

Effect of HMG-Co-A Reductase Inhibitors on Cardiac Autonomic Neuropathy in Diabetic Patients

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Abstract

Objective: To observe the effect of statins on cardiac autonomic neuropathy in patients with diabetes and to study the correlation between cardiac autonomic neuropathy as assessed by cardiac autonomic reflex tests (CARTs) and by Composite Autonomic Symptom Scale (COMPASS)-31. **Materials and Methods:** A cross-sectional observational study was conducted on 62 patients having Type 2 diabetes mellitus for more than 5 years. Patients were randomized into two groups, one group received standard antidiabetic therapy and other group received standard antidiabetic along with statin medication at least for more than 1 year. Each patient underwent CART and heart rate variability to assess autonomic dysfunction. In addition, COMPASS 31 questionnaire was used to evaluate symptoms subjectively. Statin Experience Assessment Questionnaire was used to note adverse effects of statins. Chi-square test, Spearman correlation test, and Mann-Whitney *U*-test were used for statistical analysis. **Results:** A significant difference in severity of cardiac autonomic dysfunction was observed between two groups as measured by CART ($P = 0.016$) and COMPASS-31 questionnaire ($P = 0.008$). Moreover, COMPASS score of >16 was observed in patients with advanced cardiac autonomic neuropathy. A significant correlation was found between COMPASS 31 score and CART results ($r = 0.29$, $P = 0.02$). **Conclusion:** Our study highlights the potential utility of statins in curbing progression of cardiac autonomic neuropathy and can be safely administered in patients with Type 2 diabetes mellitus. COMPASS 31 questionnaire can be used as an effective screening tool for CART referral, facilitating the early detection of cardiac autonomic neuropathy.

Keywords: Cardiac autonomic reflex test, composite autonomic symptom scale, heart rate variability, pleiotropic mechanism, statins

INTRODUCTION

India is regarded as the diabetes capital with second-largest population of 73 million diabetic patients found in 2017, and this number is expected to be double 134 million by 2045.^[1] Of the many serious complications of long-standing diabetes is diabetic autonomic neuropathy, a condition arising due to sympathetic and parasympathetic denervation of autonomic fibers, causing impairment of multiple organ systems such as cardiovascular, gastrointestinal, genitourinary, sudomotor, and visual.^[2] Diabetes-induced cardiovascular autonomic neuropathy (CAN) encompasses damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics.^[3] Clinical manifestations of CAN include resting tachycardia, orthostasis, exercise intolerance, intraoperative cardiovascular liability, and hypothermia. CAN has a definite prognostic role in cardiovascular events such as coronary artery disease, stroke,

and silent myocardial infarction. The prevalence rates of CAN increase with age and duration of diabetes mellitus. The diabetes control and complication trial has reported rates as high as 35% in Type 1 diabetes mellitus and 44% in Type 2 diabetes mellitus, with a prevalence rate of up to 60% in long-standing diabetics.^[4] Autonomic dysfunction is initially subclinical and becomes symptomatic only in the later stages of the disease. Thus, if diagnosed early, further progression can be attenuated by possible drug intervention and intensifying glycemic control, and thus adverse cardiac events can be prevented.

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HMG Co-A reductase inhibitors (statins), a class of lipid-lowering drugs, are currently the drugs of choice for reducing the risk of cardiovascular mortality and morbidity in diabetic patients, by their lipid lowering and possibly pleiotropic mechanisms. They also have shown to decrease the progression of neuropathy and autonomic dysfunction in patients of arrhythmia and heart failure.^[5] However, very few studies have been conducted, especially in India, on the effect of statins on autonomic modulation concerning decrease in the progression of autonomic neuropathy by their pleiotropic mechanism of action being relatively unexplored leading to a research gap.

A few reports, on the contrary, state increased risk of precipitation of diabetes mellitus and peripheral neuropathy by statins, which may be related to inhibition of ubiquinone or excessive depletion of cholesterol of nerve membrane required for formation of myelin sheath.^[6] Known adverse drug reactions (ADRs) such as hepatotoxicity, myalgia, and myositis raise a question of risk-benefit ratio, widening the research gap.

This paucity of data creates a question whether statins really prevent CAN or do they predispose to it. The potential therapeutic intervention of CAN by statins remains untapped, and thus this study aims at determining the potential efficacy of statins as a treatment option for CAN.

The primary objective of the study was to assess the effect of statins on CAN in diabetic patients using heart rate variability-cardiac autonomic reflex tests (HRV-CART) and Composite Autonomic Symptom Scale (COMPASS)-31 questionnaire. Secondary objectives first was to study the correlation between CAN as assessed by an objective test (CART) and by COMPASS 31 – a subjective test for autonomic neuropathy, as HRV-CART technology is not available at primary healthcare level. This tool will be useful to further refer patients for CART. The other secondary objective was to note ADRs of statins in diabetic patients.

MATERIALS AND METHODS

Institutional Ethics Committee (IEC) approval was obtained before starting the study (IEC Approval No – 2019/520). The sample size was estimated considering $\alpha=0.05$, and statistical power at 80% and the medium effect size (0.51) as proposed by Quintana.^[7] This cross-sectional observational study was conducted in a tertiary care hospital on 62 consenting patients during the period of April to September 2019. Patients of either gender, between 40 and 80 years of age, having Type 2 diabetes mellitus for more than 5 years (having hemoglobin A1C [HbA1C] value 7%–9%) and with or without statin therapy for more than 1 year, were included in the study. Exclusion criteria comprised subjects with severe concomitant diseases (malignancies, hyperthyroidism, hepatic disease, and renal failure), pregnancy, subjects with significant neurological diseases or neuromuscular disorders (e.g., Parkinson's disease, epilepsy, and multiple sclerosis), and factors affecting HRV

like previous myocardial infarction, cardiac arrhythmias, cerebrovascular accident, congenital heart disease, pacemaker, drugs such as tricyclic antidepressants and beta blockers.

Patients were divided into two groups as diabetic patients with statin therapy and diabetic patients without statin therapy. Case record form was used to note demographic data (age and gender), relevant medical history including history of medications and adverse effects, biochemical investigations such as fasting and postprandial blood glucose level, HbA1C value was also recorded.

Each patient performed HRV-CART as recommended by Toronto Consensus panel on diabetic neuropathy, and HRV analysis was done as per standard guidelines laid by HRV task force.^[8]

In this noninvasive technique, a high sampled electrocardiogram (1 KHZ) was recorded using an ambulatory HRV device for 21 min (15 min in supine position, 5 min in standing position followed by 1-minute long, deep breathing challenge). A tilt table was used for testing orthostatic hypotension, while the patient changes his/her position from supine to standing. Chronovisor Dx data acquisition system was used for data acquisition, and automated report of HRV-CART was generated.

CART parameters used for analysis were resting heart rate, heart rate response to standing (R-R interval), heart rate response to deep breathing in sitting position, and blood pressure response to standing. CART is analyzed as normal when all parameters of CART are normal, it is diagnosed as early CAN when CART denotes a single abnormal parameter and as definite CAN when CART denotes 2 or more abnormal parameters.^[9]

HRV parameters used for analysis were standard deviation of the NN interval (SDNN) (interbeat interval of normal sinus beats), total power (TP), low-frequency (LF) (ms^2), and LF (nu)-power in low frequency range 0.04–0.15 Hz which is predominantly indicative of sympathetic function, high-frequency (HF) (ms^2), and HF (nu)-power in high frequency range 0.15–0.4 Hz which is predominantly indicative of parasympathetic function and LF/HF ratio-ratio LF (ms^2)/HF (ms^2).

Each patient filled the COMPASS 31 Questionnaire.^[10] It is a subjective test and assesses autonomic neuropathy in six organ system domains, namely, orthostatic, vasomotor, secretomotor, gastrointestinal, genitourinary, and pupillomotor. It comprises 31 multiple choice questions. The patient is asked to fill the questionnaire based on the presence and severity of his/her symptoms of autonomic neuropathy.

Each patient filled the Statin Experience Assessment Questionnaire (SEAQ).^[11]

SEAQ consists of 15 questions of which six questions are to assess the severity of ADRs of statins, seven questions to assess severity of their impact on daily activities and two questions to

note whether the patient is likely to discontinue the medication. The patient was asked to rate the severity on a scale of 0–10, 0 being the least and 10 being the most severe. It was used to note the ADRs of statins and their impact on daily activities.

Statistics

Statistical analysis of the results was performed using Epi info™ version 7.2.2.16 software developed by Centres for Disease Control and Prevention (CDC) in Atlanta, Georgia (US). Data were expressed as mean $\pm$ standard deviation. Chi-square test, Mann–Whitney U-test, and Spearman correlation test were used for analysis. The 0.05 level of probability was used as a criterion of significance.

RESULTS

The present study was carried out in medicine inpatient and outpatient department in a tertiary care hospital. A total of 80 patients having Type 2 diabetes mellitus for more than 5 years were screened. Among them, 66 patients were enrolled as per study criteria. Final analysis was done with 62 patients, 31 in each group. Group 1 consisted of patients on statin therapy for at least 1 year and Group 2 consisted of patients not on statin therapy. Four patients were not considered for final analysis as two were not able to perform CART accurately and two had taken medications before the test.

As per Table 1, the demographic data reveal duration of diabetes – 6–10 years and HbA1c values between 7 and 9. The difference in CART result values between two groups is statistically significant ($P = 0.016$ using Chi-square test). Nine patients from statin group have normal CART value compared to two patients from nonstatin group [Table 2]. As per Table 3, although the difference in HRV parameters between two groups is statistically not significant, a trend of increased HRV parameters (SDNN, TP, LF (ms^2), HF (ms^2),

LF (nu), and LF/HF) is seen in the statin group. As seen in Table 4, COMPASS 31 questionnaire analysis shows that statin group has a significantly lower cardiovascular domain score (orthostatic intolerance); $P = 0.0075$ as well as a significantly lower total COMPASS 31 score ($P = 0.0081$). P values are calculated using Mann–Whitney U-test. Other domains of COMPASS 31 questionnaire did not show statistically significant differences in score although a trend of lower scores in the statin group was seen.

A higher COMPASS 31 score is correlated well with definite CAN as diagnosed from CART using Spearman

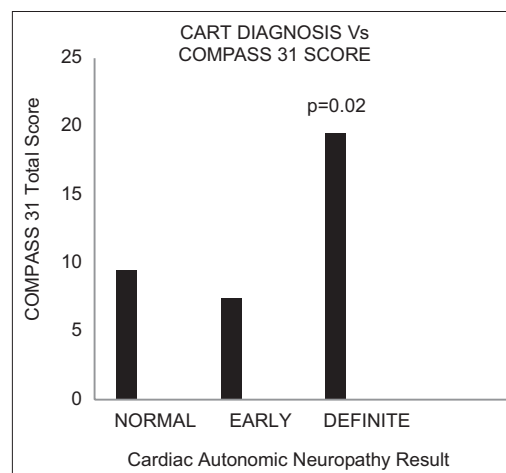


Figure 1: Correlation between cardiovascular autonomic neuropathy result and composite autonomic symptom score-31 score. Using spearman correlation test, $r = 0.29$, $*P = 0.02$. *Statistically significant $P < 0.05$. CAN = Cardiac autonomic neuropathy diagnosed as normal, early cardiac autonomic neuropathy and definite cardiac autonomic neuropathy based on cardiac autonomic reflex test, COMPASS 31 = Composite Autonomic Symptom Score-31

Table 1: Baseline characteristics of the study population ($n=62$)

	Mean $\pm$ SD	
	Group 1 - statin ($n=31$)	Group 2 - nonstatin ($n=31$)
Mean age ($P=0.0137$)*	65.2 $\pm$ 19.6	58.8 $\pm$ 20.04*
Gender ($P=0.2031$) #		
Male	12	17
Female	19	14
HbA1c ($P=0.59$)	7.67 $\pm$ 1.11	7.75 $\pm$ 1.74
Duration of diabetes (years) ($P=0.7365$)		
6-10	14	15
11-15	8	8
16-20	5	7
20-25	4	1
Drugs		
Metformin	5	3
Sulfonylurea + others	5	4
Metformin + sulfonylurea	11	13
Insulin + oral hypoglycemic agents	10	11

P values are calculated using Mann–Whitney U-test. * P value is significant. $P < 0.05$ as age compared between Group 1 and Group 2, # P values for comparing gender between two groups are calculated using Chi-square test. SD=Standard deviation, HbA1C=Hemoglobin A1c

correlation test, statistically significant values were obtained – $r = 0.29$, $P = 0.02$ [Figure 1]. SEAQ assessment scores did not show clinically impairing ADRs of statins as seen in Figure 2. No patient wished to discontinue statin treatment due to ADRs.

DISCUSSION

The present cross-sectional observational study was designed to assess the effects of statins on CAN in diabetic patients.

Table 2: Cardiac autonomic reflex test results comparing statin and nonstatin groups

CART result	Group 1 - statin (n=31)	Group 2 - nonstatin (n=31)
Normal (no CAN detected)	9	2
Early CAN	19	19
Definite CAN	3	10

CAN=Cardiac autonomic neuropathy, CART=Cardiac autonomic reflex test

Table 3: Heart rate variability analysis: Comparing statin and nonstatin groups

HRV indices	Mean ± SD	
	Group 1 - statin (n=31)	Group 2 - nonstatin (n=31)
SDNN	25.8±32.2	23.3±13
TP	583.5±1656	441.9±1311
LF (ms ²)	123.1±398.6	121.3±460.8
HF (ms ²)	155.7±636.8	100.5±335
LF (nu)	55.9±52.2	48.3±44
HF (nu)	44.1±52.2	51.4±45
LF/HF	2.5±5.6	1.5±3.4

P values are calculated using Mann-Whitney U-test. No significant difference is observed between Group 1 and Group 2. SDNN=Standard deviation of the NN interval, TP=Total power, LF=Low-frequency component, HF=High-frequency component, nu=Normal units HRV=Heart rate variability, SD=Standard deviation

Table 4: Composite autonomic symptom score-31 questionnaire analysis

Domain	Mean ± SD	
	Group 1 - statin (n=31)	Group 2 - nonstatin (n=31)
Orthostatic intolerance (cardiovascular)	3.83±12.8	10.37±21*
Vasomotor	0	0.12±1.6
Secretomotor	2.23±6	3.73±7.4
Gastrointestinal	2.31±6.8	4.17±8
Bladder	1.06±3.2	1.11±4.4
Pupillomotor	0.51±2	0.81±2
Total score	7.12±18.4	12.6±20.6*

*P value is significant. $P < 0.05$. P values are calculated using Mann-Whitney U-test. In the comparison between Group 1 and Group 2, a significant P value can be observed in the orthostatic domain ($P = 0.0075$) and in the total score. ($P = 0.0081$). SD=Standard deviation

In our study, CAN was found to be present in 73% of the patients. CART results showed that only three patients from statin group were detected with definite CAN as against ten patients from nonstatin group as shown in Table 2. Thus, statin shows a protective role in the development of CAN and may prevent progression from early stage to definite stage of CAN.

In the HRV analysis, both time and frequency domain indices showed a trend of increase HRV in the statin group [Table 3] indicating a better sympathetic-parasympathetic modulation, supporting the hypothesis of beneficial action of statin in preventing autonomic dysfunction.

Results of COMPASS 31 questionnaire [Table 4] also demonstrated similar results by a significantly lower total score ($P = 0.0081$) and cardiovascular domain score ($P = 0.0075$) in statin group indicating protective action of statins in the development of CAN.

Similar to our study, the prevalence of CAN is 70% in a study conducted by Bhuyan *et al.* in India.^[12] Birajdar *et al.* mentioned the prevalence of CAN to be 58%.^[13] Spallone *et al.* also mentioned that definite CAN is present in one-fifth of diabetic patients.^[12]

Few human studies have demonstrated a significant improvement in time and frequency domain indices of HRV with atorvastatin in heart failure patients.^[14,15] In these studies, atorvastatin was given for duration ranging from 3 months to more than 2 years. On the contrary, few studies found no effect of statins on HRV, but most of these studies were based on patients having hyperlipidemia and nonischemic cardiomyopathy or heart failure.^[16] None of the above studies were exclusively based on diabetic patients and effects of statins on CAN such as our study.

Above data suggest that treatment with statin improves autonomic function, as reflected by an increase in HRV level. This may be one of the reasons for the reduction in adverse clinical events reported by the landmark survival studies with

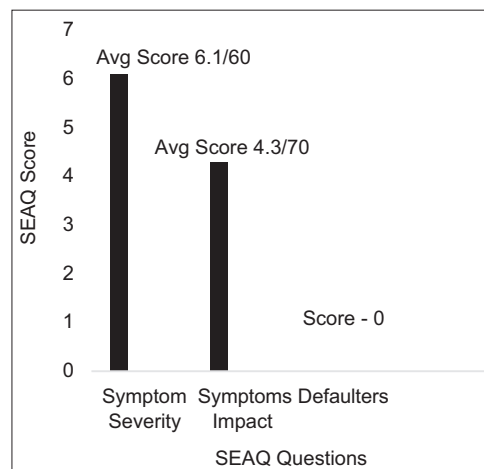


Figure 2: Statin experience assessment questionnaire analysis

statins in primary and secondary coronary artery disease.^[17] It is well known that, in coronary artery disease, there occurs decrease in HRV which may lead to ventricular arrhythmias and sudden cardiac death.^[18] This adverse effect could be prevented by the use of statins.

The probable mechanisms by which statins exert their beneficial effects on HRV are not known but are possibly due to their pleiotropic mechanism of action which consists of vascular, central, and anti-inflammatory and immunomodulatory action.

Hyperglycemia-induced activation of the polyol pathway causes direct neuronal damage and activation of protein kinase C, leading to vasoconstriction and neuronal ischemia.^[19] Accumulation of advanced glycation end-products in vasa nervorum leads to nerve hypoxia and altered neural function. One mechanism of reduced neuronal blood flow is the inhibitory effect of superoxide anion on nitric oxide (NO) synthase. It has been shown that NO synthase is reduced in experimental diabetic neuropathy and statin prevent this inhibition by reducing oxidative stress and by its endothelium dependent vasodilating property.^[20] Statins restore vasa nervorum. This effect appears to be mediated through an NO-dependent pathway.

Central action of statins improves autonomic dysfunction by decreasing adrenergic outflow in central brain regions involved in sympathetic and parasympathetic modulation. Lie Gao *et al.* first demonstrated that there is an intense-free radical stress in the autonomic areas of the brain in the heart failure state, characterized by upregulation of angiotensin receptors and NADPH oxidase subunits in the rostral ventrolateral medulla as well as NADPH-dependent superoxide anion production.^[21] This group subsequently linked autonomic improvement to an effect of simvastatin on inhibition of central angiotensin II and the superoxide pathway.

In our study, most of the patients were on atorvastatin-lipophilic statin which is able to diffuse passively across extrahepatic cell membranes and consequently has a greater potential to cross the blood-brain barrier and interact with central brain regions involved in the generation or modulation of efferent sympathetic and parasympathetic activity.^[22] This action is reflected by better CART results, i.e., statistically significant lower incidence of CAN in statin Group.

CAN has been associated with increased inflammatory markers such as C-reactive protein, interleukin-6, tumor necrosis factor alpha, and adipose-tissue inflammation.^[23] Although the exact mechanism is unclear, the relation between neuropathy and inflammation is bidirectional, i.e., one can precipitate the other, thus creating a vicious cycle. Vinik *et al.* suggested that the inflammatory response is controlled by a neural circuit, in which the afferent arc consists of nerves that sense injury and transmit the information through the vagus nerve to the brain stem, which in turn activates the cholinergic anti-inflammatory pathways modulating the response.^[24] Statin was reported to ameliorate inflammation in many studies.^[25,26] Thus, statins

possess an anti-inflammatory, immunomodulatory effect and decrease oxidative stress, thereby contributing to overall cardiovascular benefit.

Rodrigues *et al.* published an interesting study in 2010 proving that reduced HRV (marker of CAN) predicts the progression of coronary artery calcification in adults with and without Type 1 diabetes mellitus, suggesting that autonomic neuropathy leading to pro-inflammatory state could represent one pathway, leading to atherosclerosis progression.^[27] Additional anti-inflammatory action of statin may be beneficial for reducing atherosclerosis apart from its lipid-lowering effect. Thus, pleiotropic protective action of statins on CAN may be the reason for beneficial effect of statins on CAN and subsequently reducing cardiovascular morbidity and mortality.

Composite Autonomic Symptom Scale 31 questionnaire

COMPASS 31 questionnaire studies have shown sensitivity of 75% and 70% for early CAN and definite CAN, and a specificity of 65% and 67%, respectively.^[28] In our study, COMPASS 31 Questionnaire score analysis showed a significantly lower total score and cardiovascular domain score indicating a cardioprotective effect of statins. A COMPASS 31 score of >16 is considered indicative of CAN and was observed in patients who were diagnosed with definite CAN from the objective test CART. A higher total COMPASS 31 score is correlated with definite CAN as diagnosed from CART. This study thus concludes that COMPASS 31 is an effective screening tool for CAN and can be used for referral of patients for CART, since HRV-CART technology may not be available at primary health-care level.

In our study, none of the patients showed any severe or clinically impairing adverse effect of statin requiring withdrawal of the medication, as assessed from SEAQ. Both symptom severity and symptoms impact score were low. Few patients complained of fatigue and muscle weakness, but it did not affect their daily activities. Low-dose atorvastatin (10/20 mg) and small sample size of our study could be the probable reasons for the limited adverse effects reported. Similar to our finding, overall many major statin trials including large meta-analyses have concluded that severe musculoskeletal side effects from statin use are rare, and that the overall benefits of statin therapy outweigh this small risk.^[29,30] However, patients with multiple medical comorbidities are at increased risk of adverse effects from long-term statin use.

Limitation

It was a cross-sectional study. Cohort studies and randomized control trials are further needed to confirm this beneficial effect of statins. Some patients were concurrently prescribed other drugs which may have an effect on CAN in the long run. Only atorvastatin (lipophilic) was used, so the results cannot be extrapolated to other statins, e.g., hydrophilic statins.

CONCLUSION

This study states that statins have a protective effect in

preventing the development of cardiac autonomic neuropathy in diabetic patients and can be safely administered to patients of Type 2 diabetes mellitus without expecting any clinically impairing ADRs. This may reduce the incidence of adverse cardiac events in diabetic patients. Analysis of COMPASS 31 questionnaire showed that symptoms of autonomic neuropathy like orthostatic hypotension were significantly higher in the nonstatin group. It also showed that a higher COMPASS 31 questionnaire score indicative of neuropathy, correlated well with patients diagnosed as definite CAN from CART. Thus, patients having a total score of >16 can be referred for CART. COMPASS 31 questionnaire can be used as an effective bedside screening tool for CART referral, thus facilitating early diagnosis of CAN.

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Conflicts of interest

There are no conflicts of interest.

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