risk factors for diabetes in statin-treated persons include underlying risk for diabetes at baseline (specifically features of metabolic syndrome), the intensity of statin therapy, certain genetic traits independent of diabetes risk, and adherence to lifestyle factors [105] . Limited data suggest statins modestly worsen hyperglycemia and A1c levels in those with pre-existing diabetes or glucose intolerance. The precise mechanism(s) of diabetogenesis with statin therapy are unclear, but impaired insulin sensitivity and compromised β cell function via enhanced intracellular cholesterol uptake due to inhibition of intracellular cholesterol synthesis by statins, as well as other mechanisms, may be involved [106] . Furthermore, while statins are known to have anti-inflammatory effects, it is hypothesized that, under dysmetabolic conditions, they might have pro-inflammatory effects via induction of certain inflammasomes. This concept requires further elucidation in the human . Finally, it is clear that the risk–benefit ratio for cardiovascular disease events is strongly in favor of statin therapy in those at risk, despite the emergence of new diabetes. Adherence to lifestyle regimen is critical in the prevention of new diabetes on statins [107] .

5.2 Risk of hyperglycemia and new onset diabetes in patients of statin therapy

The present study showed that patients on statin therapy had significantly high rate of hyperglycemia and new onset diabetes. In addition, this study showed that duration of using statin and the dose had significant positive association with the development of diabetes mellitus in patients who were not originally known to have diabetes mellitus.

A clinically relevant concern with statin therapy is a significantly increased risk of new-onset diabetes in patients on statin therapy. The JUPITER trial reported a 25% increase with rosuvastatin 20 mg, over a median follow-up of 1.9 years, compared to those on placebo (Ridker et al., 2008) [(79)] . Since then, several meta-analyses have confirmed a smaller but significant increase with various statins[(44)] . The analysis by Sattar *et al.* in 91,140 subjects showed a 9% overall risk in 13 RCTs over a mean period of 4.0 years (odds ratio [OR] 1.09; 95% CI 1.02–1.17) (Sattar *et al*., 2010) [(80)] . In a subsequent meta-analysis of five intensive-dose statin trials, Preiss *et al.*reported a significant increase in diabetes incidence with more intensive use. moderate-dose statin (OR 1.12; 95% CI 1.04–1.22) in 32,752 subjects over a mean follow-up of 4.9 years (Preiss *et al*., 2011) [(81)] . In general, there was no relationship between % LDL-C reduction and incident diabetes. Further analysis of baseline characteristics of the various trials reported a strong relationship between features of metabolic syndrome or pre-diabetes (age, body mass index [BMI], hypertension, fasting glucose, and triglycerides) at baseline and subsequent development of diabetes (Waters *et al*., 2011; Ridker *et al*., 2012; Waters *et al*., 2013) [(82-84)] .

Of note, the risk–benefit ratio for CVD still clearly favored statin therapy in various studies, including JUPITER, in primary prevention (Ridker et al., 2012) [(83)] ,and in several secondary prevention studies (Waters *et al*., 2011; Ridker *et al*.,

2012; Waters *et al*., 2013) [82-84] , and a meta-analysis of secondary prevention studies by Preiss *et al.*(2011) [81] . Thus, regardless of whether or not diabetes was diagnosed during statin therapy, the CVD outcomes were reduced on statin therapy compared to those observed with placebo. Another meta-analysis by Navarese *et al.* is the largest so far: it includes 17 RCTs (more than 113,000 patients). It compared new-onset diabetes in patients receiving statin vs. placebo, or high-dose vs. moderate-dose statins (Navarese et al., 2013) [85] . The lowest risk was seen with pravastatin 40 mg compared to placebo (OR 1.07; 95% CI 0.83–1.30), whereas rosuvastatin 20 mg was associated with the highest risk (OR 1.25; 95% CI 0.82–1.90) and atorvastatin 80 mg was intermediate (OR 1.15; 95% CI 0.9–1.50), even though none of these differences achieved statistical significance. Simvastatin also appears to be associated with higher risk compared to pravastatin. These differences among various statins persisted after adjustments for reduction in cholesterol. These findings suggest possible molecule-specific effects on diabetogenesis, although the data thus far are inconclusive. The effects of the newest statin, pitavastatin, are not available in a large enough cohort. In a recent meta-analysis of 15 short-term RCTs of pitavastatin, most of 12 weeks' duration, total follow-up 1600 person-years, there was no significant difference in the risk for diabetes (OR 0.70; 95% CI 0.30–1.61) compared to placebo (Vallejo-Vaz *et al*., 2015) [86]. If confirmed in a larger RCT, it will raise the possibility of differences in pharmacodynamics and drug-drug interactions on diabetogenecity. These analyses revealed considerable variability among studies and with various statins, with HRs ranging from 1.19–1.57 but statistically significant, after follow-up durations of 3–6 years. In the Women's Health study, the women were older than several other populations and generally on moderate-dose therapy, yet the HR was 1.48 (Culver *et al*., 2012) [87]. In the largest study of over 2 million subjects in the UK, there was a significant time-dependent increase in diabetes risk (HR 1.57; 95% CI 1.55–

1.60), which increased further (HR 3.63; 95% CI 2.44–5.38) in those who were followed for up to 15–20 years (Macedo *et al*., 2014) [88]. In one study in patients following myocardial infarction, there was no difference in intensive- vs. moderate-dose statin therapy (Ko *et al*., 2013) [89], although the CVD outcomes were reduced with the more intensive approach. One caveat with all of the observational studies is that, despite multifactorial adjustments, some differences in the cohort characteristics may not be fully accounted for. In particular, it should be noted that the risk for diabetes according to presence of pre-existing diabetes risk factors, as observed in the several analyses of RCTs (Waters *et al*., 2011; Ridker *et al*., 2012; Waters *et al*., 2013) [82-84], was not adequately examined in the various observational studies, a major limitation in those studies, compared to RCTs. There are some observations of interest from a few studies in patients with pre-existing glucose intolerance or diabetes. In the study by Castro *et al.* (2016) [90]. The HR for progression to diabetes was similar in those with normoglycemia, or impaired fasting glucose at baseline, but both groups showed similar reduction in mortality after a 6-year follow-up. In a meta-analysis of nine RCTs in 9696 patients with type 2 diabetes, with a mean follow-up of 3.6 years, there was a modest but significant increase in mean A1c level of 0.12% (95% CI 0.04–0.20) (Erqou *et al*., 2014) [91]. In one cross-sectional study in patients with type 1 diabetes (n=1093), statin use was associated with a similar 0.2% increase in mean A1c after multivariate adjustments (Jensen *et al*., 2016) [92].

5.3 Possible mechanism of diabetes induction following statin therapy

The precise mechanism(s) for statin-induced diabetes remain unclear, although the majority of patients developing diabetes have pre-diabetes or features of metabolic syndrome indicating high risk for diabetes at baseline (Waters *et al*.,

2011; Ridker *et al*., 2012) [82, 83]. It has been controversial whether chemical differences and pharmacodynamic differences in statins or more intensive statin therapy are more likely to precipitate diabetes. In the analysis by Preiss *et al.*, intensive statin therapy led to a greater increase in diabetes (Preiss *et al*., 2011) [81]. This was also confirmed in other meta-analyses by Carter *et al.* (2013) [93] and Dormuth *et al. (2014)* [94]. However, this was not confirmed in a propensity score-matched cohort of patients with myocardial infarction who were prescribed intensive- or moderate-dose statins and followed for 5 years (new diabetes in 13.6 vs. 13.0%) (Ko *et al*., 2013) [89]. The reported lack of new diabetes in pitavastatin-treated subjects is intriguing in view of the relatively small and short-term studies with this newest statin so far (as discussed above) (Vallejo-Vaz *et al*., 2015) [86]. Another intriguing observation is that in the fairly large cohort of the heart outcomes prevention evaluation (HOPE-3) trial (n=12,705), there was no increase in the risk for new diabetes (HR 1.02; 95% CI 0.85–1.23) compared to a 25% increase with rosuvastatin 20 mg in JUPITER (Ridker *et al*., 2008) [83]. Whether this relates to the differences in the intensity of statin therapy, risk factors for diabetes at baseline, or perhaps genetic differences in the multi-ethnic HOPE-3 cohort is worth exploring. Several mechanisms have been postulated underlying the derangements in glucose metabolism by statins. There is some evidence for the detrimental effects of statins on both insulin sensitivity and β cell secretion. In the large metabolic syndrome in male (METSIM) observational study of more than 8000 men, simvastatin and atorvastatin were related to a dose-dependent increase in post-glucose load, an increase in glycemia, a mean decrease in insulin sensitivity by 24%, and a decline in insulin secretion by 12% (Cederberg *et al*., 2015) [95]. Similarly, in a small study in 28 patients with polycystic ovary syndrome (PCOS), treatment with atorvastatin 20 mg compared to placebo over 6 months led to a decrease in insulin sensitivity despite a decrease in the inflammatory marker C-

reactive protein (CRP) (Puurunen *et al*., 2013) [(96)]. A number of potential deleterious effects of statins on β cell function have been proposed, including the effects of increased influx of cholesterol due to inhibition of HMG-CoA-mediated intracellular cholesterol synthesis, inhibition of ubiquinone (CoQ 10) synthesis leading to mitochondrial oxidative stress, and β cell apoptosis (Sampson *et al*., 2011) [(97)]. Statins are generally thought to have anti-inflammatory effects (Ridker *et al*., 2008) [(83)]. However, a recent novel hypothesis posits that under certain conditions, statins may activate inflammasome NLRP3(regulated interleukin 1B) from macrophages or adipocytes in the presence of endotoxins, leading to interleukin-1β-mediated insulin resistance (Henriksbo *et al*., 2014) [(98)]. This hypothesis requires confirmation in human studies, as adipose tissue is not a major glucose-metabolizing tissue. A provocative possibility is that the altered gut microbiome, in the presence of obesity or other dysmetabolic states, might provide the endotoxin lipopolysaccharide (LPS) that may mediate the paradoxical pro-inflammatory effect of statins by activation of inflammasomes (Mitchell and Marette, 2014) [(99)]. However, under physiological circumstances, a moderate decrease in insulin sensitivity should be compensated for by enhanced insulin secretion by β cells. Thus, ultimately, the direct or indirect effects of statins on β cell function may play an important role in diabetogenesis, particularly in those already at increased risk. An exciting new observation is that a genetic polymorphism leading to a reduced activity of HMG-CoA reductase is associated with lower LDL-C, a significant increase in body weight, and features of insulin resistance (Swerdlow *et al*., 2015) [(100)]. This observation was validated in the randomized statin trials, and one particular allele was associated with a significant increase in the risk of new diabetes (OR 1.12; 95% CI 1.06–1.18). Since statins inhibit HMG-CoA reductase as their mode of action, this may at least partly explain their diabetogenic effect. Finally, a mundane and more simplistic

nutritional explanation has been reported by the long-term data in the NHANES study. In a cross-sectional follow-up of more than 27,000 adults followed over 10 years, it was shown that those on statins liberalized their fat and total caloric intake and gained weight over time compared to those not on statins (Sugiyama *et al*., 2014) [(101)]. Thus, the progression to diabetes could be explained by lifestyle-induced worsening in insulin sensitivity. It is possible that this and the other postulated mechanisms could co-exist.

5.4 Worsening already existing impaired glucose tolerance

In the present study, significant association was found between body mass index and rate of diabetes in patients with statin therapy. This may be explained by the possible role of statin in worsening pre-existing glucose intolerance in overweight and obese patients who may have metabolic syndrome that is characterized by resistance to insulin action. As summarized above, there appears to be a significant relationship between statin use and the development of new diabetes over the course of several years. This has resulted in an understandable concern about the need to be more vigilant in the use of statins in primary prevention, particularly in those at low absolute risk of CVD. However, the outcome data, particularly from the RCTs, remind us that the subsequent events are also significantly reduced in those with statin-induced diabetes (Waters *et al*., 2011; Ridker *et al*., 2012; Waters *et al*., 2013) [(82-84)]. Sattar *et al.*calculated, based on their meta-analysis of 13 RCTs, that treatment with statins compared to placebo in 255 subjects over 4 years will cause one new case of diabetes while preventing 5.4 major CVD events (Sattar *et al*., 2010) [(80)]. Similarly, Preiss *et al.* estimated that intensive statin therapy, compared to moderate-dose statins, in those with prior CVD will prevent around three new events per year in ~500 subjects while

resulting in one additional case of diabetes (Preiss et al., 2011) [81]. Finally, Ridker *et al.* reported that in the JUPITER trial, despite a 25% increase in the relative risk for new diabetes with rosuvastatin 20 mg, the major CVD event rate reduction in those who developed diabetes (HR 0.63; 95% CI 0.25–1.60) was consistent with event reductions in the trial as a whole (HR 0.56; 95% CI 0.46–0.69) (Ridker *et al*., 2012) [83]. Moreover, the risk of developing diabetes in that trial was almost entirely confined to those with pre-existing features of metabolic syndrome or pre-diabetes (Ridker *et al*., 2012) [83], with similar data from other trials (Waters *et al*., 2012) [82]. Also, in JUPITER, in those with risk factors for diabetes, 134 vascular events or deaths were avoided for every 54 new cases of new diabetes. Finally, in recent data from a cohort of more than 15,000 propensity-matched subjects who initiated statin therapy and were followed for a median of 2.7 years, there was no increase; in fact, there was a significant decrease in the development of microvascular complications (retinopathy and neuropathy) in those developing diabetes compared to a matched non-diabetic cohort (Nielsen *et al*., 2014) [102]. Thus, it seems quite clear that statin treatment should not be withheld in those at high risk of CVD for the relatively minor concern of progression to diabetes. In fact, the data described above indicate that in the presence of multiple risk factors for diabetes or metabolic syndrome at baseline in the at-risk population, a modest diabetogenic effect of statin therapy may lead to progression from pre-diabetes to diabetes. This should therefore prompt advice for lifestyle intervention, already known to prevent or delay progression to diabetes, and should be implemented prior to statin initiation. Moreover, the observations from the NHANES survey stated above (Sugiyama *et al*., 2014) [101], that those on statin therapy generally increased their caloric intake and fat intake leading to progressive weight gain, i.e. factors known to be predictors of diabetes, further

emphasize the need for lifestyle counseling as the integral component of both diabetes and CVD event reduction.

Conclusions and Recommendations

Conclusions

1. Statin use appears to be associated with diabetes mellitus among the study group.
2. Statin appears to act by convertig already glucose intolerant patients overt diabetes by increasing insulin resistance.
3. Patients on high dose statin are more liable for developing diabetes mellitus.
4. There is no significant difference between the types of statin in the study.

Recommendations

1. Any patient on statin therapy should be followed up by regular checking of FBS and HbA1c for the possibility of developing type 2 diabetes mellitus, especially patients who are overweight or obese.
2. Any dyslipidemic patient who develops diabetes should be advised to follow restricted dietary measures , regular exercise and substitute statin by other class of lipid lowering agents.
3. A larger study with larger sample size is requested.
4. Further analytic study such as (cohort, RCTs and case control study) are requested to identify the causality of statin use in developing diabetes among Iraqi dyslipidemic patients.
5. Assessment of types of inflammatory mediators that may increased by statin therapy and predispose to hyperglycemia.

Limitations

1. The cross sectional study may be prone to non-response bias if participants who consent to take part in the study differ from those who do not, resulting in a sample that is not representative of the population.

2. Because data on each participant are recorded only once it would be difficult to infer the temporal association between a risk factor and an outcome. Therefore, only an association, and not causation, can be inferred from a cross sectional study.

Appendix

The questionnaire form

The name

The form number

Address

Urban

rural

Age

20-39

40-59

≥60

The gender

Male

female

The education

Illiterate

primary

secondary or higher

MARITAL STATUS

Married

not married

divorced

Smoking history

Smokers

per day 20≤

per day 20>

Non-smokers

ALCOHOL DRINKER

Yes

No

BMI

Normal

Over weight

Obese

Exercise

Yes

Daily

More 3 hour / week

Do you have diabetes

Yes

no

Family history of diabetes

Positive

Negative

diabetic Relative

Father

Mother

Brother or sister

Wife or husband

RBS checking

Last RBS

Yes

<110 mg/dl

110-150

151-200

> 200

HT

Yes

No

BP assessment

Daily

3days/week

Weekly

Monthly

IHD

- Yes

Angina

MI

Other

- No

Family history

- Positive

Sudden death

MI

Heart failure

Stroke

- Negative

Serum lipid assessment

Yes

No

Duration of statin use

One month or less

UP to 6 months

One year or more

Drug used

Atrovastatin

Simvastatin

Rosuvastatin

Fluvastatin

Dose

10 mg

20 mg

40 mg

80 mg

Time of statin intake

Night

Day

Adverse effects

Present

Arthlagia

Myalgia

Hematuria

Investigation

Renal function test

YES NO

Liver Function test

YES NO

ECG

YES NO

استمارة استبيان لخطر ارتفاع السكر في الدم لدى المرضى الذين يتناولون علاج الستاتين

❖ اسم المريض الثلاثي : .....

❖ رقم الاستبانة .....

❖ العنوان :

☐ مدينة ☐ ريف

❖ عمر المريض :

☐ (٢٠_٣٩) ☐ (٤٠_٥٩) ☐ ٦٠≤

❖ جنس المريض:

☐ ذكر ☐ انثى

❖ المستوى التعليمي:

☐ غير متعلم ☐ الابتدائية غير مكتملة ☐ ابتدائي ☐ الثانوية أو اعلى

❖ الحالة الزوجية :

☐ متزوج ☐ اعزب ☐ مطلق

❖ **هل أنت مدخن ؟**

☐ نعم ☐ لا

❖ **اذا كانت الاجابة نعم :**

☐ أكثر من ٢٠ سيجارة ☐ أقل من ٢٠ سيجارة

❖ **هل تتناول الكحول؟**

☐ نعم ☐ لا

❖ **ماهو وزنك وطولك الحالي؟ (الوزن / مربع الطول)**

☐ طبيعي (≤٢٤,٩) ☐ وزن زائد عن الطبيعي(٢٥-٢٩,٩)

☐ بدين (≤٣٠)

❖ **هل تمارس الرياضة ؟**

☐ لا امارس ☐ امارس

❖ **اذا كانت الاجابة (نعم) كم ساعة في الاسبوع ؟**

☐ يوميا ☐ <٣ ساعة ☐ ≤٣ ساعة

❖ **هل تعاني من السكر ؟**

☐ نعم ☐ لا

❖ هل يوجد من أفراد أسرتك مصاب بالسكري ؟

☐ نعم ☐ لا

❖ اذا كانت الاجابة نعم :

☐ الوالد ☐ الوالدة ☐ الأخوة أو الأخوات ☐ الزوجة

❖ هل قمت بعمل فحص السكر في الدم سابقا ؟

☐ نعم ☐ لا

❖ اذا كانت الاجابة (_نعم) ماهي القراءة ؟

☐ اقل او يساوي ١١٠ ☐ ١١٠-١٥٠ ☐ ١٥١-٢٠٠ ☐ أكثر من ٢٠٠

❖ هل تعاني من اعراض عينية؟

☐ نعم ☐ لا

☐ رؤية غير واضحة ☐ كثرة التبول

☐ الشعور بنعاس عام ☐ صداع

☐ لا اعاني من هذه الاعراض

❖ ما هو رقم سكر الدم عند الصيام المقاس حاليا ؟

☐ اقل من ١٢٥ ☐ اكثر او يساوي ١٢٦

❖ ما هو رقم سكر الدم العشوائي المقاس حاليا ؟

☐ اقل او يساوي ١٤٠ ☐ ١٤١-٢٠٠ ☐ اكثر او يساوي ٢٠٠

❖ هل لديك أمراض أخرى مرافقة ؟

☐ بدانة ☐ ارتفاع ضغط ☐ ارتفاع شحوم

❖ هل تعاني من ارتفاع ضغط الدم المزمن؟

☐ نعم ☐ لا

❖ اذا كان الجواب (نعم) هل تقوم بقياس ضغط الدم ؟

☐ يومياً ☐ أربعة أيام بالأسبوع ☐ مرة بالأسبوع ☐ شهريا

❖ هل قمت سابقا بفحص نسبة الدهون في الدم ؟

☐ نعم ☐ لا

❖ هل تعاني من امراض نقص تروية القلب؟

☐ نعم ☐ لا

❖ اذا كانت الاجابة (نعم) ماهي الامراض القلب التي تعاني منها ؟

☐ الذبحة الصدرية ☐ احتشاء عضلة القلب ☐ غيرها

❖ هل لديك تاريخ وراثي للحالات التالية ؟

☐ موت مفاجئ ☐ احتشاء عضله القلب

☐ عجز في القلب ☐ الجلطة الدماغية

☐ لا يوجد تاريخ وراثي

❖ هل تستخدم علاج الدهون (statin)؟

☐ نعم ☐ لا

❖ اذا كانت الاجابة (نعم) كم هي المده لاستخدامك علاج ارتفاع الدهون؟

☐ شهر واحد فقط ☐ ثلاثه اشهر ☐ سنة او اكثر

❖ ماهو نوع علاج ارتفاع الدهون (statin) الذي تستعمله؟"

☐Atorvastatin ☐Rosuvastatin

☐Simvastatin ☐Fluvastatin

❖ ماهي جرعة علاج ارتفاع الدهون (statin) الذي تستعمله؟

☐ ١٠ ملغم ☐ ٢٠ ملغم ☐ ٤٠ملغم ☐ ٨٠ ملغم

❖ ماهو وقت استخدام العلاج ؟

☐ ليلا ☐ نهارا

❖ ماهي الاثار الجانبيه او الاعراض التي ظهرت عليك بعد استخدام علاج ارتفاع الدهون (statin) ؟

☐ الم بالمفاصل ☐ الم بالعضلات ☐ دم في الادرار ☐ اسهال

☐ لا توجد اي مما ذكر

❖ هل قمت باجراء تحاليل وظائف الكلى ؟

☐ نعم ☐ لا

❖ هل قمت باجراء تحاليل وظائف الكبد ؟

☐ نعم ☐ لا

❖ هل قمت باجراء تخطيط القلب ؟

☐ نعم ☐ لا

References

References

1 American Diabetes Association (ADA). Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 2010; 33(1):S62-S69.

2 Kharroubi AT and Darwish HM. Diabetes mellitus: The epidemic of the century. *World Journal of Diabetes*. 2015; 6(6):850-867.

3 Thomas CC and Philipson LH. Update on diabetes classification. *Med Clin N Am*. 2015; 99:1-16.

4 Atkinson MA. The Pathogenesis and Natural History of Type 1 Diabetes. *Cold Spring Harbor Perspectives in Medicine*. 2012; 2(11):a007641.

5 Paschou SA, Papadopoulou-Marketou NA, Chrousos GP, *et al*. On type 1 diabetes mellitus pathogenesis. *Endocrine Connections*. 2018;7(1):R38-R46.

6 Kopan C, Tucker T, Alexander M, et al. Approaches in Immunotherapy, Regenerative Medicine, and Bioengineering for Type 1 Diabetes. *Frontiers in Immunology*. 2018; 9:1354.

7 Olokoba AB, Obateru OA, Olokoba LB. Type 2 Diabetes Mellitus: A Review of Current Trends. *Oman Medical Journal*. 2012; 27(4):269-273.

8 Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present and future. *Lancet*. 2014; 383 (9922):1068-1083.

9 Tumbo JM and Kadima FN. Screening of long-term complications and glycaemic control of patients with diabetes attending Rustenburg Provincial Hospital in North West Province, South Africa. *African Journal of Primary Health Care & Family Medicine*. 2013; 5(1):375.

10 Lotfy M, Adeghate J, Kalasz H, *et al*. Chronic complications of diabetes mellitus: a mini review. *Curr Diabetes Rev*. 2017;13: 3–10.

11 Chait A and Bornfeldt KE. Diabetes and atherosclerosis: is there a role for hyperglycemia?. *Journal of Lipid Research*. 2009; 50 (l):S335-S339.

12 Kanter JE and Bornfeldt KE. Inflammation and Diabetes-Accelerated Atherosclerosis: Myeloid Cell Mediators. *Trends in endocrinology and metabolism: TEM*. 2013; 24 (3):137-144.

13 Kanter JE, Averill MM, LeBoeuf RC, *et al.* Diabetes-Accelerated Atherosclerosis and Inflammation. *Circulation research*. 2008; 103(8):e116-e117.

14 Rahal AJ, ElMallah AI, Poushuju RJ, et al. Do statins really cause diabetes?: A meta-analysis of major randomized controlled clinical trials. *Saudi Medical Journal*. 2016; 37(10):1051-1060.

15 Ganda OP. Statin-induced diabetes: incidence, mechanisms, and implications. *F1000Research*. 2016;5:14-21.

16 Yoon D, Sheen SS, Lee S, *et al.* Statins and risk for new-onset diabetes mellitus: A real-world cohort study using a clinical research database. Zhou. W, ed. *Medicine*. 2016; 95(46):e5429.

17 Chogtu B, Magazine R, Bairy K. Statin use and risk of diabetes mellitus. *World Journal of Diabetes*. 2015; 6(2):352-357.

18 Klop B, Elte JW, Castro Cabezas M. Dyslipidemia in Obesity: Mechanisms and Potential Targets. *Nutrients*. 2013; 5(4):1218-1240.

19 Peng J, Luo F, Ruan G, *et al.* Hypertriglyceridemia and atherosclerosis. *Lipids in Health and Disease*. 2017;16:233.

20 López-Soldado I, Avella M, Botham KM. Differential influence of different dietary fatty acids on very low-density lipoprotein secretion when delivered to hepatocytes in chylomicron remnants. *Metabolism*. 2009; 58(2):186-195.

21 Anand SS, Hawkes C, de Souza RJ, *et al*. Food Consumption and its impact on Cardiovascular Disease: Importance of Solutions focused on the globalized food system: A Report from the Workshop convened by the World Heart Federation. *Journal of the American College of Cardiology*. 2015; 66(14):1590-1614.

22 Lund-Katz S and Phillips MC. High Density Lipoprotein Structure–Function and Role in Reverse Cholesterol Transport. *Sub-cellular biochemistry*. 2010; 51:183-227.

.**23 Chait A and Brunzell JD.** Acquired hyperlipidemia secondary dyslipoproteinemias. *Endocrinol. Metab. Clin. North Am*. 1990; 19 (2): 259–78.

24 Grossman DC, Moyer VA, Melnyk BM; U.S. Preventive Services Task Force. The anatomy of a US Preventive Services Task Force Recommendation:

lipid screening for children and adolescents. *Arch Pediatr Adolesc Med*. 2011; 165(3):205-10.

25 **Paul M. Paulman, Audrey A.Paulman.** ***et al*** Taylors manual of family medicine, chapter17 , 17-4 *4th edition copyright 2015*

26 Nordmann A.J., Nordmann A., Briel M. ***et al.*** Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: A meta-analysis of randomized controlled trials. *Arch. Intern. Med*. 2006; 166:285–293.

27 Golomb BA and Evans MA. Statin Adverse Effects: A Review of the Literature and Evidence for a Mitochondrial Mechanism. *American journal of cardiovascular drugs : drugs, devices, and other interventions*. 2008; 8(6):373-418.

28 Bitzur R, Cohen H, Kamari Y, ***et al.*** Triglycerides and HDL Cholesterol: Stars or second leads in diabetes? *Diabetes Care*. 2009;32(2):S373-S377.

29 Basu S, Sussman JB, Hayward RA. Black-White Cardiovascular Disease Disparities After Target-Based Versus Personalized Benefit–Based Lipid and Blood Pressure Treatment. *MDM Policy and Practice*. 2017; 2(2):2381468317725741.

30 Sirtori CR. The pharmacology of statins. *Pharmacol Res*. 2014;88:3–11

31 Laufs U, Custodis F, Böhm M. HMG-CoA reductase inhibitors in chronic heart failure: potential mechanisms of benefit and risk. *Drugs*. 2006; 66(2):145–154.

32 Naci H, Brugts J, Ades T. Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials. *Circ Cardiovasc Qual Outcomes*. 2013; 6 (4): 390–9

33 Liu J, Zhang J, Shi Y, Grimsgaard S. Chinese red yeast rice (*Monascus purpureus*) for primary hyperlipidemia: a meta-analysis of randomized controlled trials. *Chinese Medicine*. 2006; 1:4-12.

34 McKenney JM, Jones PH, Adamczyk MA. Comparation of the efficacy of rosuvastatin versus atorvastatin, simvastatin, and pravastatinin in achieving lipid goals: results from STELLAR trial. *Curr Med Res Opin*. 2003;19: 689–698.

35 Toda T, Eliasson E, Ask B. Roles of different CYP enzymes in the formation of specific fluvastatin metabolites by human liver microsomes. *Basic Clin Pharmacol Toxicol*. 2009; 105(5):327-32.

36 Vaughan CJ, and Gotto, AM. Update on statins. *Circulation*. 2004; 110: 886–892.

37 **Elsevier/Saunders** Williams textbook of endocrinology (12th ed.).. pp. 1371–1435. ISBN 978-1-4377-0324-5.

38 Cooke DW, Plotnick L. Type 1 diabetes mellitus in pediatrics. *Pediatrics in Review*. 2008; 29 (11): 374–84

39 American Diabetes Association. Standards of medical care in diabetes—2015. *Diabetes Care*. 2015; 38 (l):S1-S89.

40 Baigent C, Keech A, Kearney PM. Cholesterol Treatment Trialists C Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet,* 2005; 366: 1267-1278

41 Tajima N, Kurata H, Nakaya N, *et al.* Pravastatin reduces the risk for cardiovascular disease in Japanese hypercholesterolemic patients with impaired fasting glucose or diabetes: diabetes subanalysis of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study. Atherosclerosis. 2008;199:455-462.

42 American Diabetes Association. Position statement: dyslipidemia management in adults with diabetes. 2004; *Diabetes Care*; 27(1):S68–S71

43 Mills E, Wu P, Chong G, *et al.* Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170 255 patients from 76 randomized trials. *Q J Med*. 2011;104:109–124.

44 Sattar N., Preiss D., Murray H.M., et al. Statins and risk of incident diabetes: A collaborative meta-analysis of randomised statin trials. *Lancet*. 2010;375:735–742.

45 Waters DD. Diabetes - Symptoms and causes Learn more about the different types of this blood sugar disorder, who's at risk and how each can be treated. *J Am Coll Cardiol*. 2011; 57: 1535–45

46 Rajpathak SN, Kumbhani DJ, Crandall J, *et al.* Statin therapy and risk of developing type 2 diabetes: a meta-analysis. *Diabetes Care*. 2009;32(10):1924-1929.

47 Culver AL, Ockene IS, Balasubramanian R, et al. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. *Arch Intern Med*. 2012; 172(2):144-152.

48 Carter AA, Gomes T, Camacho X, *et al.* Risk of incident diabetes among patients treated with statins: population based study. *BMJ*. 2013; 346:f2610.

49 Ridker PM, Danielson E, Fonseca FA, *et al.* Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008; 359:2195–2207.

50 Shepherd J, Blauw GJ, Murphy MB, et al; PROSPER Study Group. Pravastatin in elderly individuals at risk of vascular disease: a randomised controlled trial. *Lancet* 2002; 360:1623–1630.

51 Preiss D, Seshasai SR, Welsh P, *et al.* Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA*. 2011; 305:2556–2564.

52 Collins R, Armitage J, Parish S. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; 361:2005–2016.

53 Sabatine MS, Wiviott SD, Morrow DA, *et al.* High-dose atorvastatin asssociated with worse glycemic control: A PROVE-IT TIMI 22 substudy (Abstract). *Circulation* 2004;110:S834.

54 Nakata M, Nagasaka S, Kusaka I, *et al.* Effects of statins on the adipocyte maturation and expression of glucose transporter 4 (SLC2A4): implications in glycaemic control. *Diabetologia* 2006; 49:1881–1892

55 Ishikawa M, Namiki A, Kubota T, *et al.* Effect of pravastatin and atorvastatin on glucose metabolism in nondiabetic patients with hypercholesterolemia. *Intern Med*. 2006; 45:51–55.

56 Thakker D , Nair SR , Shukla H , *et al*. Statin use and risk of developing diabetes in cardiovascular disease: systematic literature review and meta-analysis. *Value Health*. 2014;17:A478.

57 Sever PS, Dahlöf B, Poulter NR, *et al.* Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003;361:1149–58.

58 Diabetes Atorvastin Lipid Intervention (DALI) Study Group. The effect of aggressive versus standard lipid lowering by atorvastatin on diabetic dyslipidemia: the DALI study: a double-blind, randomized, placebo-controlled trial in patients with type 2 diabetes and diabetic dyslipidemia. *Diabetes Care*. 2001; 24:1335–1341.

59 Sato H, Carvalho G, Sato T, *et al.* Statin intake is associated with decreased insulin sensitivity during cardiac surgery. *Diabetes Care*. 2012;35:2095–2099.

60 Koh KK, Quon MJ, Han SH, *et al.* Atorvastatin causes insulin resistance and increases ambient glycemia in hypercholesterolemic patients. *J Am Coll Cardiol* 2010; 55:1209–1216.

61 Kanda M, Satoh K, Ichihara K. Effects of atorvastatin and pravastatin on glucose tolerance in diabetic rats mildly induced by streptozotocin. *Biol Pharm Bull*. 2003; 26:1681–1684

62 Nakata M, Nagasaka S, Kusaka I, *et al.* Nakata M, Nagasaka S, Kusaka I, Matsuoka H, Ishibashi S, Yada T. Effects of statins on the adipocyte maturation and expression of glucose transporter 4 (SLC2A4): implications in glycaemic control. Diabetologia. 2006; 49(8):1881–1892.

63 Ishikawa M, Namiki A, Kubota T, *et al.* Effect of pravastatin and atorvastatin on glucose metabolism in nondiabetic patients with hypercholesterolemia. *Intern Med*. 2006; 45:51–5.

64 Yada T, Nakata M, Shiraishi T, *et al.* Inhibition by simvastatin, but not pravastatin, of glucose-induced cytosolic Ca2+ signalling and insulin secretion due to blockade of L-type Ca2+ channels in rat islet beta-cells. *Br J Pharmacol*. 1999; 126:1205–1213.

65 Puurunen J, Piltonen T, Puukka K, *et al.* Statin therapy worsens insulin sensitivity in women with polycystic ovary syndrome (PCOS): a prospective, randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab*. 2013; 98(12):4798–807.

66 Sampson UK, Linton MF, Fazio S. Are statins diabetogenic? *Curr Opin Cardiol*. 2011; 26(4):342–7.

67 Henriksbo BD, Lau TC, Cavallari JF, *et al.* Fluvastatin causes NLRP3 inflammasome-mediated adipose insulin resistance. *Diabetes*. 2014;63(11):3742–7.

68 Mitchell P and Marette A. Statin-induced insulin resistance through inflammasome activation: sailing between Scylla and Charybdis. *Diabetes*. 2014; 63(11):3569–71.

69 Sugiyama T, Tsugawa Y, Tseng CH, *et al.* Different time trends of caloric and fat intake between statin users and nonusers among US adults: gluttony in the time of statins? *JAMA Intern Med*. 2014; 174(7):1038–45.

70 Swerdlow DI, Preiss D, Kuchenbaecker KB, *et al.* HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials. *Lancet.* 2015; 385(9965):351–61.

71 Goldfine AB. Statins: is it really time to reassess benefits and risks? New *Engl J Med*. 2012; 366:1752-5.

72 Mihaylova B, Emberson J, Blackwell L, *et al.* The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012; 380:581–590.

73 Macedo AF, Douglas I, Smeeth L, *et al.* Statins and the risk of type 2 diabetes mellitus: cohort study using the UK clinical practice research datalink. *BMC Cardiovasc Disord*. 2014; 14:85.

74 Seshasai SR, Kaptoge S, Thompson A, *et al.* Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med*. 2011; 364:829–841.

75 Belalcazar LM, Raghavan VA, Ballantyne CM. Statin-induced diabetes: will it change clinical practice? *Diabetes Car*e. 2009; 32:1941–1943.

76 Belalcazar LM, Raghavan VA, Ballantyne CM. Statin-induced diabetes: will it change clinical practice? *Diabetes Care*. 2009; 32:1941–1943.

77 Axsom K, Berger JS, Schwartzbard AZ. Statins and diabetes: the good, the bad, and the unknown. *Curr Atheroscler Rep*. 2013; 15:299.

78 Sukhija R, Prayaga S, Maashdeh M, *et al*. Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients. *J Investig Med*. 2009;57:495–499.

79 Ridker PM, Danielson E, Fonseca FA, *et al*. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* 2008; 359(21):2195–207.

80 Sattar N, Preiss D, Murray HM, *et al*. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet.* 2010; 375(9716):735–42.

81 Preiss D, Seshasai SR, Welsh P, *et al*. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA.* 2011; 305(24):2556–64.

82 Waters DD, Ho JE, DeMicco DA, *et al*. Predictors of new-onset diabetes in patients treated with atorvastatin: results from 3 large randomized clinical trials. *J Am Coll Cardiol.* 2011; 57(14):1535–45.

83 Ridker PM, Pradhan A, MacFadyen JG, *et al*. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet.* 2012; 380(9841):565–71.

84 Waters DD, Ho JE, Boekholdt SM, *et al*. Cardiovascular event reduction versus new-onset diabetes during atorvastatin therapy: effect of baseline risk factors for diabetes. *J Am Coll Cardiol.* 2013; 61(2):148–52.

85 Navarese EP, Buffon A, Andreotti F, *et al*. Meta-analysis of impact of different types and doses of statins on new-onset diabetes mellitus. *Am J Cardiol.* 2013; 111(8):1123–30.

86 Vallejo-Vaz AJ, Kondapally Seshasai SR, Kurogi K, *et al*. Effect of pitavastatin on glucose, HbA1c and incident diabetes: A meta-analysis of randomized controlled clinical trials in individuals without diabetes. *Atherosclerosis.* 2015; 241(2):409–18.

87 Culver AL, Ockene IS, Balasubramanian R, *et al*. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. *Arch Intern Med.* 2012; 172(2):144–52.

88 Macedo AF, Douglas I, Smeeth L, *et al.* Statins and the risk of type 2 diabetes mellitus: cohort study using the UK clinical practice pesearch datalink. *BMC Cardiovasc Disord.* 2014; 14:85.

89 Ko DT, Wijeysundera HC, Jackevicius CA, *et al.* Diabetes mellitus and cardiovascular events in older patients with myocardial infarction prescribed intensive-dose and moderate-dose statins. *Circ Cardiovasc Qual Outcomes.* 2013; 6(3):315–22.

90 Castro MR, Simon G, Cha SS, *et al.* Statin Use, Diabetes Incidence and Overall Mortality in Normoglycemic and Impaired Fasting Glucose Patients. *J Gen Intern Med.* 2016; 31(5):502–8.

91 Erqou S, Lee CC, Adler AI. Statins and glycaemic control in individuals with diabetes: a systematic review and meta-analysis. *Diabetologia.* 2014; 57(12):2444–52.

92 Jensen MT, Andersen HU, Rossing P, *et al.* Statins are independently associated with increased HbA1c in type 1 diabetes--The Thousand & 1 Study. *Diabetes Res Clin Pract.* 2016; 111:51–7.

93 Carter AA, Gomes T, Camacho X, *et al.* Risk of incident diabetes among patients treated with statins: population based study. *BMJ.* 2013; 346:f2610.

94 Dormuth CR, Filion KB, Paterson JM, *et al.* Higher potency statins and the risk of new diabetes: multicentre, observational study of administrative databases. *BMJ.* 2014; 348:g3244.

95 Cederberg H, Stančáková A, Yaluri N, *et al.* Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6 year follow-up study of the METSIM cohort. *Diabetologia.* 2015; 58(5):1109–17.

96 Puurunen J, Piltonen T, Puukka K, *et al.* Statin therapy worsens insulin sensitivity in women with polycystic ovary syndrome (PCOS): a prospective, randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab.* 2013; 98(12):4798–807.

97 Sampson UK, Linton MF, Fazio S. Are statins diabetogenic? *Curr Opin Cardiol.* 2011; 26(4):342–7.

98 Henriksbo BD, Lau TC, Cavallari JF, *et al.* Fluvastatin causes NLRP3 inflammasome-mediated adipose insulin resistance. *Diabetes*. 2014; 63(11):3742–7.

99 Mitchell P and Marette A. Statin-induced insulin resistance through inflammasome activation: sailing between Scylla and Charybdis. *Diabetes*. 2014; 63(11):3569–71.

100 Swerdlow DI, Preiss D, Kuchenbaecker KB, *et al.* HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials. *Lancet.*2015; 385(9965):351–61.

101 Sugiyama T, Tsugawa Y, Tseng CH, *et al.* Different time trends of caloric and fat intake between statin users and nonusers among US adults: gluttony in the time of statins? *JAMA Intern Med.*2014; 174(7):1038–45.

102 Nielsen SF and Nordestgaard BG. Statin use before diabetes diagnosis and risk of microvascular disease: a nationwide nested matched study. *Lancet Diabetes Endocrinol.* 2014; 2(11):894–900.

103 Solis-Herrera C, Triplitt C, Reasner C, *et al.* Classification of Diabetes Mellitus. [Updated 2018 Feb 24]. In: De Groot LJ, Chrousos G, Dungan K, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279119/

104 Aiman U, Najmi A, Khan RA. Statin induced diabetes and its clinical implications. *Journal of Pharmacology & Pharmacotherapeutics*. 2014;5(3):181-185.

105 Thakker D, Nair S, Pagada A, *et al.* Statin use and the risk of developing diabetes: a network meta-analysis. Pharmacoepidemiol Drug Saf 2016;25:1131-49.

106 Ganda OP. Statin-induced diabetes: incidence, mechanisms, and implications. *F1000Research*. 2016;5:F1000 Faculty Rev-1499.

107 Yoon D, Sheen SS, Lee S, *et al.* Statins and risk for new-onset diabetes mellitus: A real-world cohort study using a clinical research database. Zhou. W, ed. *Medicine*. 2016;95(46):e5429.

108 Baigent C,Keech A,Kearney PM, *et al*. ,cholesterol treatment trilists,(CTT)

Collaborators. Efficacy and Safety of cholesterol lowering treatment : prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statin. Lancent 2005

الخلاصه

خلفية

عسر شحميات الدم هو عامل خطر رئيس يساهم في التسبب بتصلب الشرايين والمضاعفات المرتبطة القلب والأوعية الدموية والسكتات الدماغية. أدى التحكم في عسر شحميات الدم إلى انخفاض كبير في معدلات المراضة والوفيات المرتبطة بأحداث نقص تروية القلب ، وبالتالي أصبح استخدام الستاتين كطريقة أولية في السيطرة على عسر شحميات الدم اتجاهًا معتادا في ممارسة الطب. وبسبب ندرة المقالات العراقية المنشورة التي تصف العلاقة بين الارتفاع في سكر الدم وحتى مرض السكري الصريح ، فقد صُممت الدراسة الحالية للتحقيق في العلاقة بين الاستخدام المزمن للعلاج بالاستاتين وتطور ارتفاع السكر في الدم أو مرض السكري في مجموعة من المرضى العراقيين الذين يتناولون أدوية الستاتين لغرض السيطرة على عسر شحميات الدم .

الهدف من الدراسة

لدراسة العلاقة بين استخدام الستاتين ، من حيث استخدام دواء ستاتين معين ,مدة العلاج وجرعة العلاج ، والاصابه بارتفاع السكر في الدم أو السكري صريح في مجموعة من المرضى العراقيين الذين يتناولون عقاقير الستاتين المختلفة.

المرضى وطرق العمل

صُممت الدراسة لتكون دراسة مقطعية مستعرضة تضم مجموعة من 220 مريضاً عراقياً على علاج الستاتين للسيطرة على عسر شحميات الدم . تم اختيار المرضى بطريقة عشوائية من مجموع المرضى الذين يزورون المستشفى ومراكز الرعاية الصحية الأولية. تم استبعاد أي مريض تم تشخيصه بالفعل من قبل أخصائي لمرض السكري قبل البدء في علاج الستاتين من هذه الدراسة. أجريت الدراسة في مستشفى الديوانية التعليمي ومراكز الصحة الأولية للصحة. تأريخ بداية جمع البيانات في 20 أذار 2018 وانتهت في 10 حزيران 2018. وكان ما مجموعه 83 يوما طول الفترة المطلوبة لجمع البيانات من المرضى المعنيين.

النتائج

المرضى الذين يتناولون دواء الستاتين والذين أصيبو بداء السكري، يمثلون 45 من أصل 220 مريضا بنسبة(20.5 ٪). أظهر مؤشر كتلة الجسم ، ومدة استخدام الستاتين وجرعة دواء الستاتين ارتباطًا كبيرًا مع داء السكري ، في حين لم يكن لأي متغير آخر تأثيرًا كبيرًا على معدل انتشار داء السكري.

استنتاج

يعتبر علاج الستاتين مسؤولاً جزئياً على الأقل عن الاصابة بأرتفاع السكر أو مرض السكري الصريح لدى المرضى من خلال هذه الدراسة.

اقرار المشرف

اني الاستاذ المساعد الدكتور حسن راجي جلاب المشرف على رسالة طالبة الدبلوم العالي (المعادل للماجستير) نور خالد محمد , قد أطلعت على رسالة الطالبة المذكورة والتي انجزت تحت اشرافي , اقر واؤيد صلاحيتها للمناقشة لاستيفائها كافة المتطلبات العلمية لدرجة الدبلوم العالي .

التوقيع:

المشرف : الاستاذ المساعد الدكتور حسن راجي جلاب .

مصادقة

اني رئيس فرع طب الاسرة والمجتمع في كلية الطب / جامعة القادسية , اصادق على اقرار المشرف على رسالة طالبة الدبلوم العالي (المعادل للماجستير) نور خالد محمد , واعتبر الرسالة صالحه للمناقشة من قبل اللجنة الممتحنة لهذا الغرض .

التوقيع:

م.د. علي عبد الحسين موسى

رئيس فرع طب الاسرة والمجتمع

جمهورية العراق
وزارة التعليم العالي والبحث العلمي
جامعة القادسية
كلية الطب
فرع طب الأسرة والمجتمع

ارتفاع نسبة السكر في الدم لدى المرضى الذين يتناولون علاج الستاتين

رسالة مقدمة الى

مجلس كلية الطب / جامعة القادسية

وهي جزء من متطلبات نيل شهادة الدبلوم العالي المعادل للماجستير في طب الاسرة

مقدمة من قبل

نور خالد محمد

بكالوريوس طب وجراحه عامة

باشراف

الاستاذ المساعد

الدكتور حسن راجي جلاب

اختصاصي طب الاسرة

2018 A.D. 1440 A.H.