

## ANALYSIS OF DIGESTIVE DISORDERS DUE TO STATIN THERAPY IN HYPERCHOLESTRIMIA; A COHORT STUDY AMONG DIABETIC AND NON DIABETIC PATIENTS

KIRAN RAFIQ<sup>1</sup>, ZAFAR SAIED SAIFY<sup>2</sup>, ARFA AKRAM<sup>3</sup>, ANWARI SYEDA<sup>4</sup>, SHEIKH MUHAMMAD SAAD<sup>1</sup> AND MOHAMMAD USMAN KHAN<sup>1</sup>

<sup>1</sup>Institute of Pharmaceutical Sciences, Jinnah Sindh Medical University, Karachi.

<sup>2</sup>International Center of Chemical & Biological Sciences, University of Karachi.

<sup>3</sup>Department of Pharmaceutical Chemistry Faculty of Pharmacy,  
Federal Urdu University of Arts Science & Technology

<sup>4</sup>Afzal Memorial Trust- Helping Blood Disorders, Karachi.

### خلاصہ

سٹاٹن (Statin) چکنائی کی سطح کو کم کرنے والی ادویات ہیں جو عمومی طور پر دل کے دورے اور دوسرے امراض قلب کے ممکنہ خطرات کو روکنے کے لئے تجویز کی جاتی ہیں۔ ایک تحقیق کے مطابق قلبی امراض میں مبتلا سٹاٹن استعمال کرنے والے 40% فیصد مریض پیوند کاری سے گزرتے ہیں جبکہ سٹاٹن استعمال نہ کرنے والے 80% مریض پیوند کاری کراتے ہیں۔ عمومی طور پر سٹاٹن بلند فشار خون کی روک تھام کرنے والی ادویات کے ہمراہ تجویز کی جاتی ہیں اور مریض ذیابیطس کا بھی شکار ہے تو کی ادویات کا مجموعہ دیا جاتا ہے تاکہ ممکنہ طبعی بے ترتیبیوں کا مقابلہ کیا جاسکے لیکن اجتماعی طور پر یہ تمام ادویات ناپسندیدہ اثرات مرتب کرتی ہیں اور خاص طور پر نظام ہضم کو متاثر کرتی ہیں۔ موجودہ تحقیق کا ہدف نظام ہضم کی بے ترتیبیوں کا اصل سبب دریافت کرنا ہے کہ آیا یہ لگاؤ کا سبب سٹاٹن ہیں یا مریض کی طبعی تبدیلیاں اس لگاؤ کی ذمہ دار ہیں۔ اس مقصد کے لئے یکساں مرض کے حامل گروہ کا انتخاب کیا گیا اور ان کی بیماری کی تفصیلات اور تجویز کردہ ادویات کے متعلق معلومات کو جمع کیا گیا۔ مریضوں کو "کیس" اور "کنٹرول" (2) گروہوں میں تقسیم کیا گیا جن میں سے دونوں گروہوں کے مریضوں میں ہائی کولیسٹرول (چکنائی) اور بلند فشار خون کا مرض موجود تھا لیکن صرف "کیس" گروہ کے مریض ذیابیطس کے حامل تھے۔ موجودہ تحقیق کے نتائج کے مطابق "کیس" گروہ کے 67% فیصد مریضوں میں جو کہ ذیابیطس کے بھی حامل تھے انہضامی بے ترتیبیاں پائی گئیں جبکہ بغیر ذیابیطس کے مریضوں میں اس طرح کے اثرات نہیں پائے گئے اور اس طرح خطرے کا تناسب 0.24-10 اخذ کیا گیا۔ موجودہ تحقیق اس خیال سے متفق ہوتی ہوئی پائی گئی کہ سٹاٹن انہضامی بے ترتیبیوں کا ذمہ دار نہیں اور اس طرح نتائج سٹاٹن کے متعلق خیال کو غلط ثابت کرتے ہیں جیسا کہ تحقیق کے مطابق ناپسندیدہ اثرات کا صرف ذیابیطس کے حامل گروہ میں مشاہدہ کیا گیا لہذا سٹاٹن استعمال کرنے والے ذیابیطس کے مریضوں کو صرف ناپسندیدہ اثرات کا سامنا کرتے ہیں جو کہ دراصل ذیابیطس کے باعث طبعی بے ترتیبیوں کا انجام ہے اور جو کہ تنظیم انہضام کو مزید بے ترتیب کر دیتا ہے۔

### Abstract

Statins are cholesterol-lowering drugs, commonly prescribed for the significant decline of high risks leading to arrhythmia and other cardiac issues. A study conducted reveals that 40% of population among the patients of cardiovascular, got arterial fibrillation with statins and 80% without statins that are mostly prescribed along with antihypertensive and if patient is diabetic, a regime of medicine is given for the management of all probable disorders and that sometimes may lead to undesired effects specifically regarding gastric. The present study is conducted to focus the root cause of digestive disorders as either medicine or condition. In present study the method adopted was cohort study and for the purpose prescription and history of case and control groups that were both hypercholestrimic and hypertensive but diabetic and non diabetic respectively. The study out comes reveal that 67% of case group reported the after effects of digestive disorders, however interestingly no such effects were observed from control group. Data analysis showed 0.24 risk ratio. The study outcomes helped to establish the idea that statins are not accountable for digestive disorders and the outcome nullify the delusion about that specific undesired effect of statins as that were only observed in diabetic patients since diabetes itself a metabolic and comorbid disorder blamed for aggravating the digestion.

### Introduction

Hypercholesterolemia, elevated saturation of cholesterol, triglycerides and LDL in the blood, may be due to a genetic disorder, highly accountable and associated with a greatly increased jeopardy of coronary heart disease (Marks *et al.* 2003). High lipid profile is the most commonly occurring diseases especially in the developing countries, may be due to increased intake of dietary lipids, lack of exercise and to some extent anxiety (Jansen *et al.* 2004). The outcome of that excess leads to the deposition of lipids in blood vessels that becomes harmful and lethal as causes thrombus and may than myocardial infarction, characterized by

hardening and narrowing the blood vessel thus, reducing the blood flow (Ye *et al.* 2012). For therapy and management of Hypercholesterolemia, Statins, Hydroxyl Methyl Glutaryl co enzyme A reductase inhibitors, are prescribed as a first preference treatment that works by inhibiting the enzyme HMG Co-A. The enzyme is vital in the mevalonic acid and the inhibition of the enzyme causes the halt in conversion of HMG Co-A into Mevalonic Acid and the pathway is stopped. This results in reduced formation of cholesterol (Ford *et al.* 2004, Haubing *et al.* 2016) thus the body makes use of the dietary cholesterol and ultimately the cholesterol and triglycerides levels come back to normal (Hwang *et al.* 2018). The promising moiety, statin, is available in different approved forms with a slight change in molecule and efficacy as like atorvastatin (Lipitor), fluvastatin (Lescol, Lescol XL), simvastatin (Zocor), pitavastatin (Livalo), lovastatin (Mevacor, Altoprev), rosuvastatin (Crestor) and pravastatin (Pravachol) (medicinenet.com/statins). The first and common symptom of hypercholesterolemia is hypertension, a “continual state of elevated blood pressure event at rest, as plaques of cholesterol make the lumen of blood vessels narrower causes the heart to generate more pressure for effective perfusion and thus a rise up is observed in blood pressure. To manage the indicative effect of hypercholesterolemia, anti-hypertensives like  $\beta$ -Blockers are also prescribed, that work by inhibiting the  $\beta_1$  and  $\beta_2$  receptors in the heart (Philip, 2015, Mancusi, 2016). These are adrenergic receptors that bind with epinephrine and norepinephrine to give increasing force of contraction thus to increase blood pressure, whereas the  $\beta$  blockers are antagonistic to these receptors and help in reducing blood pressure. Interestingly diabetes is a group of disorders that result from persistent elevated blood glucose levels. One of its influences is on the digestion as it is seen that motility of digestive system becomes reduced (Abrams, 1982, Gylling & Miettinen, 1997). As diabetes either type 1 or 2 is accountable for accompanying the metabolic disorders as well as due to hyperlipidemia the state of disease may become more worst. Likewise, progression of hypercholesterolemia may possibly a forewarning of diabetes in future prospect. While, furthermore, the condition of high cholesterol level is frequently prevalent in prediabetics, consequently, in non hyperglycemia, alteration in insulin action is highly associated with this lipid abnormality. As diabetes is co morbid disease and accountable for multimetabolic disorders along with lipoprotein abnormalities with associated increased risk of coronary artery disease. All the allied consequences are required to essentially managed for healthy and normal life via diet, physical activity and medicine. To overcome all the possible outcomes, a regime of medicine is prescribed including antidiabetic, antihypertensive along with statins that may lead to undesirable effects, beyond the understanding that either these outcomes are consequences of disease or due to drug effects on body. As like a very commonly reported effect of statin is heartburn, acidity and myalgia (Scoppola, 1995, Choung, 2012, Klaus and Bielefeldt, 2012). However these observations are more generally found in diabetic patients taking statins and that should be managed. The issue is focused in present study to analyze the actual cause of the reported coming effects regarding treatment.

## Materials and Methods

The present study was conducted to measure the consequences due to statin appeared in patients of hyperlipidemia in diabetic and non diabetic patients and to catch the root cause of apparent disagreeable effects. The method adopted was cohort study and the prescription along with history of patients was analyzed. For the purpose study was carried out during the period of November, 2016 till September, 2017. The study population was divided into two groups, each having forty participants. One group, considered controlled one, was of the patients suffering from cardiac disorder, hypercholesterolemia and hypertension and were prescribed statin for their high cholesterol level along with antihypertensive, whereas the case group, was also prescribed the same medicine along with hypoglycemic due to having diabetes. The study was prescription based as of forty patient's prescriptions from physicians and doctors were collected during the study duration as to observe the follow up also specifically the patients complain regarding unwanted outcome of treatment and the change in prescribed medicine carried out by the concerned doctors as in case of statin patient usually found to complain of acidity and ulcer as if it is due to statins.

### Study population

The study population was the population of patients who visits for regular follow up to the OPD of different hospitals and clinical settings in Karachi.

### Study subjects

Patients who experienced hypercholesterolemia and were usually prescribed statins for management diabetic and non diabetic both.

### Study period

The study period was from November, 2016 till September, 2017. The first five months were used as a screening period and prescription of hyperlipidemic patients were included in the study. In later three months,

feed back with revised prescription were collected from concerned physicians and in remaining period data was compiled and analyzed.

**Setting:** different hospitals and clinics around Karachi.

**Inclusion Criteria:** The patients, those who are suffering from Hypercholesterolemia, Hypertension and Diabetes.

**Study Type:** Case-control study

**Sample:** Two groups of forty participants each were considered. One group of case series consisting of patients having hypercholesterolemia, hypertension and Diabetes, while the other group (Control) patients were non diabetic, hypercholesterolemic and hypertensive.

**Sample Selection:** random

**Instrument:** Prescriptions and history of patients were collected from clinical settings during the study period.

**Data Evaluation:** MS Excel 2007, Cohort study statistical calculation.

**Result**

The study covered the two group, patients of case group were diabetic and were prescribed, antihypertensive, beta blockers, antidiabetic and statin. The other control group were non diabetic however had hypertension, cardiac issue and hypercholesterolemia, were prescribed antihypertensive, beta blockers and statin. The outcome of study reveals (Table -1) that 27 patients out of forty in case group complained for digestive disorders along with hyperacidity 13 of the same group did not find any fault in treatment, whereas all the patients in control group that were also 40 sample size did not exhibit any undesired effect in statin therapy. The data outcome reveals the incidence density of frequency of digestive disorders among the diabetic and non diabetic was found zero with also zero risk ratio (Figures-1&2). The attributed risk was analyzed as -0.24. The overall data analysis showed that frequency of undesired effect regarding digestion due to statin is very low when studied on control and case group.

**Table-1: Patient’s Response for Statins regarding Digestive Disorders**

	<b>Case Group</b> (Hypercholesterimic, hypertensive, Cardiac & Diabetic)	<b>Controlled Group</b> (Hypercholesterimic, hypertensive, Cardiac & Non Diabetic)	<b>Total Exposure</b>
<b>Exposed</b>	27	0	27
<b>Non Exposed</b>	13	40	53
	40	40	80

\*Exposed; The patients who complained hyperacidity and ulcer while taking statin

\*Non exposed; The patients who did not complain hyperacidity and ulcer while taking statin.

**Incidence Density**

Among exposed;  $27/27 = 0$

Among non-exposed;  $13/53 = 0.24$

**Incidence Density Ratio (Risk Ratios or Relative Risk)**

$0/0.24 = 0$

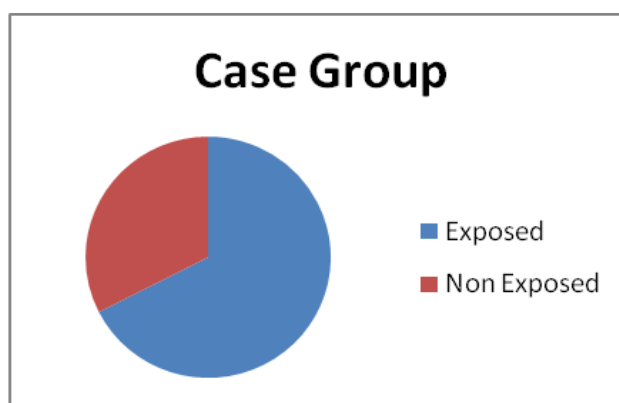
**Attributed Risk**

$0 - 0.24 = -0.24$

**Discussion**

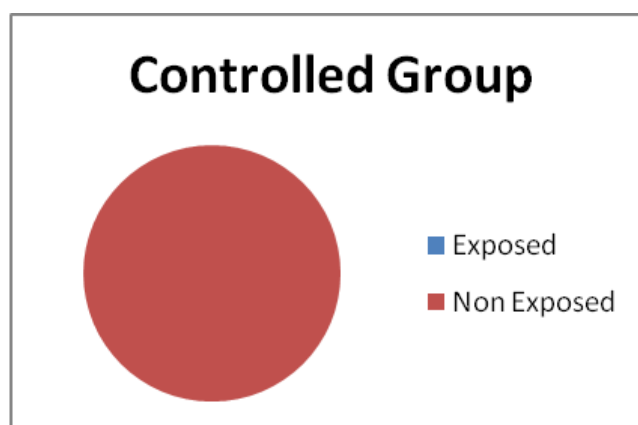
In all over the world statins medicine are widely prescribed to control hypercholesterolemia and highly accountable for reducing vascular inflammation and lipid deposition. It has also been proved through various studies as like CARE (cholesterol and recurrent events) and AFCAPS (Air Force coronary atherosclerosis prevention study) WOSCOPS (West of Scotland coronary prevention study) that statin significantly increase survival rate by reducing 30% coronary diseases. Hence statin was established as strong preventing treatment to the limit that doctors and physicians commonly prescribed to evade the severity of disease and if patient is suffering from hypertension, cardiac issue and diabetes, a regime of medicine is also prescribed along with statins that sometimes and in some cases may lead to undesired effects, however in present study the data collected to focus the reason of unwanted effects regarding gastric problem in patients taking statins. For the purpose study was carried out on case and control groups, diabetic and non diabetic respectively. According to

the result outcome complications were observed more among the patients of case group but no such effects were exhibited from the control one, non diabetic. The outcomes exhibit that the chances of statin of being responsible for hyperacidity in patients of hypercholestrimia are very low and the coming effects were observed in patients suffering from diabetes. Diabetes is a co morbid disease and a group of disorders itself and mostly entangled with conditions like hyperlipidimia and hypertension and also has established as underlying cause leading to different microvascular and macrovascular disorders. Consequently diabetes can be accountable for the complications associated with digestion and it also indicates that gastric discomforts can be exacerbated by diabetes (Rayner and Samsom, 2001) and the prescriber should take care in administering the dosage and their aftermath. As due to diabetes a condition develops called gastroparesis regarding the functioning of stomach . Normally the vagus nerve stimulation directs the contraction of stomach muscles converting meal into tiny particles and blending with acids and pepsin than make it move down towards intestine through pyloric sphincter within maximum normally four hours. However diabetes accounts for the damage of vagus nerve accordingly the process of emptying stomach becomes longer in patients specifically having hyperglycemia for a longer period leading digestive disorders and upset stomach commonly symptomize by nausea, bloating, a feeling of fullness and heartburn and along the situation acid secretion goes on and may worsen the condition. All these facts supports the data figures according to that effects of statin were found in all diabetic cases but not in non diabetic that nullify the assumption of digestive disturbances and hyperacidity due to statins (Fend and Chuang, 2015). Although the simultaneous dosing with antacid can significantly minimize the undesired responses. Diet habit can also play an important role for curing the condition as like low intake of high fiber diet and more of fruits , vegetables, grains and specifically avoid fat.



**Figure-1: Frequency of Digestive Disorders for Statins (Case Group)**

“In Case Group (Diabetic), the majority of patients were reported for complaining hyperacidity and ulcer while taking statin”



**Figure-2: Frequency of Digestive Disorders for Statins (Controlled Group)**

“In Controlled Group (Non-Diabetic), the majority of patients were reported for complaining ‘NO’ hyperacidity and ulcer while taking statin”

## Conclusion

According to the study outcomes the present data reveals the zero chances of occurring hyperacidity in hyperchlorimic patients taking statins, however prolong hyperglycemic effect in such patients exhibits digestive disorders. Furthermore research support the fact that improper diet and lack of exercise also played a major role in the digestive problems of the case group and to overcome these problems, patients should be prescribed PPI, proton pump inhibitors along Statins and  $\beta$  Blockers to the Diabetic Patients who have encountered Hypercholesterolemia and Hypertension. Moreover controlled diet plan, proper workout and induction of a Proton Pump Inhibitor will efficiently abolish the general assumption about statin of being risk for digestion. Further certain medications may create worsen state of gastroparesis. In community health care system, physician and pharmacist should ensure the line of treatment with negligible harmful effects and if there, should be controlled by prescribing with best possible medicine.

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