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Research Article

EFFECT OF METFORMIN ON HEART RATE VARIABILITY IN NEWLY DIAGNOSED TYPE 2 DIABETES MELLITUS PATIENTS AT A TERTIARY CARE HOSPITAL

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ABSTRACT

Objectives: There is a worldwide epidemic of type 2 diabetes mellitus (T2DM). It is associated with cardiovascular autonomic neuropathy. Heart rate variability (HRV) is the gold standard for its measurement. Thus, effect of metformin therapy on HRV was evaluated in newly diagnosed T2DM patients.

Methods: This was a prospective and observational study carried out from January 2020 to September 2021 in the medicine outpatient department of a tertiary care hospital in Gujarat, India. The study included newly diagnosed T2DM patients of both genders aged 18–70 years. Baseline HRV parameters were recorded by performing electrocardiogram for a fixed duration of 5 min. Follow-up was done after 6 months of metformin 500 mg monotherapy. Time domain analysis was done using square root of mean square of successive R-R interval difference (RMSSD) and frequency domain analysis was done using low-frequency/high-frequency (LF/HF) ratio. Paired *t*-test was used for analysis. $p<0.05$ was considered statistically significant.

Results: Total 30 patients were included in the study. The average age of participants was 43.5±4.5 years. The highest number of patients were from age group between 41 and 50 years (33.3%). There were more number of females (56.7%) compared to males (43.3%). There was an increase in the RMSSD value after metformin treatment, but it was not statistically significant ($p=0.308$). In frequency domain analysis, there was no significant improvement in LF, HF, as well as LF/HF ratio ($p=0.655$).

Conclusion: There was a minor improvement in HRV parameters after 6 months of metformin therapy, but it was not statistically significant. Further studies with larger sample size should be planned with one or more oral hypoglycemics.

Keywords: Autonomic nervous system, Diabetes mellitus, Heart rate variability.

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INTRODUCTION

There has been a steady increase in the global prevalence of type 2 diabetes mellitus (T2DM), a chronic endocrinal metabolic disorder [1]. Based on 2019 estimates, there are approximately 77 million cases of diabetes mellitus (DM) in India, which is expected to double by 2045, making it the fastest growing disease in India [2]. T2DM is the most common form of diabetes and is associated with many multiorgan complications. Cardiovascular complications such as stroke and myocardial infarction are major cause of morbidity and mortality in diabetic patients [3]. One of the factors associated is autonomic neuropathy occurring due to impaired glucose metabolism which also affects the nerves innervating the heart and blood vessels. This leads to dysfunctional heart rate. An imbalance between the parasympathetic and the sympathetic activity reflects a disorder of the automatic nervous system (ANS). Heart rate variability (HRV) measurement is considered gold standard for assessing the autonomic dysfunction [4].

The time interval between two heartbeats is HRV. It is a physiological phenomenon. Variation in "RR interval" of each heartbeat is used to determine it. It is one of the well-known parameters to assess functional aspect of ANS. It has been observed that duration of RR interval continually fluctuates even at rest. These fluctuations are a result of extremely complex neural mechanisms which are mainly based on interaction between the parasympathetic and sympathetic nervous systems [5]. It has also been reported in a recent systematic review that, T2DM significantly alters the autonomic activity. It strongly decreases the HRV which denotes a decrease in both the sympathetic and parasympathetic activities [4]. There is a dearth of data related to the effect of oral hypoglycemic drugs on HRV indices in T2DM patients, especially with metformin monotherapy. Thus, in view of this background, this study was conducted with an aim to evaluate the effect of metformin treatment on the HRV parameters in patients of T2DM. To achieve this, time domain analysis and frequency domain analysis of HRV parameters was carried out.

METHODS

This was a prospective and observational study conducted at a tertiary care hospital in Surat, Gujarat for 1 year and 9 months from January 2020 to September 2021. The study was conducted in the department of medicine. It was started after getting approval of the Institutional Ethical Committee. Study population included newly diagnosed DM patients started on metformin therapy. The diagnosis of T2DM was solely based on the attending physician's discretion. The selection was based on following inclusion and exclusion criteria –

Inclusion criteria

The following criteria were included in the study:

- Newly diagnosed adult T2DM patients of either gender aged between 18 and 70 years started on single drug anti-diabetic therapy with metformin.
- Not exposed to earlier treatment with metformin or any other oral hypoglycemic drugs and any other drugs which may affect glucose tolerance test (GTT) for T2DM.
- Patients willing to give informed consent.

Exclusion criteria

The following criteria were excluded from the study:

- Patients with comorbid conditions such as acquired immunodeficiency syndrome, cardiovascular disease, and renal disorders, or who are taking any concurrent medications for these diseases.
- Patients on any other medications which may affect GTT.

Study procedure

The patients fulfilling the inclusion criteria were explained the study procedure and its objectives in detail and written informed consent of the participant was taken before enrolling them in the study. Demographic details of the patients were noted and general examination was carried out. This was followed by a baseline or pre-treatment estimation of HRV. To estimate HRV, after 20 minutes of rest, electrocardiogram (ECG) was taken using Physiopac Digital Polygraph software for a fixed duration of 5 min. HRV was calculated by root mean square deviation of successive differences between adjacent RR intervals (RMSSD), low frequency (LF), high frequency (HF), and LF and HF ratio. All the patients were prescribed Metformin at the dose of 500 mg 2 times a day. Follow-up HRV assessments were done on 6th month. Follow-up ECG recording for HRV estimation was also taken by same method and duration. Follow-up values after 6 months of metformin treatment were compared with pre-treatment values of same patient, so pre-treatment values of RMSSD, LF, HF, and LF/HF were considered as baseline.

Time domain analysis

Parametric analysis was used to determine the time domain variables. The measures derived were as follows:

- Standard deviation of NN intervals
- Square root of mean square of successive RR interval difference (RMSSD)
- Number of interval differences of successive R-R intervals <50 ms (NN50)
- Proportion derived by dividing NN50 by total number of R-R intervals (pNN50)

For HRV analysis, out of all of the above parameters, RMSSD value was taken into consideration in this study.

Frequency domain analysis

Frequency of 256 Hz was used to take the ECG. In a particular duration of 5 min, amplitude criterion was used to detect the R-wave of QRS complex and RR intervals were measured. The duration was fixed at 5 min [6]. To obtain the frequency spectrum of HRV, fast Fourier transformation of the RR intervals verses time plot was done at the sampling rate of four Hz. The following frequency ranges were categorized

- ≤0.04 Hz – very LF
- 0.04–0.15 Hz – LF
- 0.15–0.40 Hz – HF.

The data were obtained in terms of powers of LF and HF and the ratio of LF/HF. The power of HF is associated with parasympathetic control and that of LF is equated with sympathetic control. For HRV analysis, the ratio of LF/HF was considered in this study.

Data analysis

The data were entered and analyzed using the Statistical Package for the Social Sciences 23.0 software. All values were expressed as mean±SD. Paired *t*-test was used for statistical analysis. p<0.05 was taken as statistically significant.

RESULTS

Thirty participants were included in this study. The average age of study participants was 43.5±4.5 years. Fig. 1 shows the age distribution of the study population. The highest number of patients were from age group between 41 and 50 years (33.3%, n=10). The gender distribution of the study population revealed a higher number of females (56.17%, n=13), number of males (43.3%, n=10).

Time domain analysis

As depicted in Fig. 2, using the paired sample *t*-test, there was no significant difference reported in RMSSD value before (M=29.70, SD=22.82, SEM=4.16) and after (M=45.50, SD=87.46, SEM=15.96) metformin administration (t [29] = −1.037, p=0.308).

Frequency domain analysis

A paired sample *t*-test revealed no significant difference in the LF (p=0.655) as well as HF (p=0.655) before and after metformin administration in the study population. Furthermore, as shown in Fig. 3, there was no significant difference in LF/HF ratio value before (M=5.41, SD=2.46, SEM=0.45) and after (M=5.16, SD=1.62, SEM=0.29) metformin administration (t [29]=0.451, p=0.655).

DISCUSSION

T2DM is one of the most common endocrine disorders encountered worldwide. It is associated with significant micro and macrovascular complications [7,8]. In addition to that, there is associated autonomic dysfunction due to the damage to autonomic nerve fibers due to altered glucose metabolism. This causes cardiovascular autonomic neuropathy. Thus, diabetes decreases HRV by decreasing both the sympathetic as well as parasympathetic activity [4]. Decreased HRV is a consistent and independent risk factor for cardiac mortality. It is a non-invasive procedure to easily evaluate the autonomic system activity. Oral hypoglycemic drugs are prescribed to control the blood sugar levels which, in turn, can positively affect the autonomic activity and improve

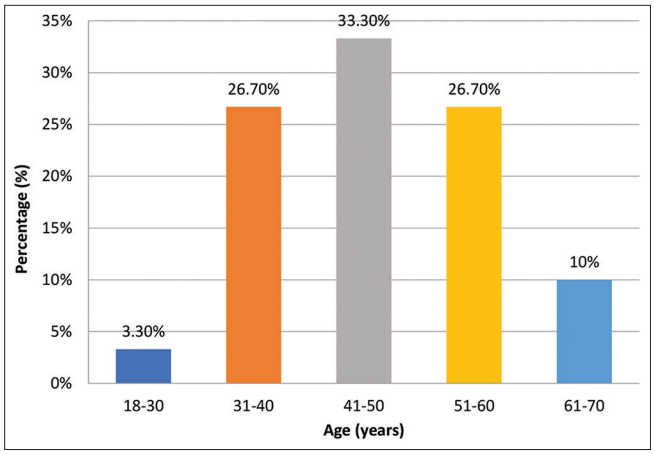

Fig. 1: Age distribution of the study population (n=30)

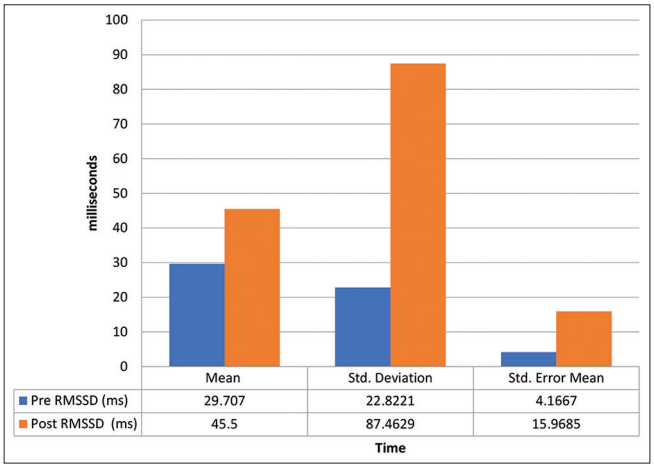

Fig. 2: Effect of metformin on RMSSD measured during follow-up visit compared with baseline. (n=30, RMSSD – square root of mean square of successive R-R interval difference)

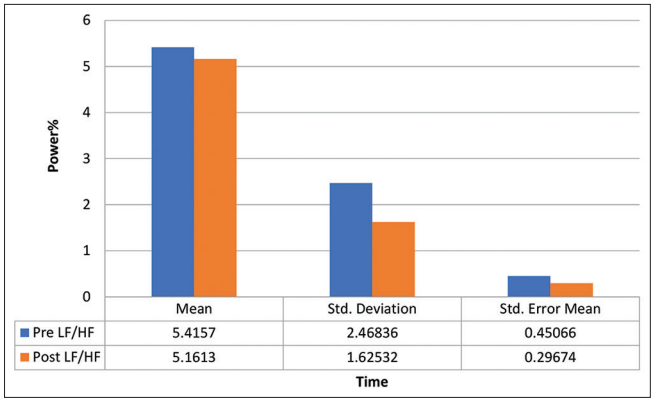

Fig. 3: Effect of metformin on low-frequency/high-frequency (LF/HF) measured during follow-up visit compared with baseline. (n=30, LF/HF)

the HRV parameters. Thus, this study was conducted to study the effects of 6 months' metformin treatment on HRV in patients of T2DM.

An average increase of 15.79 ms was observed in mean RMSSD value after 6 months of metformin treatment. However, it was not statistically significant (p=0.308). This was similar to the findings of study by Kilit *et al*. involving analysis of HRV in T2DM patients treated with combination of metformin and rosiglitazone, which reported no significant differences in HRV parameters like RMSSD in the patients [9]. Extremely low RMSSD signifies true autonomic dysfunction. Although there are no established normal values for HRV parameters yet; but, van den Berg *et al*. reported a continuous decrease in RMSSD values from birth to old age; RMSSD values fall between 24.4 and 48.5 ms for the age group of 20–59 years [10].

It was noted that there was an average reduction in mean LF value of 1.91 power% after 6 months of metformin treatment; but, the reduction was not statistically significant (p=0.655). LF component corresponds to the sympathetic branch of autonomic nervous system. Increased LF suggests increased sympathetic cardiac functioning. Although there are no established normal values for HRV parameters; yet, Sammito *et al*. reported a range of LF/HF ratio from 38.51 to 68.07 power% for the age group of 20–60 years [11]. There was an average increase of 0.72 power% in mean HF value after 6 months of treatment. However, this increment in mean HF value was not statistically significant (p=0.655). HF component corresponds to the parasympathetic branch of autonomic nervous system. Sammito *et al*. reported HF values between 16.41 and 31.92 power% for the age group of 20–60 years [11]. A recent study evaluating the effects of combination treatment of metformin with either liraglutide or glimepiride reported similar results with no significant changes in RMSSD, LF, and HF and LF/HF ratio with the oral hypoglycemic drugs [12].

There was an average reduction of 0.25 power % in the mean LF/HF ratio after 6 months' treatment with metformin. However, it was not statistically significant (p=0.655). This was in contrast to the findings of Manzella *et al*. which reported a significant reduction in LF/HF ratio with metformin (p=0.02) [13]. Cardiac autonomic balance is indicated by LF/HF ratio. Increase in this ratio indicates an imbalance between cardiac sympathetic and parasympathetic activity. Although there are no established normal values for HRV parameters; yet, Sammito *et al*. reported a range of LF/HF ratio from 3.63 to 8.32 power % for the age group of 20–60 years [11].

Overall, no statistically significant increase or decrease in HRV after treatment with metformin was reported in the results of this study. This could be due to a few limitations in the study methodology. The most important is the small sample size, which was due to the COVID-19 pandemic which resulted in nationwide lockdown and stoppage of routine outpatient services in out hospital. Due to the small sample size, the results could not be reported with conclusively in one direction and are not suitable to generalize for large population. Second, due to limited infrastructure and for patient convenience, HRV measurement was limited to 5 minutes only. This recording time is not ideal to explain the changes in HRV in detail. Furthermore, follow-up was only done once after 6 months. Future studies with multiple follow-ups for longer duration could be designed to generate more accurate and reliable results.

CONCLUSION

It could be concluded from the present study that metformin did not have any significant impact on HRV in newly diagnosed T2DM patients. There were no significant changes in RMSSD, LF, HF, and LF/HF ratio. As HRV reflects the sympathovagal balance in an individual with diabetes, this area needs to be explored. Future prospective studies should be carried out with larger sample size to evaluate the effects of various oral hypoglycemic drugs on the HRV parameters in T2DM patients. This will help in the early recognition of diabetic patients at high risk of cardiovascular dysfunction.

AUTHORS CONTRIBUTIONS

All the authors contributed equally toward the study starting from literature review, identifying the research gap, research proposal writing, data collection and analysis, manuscript writing, and publication.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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