

Reverse Dipping of Blood Pressure in Patients of Hypertension with and without Type 2 Diabetes Mellitus

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ABSTRACT

Objective: To determine the frequency of reverse dipping among hypertensive patients with and without type 2 Diabetes Mellitus (T2DM).

Methodology: This descriptive, cross-sectional study was conducted at Medical Unit of Pakistan Ordinance Factories Hospital Wah Cantt from April 2020 to April 2021 after institutional ethical review board approval. Ninety patients with hypertension of both sexes, aged 18-85 years were enrolled using non-probability consecutive sampling technique. Blood sample for fasting and random glucose levels were gathered. Ambulatory Blood Pressure was monitored for 24 hours by installing the monitor (Ambulatory Blood Pressure Monitor ABPM50 Contec China, Product Code: ABPM50) on non-dominant arm, measuring at 30 minutes intervals during the day (from 7:00 AM to 11:00 PM) and at 60-minute intervals during the night (from 11:00 PM to 7:00 AM). All the data was recorded and analyzed.

Results: Mean age was 51.18 ± 10.1 years with 54 (60.0%) were male and 36 (40.0%) females. Mean fasting blood glucose and mean random blood glucose levels were 87.32 ± 13.2 mg/dl and 152.76 ± 21.8 mg/dl respectively. T2DM was seen in 38 (42.2%) patients. Blood pressure reverse dipping was found in 34 (37.7%) hypertensive patients. Frequency of blood pressure reverse dipping among hypertensive patients with and without T2DM was found to be 63.1% and 19.2% respectively (p-value <0.001).

Conclusion: Reverse Dipping was seen in more than one-third of the patients with hypertension having a statistically significant association with T2DM.

KEYWORDS: Hypertension, Reverse Dipping, Type 2 Diabetes Mellitus, Blood Pressure.

INTRODUCTION

Diabetes Mellitus is becoming the epidemic of present age in terms of incidence and prevalence.¹ Type 2 Diabetes Mellitus (T2DM) is a multifactorial and chronic disease, characterized by

hyperglycemia caused by variable degrees of insulin deficiency and insulin resistance.¹ Poor control of diabetes mellitus leads to complications in cardiovascular, renal and retinal systems which affects the quality of life in patients.^{2,3} There are numerous other studies depicting the disease burden, morbidity and disability caused by T2DM in Pakistani population.^{4,5} A large number of patients with T2DM are also found to have hypertension, which shows substantial overlap in etiology and pathological mechanism of the two, such as obesity, insulin resistance and hyperglycemia.^{6,7,8} T2DM sympathetically activates intrarenal renin-angiotensin system which causes rise in blood pressure.^{1,6} Blood pressure (BP) and its circadian rhythm variation also play a role as risk factors for T2DM.⁹ Blood pressure fluctuates in a circadian rhythm, peaking in the early morning hours on average, and dipping

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approximately 10-20% during sleep.⁹ Suprachiasmatic nucleus (SCN) in the anterior hypothalamus is the center where circadian rhythms originate.⁹ It is postulated that the autonomic nervous system also plays a role in translating blood pressure according to the rhythm. The usual pattern of BP variability is nocturnal BP dipping. In healthy subjects, BP at night (sleep) is 10% to 20% less than diurnal (waking) BP. However, abnormal BP dipping patterns either by having less nocturnal dipping (0%–10%, decrease) or even rise in BP in sleep is associated with higher cardiovascular morbidity and mortality and damage to end organs such as brain and kidneys. Therefore, patients can be categorized depending on their blood pressure as extreme dippers, dippers, non-dippers and reverse dippers. Ambulatory blood pressure monitoring (ABPM) correlates more closely to organ damages than clinic blood pressure. Ideal 24-hour blood pressure (BP) control not only consists of control of average daily BP, but also its diurnal and nocturnal variability. Various studies show that non-dipping pattern is more commonly associated with T2DM. Hence, the concomitant risk of cardiovascular accidents is also elevated significantly as compared to patients exhibiting normal dipping.^{9,10} A study conducted on Chinese population showed T2DM to be more common in reverse-dipper patients as compared to dipper and non-dipper patients.

As a consequence of abnormal alterations in blood pressure, arterial elasticity is reduced and wall damage appears which can lead to cholesterol and fat deposition on those lesions and eventually to obstruction of the vessels which is the basis of most of the target organ damages induced by abnormalities in blood pressure.^{11,12} Recent studies also show reverse dipper blood pressure pattern to be linked to renal dysfunction and cardiovascular accidents; it additionally contributes to carotid plaque formation and lacunar infarction in hypertensive patients as well as end organ damage.^{11,12} In the study conducted by Najafi et al.¹³ the prevalence of non-dipping nocturnal pattern

was seen in 54.2% of participants and reverse dipping pattern in 28.6%, demonstrating diabetic neuropathy, CVD and retinopathy in T2DM patients to be positively associated with non-dipping and rising pattern of BP. However, limited data is available which shows relationship of T2DM with raised nocturnal blood pressure in Southeast Asian population including Pakistan. The rationale of present study was to find out the link of reverse dipping blood pressure pattern in hypertensive patients with and without T2DM in Pakistani patients. The study results may help the treating physician to more tightly control blood sugar in diabetic patients and start targeted antihypertensive therapy aimed at restoring normal circadian rhythm of blood pressure.

METHODOLOGY

This descriptive, cross-sectional study was conducted at Medical Unit of Pakistan Ordnance Factories Hospital Wah Cantt from April 2020 to April 2021 to determine the frequency of reverse dipping among hypertensive patients with and without T2DM. Approval for study was taken from institutional ethical committee of Wah Medical College, dated 4th May 2019. Hypertension was defined as mean clinic systolic blood pressure (SBP) of ≥ 130 mmHg or diastolic blood pressure (DBP) of ≥ 80 mmHg; or mean SBP during a 24-hour period ≥ 125 mmHg or mean DBP ≥ 75 mmHg; or SBP > 140 mm Hg or DBP > 90 mm Hg in at least 2 previous clinical visits. T2DM was defined as fasting blood glucose of ≥ 126 mg/dl or 2-hour blood glucose of ≥ 200 mg/dl. Normally blood pressure shows a circadian rhythm, with 10-20% lower nocturnal values as compared to day values. Reverse dipping was defined as higher night time blood pressures, 10-20% higher systolic blood pressure values as compared with daytime values. Keeping confidence level 95% and margin of error 10%, a sample size of 90 was calculated using anticipated frequency of 28.6%¹³ using online Open Epi sample size calculator available at www.OpenEpi.com. Using non-probability,

consecutive sampling technique, 90 hypertensive patients with and without T2DM of both sexes, aged 18-85 years were enrolled. Demographic information was collected upon enrollment in study after written informed consent. For fasting glucose level, blood samples were taken early in the morning at least 10 hours after the last meal from an antecubital vein. For random glucose level, blood samples were taken any time throughout the day irrespective of meal time from an antecubital vein. The samples were analyzed with the help of an automatic biochemical analyzer. Ambulatory blood pressure was monitored for 24 hours by installing the monitor (Ambulatory blood pressure Monitor ABPM50 Contec China, Product Code: ABPM50) on non-dominant arm, measuring at 30 minutes intervals during the day (from 7:00 AM to 11:00 PM) and at 60 minutes intervals during the night (from 11:00 PM to 7:00 AM). All the data was recorded. Patients with evidence of recent stroke or myocardial infarction in previous 6 months, patients who could not tolerate ambulatory blood pressure monitoring, patients having history of cardiac arrhythmia, congestive heart failure, hepatic failure or kidney failure and pregnant females were excluded from the study.

Data was entered and analyzed using the statistical package for social sciences (IBM SPSS version 23). Descriptive statistics were utilized to explain results of demographic profile. Mean $\pm$ SD were used for age, fasting blood glucose and random blood glucose. Frequency and percentage were used for gender, status of T2DM and reverse dipping. Chi-square was used to compare the results and p-value of <0.05 was considered statistically significant.

RESULTS

A total of 90 hypertensive patients were included in the present study. In the present study, blood pressure reverse dipping among hypertensive patients was found in 34 (37.7%) patients. Male to female ratio was 1.5:1 in our study. Out of the 90 patients, 54 (60.0%) were male and 36 (40.0%) females. The mean age of patients was 51.18 ± 10.1

Table 1: Demographic and Clinical parameters of the patients (n=90)

Demographic and Clinical Parameters	Results
Mean $\pm$ SD age	51.18 $\pm$ 10.1 years
Mean $\pm$ SD fasting blood glucose level	87.32 $\pm$ 13.2 mg/dl
Mean $\pm$ SD random blood glucose level	152.76 $\pm$ 21.8 mg/dl
Age groups:	
18-50 years n (%)	59 (65.5%)
51-85 years n (%)	31 (34.4%)
Sex groups:	
Male n (%)	36 (40.0%)
Female n (%)	54 (60.0%)
Type 2 Diabetes Mellitus:	
Present n (%)	38 (42.2%)
Absent n (%)	52 (57.7%)
Blood Pressure Reverse Dipping	
Present n (%)	34 (37.7%)
Absent n (%)	56 (62.2%)

years with 59 (65.5%) patients aged 18 to 50 years as shown in Table 1. T2DM was seen in 38 (42.2%) patients. Mean fasting blood glucose level was 87.32 ± 13.2 mg/dl and mean random blood glucose

Table 2: Comparison of Type 2 Diabetes Mellitus and Blood Pressure Reverse Dipping (n=90)

Type 2 Diabetes Mellitus	Blood Pressure Reverse Dipping		p-value
	Present n (%)	Absent n (%)	
Present n (%) 38 (42.2%)	24 (63.1%)	14 (36.8%)	<0.001
Absent n (%) 52 (57.7%)	10 (19.2%)	42 (82.7%)	

P value ≤ 0.05 taking significant

level was 152.76 ± 21.8 mg/dl as shown in Table 1. On stratification of data, frequency of Blood Pressure Reverse Dipping among hypertensive patients with and without T2DM was found to be 63.1% and 19.2% respectively having p-value <0.001 (significant) as shown in Table 2.

DISCUSSION

Limited data is available which shows relationship of T2DM with raised nocturnal blood pressure in southeast asian population including Pakistan.^{14,15} To the best of our knowledge the only Pakistani study available on BP reversibility revealed frequency of increased morning surge 80.5% in SBP and 69% in DBP. On comparison of participants with normal morning surge and increased morning surge in SBP, there was a significant difference in non-dipping status (13.4% vs. 18.3%, $p=0.001$). Zhu et al.¹⁶ assessed the cross-country differences in 24-h ambulatory, daytime, and nighttime systolic blood pressure (SBP) among rural population with uncontrolled clinic hypertension in Bangladesh, Pakistan, and Sri Lanka to show 56.5% exhibited ambulatory hypertension with wide variation across countries: 72.6% (Bangladesh), 50.0% (Pakistan), and 51.0% Sri Lanka. From India Kaul et al.¹⁷ reported the prevalence of reverse dippers increased with age from 7.3% in ≤ 30 years old patient group to 34.2% in >80 years old patient group. Dippers prevalence decreased from 42.5% in ≤ 30 years old patient group to 17.9% in >80 years old patient group. However, these studies did not evaluate link with T2DM. Therefore, we conducted this study to determine the frequency of reverse dipping among hypertensive patients and to compare frequency of reverse dipping among hypertensive patients with and without T2DM.

In present study, frequency of reverse dipping among hypertensive patients is found in 34 (37.78%) patients. Comparison of frequency of reverse dipping among hypertensive patients with and without T2DM was found to be 63.16% and 19.23% respectively (p -value <0.001). The findings

of our study are in accordance with various other studies which show an increased presence of blood pressure reverse dipping in hypertensive patients with diabetes when compared to non-diabetics. In the study conducted in Iran by Najafi et al.¹³ the prevalence of non-dipping nocturnal pattern was seen in 54.2% of participants and reverse dipping pattern in 28.6%, demonstrating diabetic neuropathy, cardiovascular disease (CVD) and retinopathy in T2DM patients to be positively associated with non-dipping and rising pattern of BP. In India Nandhini et al.¹⁸ revealed 34% diabetic patients to have an abnormal pattern of blood pressure that included non-dipping and reverse dipping patterns. Duration of diabetes and severity of HbA1c had a direct correlation with abnormal pattern of blood pressure variability that included non-dippers and reverse dippers.¹⁸ Numerous other studies have also shown T2DM to be more common in reverse-dipper patients as compared to dippers and non-dippers.^{19,20}

Hypertension is a major and well-recognized risk factor in development of cerebrovascular and cardiovascular accidents.^{21,22} A non-invasive examination technique, ambulatory blood pressure monitoring (ABPM) helps to monitor intermittent blood pressure over 24 hours while the patient continues to perform routine activities and sleep aiding the clinician by providing diagnostic information regarding fluctuations of blood pressure and by providing prognostic information that help to predict risk of end organ damage and all-cause mortality.²³ Patients with reverse dipping of blood pressure are at increased risk of cardiovascular accidents, kidney damage and cerebral lacunar infarction, highlighting a possible association with atherosclerosis.^{24,25}

CONCLUSION

In the present study, reverse dipping was seen in more than one-third of the patients with hypertension. Furthermore, reverse dipping had a statistically significant association with T2DM. Therefore, we recommend that proper diabetic

control and targeted antihypertensive therapy should be done promptly, to help restore normal circadian blood pressure rhythm thereby reducing disease morbidity and mortality.

Limitations: The present study has some limitations as well which need to be considered. Based in a single center, the present study had a relatively small sample size and therefore the results may not be applicable to the general population. Case-control and cohort studies are better options to determine the association of reverse dipping of blood pressure in hypertensive patients with presence or absence of co-existing T2DM but they require more resources and time. Using the results of our study as baseline data, researchers could plan more studies and generate further evidence regarding association of reverse dipping blood pressure to not only T2DM but also to hypertension related end organ damage so that specific targeted therapies may be designed for such patients to reduce the disease burden, morbidity and mortality.

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REFERENCES

1. Song Z, Yang R, Wang W, Huang N, Zhuang Z, Han Y, et al. Association of healthy lifestyle including a healthy sleep pattern with incident type 2 diabetes mellitus among individuals with hypertension. *Cardiovasc Diabetol*. 2021;20(1):e239. doi: 10.1186/s12933-021-01434-z.
2. Chowdhry MAT, Butt NI, Shakeel H, Gondal MNF, Saeed H, Tahir H. Is lack of patient knowledge a cause of poorly controlled diabetes mellitus? *Pak J Med Health Sci* 2021;15(9): 2302-2304. <https://doi.org/10.53350/pjmhs211592302>.
3. Seleshi T, Alemneh T, Mekonnen D, Tesfaye D, Markos S, Getachew Y, et al. Assessment of subclinical left ventricular systolic and diastolic dysfunction in patients with type 2 diabetes mellitus under follow-up at Tikur Anbessa specialized hospital, Ethiopia: a case-control study. *BMC Cardiovasc Disord*. 2024;24(1):201. doi: 10.1186/s12872-024-03850-x.
4. Butt NI, Mahmood K, Kanwal N, Ashfaq F. Acanthosis Nigricans in Patients with Type 2 Diabetes Mellitus at a Tertiary Care Hospital of Lahore. *Jour Bahria Uni Med & Den Colg*. 2023;13(01):13–17. doi.org/10.51985/JBUMDC202266.
5. Mehmood K, Khalid S, Butt NI, Ashfaq F, Khan AA. Anton's Syndrome in Occipital Lobe Infarction. *Pak J Ophthalmol*. 2021;37(3):338-340. doi: 10.36351/pjo.v37i3.1228.
6. Sanchez R, Musso C. Hypertension and Diabetes: An Old Association to be Aware. *Curr Hypertens Rev*. 2021;17(2):84. doi: 10.2174/157340211702211025101445.
7. Anwar A, Butt NI, Ashfaq F, Aftab S, Nasim H, Khan FA. Elevated CRP level in metabolic syndrome. *Rawal Med J*. 2022;47(4): 837-840.
8. Zia N, Aftab S, Butt NI, Ashfaq F, Anser A, Saeed S. Prevalence of Silent Cardiac Ischemia in Type 2 Diabetes Mellitus. *Pak Heart J*. 2021;54(02):162-166. <https://doi.org/10.47144/phj.v54i2.2093>.
9. Tian H, Zhao X, Zhang Y, Xia Z. Research progress of circadian rhythm in cardiovascular disease: A bibliometric study from 2002 to 2022. *Heliyon*. 2024;10(7):e28738. doi: 10.1016/j.heliyon.2024.e28738.
10. Felicio J, Moraes L, Lemos G, Souza Í, Vieira G, Silva L, et al. High dose cholecalciferol supplementation causing morning blood pressure reduction in patients with type 1 diabetes mellitus and cardiovascular autonomic neuropathy. *Sci Rep*. 2024;14(1):6374. doi: 10.1038/s41598-024-56934-1.
11. Rasheed A, Butt NI, Yasin F, Aslam H, Shahid K, Kanwal N. Frequencies of Non-Alcoholic Fatty Liver Disease and Metabolic Syndrome in Lean Individuals. *Liaquat National Journal of Primary Care*. 2024;6(1):8-13. doi:10.37184/lnjpc.2707-3521.5.42.
12. Cömerter D, Baysal T, Doğan S, Erdem A, Çınar T. Comparison of choroidal thickness and choroidal vascular index in normotensive dippers and nondippers. *Rev Assoc Med Bras (1992)*. 2024;70(1):e20230950. doi: 10.1590/1806-9282.20230950.
13. Najafi MT, Khaloo P, Alemi H, Jaafarinia A, Blaha MJ, Mirbolouk M, et al. Ambulatory blood pressure monitoring and diabetes complications: Targeting morning blood pressure surge and nocturnal dipping. *Medicine (Baltimore)*. 2018;97(38): e12185. doi: 10.1097/MD.00000000000012185.
14. Hameed I. Nocturnal Blood Pressure Assessment, an Entity of High Prognostic Value, Not Utilized to Its Potential in Clinical Practice. *Pak Heart J*. 2023;56(1):3-11. doi: 10.47144/phj.v56i1.2469.
15. Riaz M, Shah G, Asif M, Shah A, Adhikari K, Abu-Shaheen A. Factors associated with hypertension in Pakistan: A systematic review and meta-analysis. *PLoS One*. 2021;16(1):e0246085. doi: 10.1371/journal.pone.0246085.
16. Zhu A, Ostbye T, Naheed A, de Silva HA, Jehan I, Gandhi M, et al. Ambulatory blood pressure levels in individuals with uncontrolled clinic hypertension across Bangladesh, Pakistan, and Sri Lanka. *J Clin Hypertens (Greenwich)*. 2024. (Epub ahead of print). doi: 10.1111/jch.14787.
17. Kaul U, Omboni S, Arambam P, Rao S, Kapoor S, Swahney JPS, et al. Blood pressure related to age: The India ABPM study. *J Clin Hypertens (Greenwich)*. 2019;21(12):1784-1794. doi:10.1111/jch.13744.
18. Nandhini H. Abnormal Dipping Pattern of Blood Pressure in Diabetics-A Study. *J Assoc Physicians India*. 2022;70(4):11-12. PMID: 35443358.
19. Laugesen E, Svendsen AN, Vernstrøm L, Halkjær L, Dons-Jensen A, Funck KL, et al. Feasibility of Arteriograph 24 for evaluation of 24-hour pulse wave velocity and central blood pressure in patients with type 2 diabetes and non-diabetic controls. *Blood Press Monit*. 2024;29(2):82-88. doi: 10.1097/MBP.0000000000000689.

20. Sesa-Ashton G, Carnagarin R, Nolde JM, Muenta I, Lee R, Macefield VG, et al Salt sensitivity risk derived from nocturnal dipping and 24-h heart rate predicts long-term blood pressure reduction following renal denervation. *J Hypertens.* 2024;42(5):922-927. doi: 10.1097/HJH.0000000000003655.
21. Nasim H, Butt NI, Ashfaq F, Anwar A, Aftab S, Muaaz M. Frequency of Modifiable Risk Factors in Ischemic Stroke Patients at a Tertiary Care Hospital in Lahore Pakistan. *PJMR.* 2023; 62(2):53-58.
22. Condoleo V, Maio R, Cassano V, Bonfrate L, Pelaia C, Armentaro G, et al. Association between non-dipping blood pressure pattern and different glucometabolic profile during oral glucose tolerance test. *Intern Emerg Med.* 2024;19(1):81-89. doi: 10.1007/s11739-023-03442-1.
23. Hegde SB, Aroor S, Anupama YJ, Hegde SN, Prajapati H, Verberk WJ. A comparative analysis of ambulatory blood pressure characteristics in acute stroke and non-stroke Indian patients. *Blood Press Monit.* 2023;28(6):295-302. doi: 10.1097/MBP.0000000000000664.
24. Afzal H, Butt NI, Ashfaq F, Habib O, Anser A, Aftab S. Obstructive sleep apnea in type 2 diabetes mellitus. *Rawal Med J.* 2023; 48(1): 20-22.
25. Habas E Sr, Akbar RA, Alfitori G, Farfar KL, Habas E, Errayes N, et al. Effects of Nondipping Blood Pressure Changes: A Nephrologist Prospect. *Cureus.* 2023;15(7):e42681. doi: 10.7759/cureus.42681.

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