ORIGINAL ARTICLE

Therapeutic Review of Metformin and Sulfonylureas Regimen for Protection of Cardiac Autonomic Neuropathy in Type 2 Diabetes Mellitus

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ABSTRACT

Background: Cardiovascular autonomic neuropathy (CAN) is an important progressive complication of type 2 diabetes mellitus (T2DM). Therapeutic salvation of CAN is usually not practiced either due to lack of awareness or no consensus treatment is available for its management.

Methods: A prospective, observational, open label, non-randomized cohort study enrolling 63 patients of T2DM, examined thrice clinically and for CAN in 6 months followup. The CAN score in each patients and its relation to metformin plus sulfonylureas regimen over 6 months was analyzed. Possible influences of age, obesity (BMI), duration of diabetes, glycosylated hemoglobin (HbA1c) level and coexistent peripheral neuropathy on occurrence of CAN were also studied.

Results: The prevalence of CAN was as high as 62% in our (North Indian) patients. Univariate analysis showed a significant association between CAN and higher age ($p<0.002$), obesity (BMI) ($p<0.001$), HbA1c ($p<0.0001$), duration of diabetes ($p<0.001$), hypertension ($p<0.004$), peripheral neuropathy ($p<0.001$) and erectile dysfunction ($p<0.001$), but only obesity (BMI), HbA1c, duration of diabetes, peripheral neuropathy and erectile dysfunction showed independent risk on multivariate analysis. Metformin plus sulfonylureas regimen targeting normal level of HbA1c (<7) resulted in improvement of CAN. Although various factors affect outcome of CAN independently such as obesity (BMI), duration of diabetes and HbA1c, we got 40% improvement in CAN in patients with dysglycemia (HbA1c >10) with combination regimen.

Conclusions: The prevalence of CAN in T2DM is fairly high (62%) in North Indian population. Higher HbA1c, longer diabetes duration and obesity (BMI) are significant risk factors. Although there is improvement in glycemic level of patients receiving metformin plus sulfonylureas therapy, but overall improvement of CAN needs more elucidation of pathogenesis of diabetic autonomic neuropathy and new insights and agents of therapy. (J Clin Prev Cardiol. 2013;2(4):178-84)

Keywords: cardiac autonomic neuropathy (CAN); type 2 diabetes mellitus (T2DM); glycosylated hemoglobin (HbA1c); body mass index (BMI)

Introduction

Type 2 diabetes mellitus (T2DM) increases the risk of heart disease, stroke and microvascular complications such as blindness, renal failure and peripheral neuropathy (1). T2DM is one of the important causes of neuropathy. Neuropathy often leads to increased morbidity and mortality in patients with T2DM. While sensory neuropathy damages the sensory nerves in the extremities, diabetic autonomic neuropathy (DAN) damages the nerves supplying the heart, all internal organs and other processes that are not under direct conscious control. DAN is among the least recognized and understood complications of diabetes, despite its significant negative impact on survival and quality of life in people with diabetes (2–4). 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 (5). CAN is a significant cause of morbidity and mortality associated with a high risk of cardiac arrhythmias and sudden death (4). The clinical manifestations are exercise intolerance, orthostatic hypotension, painless (silent) myocardial ischemia, etc. The incidence of silent myocardial ischemia is very high and CAN appears to be the most

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probable reason for absence of pain (6). DAN has a slow and insidious onset and many patients suffer from the condition unknowingly for years. Many studies using different end-points report prevalence rates of 1–90% (2), although an estimated 30–40% of those are in the pre-symptomatic stage and are, therefore, unlikely to know of their condition.

Attainment and maintenance of near-normal glycemia reduces the risk of long-term complications of diabetes. Despite lifestyle and pharmacological interventions, glucose level increases over time in T2DM, probably as a consequence of decline in β-cells function. The progressive nature of T2DM makes it difficult to maintain target levels of HbA_{1c} with traditional glucose-lowering agents and generally necessitates escalation of drug doses and use of combination therapy or insulin. The present study is to investigate the relation between HbA_{1c} levels and CAN with conventional therapeutics (metformin plus sulfonylureas), and gather preliminary insight to determinants averting or reverting CAN in patients with T2DM.

Methods

The present study was conducted prospectively in the Department of Pharmacology in association with Department of Endocrinology & Metabolism, Institute of Medical Sciences (IMS) and associated Sir Sunderlal Hospital (SSLH), Banaras Hindu University (BHU), Varanasi, over a period ranging from February 2008 to June 2009 under routine care of Department of Endocrinology.

Patients

Eligible patients were between the ages of 30 and 65 years with diagnosed T2DM, noncritical and ambulatory, attending the diabetic clinic during study period. Cases prescribed initial pharmacotherapy of metformin and sulfonylurea drugs for diabetes were selected. Comorbidity of hypertension alone was accepted along with necessary treatment. Diabetic patients with known serious cardiovascular, respiratory, renal, hepatic and cerebrovascular disease and electrolyte imbalance and those who were not willing to participate were excluded. The control group comprised of 10 subjects who were nondiabetic, healthy adults and matched for age, sex and other baseline characteristics that were present in the study group. Informed consent was obtained from each participant and the study was approved by Institutional Ethics Committee (IEC).

Study Design

This is a prospective, observational, open-label, nonrandomized cohort that examined the effects of basic sugar controlling regimen of metformin and sulfonylureas on CAN. Profile of autonomic dysfunction elaborated with reference to standard value obtained in nondiabetic, healthy adults (control) in similar age range. The profile of autonomic dysfunction compared for generally assumed determinants viz. age, sex, obesity (BMI), HbA_{1c}, duration and control of diabetes and antidiabetic regimens. Sixty-three patients who satisfied the eligibility criteria were studied, out of which 41 turned up in first followup while only 30 patients in second followup.

Study Procedure

All the patients were evaluated with a detailed history and clinical examinations. Baseline hematological and biochemical investigations were done in all the cases on all three occasions. Particular emphasis was given on assessment of cardiac autonomic dysfunctions. The following five tests for detecting CAN were used in each of the enrolled participants using four leads cardiac monitor: (1) resting heart rate (HR>100 beats/min was taken as abnormal); (2) heart rate response to deep breathing (ECG was recorded continuously while the patient was taking breath at a regular rate of 6–12 breaths/min and a difference in heart rate <15 beats/min between inspiration and expiration was considered abnormal); (3) heart rate variability to posture (HR was recorded in supine posture and immediately after standing; a ratio of RR interval at 30th and 15th beat was calculated; ratio of <1.04 was considered abnormal); (4) BP for postural or orthostatic hypotension (BP was recorded in supine posture and again just after 2 min of standing; a fall in systolic BP of >20 mmHg and diastolic BP of >10 mmHg were considered abnormal); (5) diastolic blood pressure response to an isometric exercise (the patient was asked to squeeze a ball in his or her left hand for about 5 min and an increase in diastolic blood pressure <10 mmHg was considered abnormal). This is a modification of original Ewing's criteria (7) for assessment of CAN, wherein Valsalva method was replaced with resting heart rate parameter given in Table 1.

Table 1.

Interpretation of autonomic function tests (AFT) as normal, borderline or abnormal depending on the value of the parameter measured and score as points are given in bracket

Tests	Predominant AFT	Normal (0)	Borderline (0.5)	Abnormal (1)
1. Resting heart rate/min	Parasympathetic	<100	100–110	>110
2. Deep breathing test (max–min heart rate beats/min)	Parasympathetic	>15	10–15	<10
3. Heart rate response to standing (30:15 ratio)	Parasympathetic	>1.04	1.00–1.04	<1.00
4. BP response to standing (fall in SBP in mmHg)	Sympathetic	<10	10–20	>20
5. BP response to sustained hand grip (increase in DBP in mmHg)	Sympathetic	>15	10–15	<10

A scoring system like the one suggested by Bellavere *et al*. (8) was also utilized to assess the extent of autonomic nervous damage. The total points from each of these five tests were added and CAN Score was categorized as follows: CAN score 0 (total points 0), CAN score 1 (total points 0.5–1.5), CAN score 2 (total points 2–3) and CAN score 3 (total points ≥3.5). CAN was considered absent, early, definite or severe if the CAN score were 0, 1, 2 or 3, respectively.

Neurological Assessment

Each participant was also examined for presence or absence of neuropathy by testing for abnormal pin-prick sensations in the limbs, abnormality of position sense in the big toe, and the absence of Achilles tendon reflex.

BMI

Weight and height were recorded and the BMI was calculated by the formula: weight (kg) divided by square of height (m^2).

Baseline investigations

Complete hemogram, blood sugar (fasting and post prandial, 2 hours) were done.

HbA1c estimation

With all aseptic precautions 4 ml of venous blood was drawn from the antecubital vein with a sterilized plastic disposable syringe. After collection of blood sample 2 ml of whole blood was taken immediately in a test tube containing EDTA anticoagulant for estimation of HbA_{1c}. Percentage of HbA_{1c} was measured in whole blood by kit DS-V Analyzer using a modified HPLC method.

Statistical analyses

All values (data) were expressed as mean±SD. Mean values were compared using independent *t*-test. The χ^2 was used appropriately to compare frequencies between the different groups. *P*-value <0.05 was considered to be statistically significant. To compare among groups, repeated measure ANOVA (RMANOVA) with Wilks' lambda test was performed as the test of significance. The Pearson's correlation coefficient was done to observe relationship among different variables. To analyze the data, SPSS 16 Package was used.

Results

Out of the 63 patients who satisfied the inclusion criteria, only 30 patients followed up to second followup and the analysis was done as per protocol. The male-to-female ratio was 60:40. The median age was 50 years (34–65 years), median BMI was 24.1 (18.9–37.6), median duration of diabetes was 5 years (2–15 years).

Table 2 depicts that there was significant difference of CAN scores in <50 and >50 years age group at the time of inception and at first followup, but waned in second followup. There was significant difference in CAN scores of BMI <25 and >25 not only at inception but at all followup. Similar results were obtained for parameters such as HbA_{1c} and duration of diabetes. In case of hypertension, peripheral neuropathy and erectile dysfunction (ED) parameter there were significant differences of CAN scores in respective groups at the time of inception and first followup with some changes in second followup.

Table 2.

Relation of CAN scores with various parameters

Serial No.	Variable	Parameter	No. of Patients	CAN Score at Reporting Mean (SD)	CAN Score at First Followup Mean (SD)	CAN Score at Second Followup Mean (SD)
	Age	<50	14	1.5 (1.33)	1.4 (1.39)	1.4 (1.24)
		>50	16	2.9 (0.86)	2.6 (1.25)	2.2 (1.44)
		p value		0.002	0.023	0.122
	BMI	<25	13	1.2 (1.07)	0.9 (1.11)	0.9 (0.92)
		>25	17	3.0 (0.76)	2.9 (0.97)	2.5 (1.31)
		p value		0.001	0.001	0.001
	HbA_{1C}	<10	10	0.8 (0.85)	0.6 (0.77)	0.6 (0.72)
		>10	20	2.9 (0.75)	2.8 (1.08)	2.5 (1.17)
		p value		0.0001	0.0001	0.0001
4.	Duration of diabetes	< 5	13	1.2 (1.12)	0.8 (1.01)	0.8 (0.83)
		>5	17	3.0 (0.78)	3.0 (0.75)	2.7 (1.14)
		p value		0.001	0.001	0.001
5.	Hypertension	Absent	17	1.6 (1.29)	1.5 (1.38)	1.5 (1.31)
		Present	13	3.0 (0.87)	2.8 (1.18)	2.3 (1.37)
		p value		0.004	0.013	0.087
6.	Peripheral neuropathy	Absent	15	1.5 (1.23)	1.1 (1.06)	1.2 (1.22)
		Present	15	3.0 (0.81)	3.0 (0.79)	2.5 (1.23)
		p value		0.001	0.001	0.005
7.	Erectile dysfunction	Absent	17	1.5 (1.15)	1.3 (1.19)	1.3 (1.14)
		Present	13	3.3 (0.56)	3.1 (1.02)	2.6 (1.38)
		p value		0.001	0.001	0.010

Table 3 depicts that all patients above 50 years had some grades of CAN while 64% (9 out of 14) below 50 years of age had dysfunction at reporting. By the time of second followup with institution of therapy, older patients exhibited more correction.

There was no gender predilection for occurrence of CAN. The rate of improvement or deterioration in CAN was similar in male and female patients, during the observation up to second followup.

Table 3.

Relation of CAN score with age and therapeutic correction of CAN

Age	Patients Showing Change with Therapy		
	Improvement	No Improvement	Deterioration
<50	4/14 (28.6%)	6/14 (42.8%)	4/14 (28.6%)
>50	6/16 (37.5%)	10/16 (62.5%)	0 (100%)

Table 4 depicts that patients with BMI within normal range had 64% (9 out of 14) prevalence of CAN at first reporting. All patients with excess BMI suffered CAN; in contrast BMI drastically reflected association with presenting severity of CAN. Thus excess BMI cases had nearly double severity of that seen in those with normal range BMI. Only minor difference was seen in improvement rates of CAN (39% and 29%).

Table 4.

Relation of CAN score with BMI and therapeutic correction of CAN

BMI	Patients Showing Change with Therapy		
	Improvement	No Improvement	Deterioration
<25	5/13 (39.0%)	2/13 (15.3%)	4/13 (30.6%)
>25	5/17 (29.0%)	11/17 (64.7%)	1/17 (5.8%)

Table 5 depicts that none of the patients with HbA_{1c} <7 presented with autonomic neuropathy. All those with

HbA_{1c} >10 had CAN. Severity of CAN was much higher in patients with HbA_{1c} >10 compared to those with values HbA_{1c} <10 at the time of reporting. Recovery profiles reveal 62% of patients exhibiting HbA_{1c} <10 becoming free of CAN by second followup. Recovery rate of CAN was lower (38%) in patients with HbA_{1c} >10. Apparently improvement had no bearing with initial severity of CAN in the either group.

Table 5.

Relation of CAN score with HbA_{1C} and therapeutic correction of CAN

HbA_{1C}	Patients Showing Change with Therapy		
	Improvement	No Improvement	Deterioration
<7	0	0	1/4 (25%)
7–10	8/13 (61.5%)	4/13 (30.7%)	0
>10	5/13 (38.4%)	8/13 (61.5%)	0

Table 6 depicts that there is strong relation between duration of diabetes and occurrence of CAN. All the cases of diabetes with >5 years of duration presented with abnormal CAN score. The severity of CAN present at first reporting exhibited progressive deterioration with duration of diabetes. Improvement through the second followup of instituted therapy occurred in all categories but was best seen in cases less than 5 years duration of diabetes. Cases with recent (1 year) duration of diabetes had marked instances of worsening of CAN than any other group despite institution of therapy.

Table 6.

Relation of CAN score with duration of diabetes and therapeutic correction of CAN

Duration of Diabetes	Patients Showing Change with Therapy		
	Improvement	No Improvement	Deterioration
Up to 1 year	3/6 (50%)	0	3/6 (50%)
>1–5 years	5/9 (55.5%)	4/9 (44.5%)	0
>5–10 years	3/10 (30.0%)	6/10 (60.0%)	1/10 (10.0%)
>10 years	2/5 (40.0%)	3/5 (60.0%)	0

Prevalence of CAN was found in all diabetic with hypertension (either systolic or diastolic). While 66% of nonhypertensive diabetic had some grade of CAN. Severity of CAN was markedly higher in hypertensive diabetic as opposed to nonhypertensive diabetic. Nevertheless recovery following therapy at second followup was as good or slightly higher in case of diabetes with hypertension. Interestingly, none of the hypertensive patients suffered further deterioration of CAN score during study while in nonhypertensive deterioration occurred in nearly even number of patients as showing improvement.

Table 7 depicts that appraisal of cases with symptoms of peripheral neuropathy shows strong relation with CAN. Whenever apparent sign of peripheral neuropathy was detected, it was consistently present with CAN in diabetic patients. It is evident that rate of improvement in CAN following hypoglycemic therapy was similar in patients with or without signs of peripheral neuropathy.

Table 7.

Relation of CAN score with peripheral neuropathy and therapeutic correction of CAN

Subjective Symptoms	Patients Showing Change with Therapy		
	Improvement	No Improvement	Deterioration
Absent	6/12 (50.0%)	4/12 (33.3%)	2/12 (16.6%)
Present	8/15 (53.3%)	6/15 (40.0%)	1/15 (6.6%)

ED always accompanied CAN. However, CAN could occur in absence of ED. Improvement of CAN was marginally better in patients with ED.

Discussion

Among the patients with T2DM, higher age, BMI, HbA_{1c}, duration of disease over 10 years and peripheral neuropathy were the factors associated with higher risk of CAN in univariate analyses, while gender difference posed no additional risk. Higher BMI, HbA_{1c}, duration of diabetes over 10 years significantly increased the risk for higher CAN.

1. The high prevalence of CAN (62%) among the patients with diabetes was similar to previous observations by Mehta *et al.* (9) (57.5%), Pappachan *et al.* (10) (60%) and Nanaiah *et al.* (11) (63.3%). Although Nanaiah *et al.* (11) reported prevalence of CAN in Asian Indian patients with a special condition of fibrocalculous pancreatic diabetes. There are large variations in prevalence reported as Sinha *et al*. (12) suggest 43.5%. It is probably because of difference of socioeconomic or BMI or duration of diabetes or control of dysglycemia in groups under study.

2. All patients above 50 years had some grades of autonomic neuropathy while 64% (9 out of 14) below 50 years of age had dysfunction at reporting. By the time of second followup with institution of therapy, older patients exhibited more correction. Rodrigues *et al.* (13) also support that older age is one of the factors of CAN severity, but in T1DM factors which actually play in the development of autonomic neuropathy are still poorly defined. Impact of metabolic changes with increasing age on neural circulation causing reduced blood flow and hypoxia could be the important factors (14). In the EURODIA (15), prospective complication study that examined 956 patients with T1DM, higher age of the patients at baseline posed a statistically significant risk for future development of CAN. In our cohort of patients with T2DM we found the similar association with higher age.

3. Male patients were showing slightly lower mean CAN score in comparison to females though the difference was not statistically significant. Sinha *et al.* (12) reported higher occurrence in males, but the difference was not statistically significant.

4. Patients with BMI within normal range had 60% occurrence of CAN at first reporting. All patients with excess BMI (>25) suffered CAN. The >25 BMI cases had nearly double severity of that seen in those with <25 BMI. Rodrigues *et al.* (13) and Colhoun *et al*. (16) also reported relation with BMI in heart rate variation (cardiac autonomic dysfunction) in T1DM patients.

5. Appraisal of patients, when by stratifying those exhibiting HbA_{1c} value; under 10 and above it, it was seen that CAN had strong relation with higher HbA_{1c} level. Rodrigues *et al.* (13) and Colhoun *et al.* (16) also reported relation with BMI in heart rate variation (cardiac autonomic dysfunction) in T1DM patients.

6. Longer duration of disease was found to be an important risk factor for the development of CAN among 105 Vietnamese patients studied by Thi *et al.* (17) and is one of the findings in our study.

7. Significant risk for future development of CAN in diabetes patients with peripheral neuropathy at the time of initial evaluation was observed in the EURODIAB (15) study. Our finding of higher prevalence of CAN in those with peripheral neuropathy in T2DM also adds to the existing evidence of the association between these two disease entities.

8. ED always accompanied CAN. However, CAN could occur in absence of ED. Improvement of CAN was marginally better in patients with ED. Kempler *et al.* (18) also suggest that ED correlates significantly with the severity of CAN among T1DM patients. Although ED is associated with autonomic neuropathy, ED prevalence in patients with CAN and the prevalence of CAN among patients with ED have not been analyzed in large epidemiological studies.

The major benefit because of metformin plus sulfonylureas therapy was not significant in our study, which was primarily made to find out other indications for established combination therapy.

The study has few important limitations. The sample size was relatively small and on the top of it, followup was not satisfactory. Since this is an observational study planned for two followups, specific combination of particular sulfonylurea was not made, which could have further reduced the number of study subjects.

Conclusion

CAN is a common complication of T2DM. Higher age, BMI, HbA_{1c}, duration of disease over 10 years and peripheral neuropathy were the factors associated with higher risk of CAN in diabetics. Glycemic control is one of the most important factors which have to be properly taken care in order to prevent/delay either initiation or progression of CAN in T2DM. Although there was improvement in CAN with glycemic control, the quantum of benefit by metformin plus sulfonylureas therapy was not very promising.

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None

Conflict of Interest

None

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