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IS NON DIPPING HYPERTENSION ASSOCIATED WITH DYSLIPIDEMIA, TYPE 2 DIABETES OR CHRONIC KIDNEY DISEASE ?

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Abstract

Background and aims. *Hypertension and dyslipidemia (DLP) increase the risk of cardiovascular diseases (CVD), especially in patients with chronic kidney disease (CKD). A non dipping pattern is very common in CKD. The aim of the study was to determine whether there is a difference between dipping/non dipping hypertension in subjects with CKD and DLP with or without lipid-lowering therapy (LLT).* ***Material and methods****. We performed a retrospective study that included 129 subjects from the Nephrology-Hypertension Out-patient Department of the University Campus Bio-Medico, Rome from January 2011 to April 2013.* ***Results****. From a total of 129 CKD subjects, 73 (56.59%) subjects had a non dipping pattern and 56 (43.41%) had a dipper pattern. We found satistically significant differences between the dipping and non-dipping pattern in subjects with CKD stages 1-2 versus stages 3-4 (p=0.018). When we analyzed the association between non-dipping status with DLP and type 2 diabetes (T2D), we did not find a satistically significant result.* ***Conclusions.*** *Only CKD significantly influenced the dipping/non dipping pattern in the study group.*

key words: *dipping/non dipping pattern, hypertension, dyslipidemia, chronic kidney disease, diabetes.*

Background and Aims

Hypertension and dyslipidemia (DLP) constitute major public health problems as they increase the risk of cardiovascular diseases (CVD) [1], especially in patients with chronic kidney disease (CKD). The third National Health and Nutrition Examination Survey (NHANES III) study estimated that almost 15% of US adults (representing approximately 30 million persons) have both hypertension and DLP [2]. It was also shown that more than 60% of patients with hypertension also have DLP; conversely, approximately 50% of patients with DLP have hypertension [3]. DLP is a strong predictor of CVD and may also predict incident hypertension

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and both are conditions that coexist on a regular basis [4].

Hypertension and DLP are two of the major traditional risk factors for CVD [5] and also for CKD and may accelerate the progression of renal disease, but most importantly both of them contribute to the high cardiovascular morbidity and mortality in CKD patients. Risk of cardiovascular morbidity and mortality is increased in patients with CKD [6] and most patients with CKD will die of CVD before dialysis becomes necessary [7].

In healthy individuals blood pressure (BP) follows a circadian pattern. BP starts declining from late evening onwards, reaches a plateau level around midnight, and rises in the morning. This phenomenon of BP dipping has been documented by 24-hour ambulatory blood pressure monitoring (ABPM) [8]. During the last 15 years, ABPM has become an essential tool for the diagnosis of hypertension [9,10], subdividing these patients into "dippers" versus "nondippers" on the basis of a 10% reduction in the nocturnal mean arterial pressure. This natural circadian variation may be altered by certain metabolic and cardiovascular changes.

Nondipping BP patterns can be a useful marker of hypertension severity, if they are proven to be associated with other risk factors and complications.

A good news is that hypertension and DLP are modifiable risk factors and the treatment of hypertension and DLP results in a reduction in CVD. However hypertension and DLP are often insufficiently controlled in persons with CKD or diabetes [11]. Why? Because in DLP the implementation of therapeutic lifestyle changes is a problem, therefore those patients will require lifelong therapy with a lipid-lowering drug and in hypertension all clinician decision are made using clinic or office BP recordings. In the management of hypertension in patients with CKD, control of hypertension is very important and depends on the technique of BP measurement [12]. 24-hour ABPM may be useful for better management of hypertension in patients with CKD [13-16] and for achieving the targets of the recent guidelines. Recent evidence suggests that ABPM is a superior prognostic marker of cardiovascular [17] end points in CKD compared to BP obtained in the clinic [18-20].

The aim of our study was to determine whether there is a difference between dipping/non dipping hypertension in subjects with CKD and DLP with or without lipid-lowering therapy (LLT).

Matherial and methods

We performed a retrospective study on 129 subjects from the Nephrology-Hypertension Out-patient Department of University Campus Bio-Medico, Rome from January 2011 to April 2013. The study was approved by the ethics committee of the University. For all the subjects included in the study, the following inclusion criteria were met: subjects who had more than 70% of successful readings of ABPM, subjects with an estimated glomerular filtration rate (eGFR) calculated by CKD-EPI formula ≥15 mL/min/1.73m^2, no recent history of acute diseases, no history of oncological diseases and subjects with normal liver function. ABPM and other clinical and paraclinical data were collected.

ABPM recording

The subjects underwent 24 h ABPM with the SpaceLabs ABP UltraLite 90217. Its accuracy has been validated by official organizations in the US, UK, France and Germany. The diagnosis of hypertension was based on accepted ABPM criteria [21-24] according to the reports in Japan [25], Europe and the United States. "Dipper" was defined as a decline in the nocturnal BP of >10%, whereas "non-dipper" was defined as a decline in the

nocturnal BP of <10%. ABPM was used only for documenting dipper/non dipper pattern.

For each subject we collected the demographic data, laboratory data (serum levels of creatinine, cholesterol, TG, HDL-C, LDL-C, blood glucose, HbA1c, etc.), current therapy and medical history. eGFR was calculated by CKD-EPI formula.

Statistical Analysis

Statistical analysis was performed by the Biostatistics Department of the University of Medicine and Pharmacy of Craiova, Romania, using Microsoft Excel (Microsoft Corp., Redmond, WA, USA), together with the XLSTAT add-on for MS Excel (Addinsoft SARL, Paris, France) and IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY, USA) for processing the data.To test the normality of the data, we used the Anderson-Darling and Shapiro-Wilk tests. None of the numerical variables investigated had a normal distribution of data, globally or inside each studied group. Because the study involved a numerical comparison between 2 groups of patients that didn't have a normal (Gaussian) distribution of data, the nonparametric Mann-Whitney test was primarily used. For categorical data, in order to evaluate the significance of the association (contingency) we used Fisher test (chi-square test). P-values <0.05 were considered statistically significant.

Results

Table 1 reports the characteristics of the entire group studied and Figures 1-3 present the differences between dipping and non dipping pattern in different groups (subjects with CKD, DLP and T2D). We found satistically significant differences between the dipping and non-dipping pattern in subjects with CKD stages 1-2 versus stages 3-4 (p=0.018). When we analyzed the association between non-dipping status with DLP and T2D, we did not find a satistically significant result.

Table 1. Baseline characteristics of the study population

Total subjects	129
Age (years)	74 ± 15.56
Man	68.99% (n=89)
Woman	31.01% (n=40)
Stage CKD	
-stage 1	19.38% (n=25)
-stage 2	37.21% (n=48)
-stage 3	37.98% (n=49)
-stage 4	5.43% (n=7)
eGFR/CKD–EPI ml/min/1.73m^2	60.5 ± 20.5
Dipper/non dipper pattern	
-dipper	43.41% (n=56)
-non dipper	56.59% (n=73)
Diabetes	
-with T2D	38.76% (n=50)
-without T2D	61.24% (n=79)
Dyslipidemia	
-with dyslipidemia	82.95% (n=107)
With LLT	59.81% (n=64)
Without LLT	40.19% (n=43)
-without dyslipidemia	17.05% (n=22)

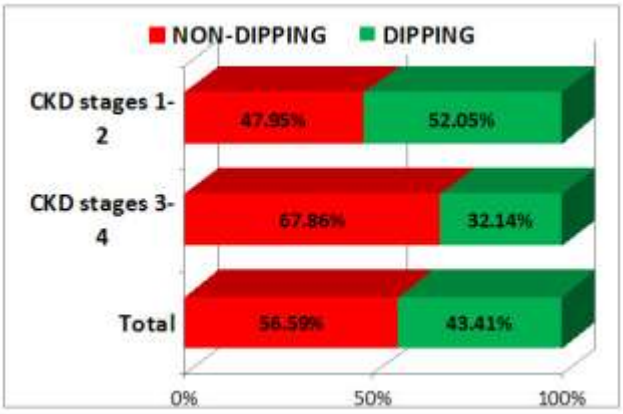

Figure 1. The differences between dipping and non dipping pattern in subjects with CKD stage 1-2 versus CKD stage 3-4 (p=0.018).

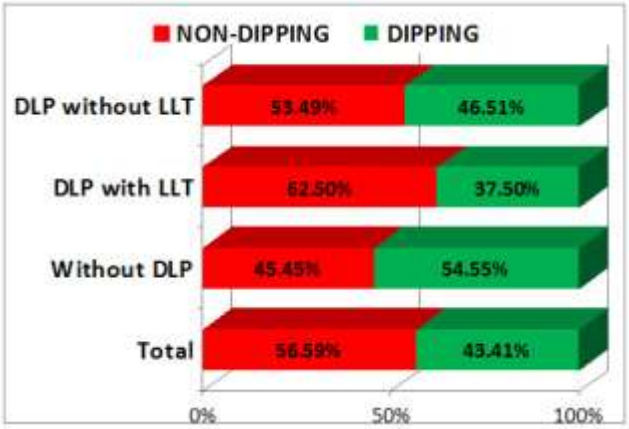

Figure 2. The relationship between dipping and non dipping pattern and DLP in the study population (p=0.230)

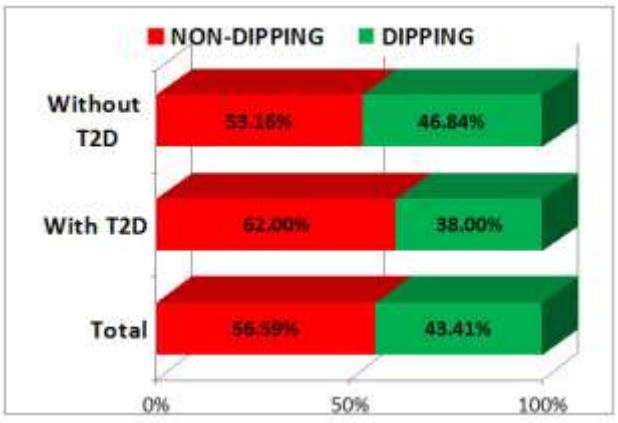

Figure 3. The differences between dipping and non dipping pattern according to the presence of T2D (p=0.211).

Table 2 reports the differences between dipping and non dipping pattern for all the analyzed parameters in subjects with DLP without LLT versus subjects without DLP.

In the dyslipidemic subjects, we found statistically significant differences between the dipping and non dipping pattern regarding the values of TG (p=0.019), as shown in Figure 4.

We also compared subjects with dipping pattern and those with non dipping pattern in the group without dyslipidemia and we found statistically significant differences between the values of LDL-C (p=0.044) and atherogenic index of plasma (AIP) calculated using a logarithmic formula comprising TG and HDL cholesterol, log(TG/HDL-C) (p=0.049), as shown in Figure 5.

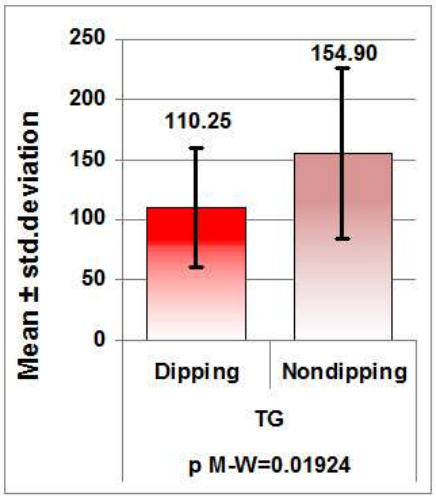

Figure 4. TG values differences between the dipping/nondipping pattern in subjects with dyslipidemia without LLT.

When we analyzed the differences between dipping and non dipping pattern in subjects with dyslipidemia and LLT, we did not find statistically significant differences between any of the studied parameters.

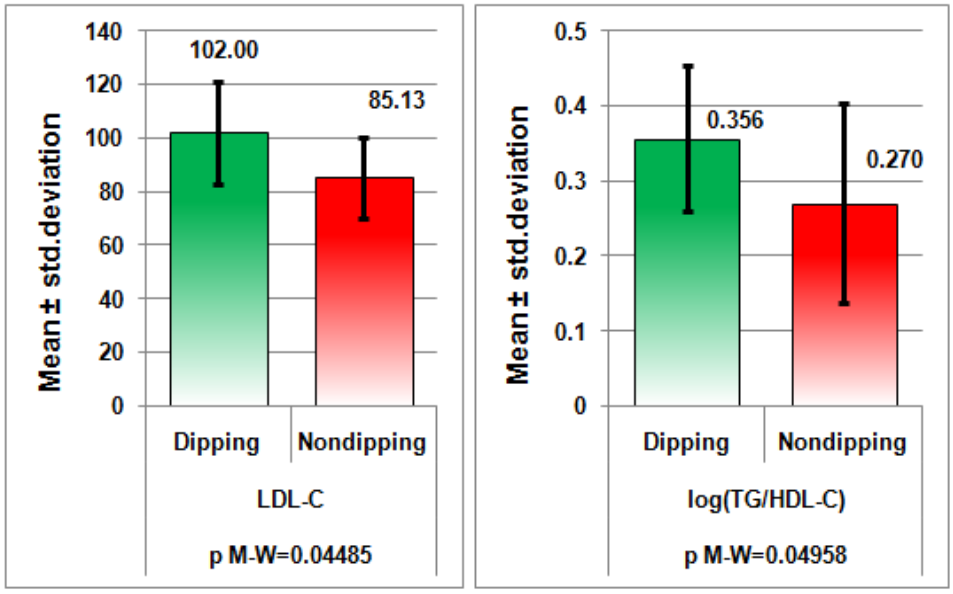

Figure 5. LDL and AIP values differences between the dipping/nondipping pattern in subjects without dyslipidemia.

Table 2. Subjects' characteristics (data presented as mean ± standard deviation).

Parameter	Subjects with dyslipidemia without LLT			Subjects without dyslipidemia		
	Dipping N=20	Non dipping N=23	p M-W	Dipping N=12	Non dipping N=10	p M-W
Age (years)	58.85±11.34	59.48±11.85	NS	55.58±15.58	54.60±18.80	NS
Creatinine(mg/dl)	1.22±0.45	1.27±0.54	NS	0.98±0.37	1.07±0.61	NS
eGFR (CKD-EPI) ml/min/1.73m^2	66.34±24.36	65.40±22.15	NS	78.83±23.46	81.30±35.44	NS
HsCRP (mg/l)	1.94 ± 2.24	0.99±1.30	NS	2.47±2.12	4.65±4.99	NS
Proteinuria (g/24h)	0.64±0.92	1.74±2.62	NS	0.13±0.15	0.45±0.28	NS
Cholesterol (mg/dl)	215.40±18.15	204.45±25.10	NS	171.42±17.79	160.30±23.80	NS
Triglycerides (mg/dl)	110.25±49.71	154.90±69.97	**p<0.05**	113.33±17.36	99.22±26.09	NS
LDL-C (mg/dl)	141.45±11.02	128.64±25.65	NS	102.00±19.16	85.13±15.29	**p<0.05**
HDL-C (mg/dl)	49.84±11.27	48.68±12.65	NS	49.92±11.38	51.56±12.63	NS
Non HDL-C= CHOL.T-HDL-C	165.16±13.98	158.14±20.12	NS	121.50±19.47	105.67±19.36	NS
CHOL.T/HDL-C	4.42±0.85	4.48±1.29	NS	3.52±0.74	3.12±0.70	NS
LDL-C/HDL-C	2.93±0.70	2.81±1	NS	2.08±0.60	1.74±0.60	NS
Log(TG/HDL-C)	0.32±0.23	0.47±0.27	NS	0.36±0.10	0.27±0.13	**p<0.05**
Blood Glucose (mg/dl)	103.83±21.25	102.00±16.58	NS	90.50±9.55	126.20±62.97	NS
HbA1c	6.10±0.89	6.70±1.66	NS	6.6±6.15	7.92±2.57	NS

NS not significantly statistic

Discussions

The results of our study proved that there is a statsitically significant difference between dipping and non dipping pattern in the subjects with CKD stages1-2 versus stages 3-4 (p=0.018). It is well known that nocturnal nondipping hypertension is very common in CKD patients and it is associated with the severity of the disease [26], increased proteinuria and inflammatory markers, such as C-reactive protein, but few studies [27] have examined the exact relationship of nocturnal non dipping hypertension with DLP in CKD patients.

When interpreting the data presented above, we must also take into consideration that it was performed in subjects with hypertension and antihypertensive medication and many studies have confirmed that it is possible to achieve a dipping pattern and improve the metabolic profile by administering antihypertensives in the evening [28]. Also many studies have shown that antihypertensive medication is associated with a significant reduction in microalbuminuria [29]. This could explain why we did not find statistically significant differences when we analyzed the values of proteinuria in any of the studied groups. We know that LLT, especially statins, have pleiotropic effects. In addition to lipid-lowering effect, statins acts also on endothelial dysfunction and may have the effect of lowering blood pressure. Also, statins have antiproteinuric effects and small studies have documented the improving dipping pattern when microalbuminuria was reduced.

Other studies have observed higher prevalence of DLP, T2D, or cardiovascular disease in non-dipping subjects [30,31]. However, in our study we did not find statistically significant differences in the subjects with T2D but we supose that this is due to the

small sample size of the study which prevents us from drawing strong conclusions. Another study conducted by Zeynep Tartan and al did not find singnificantly results when analyzing lipid parameters regarding dipping/non dipping pattern [32]. Although they showed that metabolic syndrome is a predictor of non-dipping hypertension, when the authors report their results, they emphasize the fact that there was no significant difference regarding certain lipid parameters (total cholesterol, LDL-C and HDL-C).

Conclusions

Only CKD significantly influenced the dipping/non dipping pattern in the study group.

24-hour ABPM is useful for the better management of hypertension in patients with CKD and for achieving the targets reccomandend by guidelines. Furthermore, it is the only method for documenting dipper/non dipper pattern available so far.

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