How to Cite:
Manyam, A., Gattu, N., Basutkar, S. R., Yashilha, D., Kumar, J. S., & Padmanabhan, R. (2022). To assess the variation in nocturnal blood pressure among diabetic hypertensives. *International Journal of Health Sciences*, *6*(S2), 13390–13416. https://doi.org/10.53730/ijhs.v6nS2.8533

To assess the variation in nocturnal blood pressure among diabetic hypertensives

Anandamuni Manyam
Post Graduate Medicine, SRM Medical College & Research Centre

Neha Gattu
Post graduate medicine, SRM Medical College & Research Centre

Subramanyam Rao Basutkar
Post graduate medicine, SRM Medical College & Research Centre

Yashilha D
Post graduate Medicine, SRM Medical College & Research Centre

Dr J S Kumar
Professor medicine, SRM Medical College & Research Centre

Dr R Padmanabhan
Professor and HOD Department of Nephrology, SRM Medical College & Research Centre

***Abstract*---**This research proposes the there is a strong co-relation among altered circadian rhythm in both diabetic hypertensive and non diabetic hypertensive groups. This study also shows there is statistically significant relation between absence of dipping status and left ventricular hypertrophy as evidenced by ECHO suggesting participants are at risk of developing cardiovascular diseases. This study also found that ABPM SBP, DBP, PP and MAP have significant correlation with dipping status. Hence early Identification of altered circadian variation of BP can help in diagnosing, proper risk stratification and plan of modification of treatment plan.

***Keywords*---**nocturnal blood, diabetic hypertensives, non diabetic hypertensive.

Introduction

Hypertension being the common disease during the world emerges as one of the important cause of untimely morbidity and humanity globally. Data from 2012 to 2014 studies found that the occurrence is on increase globally and also in India by occurrence of 25.3%. Due to change in the American College of Cardiology/ American Heart association (ACC/AHA) 2017 strategy these figures are expected raise as any patients with systolic blood pressure more than 130 mmHg as hypertensive compared with earlier guidelines which had a cut off of 140 mmHg to categorize patient as hypertensive. Coronary artery disease (CAD) and chronic kidney disease (CKD), strokes, myocardial infarction and heart failures are attacking more for patients due to hypertension. With appropriate non-pharmacological and pharmacological measure hypertension can be considered as a modifiable risk factor, providing substantial reduction of risk of these conditions. Hence it is pivotal for the physicians to measure blood pressure appropriately, categorize and manage hypertension. American Heart association guidelines advice initiation of antihypertensive medication based on office BP readings. Though, office appraisal give a picture of patients BP, that may not replicate real BP. Ambulatory Blood Pressure (ABPM) reading provides true readings of the patient BP over 24 hours with the added benefits of understanding the circadian rhythm unpredictability. ABPM also helps to recognize White Coat Hypertension (WCH) and Masked Hypertension are two examples of such disorders (MH). With a predictive value greater than office measurements, ABPM aids in determining the presence and severity of hypertension. Ambulatory blood pressure monitoring for 24 hours is a more exact and accurate approach of diagnosing and managing hypertension than typical clinical or office blood pressure measurements.

Given the increase in prevalence of metabolic syndrome, enlarge in life anticipation and urbanization the projected amount of people by diabetes will be doubled in the next decade. Type 2 diabetes coexisting with hypertension has a most important contact on cardiovascular and renal morbidity and humanity. Strict control of blood pressure is suggested in these patients. To prevent the complications the target blood pressure is set as low as 130/80mm Hg. Patients with type 2 diabetes have a two-to-threefold increased cardiovascular risk, and more than half of those with type 2 diabetes have hypertension. Study has revealed that diabetic patients are frequently non-dippers with raising patter during the night and are reported to be elevated hazard phenotype of hypertension. Organizations like American Society of Hypertension and International Society of Hypertension recommended the use of Ambulatory blood pressure monitoring in diabetic patient as it is closely associated with diabetic micro vascular disease such as retinopathy, neuropathy and nephropathy. Maintaining the target BP in patients in hypertensive patients, with or without diabetes has shown to reduce maximal cardiovascular events. This study we will focus on the significance of ABPM to calculate the blood pressure circadian pattern unpredictability in diabetic hypertensives and the factors associated with circadian pattern unpredictability in diabetic hypertensives. In this study, we will focus on the significance of ABPM recordings performed in hospitalized hypertensives and hypertensive diabetic patients to clarify the characteristics of circadian pattern BP unpredictability and also factors which might influence BP

unpredictability in these groups.

Gaps Identified

Prevalence of white coat hypertension in Type 2 diabetes patients is not appropriately evaluated. Post ACCORD era the need for individualized blood pressure has gained importance as the ACCORD trail found no significant prognostic benefit in cardiovascular outcomes with aggressive blood pressure control in diabetics. Though a new target level of BP in Type 2 DM is not been specified and It was postulated that absence of normal dipping pattern is connected by increased microvascular and macrovascular impediments. Nevertheless, the association of the absence of a nocturnal dipping and various factors associated in the development and progression of chronic diabetic difficulties still remains controversial. Several researchers analysed ABPM values focused on the diagnosis and development of diabetic and hypertension complications. Some studies found positive correlation, while others were not able to establish any association. More evidence on BP unpredictability and factors associated with it is needed to lead to a more precise evaluation for controlling the progression of complications. On the other hand, treated hypertensive individuals can have controlled BP in the clinic and high BP levels in ABPM, with a masked uncontrolled hypertension which needs further evaluation. Heart Outcomes Prevention Evaluation (HOPE) study found that patient taking antihypertensive in the evening have a lesser diminution in the clinic BP and important diminution in ABPM readings which need to be confirmed further in Indian population.

Objective

The objective of the study is to find circadian rhythm unpredictability in both non diabetic hypertensive and diabetic hypertensive groups and to know the possible associations and modifiable risk factors to help in diagnosing and preventing the complications due to failure of normal circadian pattern.

Review of Literature

Type 2 diabetes (T2DM) is now one of the most common non communicable disease globally(1, 2). Diabetes is one of the major risk factors by developing of complications like coronary artery diseases, stroke, diabetic retinopathy, nephropathy and neuropathy particularly when associated with blood pressure (BP) causing enormous burden on health care system with increased rates of morbidity and mortality both in developing and developed countries (2-5). Most studies have analyzed the risk factors such as diabetes duration, hyperglycaemia, arterial hypertension, dyslipidaemia, and smoking, moreover genetic factors for the progression of diabetes and hypertension complications(4-6).

Ambulatory blood pressure monitoring (ABPM) ascertains a enhanced association by diabetes complications than BP obtained in the office settings with blood pressure parameters like the 24 hours, day time, night timesystolic and diastolic blood pressure, Blood pressure loads and the attendance or nonattendance of physiological night time dipping of blood pressure(5, 7, 8). Several studies have shown that aggressive control of hypertension with diabetic patients is beneficial

in preventing growth and sequence of compliances (9-11). In patients with diabetes international guidelines recommend BP to be lowered to <130/80 mm Hg. Inspite of need for aggressive BP control in diabetes(< 130/85 mm Hg) was only 35.9%(11).

Circadian BP variations in normal diurnal rhythms such as non-dipping model during night, nocturnal hypertension and morning hypertension are considered to be high risk of initial complication in mutually non diabetic hypertensives and diabetic hypertensives(8-10, 12). In view of importance in assessing the dipping status titrating the hypertensive drugs to achieve the target several international organisations such as American society of Hypertension, American diabetic Association and international society of hypertension advocated ABPM for improving the estimation of cardiovascular, cerebrovascular and microvascular complications risk in patients with hypertension and hypertensive diabetics(1, 9, 10, 13). Compared with clinic BP, absence of nocturnal dipping of blood pressure in particular night time blood pressure Mean is associated with microvascular complications especially diabetic retinopathy (10, 14). While HTN is predominantly disturbing in diabetic patients, it seems sensible to execute ABPM in all patients by high-normal BP levels and diabetes (10). ABPM also identifies various types of hypertension including white coat hypertension and masked hypertension(9, 12, 15). A meta-analysis found predominance of white coat hypertension as being more in patients by Type 2 DM, accomplishment up to 51% of those without Type 2 DM(16, 17).

Methods

- Patient information includes demographics, weight, BMI, waist circumference, duration of hypertension and diabetes, HbA1c, dyslipidaemia, eGFR, smoking, alcohol, medical history including antihypertensives and OHA will be collected after taking patient informed consent.
- Each patient will complete a simple questionnaire at the time of the ABPM.
- Office blood pressure of each subject will be measured eight hourly using mercury sphygmomanometer and average of three readings will be considered for comparison with ABPM mean.
- Noninvasive ABPM will be performed with an automated system that meets the requirements of European society of hypertension or National heart foundation of Australia.
- Patient's baseline BP will be recorded by using ABPM with antihypertensives patient is already on.
- If the patient ABPM reading is ≥ 140/90 mm Hg, Blood pressure will be controlled according to hypertensive guidelines (JNC 7).
- Blood pressure will be recorded for all subjects after 3 days of baseline reading.
- Awake and sleep times were calculated using written diaries kept by patients during ABPM.
- What is the difference between daytime and nighttime?
  Participants' sleeping times are used to determine daytime and nighttime intervals. Daytime is defined as 0900–2100 h, whereas nighttime is defined

as 2200–0600 h. If the following criteria were not met, the ambulatory blood pressure monitoring was repeated. At least 70% of projected measures were recorded during the course of a 24-hour period. 20 genuine awake (0900 to 2100 h) 7 good sleepers (0100 to 0600 h) 30-minute intervals for blood pressure measurements

- ABPM will be done as per guidelines and data will be assessed using SPSS software.

Flow chart for planning for the study

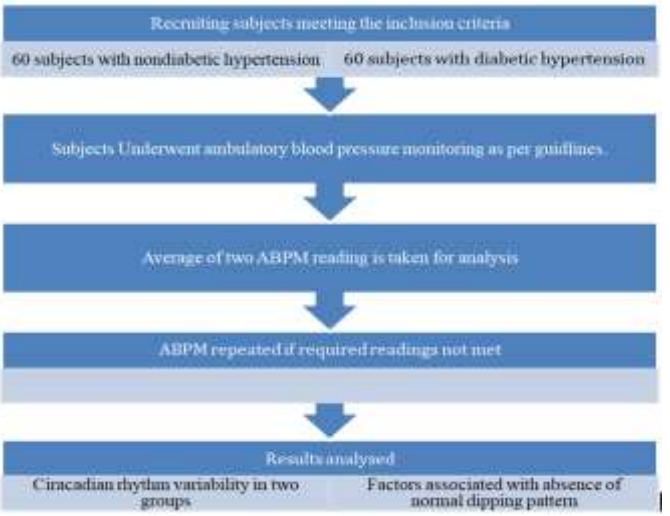

Fig.1. Flow chart for planning for the study

Inclusion Criteria

To be eligible for the study, men and women aged more than 18 years, a known hypertensive on medication or Office blood pressure ≥140/90 mmHg with diabetes criteria fulfilment.

Exclusion Criteria

- Severe renal dysfunction (creatinine authorization ≤30 ml/ min/1.73m^2) at Screening
- Acute febrile illness
- Hypertensive emergencies
- Active liver disease
- Pregnancy
- small-mindedness to ABPM and incapability to communicate and fulfill by study necessities.

Ambulatory Blood Pressure Monitoring

ABPM is initial executed in the 1960s, which was a noninvasive apparatus urbanized to measure 24 hours BP, whereas the patient moving daily routine

work. ABPM executes BP dimensions through an automatic portable device. ABPM device is attached to the patient's waist and associated to BP cuff. The cuff is tied on the patient's non-dominant arm and the BP is measured at preset period. Measurements are made at set interval during the day and night times(1, 13, 18).

"BP is recorded by the oscillometric method. Oscillations begin before the auscultatory method's first Korotkoff sound (systolic BP) and end after the fifth Korotkoff sound (diastolic BP). The mean BP is the largest oscillation captured by the device. The device's systolic and diastolic blood pressure readings are calculated using mathematical formulae.(19)." The advantages of ABPM has been described in various comprehensive literature reviews have led to recommendations for the ABPM to be used much more extensively in clinical practice.(10, 13, 19, 20) "Thresholds for hypertension diagnosis depending on ambulatory blood pressure monitoring(13, 18, 19)"

24-h avg 130/80mmHg
Awake (daytime) avg 135/85mmHg
Asleep (night-time) avg 120/70mmHg
Patterns of ambulatory blood pressure readings(21)

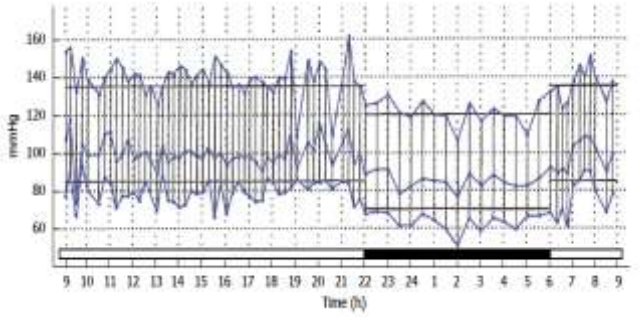

Fig.2. Patterns of ambulatory blood pressure readings

The following is an example of an ambulatory blood pressure reading that shows a typical nighttime dip: Systolic, diastolic, and mean pressures are indicated in blue in ABPM data. On the left, the Y-axis shows the pressure scale in mmHg, while the X-axis shows the time scale in hours. A dark bar indicates how long you slept.

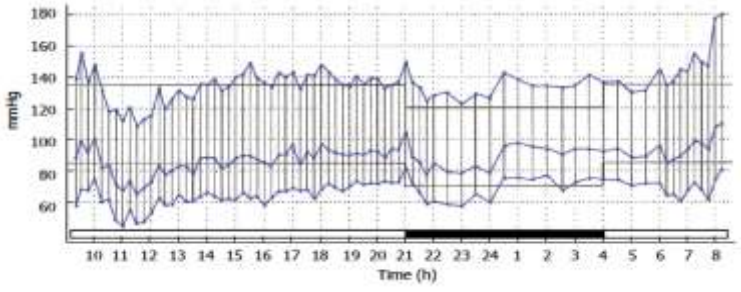

Fig.3. Ambulatory blood pressure reading presentating change in nocturnal dip(21)

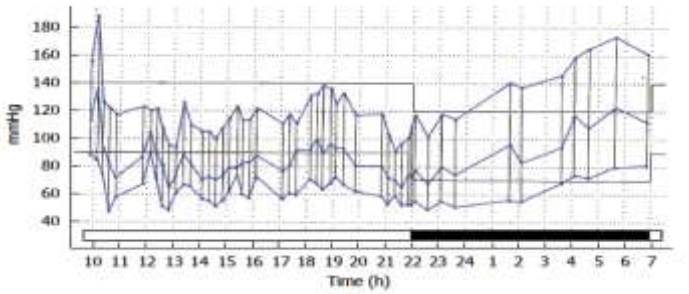

Fig.3. “ABPM reading presenting white coat hypertension by a superimpose necessary hypertension

The blood pressure only arrives at hypertension levels throughout sleep while it is probable to be clinically unobserved(21)”

“Nonattendance of Nocturnal Dipping Model of Blood Pressure Fall and Diabetes Mellitus:”

"There is a physiological diurnal swing in blood pressure, with the lowest BP levels occurring during sleep." The decline in nocturnal blood pressure is usually larger than 10% compared to the mean daytime blood pressure. A nocturnal BP decline of less than 10% or a night/day index (N/D) (nocturnal BP/daytime BP) >0.921 defines the lack of a nocturnal BP fall." (1) and (19). The absence of nocturnal blood pressure dropping is linked to a higher risk of microvascular and macrovascular problems. (8, 10, 47).

Literature review showed that increased occurrence of nonattendance of dipping patterns of BP fall in Type 2 DM individuals reaching up to 78% of individuals when compared with 39% in patients without diabetes(20, 48, 49). These findings in ABPM readings correlate with the diagnosis of cardiovascular autonomic neuropathy (10, 50, 51). Fogari et al and Ashok Duggal established that the DM patients have a advanced occurrence circadian rhythm variant abnormality in relation to normal individuals(52, 53). The changes in normal nocturnal BP fall in Type 2 DM patients is due to the alteration in circulating plasma volume because of hyperglycaemia that can interfere with blood flow distribution and renal haemodynamic(49, 54, 55). Moreover, insulin acts an significant role in the control of autonomic anxious structure (10, 54).

The absence of a nocturnal dipping is deliberate in adults of Type 2 DM patients, found no dissimilarity in relative to reins, i.e., subjects with no family history of Type 2 DM(55, 56). Though, individuals in a subgroup without diabetic with a family history of Type 2 DM who previously diagnosed with cardiac autonomic neuropathy(CAN) demonstrated a lesser nocturnal BP fall(56, 57). These findings affirms that the absence of nocturnal dipping is characteristically linked by Type 2 DM. absence of nocturnal BP fall can also present in individuals who are inclined, but without any symproms of diabetes, and is strong-minded by the diagnosis of CAN(56-58).

"Suggestion for Ambulatory Blood Pressure Monitoring In Patients by Diabetes Mellitus"

Literature review has shown ABPM has linked numerous characteristics of the 24-hour rhythm to potential triggers of target organ damage and cardiovascular problems (1, 2, 10, 13, 19). Due to its link with poor cardiovascular prognosis, current study has focused on circadian rhythm unpredictability, particularly nocturnal dipping (59, 60). Non-dippers have more subclinical and clinical cardiovascular difficulties than dippers, according to studies, and reverse-dipping patterns of nocturnal blood pressure have been discovered to be an independent predictor of cardiovascular disorders.(61-63).

Results

A total of 120 subjects, 60 subjects will be hypertensives with diabetes and 60 subjects will be hypertensives without diabetes

Variables	Non diabetic Hypertension (60)		Diabetic Hypertension (60)		p value
	Mean	SD	Mean	SD	
Age	58.98	10.59	57.56	9.07	0.43
BMI	25.29	3.06	25.98	2.73	0.91
Hemoglobin	11.91	1.72	12.51	1.86	0.07
Creatinine	0.88	0.28	0.89	0.23	0.82
EGFR	87.85	25.11	85.13	20.39	0.51
Sodium	136.53	3.71	136.96	4.01	0.54
Potassium	4.04	0.37	4.05	0.52	0.98
Total cholesterol	175.78	60.79	167.23	55.75	0.424
Triglycerides	120.33	65.96	114.06	61.56	0.59
HDL	45.667	37.02	39.5	13.9	0.23
LDL	110.25	39.75	105.73	41.48	0.54
VLDL	28.64	32.29	23.07	12.43	0.21
EF	61.86	7.01	63.3	3.78	0.16

Table 1: Descriptive Of Various Factors In Diabetic Hypertensive And Non-Diabetic Hypertensive Group

Table 2: Age Distribution In Non-Diabetic Hypertension And Diabetic Hypertension Groups

		Diabetic Hypertension (60)	Non diabetic Hypertension (60)	p value
Age groups	21-30	0	1	0.12
	31-40	3	4	
	41-50	13	8	
	51-60	23	14	
	>60	21	33	
	Total	60	60	

Table 3: Age and Gender Distribution of the Study Subjects

Age	Male		Female		Total	p value
	Frequency	Percentage	Frequency	Percentage		
21-30	1	1.55	0	0	1	0.01
31-40	6	9.23	1	1.83	7	
41-50	7	10.76	14	25.45	21	
51-60	16	24.62	21	38.18	37	
>60	35	53.84	19	34.54	54	
Total	65	100.0	55	100.0	120	

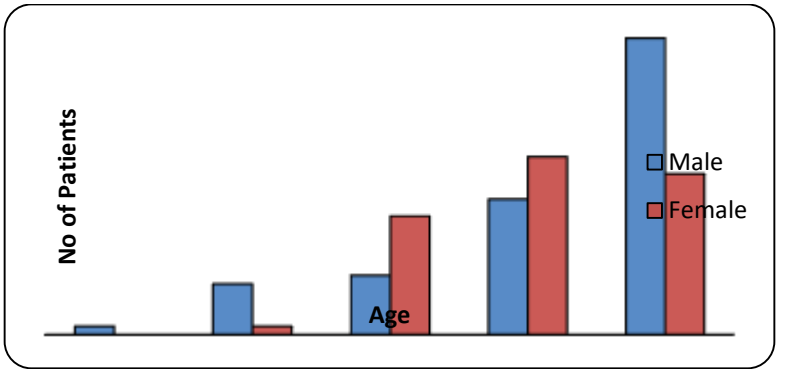

Fig.4. Distribution of Age And Gender Of Study Subjects

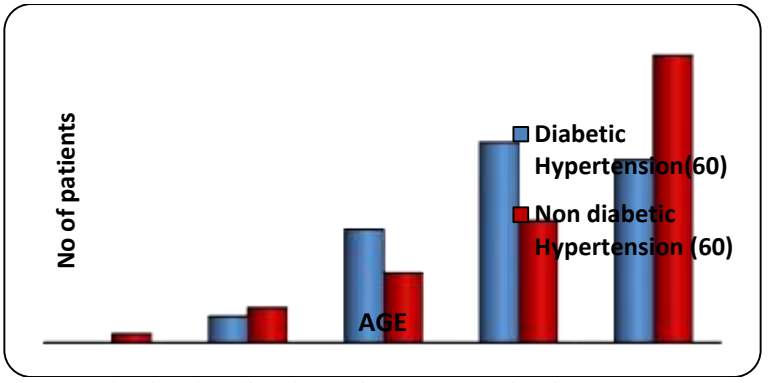

Fig.5. Distribution of Age In Both The Group

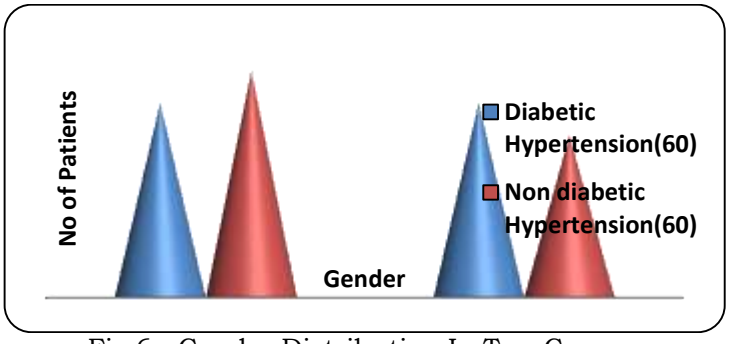

Fig.6. Gender Distribution In Two Groups

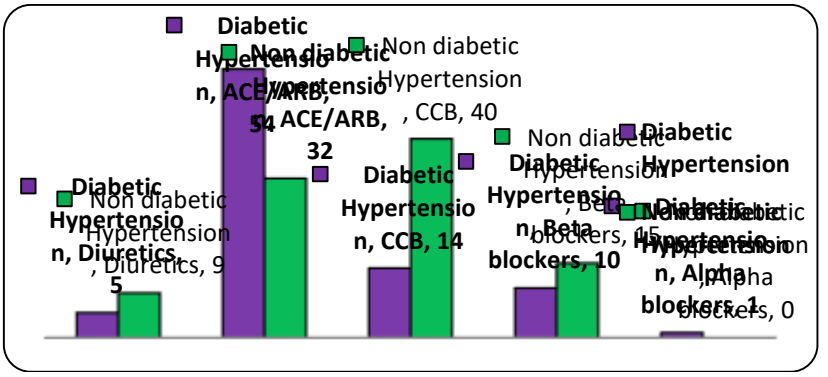

Fig.7. Distribution Of Study Subjects Based On Antihypertensive Drugs Used

Table 4: Smoking And Alcohol Consumption In Non-Diabetic Hypertension And Diabetic Hypertension Groups

		Diabetic Hypertension (60)	Non diabetic Hypertension (60)	p value
Smoker	NO	48	32	0.002
	YES	12	28	
	Total	60	60	

		Diabetic Hypertension	Non diabetic Hypertension (60)	p value
Alcoholic	NO	50	35	0.03
	YES	10	25	
	Total	60	60	

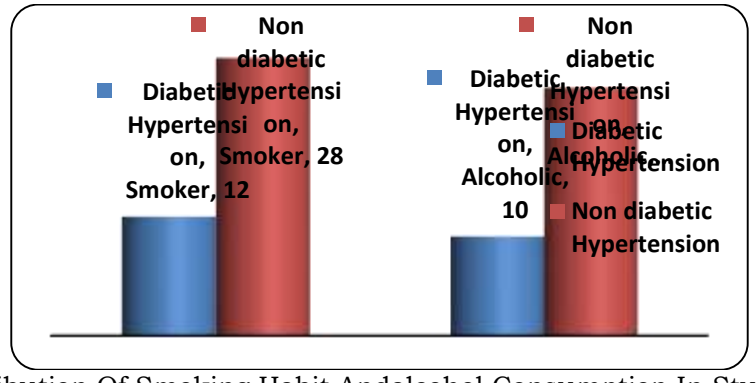

Fig.8. Distribution Of Smoking Habit Andalcohol Consumption In Study Subjects

Table 5: Dipping Status In Non-Diabetic Hypertension And Diabetic Hypertension Groups

		Diabetic Hypertension (60)	Non diabetic Hypertension (60)	p value

Dipping status	Dipper	27	27	0.83
	Extreme Dippers	4	2	
	Non-Dipper	19	22	
	Reverse Dipper	10	9	
	Total	60	60	

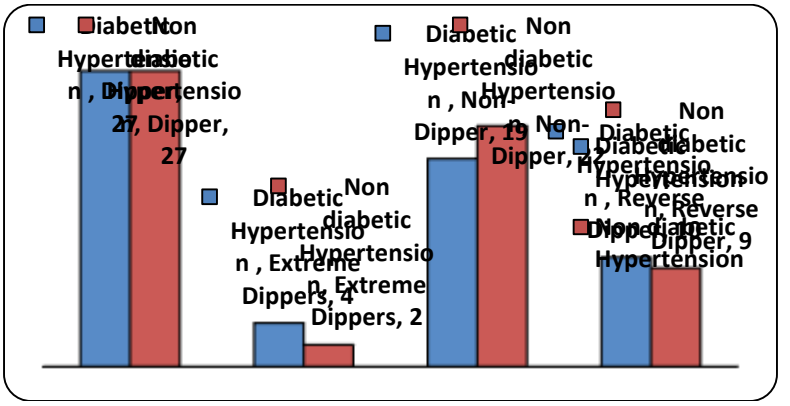

Fig.9. Prevalence Of Ciarcadian Bp Abnormalities Intwo Groups

Table 6: Distribution Of Study Subjects Based On Antihypertensive Drugs

	Frequency	Percentage
Diuretics	14	11.67
ACE/ARB	86	71.67
Calcium channel blockers	40	33.33
Beta blockers	25	20.83
Alpha blockers	1	0.83

Table 7: Distribution Of Study Subjects Based On Number Of Antihypertensive Drugs And Comparing Between Dipping Status

	Diabetic Hypertension (60)				Non diabetic Hypertension (60)			
	Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper	Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper
Monotherapy	20	2	10	7	18	1	7	3
Dual drug therapy	4	2	4	2	7	1	13	5
Triple drug therapy	3	0	1	0	2	0	2	0
Quadruple drug therapy	0	0	1	1	0	0	0	1

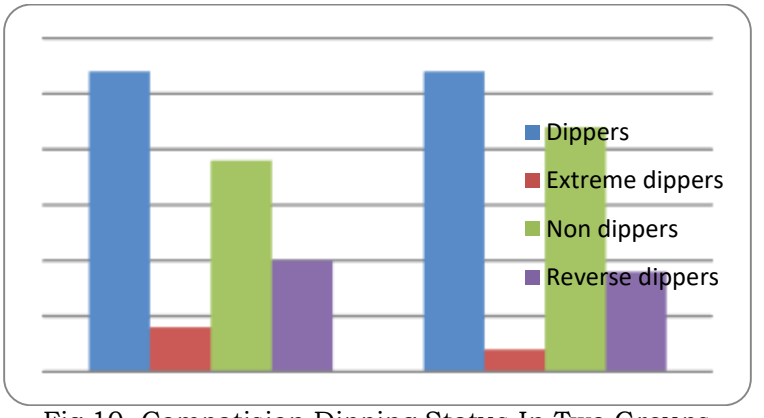

Fig.10. Compatision Dipping Status In Two Groups

Table 8: Comparison Of Dipping Status And Age Groups

		Dipping status				
		Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper	p value
Age groups	21-30	1	0	0	0	0.003
	31-40	2	0	3	2	
	41-50	12	1	8	0	
	51-60	8	2	19	8	
	>60	20	3	22	9	
	Total	43	6	52	19	

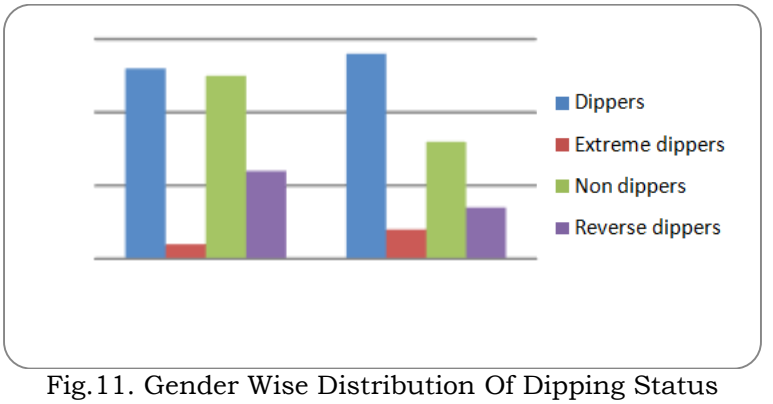

Fig.11. Gender Wise Distribution Of Dipping Status

Table 9: Comparison Of Dipping Status And Diuretics Use

		Dipping status				
		Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper	p value
Diuretics	NO	51	5	34	16	0.3
	YES	3	1	7	3	
	Total	54	6	41	19	

Table 10: Comparison Of Dipping Status And ACEI/ARB

		Dipping status				
		Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper	p value
ACE/ARB	NO	9	2	19	4	0.01
	YES	45	4	22	15	
	Total	54	6	41	19	

Table 11: Comparison Of Dipping Status And Calcium Channel Blockers

		Dipping status				
		Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper	p value
Calcium channel blockers	NO	33	4	18	11	0.37
	YES	21	2	8	54	
	Total	54	6	41	19	

Table 12: Comparison Of Dipping Status And Beta Blockers

		Dipping status				
		Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper	p value
Beta blockers	NO	47	4	31	13	0.23
	YES	7	2	10	6	
	Total	54	6	41	19	

Table 13: Comparison Of Dipping Status And Alpha Blockers

		Dipping status				
		Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper	p value
Alpha blockers	NO	53	6	41	19	0.7
	YES	1	0	0	0	
	Total	54	6	41	19	

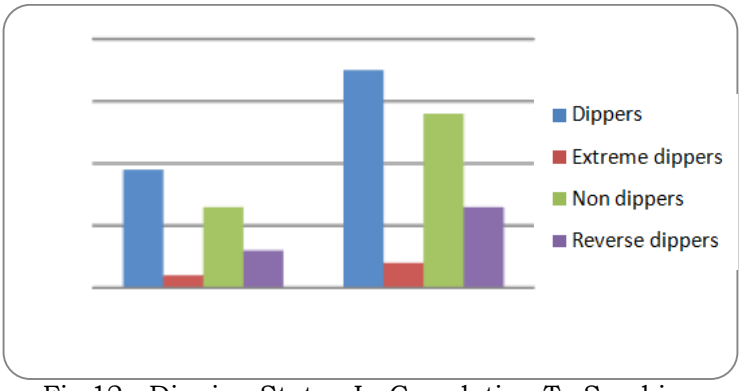

Fig.12. Dipping Status In Correlation To Smoking

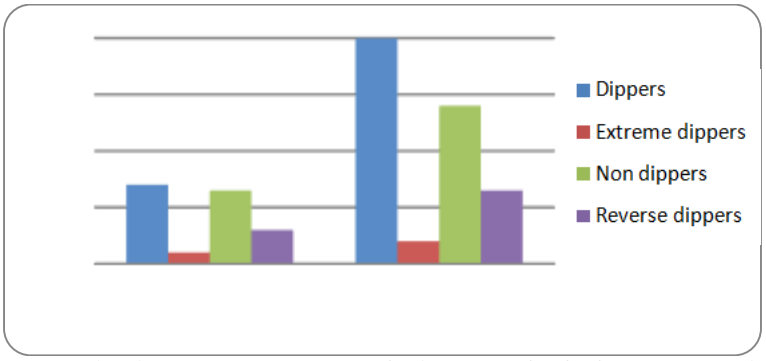

Fig.13. Dipping Status In Correlation To Alcohol Consumption

Table 14: Relationship Between Participants Diuretics Use And Dipping Status In Both Groups

		Diabetic Hypertension (60)				Non diabetic Hypertension (60)			
Variables		Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper	Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper
Diuretics	NO	26	3	17	9	25	2	17	7
	YES	1	1	2	1	2	0	5	2
	p value	0.5				0.43			

Table 15: Relationship Between Participants ACE/ARD And Dipping Status In Both Groups

		Diabetic Hypertension (60)				Non Diabetic Hypertension60)			
Variables		Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper	Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper
ACE/ARB	NO	1	0	4	1	8	2	15	3
	YES	26	4	15	9	19	0	7	6
	p value	0.22				0.01			

Table 16: Relationship Between Participants Calcium Channel Blockers And Dipping Status In Both Groups

		Diabetic Hypertension (60)				Hypertension (60)			
Variables		Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper	Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper
Calcium channel blockers	NO	20	4	15	7	13	0	3	4
	YES	7	0	4	3	14	2	19	5
	p value	0.6				0.03			

Table 17: Relationship Between Participants Beta Blockers And Dipping Status In Both Groups

		Diabetic Hypertension (60)				Non Diabetic Hypertension (60)			
Variables		Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper	Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper

Beta blockers	NO	23	3	16	8	24	1	15	5
	YES	4	1	3	2	3	1	7	4
	p value	0.9				0.1			

Table 18: Relationship Between Participants Alpha Blockers And Dipping Status In Both Groups

		Diabetic Hypertension (60)				Non Diabetic Hypertension (60)			
Variables		Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper	Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper
Alpha blockers	NO	26	4	19	10	27	2	22	9
	YES	1	0	0	0	0	0	0	0
	p value	0.7				0.74			

Table 19: Relationship Between Participants Habits And Dipping Status In Both Groups

		Diabetic Hypertension (60)				Non Diabetic Hypertension (60)			
Variables		Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper	Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper
Smokers	NO	20	3	16	9	15	1	12	4
	YES	7	1	3	1	12	1	10	
	p value	0.6				0.9			

		Diabetic Hypertension (60)				Non Diabetic Hypertension (60)			
Variables		Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper	Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper
Alcohol Consumption	NO	23	3	15	9	17	1	13	4
	YES	4	1	4	1	10	1	9	5
	p value	0.8				0.8			

Table 20: Relationship Between Participants Echo Lvh And Dipping Status In Both Groups

		Diabetic Hypertension (60)				Non-Diabetic Hypertension (60)			
Variables		Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper	Dipper	Extreme Dipper	Non-Dipper	Reverse Dipper
Echo LVH	No	22	4	6	7	22	2	10	4
	Yes	5	0	13	3	5	0	12	5
	p value	0.01				0.03			

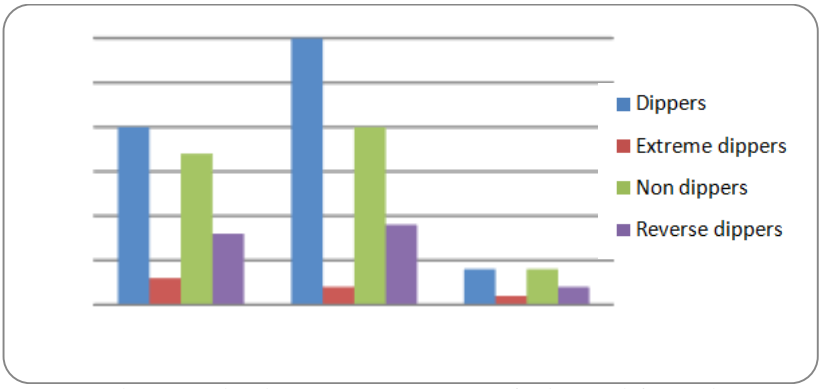

Fig.14. Dipping Status In Correlation With Bmi

Table 21: Systolic BP Variability And Dipping Status

SBP mm Hg	Dippers	Extreme dippers	Non dippers	Reverse dippers	ANOVA	P value
24 hours	144.19 ± 3.15	125.83 ± 7.53	145.63 ± 2.58	146.89 ± 3.68	1.900	0.133
Day time	142.30 ± 3.14	135.83 ± 5.53	149.24 ± 2.88	142.21 ± 3.77	1.407	<0.0001
Night time	120.20 ± 2.64	104.17 ± 3.37	140.24 ± 2.68	150.79 ± 5.15	20.306	0.0001

Table 22: Diastolic BP Variability And Dipping Status

DBP mm Hg	Dippers	Extreme dippers	Non dippers	Reverse dippers	ANOVA	P value
24 hours	88.94 ± 2.15	80.00 ± 4.71	98.24 ± 3.33	86.37 ± 5.53	3.191	0.026
Day time	86.20 ± 2.07	88.17 ± 3.68	94.80 ± 2.68	73.74 ± 1.61	8.981	0.0001
Night time	184.57 ± 110.30	64.50 ± 2.92	87.05 ± 2.26	76.21 ± 1.95	0.352	0.788

Table 23: Pulse Pressure (PP) Variability And Dipping Status

PP	Dippers	Extreme dippers	Non dippers	Reverse dippers	ANOVA	P value
24 hours	58.76 ± 2.15	49.33 ± 5.68	63.46 ± 2.58	72.37 ± 3.55	4.794	0.003
Day time	60.26 ± 2.42	53.50 ± 6.33	62.34 ± 2.36	73.16 ± 3.29	3.655	0.015
Night time	49.39 ± 1.88	40.17 ± 2.04	57.10 ± 2.04	70.42 ± 5.15	11.423	0.0001

Table 24: Mean Arterial Pressure (MAP) Variability And Dipping Status

MAP	Dippers	Extreme dippers	Non dippers	Reverse dippers	ANOVA	P value
24 hours	102.04 ± 2.27	89.83 ± 5.71	105.88 ± 2.13	103.05 ± 3.06	2.093	0.105
Day time	103.31 ± 2.33	99.00 ± 5.73	111.10 ± 2.70	98.84 ± 2.68	3.269	0.024
Night time	87.15 ± 1.97	79.17 ± 3.11	101.85 ± 2.39	102.95 ± 3.38	12.359	0.0001

Table 25: Heart Rate (HR) Variability And Dipping Status

HR	Dippers	Extreme dippers	Non dippers	Reverse dippers	ANOVA	P value
24 hours	84.22 ± 2.24	86.33 ± 7.24	86.39 ± 2.08	81.63 ± 2.71	0.492	0.689
Day time	84.09 ± 2.01	93.17 ± 7.21	89.10 ± 2.48	80.26 ± 2.49	2.300	0.081
Night time	73.94 ± 1.42	79.17 ± 5.55	77.88 ± 1.63	72.79 ± 1.83	1.846	0.143

Discussion

This study was conducted at SRM medical college Hospital and study centre, Kattankulathur between March 2018 to July 2019.A total of 120 subjects be indulged in the study who have met the inclusion and exclusion criteria. Sixty participants were allotted to diabetic hypertensive group and another sixty participants to hypertensive group. Hypertension is a major health problem globally. Improper blood pressure control is known to amplify the risks of myocardial infarction, stroke, heart failure and renal failure. Hypertension with diabetes contributes for chronic complications. Several studies are revealed that altered circadian rhythm of BP in diabetic individuals and absence of physiological nocturnal dip could contribute to higher 24 hrs mean pressure load. Early identification of circadian rhythm variations of BP can help identifying, risk stratifying and plan for non-pharmacological and pharmacological management to prevent chronic complications. Ambulatory BP monitoring helps in understand the circadian rhythm variation and assess 24 hours mean blood pressure load.

Age and Gender Distribution

It is well known fact that the risk of developing hypertension increases as the age advances. In this study maximum numbers of study participants were seen in the age group of more than 60yrs in both male and female study subjects. Table 2, Chart 1 and chart 8 shows association between dipping status and age. In this study there were more non dippers in the age group above 50 (p=0.003). A study conducted by Kyoung Shim et alshowed that the 24hours meanBPvariability has correlation with SBP(p=0.018) in female participants, but not in male

participants(64). This study has affirmed that correlation among circadian blood pressure variability is altered by gender in different manner.

Distribution of Antihypertensives Intake And Co-Relation to Dipping Status

71.67 % of study participants were using ACE or ARBs followed by 33.33% of study participants wereusing Calcium channel blockers, 20.83 study participants were on Beta blockers, 11.67% on Diuretics and 0.83% on Alpha blockers (Table 11). This study showed Comparative data of circadian rhythm abnormalities in relation to antihypertensivemedications participants were taking (Table 12). In this study we found nostatistically significant association between type of Antihypertensive drugs over absence of normal physiological dipping except for patient who were taking ACE or ARBs. We found that participants taking ACE or ARBs at the night time in contrast to the conventional intake during morning have significant statistical significance(P-0.01) (Table 18). We also found that participants taking calcium channel blockers in non-diabetic hypertensive group has statistically significant association between dipping status and CCB intake (p=0.03) (Table28). A conducted by Ramón C. Hermida and colleagues found that patients taking antihypertension medication at bed time especially ACE/ARBs showed significant reduction in risk of end organ damage, development and progression of chronic complications(65). In another study conducted by Kulakov et al, comparing ACE/ ARBs with CCB and Beta blockers found that patient taking ACE/ ARBs achieved BP target was achieved in more than 90% of the patients within 12 weeks of initiation and up titration of drugs as needed(66).A randomised control study conducted on 2,012 hypertensive patients without diabetes with mean age of 52.7 ± 13.6 years found that patients treated with ACE/ARBin the bed time has better BP mean and normal physiological dipping compared with individuals taking medication at conventional day time (32% vs 52%, $p < 0.001$). Interestingly this study also affirmed that patient on ACE/ ARB has reduced risk of developing new onset Type 2 DM(67). Confirming these finding a follow up study for 21 years in non dipping hypertensives individuals found that, these patients are at risk of developing diabetes(68).

BMI and Circadian Rhythm

This study has found no statistically significant association between dipping status and obesity (P=0.953). However, in a study byKotsis et al. found that normal physiological night time BP fall is significantly altered in overweight and obese 3,126 untreated hypertensive individuals(70). The absence of normal dipping was much more in the overweight and obese participants than in the normal weight group (72.7% versus 61.5% in the hypertensive group). Spanish Society of Hypertension registry data found that obesity was one of the determinants of abnormal dipping pattern. Another study conducted by “Jung Ho Heo and colleagues found that patients with overweight show more variable degree of blood pressure abnormalities compared to normal subjects (24 hour systolic BP variability : 15.6 ± 4.5 Vs 14.5 ± 4.0 , p= 0.001, 24 hour diastolic BP variability : 13.5 ± 4.7 Vs 12.1 ± 3.8, p<0.001, 24 hour mean BP variability : 13.6 ± 4.5 Vs 12,4 ± 3.7 p<0.001, Daytime systolic BP variability : 14.7 ± 4.9 Vs 13.5 ± 4.3, p=0.002, Daytime diastolic BP variability : 12.9 ± 5.3 Vs 11.5± 4.3 p<0.001, Daytime mean BP variability : 12.8 ± 4.9 11.5± 4.1 p<0.001). Furthermore, BMI

was associated with 24-hour systolic BP variability (p= 0.048), 24-hour diastolic BP variability (p=0.016) and 24 hours mean BPvariability(p=0.028). In contrast, Diamantopoulos et al. examined 226 (116 male and 110 female) overweight and obese subjects with newly diagnosed hypertension found no significant correlation in BMI between the dippers and non-dippers.(71)"

Dipping Status In Diabetic Hypertensives

In Type 2 DM, an abnormal circadian rhythm, that is, absence of normal dipping pattern, is frequently recorded. our study revealed that out of 120 subjects 41 participants were non dippers, among them 19 were diabetic hypertensives (Table 14, Chart 7). We also found that 10 participants were reverse dippers in diabetic hypertensive groups. This study found that, incidence of dipping status in diabetic hypertensive group. In our study there was no statistically significant difference in dipping status in both groups (p=0.83). we found that reverse dippers and extreme dippers are more in diabetic group compared to non diabetic hypertensives. Studies have shown that extreme and reverse dippers are more prone cardiovascular diseases compared with normal population(72, 73). A cross sectional study found that patients with reverse dipping was found to have moderate carotid stenosis due to atherosclerotic plaques compared with normal population (*P*=0.010)(72). These group are more prone for developing lacunar infarcts and coronary artery diseases(72).

Dipping Status And Echo LVH

This study found that statistically significant association between the dipping status and left ventricular hypertrophy (LVH) in both the groups (p=0.01and 0.03 in diabetic hypertensive and non diabetic hypertensive group respectively). A Jackson Heart study found that patients with dipping and reverse dipping abnormalities in ABPM found to have increased left ventricular mass index and an increased prevalence of left ventricular hypertrophy(74)."

Dipping Status and Its Co-Relation With Abpm And Manual Systolic BP

In this study we have recorded manual BP three readings and average was compared with the dipping status. We found that significant co-relation between average systolic BP and dipping status (P=0.033). we also found that there is statistically significant relation in all observations in ABPM systolic BP (SBP) that include 24 systolic BP, day time SBP and night time SBP with the dipping status (P=0.133, <0.0001 and 0.0001 respectively) (Table 40). These findings suggest that ABPM use plays a pivotal role in knowing the blood pressure variability and control with the drugs patient is taking.

Dipping Status In Co-Relation With ABPM Diastolic BP (DBP)

This study found that 24 hours diastolic BP and day time DBP have significant correlation with dipping status (P=0.026 and 0.0001 respectively) (88.94 ± 2.15 vs98.24 ± 3.33) (Table 41).International Verapamil-Trandolapril Study (INVEST) found that all cause mortality is increased in diabetic patients who DBP is less

than 70 mm Hg. When diastolic BP reaches 60-70mm Hg the risk increases by two folds and when reached to <60 mm Hg, risk is tripled(75-78).

Dipping Status In Co-Relation With ABPM Pulse Pressure (PP)

ABPM PP showed a statistically significant correlation between 24 hrs, day time and night time PP (P=0.003,0.015 and 0.0001 respectively) (Table 42). Patients with non-dipping status have a high PP compared to dippers (63.46 ± 2.58 vs58.76 ± 2.15). Interestingly this study also found that reverse dippers have high PP than non-dippers (72.37 ± 3.55 vs 63.46 ± 2.58) (Table 42). "A study found that patient with diabetes and hypertensive with coronary artery disease has more pulse pressure compared with the normal population(daytime pulse pressure 56.2±13.1 vs. 50.6±11.3 mmHg, p=0.003; nighttime pulse pressure 56.5±14.2 vs. 50.7±12.4 mmHg, p=0.005; 24-hour pulse pressure 54.7±13.6 vs. 49.0±12.0 mmHg, p=0.003)."Our study also found significant correlation of PP with circadian variability that signifies the need for shifting the focus from systolic and diastolic Bp to assess and risk stratify patients(79).ABPM 24hrsPP, gives correlation with progression of albuminuria (P=0.015 and 0.052, respectively) than ABPM reading and office PP. The adjusted hazards ratio (95% CI) per each 10-mm Hg increment in ambulatory pulse pressure was 1.23(1.04 to 1.42). "In another study a total of 3120 patients both diabetic and hypertensive patients were followed for a period of 7.8 yearsPatients with PP less than 45 mmHg and PP more than 55 mmHg had increased risk of future CHD event, compared with those with PP between 45 and 55 mmHg [hazard ratio (HR) = 1.33 (1.00–1.77) and HR = 1.67 (1.23–2.27), respectively](80)."In conclusion, ABPM PP may provide better information in elderly diabetic subjects to predict progression of microvascular and macrovascular complications(81).

Dipping Status In Co-Relation With ABPM Mean Arterial Pressure (MAP)

This study showed that MAP and circadian rhythm has a strong significant association. Subjects with non-dipping status found to have more MAP compared with dippers especially during night time (P=0.0001) (101.85 ± 3.38 vs 87.15 ± 1.97 respectively) (Table 43)."Studies have shown that a flattened circadian HR rhythm was independently associated with left atrial enlargement.More over HR abnormality is predictive of fatal and nonfatal cardiovascular events, independently of several confounders (hazard ratio 1.8, confidence interval: 1.13–2.86, *P*< 0.01)(82)."

Non Dippers Profile

In this study, out of 120 patients 41 patients were found to benon dippers. The profile of these group has significant difference when compared with the dippers. Non dipper are more in males than females. Patient who is on ACE/ARBs have better BP control compared with non-dippers. Even though statistically not significant patients with smoking history has a greater number of non dippers, however it is opposite in caseof subjects consuming alcohol. The fasting and postprandial blood sugars were more patients with absence of normal nocturnal dip when compared with dippers (167.93± 10.61vs 181.15± 55.58 and 198.55± 73.33 vs 221.11± 60.24 respectively). Similarly, non dippers have increased

HbA1c compared with dippers (9.12± 1.33 vs 8.5±1.48). Non dipper group have increased total cholesterol, triglycerides, low density lipoproteins(LDL) and very low density lipoproteins (VLDL)when compared with dippers. Interestingly non dippers have more high density lipoproteins (HDL) compared with dippers (41.22 ± 1.80 vs 47.68 ± 6.96).

Summary

This study was conducted on 120 patients, to assess the difference in nocturnal blood pressure in diabetic hypertensive and non diabetic hypertensive group and to assess the various factors that may affect the ABPM variables. Fisher's exact tests was used for categorical variables and ANOVA for continuous variables.In diabetic hypertensive group 27 participants were dippers, 19 were non dippers, 10 were reverse dippers and four were extreme dippers. In non diabetic hypertensive group 27 participants are dippers, were as 22 were non dippers, 9 were reverse dippers and 2 were extreme dippers. There is a significant correlation with age, use of ACE/ARBs, echo LVH findings and various ABPM parameters with dipping status of both the groups. Even though non dippers have greater lipids, FBS, PPBS and HbA1c these are not statistically significant.

Limitations

This study has several limitation. Ideally ABPM should be done when patient is doing his/ her routine activities that may give better picture compared with inpatient ABPM parameter. The reading is accomplished in small group of population which may require added studies by larger sample size to ascertain the findings. Obstructive sleep apnea (OSA) is on the common cause for non dipping patter of blood pressure. However, in this study, participants were not evaluated to rule out OSA, that may interfere study results.

Conclusion

This present study exposed there is a strong co-relation among altered circadian rhythm in both diabetic hypertensive and non diabetic hypertensive groups. This study also shows there is statistically significant relation between absence of dipping status and left ventricular hypertrophy as evidenced by ECHO suggesting participants are at risk ofdeveloping cardiovascular diseases. This study also found that ABPM SBP, DBP, PP and MAP have significant correlation with dipping status. Hence early Identification of altered circadian variation of BP can help in diagnosing, proper risk stratification and plan of modification of treatment plan.

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