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Title:

EVIDENCE OF HYPERGLYCEMIA IN PATIENTS USING STATIN THERAPY

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ABSTRACT

Objectives: Dyslipidemia is a major risk factor involved in the pathogenesis of atherosclerosis and associated cardiovascular complications and strokes. the use of statin as a primary mode in controlling dyslipidemia became and consequent cardiovascular ischemic events a usual trend in the practice of medicine. Thus, the aim of present Study is to study the association between statin use, in terms of the specific drug used the 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 the hospital and the primary health care center. 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. The beginning of data collection was dated the 20th March 2018 and ended on the 10th June 2018. A total of 83 days was the length of the period required to collect data from involved patients. Recent measurements of fasting and random blood sugar were obtained for all patients.

Results: Patients on statin fulfilling criteria for the 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%). BMI, duration of statin use and a dose of statin showed a significant association with diabetes mellitus, whereas, none of the other variables had a significant effect on the prevalence rate of diabetes mellitus.

Conclusion: Statin therapy is responsible for at least in part for the development of new-onset type 2 diabetes mellitus or worsening already existing resistance to insulin action.

Key Words: Statin, hyperglycemia

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 a 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. In a small proportion of patients with type 1 diabetes, the destruction of beta cells is of unknown etiology and hence considered idiopathic [4-6]. 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 [7,8]. The long-term complications of diabetes mellitus that are related to microvascular 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 glucose intolerance and frank diabetes 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 literature dealing with this subject justified the conductance of the current study.

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 the hospital and the primary health care center. 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 and Al-Forat primary health center. The beginning of data collection was dated the 20th March 2018 and ended on the 10th June 2018. A total of 83 days was the length of the period required to collect data from involved patients. The questionnaire form was based on the following:

- Sociodemographic characteristics of patients: Age, gender, residency, level of education, marital status, economic status, smoking, alcohol intake and body mass index (BMI).
- Information regarding statin therapy such as duration of intake, dose, specific drug and time intake of the 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.

Recent measurements of fasting and random blood sugar were obtained for all patients.

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. The prevalence rate of diabetes mellitus was expressed as a 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. Comparison of mean values between the three groups was done using one-way analysis of variance (ANOVA). The level of significance was considered at $P \leq 0.05$.

RESULTS

Sociodemographic Characteristics Of The Study Sample

Characteristics of patients enrolled in the present study are shown in table 1. Data relating to diabetes mellitus are shown in table 2. The family history of diabetes was seen in 84 (38.2%) of patients. Relative who had diabetes was father, mother, sister or brother and wife in 40 (18.2%), 20 (9.1%), 12 (5.5%) and 12 (5.5%) patients respectively. Out of 220 patients, 212 (96.4%) admitted to checking blood glucose level and accordingly the results were as follows: 200 (90.9%) had blood sugar level of 110-130 mg/dl and 12 (5.5%) had blood sugar level of 161-200 mg/dl. A 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). Hence, if FBS measurements were taken into consideration, the prevalence of diabetes in those patients taking statin therapy will be 20.5%. 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 a statin for one month or less, 16 (7.3%) patients used statin for up to 3 months, whereas 196 (89.1%) patients used to take a statin for one year or more. According to a specific drug used, 195 (88.6%) patients used atorvastatin, 20 patients used simvastatin, five (2.3%) patients used rosuvastatin and no patience used fluvastatin. According to the dose of treatment, the majority of patients were given 20 milligrams daily, those patients accounted for 134 out of 220 (60.9%). Eighty-two (37.3%) were given 40 mg daily and only four (1.8%) were given 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 of 220 (57.3%) developed side effects these side effects were in the form of arthralgia (12.7%), myalgia (42.7%) and hematuria (1.8%). The majority of patients (72.3%) used to eat lipid Rich diet, 10.9 % of patients used to eat a diet with intermediate lipid content, 12.7% of patients have considered intake of lipid-poor diet and 4.1% of patients have suffered from poor appetite, as outlined in table 3. Patients on statin fulfilling criteria for the 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%). Table 4 showed the association between diabetes mellitus and possible risk factors. BMI, duration of statin use and a dose of statin showed a significant association with diabetes mellitus, whereas, none of the other variables had a significant effect on the prevalence rate of diabetes mellitus.

Table 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	149	67.7
Female	69	31.4
Education		
Illiterate	111	50.5
Primary (not finished)	20	9.1
Primary	52	23.6
Secondary or higher	37	16.8
Marital status		
Married	220	100.0
Nor married	0	0.0
Economical status		
Low	38	17.3
Intermediate	161	73.2
Good	21	9.5
Smoking		
Smokers	130	59.1
≥20 per day	122	55.5
<20 per day	8	3.6
Non-smokers	90	40.9
Ethanol		
Yes	40	18.2
No	180	81.8
BMI		
Normal	110	50
Overweight	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 3 hour/week	15	6.8
No	204	92.7

Table 2: Data regarding diabetes mellitus

Characteristic	*n*	%
The 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
Wife or husband	12	5.5
RBS checking		
Last RBS		
Yes	212	96.4
110-130 mg/dl	200	90.9
131-160 mg/dl	0	0
161-200 mg/dl	12	5.5
No	8	3.6
Recent FBS		
<125 mg/dl	175	79.5
≥126 /dl	45	20.5
Recent RBS		
≤ 160 mg/dl	122	55.5
161-200 mg/dl	57	25.9
> 200 mg/dl	41	18.6

Table 3: Data concerning 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 3 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
	94	42.7
Diet		
Lipid-rich	159	72.3
Lipid intermediate	24	10.9
Lipid-poor	28	12.7
Loss of appetite	9	4.1

Table 4: Association between diabetes mellitus and characteristics of the 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
	Overweight	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 3 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		

DISCUSSION

The present study demonstrated that patients on statin therapy had a significantly higher rate of hyperglycemia and new-onset diabetes than the prevalence rate of diabetes in the general adult population. In addition, this study showed that duration of using statin and the dose had a significant positive correlation with the development of diabetes mellitus in patients who were not originally known to have diabetes mellitus [18]. Since several meta-analyses have long-established a lesser but important increase with several statins. The analysis by Sattar *et al.* in 91,140 topics displayed 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) [19]. In a consequent meta-analysis of five severe-dose statin trials, Preiss *et al.* stated a important increase in diabetes incidence with more intensive- vs. 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 [20]. generally, there was no correlation between % LDL-C reduction and incident diabetes. Further analysis of baseline features of the numerous trials stated a solid correlation between features of metabolic syndrome or pre-diabetes at baseline and subsequent development of diabetes [21-23].

Notable, the risk–advantage ratio for CVD quiet obviously preferred statin treatment in various revisions, including JUPITER, in primary prevention [22], and many secondary prevention studies [21-23]. Thus, nevertheless of whether or not diabetes was diagnosed during statin therapy, the CVD consequences were decreased on statin therapy matched to those observed with placebo. Another meta-analysis by Navarese *et al.* is the largest so far: it includes 17 RCTs, compared new-onset diabetes in patients getting statin vs. placebo, or high-dose vs. judicious-dose statins [24,25]. The lowermost risk was seen with pravastatin 40 mg compared to placebo (OR 1.07; 95% CI 0.83–1.30), whereas rosuvastatin 20 mg have the highest risk (OR 1.25; 95% CI 0.82–1.90) and atorvastatin 80 mg have intermediate (OR 1.15; 95% CI 0.9–1.50), even though none of these differences reached statistical worth. These data indicate likely molecule-precise effects on diabetogenesis. These data showed significant unevenness between studies and with various statins, with HRs ranging from 1.19–1.57 but statistically significant, after follow-up periods of 3–6 years. In the Female Health Care study, the women were older than several other people and generally on moderate-dose therapy, yet the HR was 1.48 [26]. In

the biggest study of over 2 million patients in the UK, there was a substantial time-dependent rise in diabetes risk (HR 1.57; 95% CI 1.55–1.60), which augmented more (HR 3.63; 95% CI 2.44–5.38) in those who were followed for up to 15–20 years [27]. In one study in patients following myocardial infarction, there was no difference in intensive- vs. moderate-dose statin therapy [28]. It is well-known that the risk for diabetes according to the existence of pre-existing diabetes risk influences, as mentioned in the several analyses of RCTs [21-23], was not sufficiently inspected in the various observational studies, a major restriction in those studies, compared to RCTs. There are some remarks of interest from some studies in patients with pre-existing glucose intolerance or diabetes. In the study by [29]. The HR for progression to diabetes was like in those with normoglycemia, or reduced fasting glucose at baseline, but both groups displayed a comparable decrease 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 important increase in the mean A1c level of 0.12% (95% CI 0.04–0.20) [30-33].

Conflicts Of Interest: There is no conflict of interest.

Ethical clearance: The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/ have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity.

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REFERENCES

1. American Diabetes Association (ADA). Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2010;33: S62-S69.
2. Kharroubi AT, Darwish HM. Diabetes mellitus: The epidemic of the century. World Journal of Diabetes 2015: 850-867.
3. Thomas CC, 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;2:007641.
5. Paschou SA, Papadopoulou-Marketou N, Chrousos GP, Kanaka-Gantenbein C. On type 1 diabetes mellitus pathogenesis. Endocrine Connections 2018;7:38-R46.
6. Kopan C, Tucker T, Alexander M, Mohammadi MR, Pone EJ, Lakey JRT. 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;27:269-273.
8. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. Lancet. 2014;383:1068-1083.
9. Tumbo JM, 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;5:375.
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, Bornfeldt KE. Diabetes and atherosclerosis: is there a role for hyperglycemia? Journal of Lipid Research. 2009;50:335-S339.
12. Kanter JE, Bornfeldt KE. Inflammation and Diabetes-Accelerated Atherosclerosis: Myeloid Cell Mediators. Trends in endocrinology and metabolism*:* TEM. 2013;24:137-144.
13. Kanter JE, Averill MM, LeBoeuf RC, Bornfeldt KE. Diabetes-Accelerated Atherosclerosis and Inflammation. Circulation research. 2008;103:116-117.
14. Rahal AJ, ElMallah AI, Poushuju RJ, Itani R. Do statins really cause diabetes?: A meta-analysis of major randomized controlled clinical trials. Saudi Medical Journal. 2016;37:1051-1060.
15. Ganda OP. Statin-induced diabetes: incidence, mechanisms, and implications. F1000Research 2016;5: 1499.
16. Yoon D, Sheen SS, Lee S, Choi YJ, Park RW, Lim H-S. Statins and risk for new-onset diabetes mellitus: A real-world cohort study using a clinical research database. Zhou. W, ed. Medicine. 2016;95:5429.
17. Chogtu B, Magazine R, Bairy K. Statin use and risk of diabetes mellitus. World Journal of Diabetes. 2015;6:352-357.
18. 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;359:2195–207.
19. Sattar N, Preiss D, Murray HM, et al. : Statins and risk of incident diabetes: a collaborative meta-analysis of randomized statin trials. Lancet. 2010;375:735–42.

20. 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;305:2556–64.
21. 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;57:1535–45.
22. 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;380:565–71.
23. 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;61:148–52.
24. Navarese EP, Buffon A, Andreotti F, et al. : Meta-analysis of the impact of different types and doses of statins on new-onset diabetes mellitus. Am J Cardiol. 2013;111:1123–30.
25. 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;241:409–18.
26. 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;172:144–52.
27. 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.
28. 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;6:315–22.
29. 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;31:502–8.
30. Erqou S, Lee CC, Adler AI: Statins and glycaemic control in individuals with diabetes: a systematic review and meta-analysis. Diabetologia. 2014;57:2444–52.
31. 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.
32. Padmavathi S, Rajkumari L, Manimekalai K. Dose And Time-Dependent Effects Of Statins On Glycemic Status And Their Association With New Onset Diabetes Mellitus. Asian Journal of Pharmaceutical and Clinical Research 2015;8:125-128.
33. Siddhi U, Panda B, Madhu B. Acute Myocardial Infarction With Vitamin B12 Deficiency And Mild Hyperhomocysteinemia: A Case Report And Review. Asian Journal of Pharmaceutical and Clinical Research 2016;9:2-4.