ORIGINAL ARTICLE

Twenty four–hour ambulatory blood pressure monitoring and lipid levels before, 3, 6 and 12 months after the onset of hemodialysis in chronic kidney disease patients: a pilot study

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Abstract

Background: Twenty four–hour ambulatory blood pressure (BP) monitoring (ABPM) is being increasingly used to evaluate the effectiveness of antihypertensive medications. We aimed to to investigate the incidence of "non–dippers" in ESRD patients before, as well after the initiation of hemodialysis, to evaluate whether start of hemodialysis is associated with a reduction in the use of antihypertensive drugs, and to correlate 24–hour ABPM with serum lipid levels, the use of lipid–lowering drugs (statins) and the development of the Metabolic Syndrome (MetS) in these patients.

Methods: Thirty patients scheduled to initiate hemodialysis (glomerular filtration rate <15 ml/min/1.73m^2) were prospectively recruited. Twenty four–hour ABPM and lipid levels were recorded before (T0), as well as 3 (T1), 6 (T2) and 12 (T3) months after hemodialysis onset.

Results: A progressively significant (p=0.025) decrease in the use of antihypertensive medications was observed in 26 of 30 patients throughout the study, whereas the remaining four patients were not hypertensive during the same period. There was a progressive increase in the use of statins for the management of dyslipidemia (p=0.015). This increase in statin use was coupled with an increase in the prevalence of the MetS in the study population (p=0.040). Patients with daily BP <135/85 mm Hg had a lower incidence of new MetS compared with patients with daily BP >135/85 mm Hg (p=0.053).

Conclusions: Patients initializing hemodialysis demonstrate a progressively increased incidence of dyslipidemia and MetS, as well as a reduction in the use of antihypertensive drugs. Optimal management of BP and dyslipidemias is essential to reduce the high cardiovascular morbidity and mortality rates in this high–risk population. Hippokratia. 2012; 16 (2): 154-158

Key words: ambulatory blood pressure monitoring, hemodialysis, dyslipidemia, statins, metabolic syndrome

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The incidence of end–stage renal disease (ESRD is globally rising[1]. Hypertension is one of the leading causes of ESRD[2,3] and a strong predictor of mortality in dialysis patients[4].

In the last few years, there is increased use of 24–hour ambulatory blood pressure (BP) monitoring (ABPM) to evaluate the effectiveness of antihypertensive medications[5]. It was supported that 24–hour ABPM offers considerable advantages compared with clinical BP monitoring[6]. In a longitudinal cohort study of 217 veterans with chronic kidney disease (CKD), 24–hour ambulatory BP was 133.5±16.6 / 73.1±11.1 mm Hg, while clinical BP was 155.2±25.6 / 84.7±14.2 mm Hg[6]. The composite renal end–point of ESRD or death occurred in 75 patients (34.5%). One standard deviation (SD) increase in systolic BP increased the risk of composite outcome by 69% for standard clinical BP measurement (hazard ratio [HR], 1.69; 95% confidence interval [CI], 1.32–2.17) compared with 88% for 24–hour ABPM (HR, 1.88; 95% CI, 1.48–2.39). The conclusion reached was that ABPM provides greater prognostic information compared with clinical BP monitoring[6].

The terms "dippers" and non–dippers" were introduced to describe the 2 distinct populations based on BP variation during the night[7]. "Non–dippers" are individuals who do not experience the normal decrease in BP during the night[7]. Whether this phenomenon occurs as a cause or as a result of CKD is still a matter of debate.

Our study had 3 aims: 1) to investigate the incidence of "non–dippers" in ESRD patients before, as well after the initiation of hemodialysis, 2) to evaluate whether hemodialysis is associated with a reduction in the use of antihypertensive drugs, and 3) to correlate 24–hour ABPM with serum lipid levels and the use of lipid–lowering drugs (statins).

Materials and Methods

Between June 2006 and June 2008, 47 ESRD

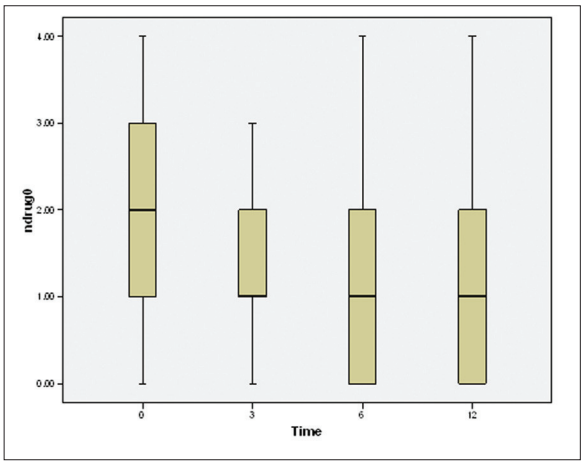

Figure 1: Mean number of antihyApertensive drugs used before, 3, 6 and 12 months after initiation of hemodialysis

patients scheduled to initiate hemodialysis (estimated glomerular filtration rate [GFR] <15 ml/min/1.73m^2), were prospectively recruited in our cohort study. During the study period, 15 patients were lost due to transfer to other hemodialysis units, while 2 patients died from cardiovascular causes (1 myocardial infarction and 1 stroke). Thus, a total of 30 patients were included in our study (14 males; 16 females; mean age±SD: 66.4±9.6 years).

BP considered normal if found <130/85 mm Hg and was measured with a sphygmomanometer according to a prespecified protocol: after 5 minutes of rest in supine position, 3 BP measurements took place with at least 1 minute intervals between them. Following these measurements, a 24–hour ABPM was employed. The same protocol was performed before the patients initiated hemodialysis (T0), as well as 3 (T1), 6 (T2) and 12 (T3) months after the onset of hemodialysis. The prescribed medications for each patient as well as their lipid levels were recorded at each measurement.

All patients signed an informed consent to enter our study. The Ethics Committee of our Hospital approved our protocol.

Serum lipid measurement

Serum lipid levels were measured at the same time intervals (T0, T1, T2 and T3). Venous blood was drown after overnight fasting in the absence of anticoagulant into Wasserman tubes and allowed to clot for 30 minutes at 4ºC. Serum was isolated from blood samples by centrifugation at 3000g for 15 minutes at 4 ºC. Serum was then stored at –80 ºC and analyzed within 2 days from collection.

Total cholesterol (TC) was determined enzymatically by the cholesterol oxidase peroxidase–amidopyrine (CHOD–PAP) method using a commercially available kit (Biosis, Hellas), with normal range 150-200 mg/dl.

Table 1: Number of patients (%) receiving antihypertensive treatment at the prespecified time intervals of the study

	T0	T1	T2	T3
Number of patients (%)	26 (87)	23 (77)	21 (70)	22 (73)*

T0: Before the initiation of hemodialysis; T1: 3 months after the onset of hemodialysis; T2: 6 months after the onset of hemodialysis; T3: 12 months after the onset of hemodialysis

* p=0.025 between T0 and T3.

Table 2: Number of patients (%) with hyperlipidemia receiving statins at the prespecified time intervals of the study

	T0	T1	T2	T3
Number of patients (%)	5 (17)	8 (27)	9 (30	10 (33)*

T0: Before the initiation of hemodialysis; T1: 3 months after the onset of hemodialysis; T2: 6 months after the onset of hemodialysis; T3: 12 months after the onset of hemodialysis

* p=0.015 between T0 and T3.

Table 3: Number of patients (%) with the Metabolic Syndrome at the prespecified time intervals of the study

	T0	T1	T2	T3
Number of patients (%)	5 (17)	7 (23)	8 (27)	11 (37)

T0: Before the initiation of hemodialysis; T1: 3 months after the onset of hemodialysis; T2: 6 months after the onset of hemodialysis; T3: 12 months after the onset of hemodialysis

* p=0.040 between T0 and T3.

After precipitation of other lipoproteins with heparin and $MnCl_2$, serum high–density lipoprotein cholesterol (HDL–C) was measured using a commercially available kit (Roche, Manheim, Germany), with normal values >45 mg/dl. Serum triglycerides (TG) were measured by the glycerol–3–phospate–oxidase peroxidase–amidopyrine (GPO–PAP) method using a commercially available kit (Biosis, Hellas), with normal range 70-170 mg/ dl. Low–density lipoprotein cholesterol (LDL–C) was estimated using the Friedewald formula: LDL–C = TC – (HDL–C + TG/5) mg/dl whereas optimal values were <160 mg/dl.

The diagnosis of the Metabolic Syndrome (MetS) was established if at least 3 of the following 5 parameters were present[8]:

1. Blood pressure >130/85 mm Hg
2. Waist circumference >102 cm for males and >88 cm for females.
3. HDL values <50 mg/dl for males and <40 mg/dl for females
4. TG values >150 mg/dl, and,
5. Fasting blood glucose values >110 mg/dl

Statistical analysis

Data are expressed as mean±SD for continuous variables and as percentages for categorical data. The Kolmogorov–Smirnov test was used to assess whether the distribution of variables followed a Gaussian pattern. Comparison of continuous variables was analyzed using the unpaired t test and Mann–Whitney nonparametric test, as appropriate. Differences in categorical variables were assessed using Pearson's chi–square test. Linear relationships between quantitative normally distributed parameters were assessed with Pearson's two–way test and Spearman's rho was used for nonparametric data. Repeated measures analysis of variance (ANOVA) was used to evaluate the fluctuation of specific parameters in time and whether this fluctuation followed a normal distribution, while the non–parametric Friedman's test was used otherwise. The association between the fluctuations of 2 independent variables was tested with Fisher's exact test. Any difference was considered significant if the null hypothesis could be rejected with >95% confidence (2–tailed $p < 0.05$). All statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS 15.0) statistical programme.

Results

Four of the 30 patients of our cohort were found with normal BP during the whole study period. For the remaining 26 patients, there was a progressive decrease in the use of antihypertensive medications (p=0.025; Table 1; Figure 1). In contrast, there was a progressive increase in the use of lipid–lowering medications (statins) for the management of dyslipidemia (p=0.015; Table 2). This increase in statin use was coupled with an increase in the prevalence of the MetS in the study cohort ($P = 0.040$; Table 3).

The number of "dippers" and "non–dippers" did not change between T0 and any time interval after the onset of hemodialysis ($P = 1.0$ between T0 and T1; p=1.0 between T0 and T2; and p=0.375 between T0 and T3). The majority of the study participants (n=21) remained "non–dippers" throughout the whole duration of the study. Additionally, 4 patients who were "dippers" at the beginning of the study remained "dippers" throughout the whole duration of the study. Only four "non–dippers" at T0 became "dippers" and only one "dipper" at T0 became "non–dipper" by the end of the study.

Patients with daily BP <135/85 mm Hg had a lower incidence of new MetS compared with patients with daily BP >135/85 mm Hg. This difference reached borderline significance (Fisher's exact test: p=0.053).

Discussion

Our study demonstrated a progressive decrease in the use of antihypertensive drugs coupled with a progressive increase in the prevalence of the MetS and hyperlipidemia requiring statin use.

Dialysis patients often have various forms of dyslipidemias, with hypertriglyceridemia being the primary lipid abnormality[9]. Dyslipidemia is a strong risk factor for cardiovascular disease. Statins may exert several beneficial actions on renal patients; examples include the reduction of residual kidney function loss rates (thus slowing the progression to renal failure) and cardiovascular event rates[9]. The reduction in cardiovascular mortality in renal patients by statin treatment was not supported in two multicentre studies, the German Diabetes and Dialysis Study (4D)[10] and the Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA)[11] . Nevertheless, in the 4D Study, statin treatment resulted in an 18% reduction of all cardiac events combined compared with placebo (relative risk 0.82, 95% CI 0.68–0.99; p=0.03)[10]. It was supported that earlier statin treatment could be associated with more beneficial effects in this high–risk population[12-14].

In a recent "simulated" trial, an observational model of the 4D study (n=5,144 type 2 diabetes dialysis patients using statins) was matched to a non–statin control group (n=5,144 non–users)[15]. In covariate– and propensity–adjusted Cox regression, statin use was associated with a decrease in the composite primary outcome of cardiac death, non–fatal myocardial infarction and stroke compared with statin non–use. Statin use was also associated with a decrease in cardiovascular mortality and all cardiac events combined[15]. The Study of Heart And Renal Protection (SHARP) also demonstrated a reduction in the incidence of major atherosclerotic events for statin use compared with non–use in a wide range of patients with advanced CKD[16]. An independent report demonstrating a beneficial effect of preoperative statin use on renal function in patients undergoing cardiac surgery further supports a nephroprotective effect of statin treatment[17]. Thus, the jury is still out regarding the

role of statins in CKD and dialysis patients.

Renal patients have mortality rates up to 10–12 times higher than the general population[18]. The Kidney Early Evaluation Program (KEEP) Study showed that the presence of CKD is associated with younger ages of cardiovascular disease[19]. Furthermore, the combination of CKD with cardiovascular diseases is associated with shorter survival rates[19]. These patients should therefore have aggressive risk factor management to reduce the high cardiovascular event, morbidity and mortality rates[18]. Adoption of regular in–hospital and home–based exercise programs may improve outcomes[20]. The beneficial effects of conservative treatment in patients with stages 4 and 5 CKD may include delaying the initiation of dialysis for over 2 years[21]. Screening for both CKD and cardiovascular disease and early initiation of protective conservative measurements was suggested to maximize the chances for slowing nephropathy progression and reduction of proteinuria[22]. It was concluded that aggressive management of traditional cardiovascular risk factors should be employed in this high–risk population, specifically rigorous hypertension control (including the use of angiotensin–converting enzyme inhibitors/angiotensin receptor blocking agents), management of hyperglycemia, hyperlipidemia and smoking cessation[22]. Statin use in CKD and dialysis patients is associated with several beneficial effects, besides improvement of cardiovascular event rates and decline in the deterioration of renal function[23].

Hypertension is one of the major risk factors for both CKD and cardiovascular disease. Patients with BP≥160/95 mmHg have a 5–fold greater decline in GFR compared with patients with BP <140/95 mmHg[24]. A stronger association between hypertension and cardiovascular diseases has been demonstrated in CKD patients[25-27]. In the Suita study[28], CKD was associated with an increased risk for stroke and myocardial infarction in a general urban Japanese population. Patients with a GFR of 50–59 ml/min/1.73m^2 had an almost 2–fold increased risk for stroke compared with patients with a GFR of ≥90 ml/min/1.73m^2 (HR, 1.9; 95% CI, 1.3–3.0). Those patients with a GFR of <50 ml/min/1.73m^2 had an even higher risk of stroke (HR, 2.2; 95% CI, 1.2–4.1)[28].

A limitation of our study is the small number of ESRD patients included (n=30). This number, however, was adequate for significant associations to be formed. Our results need to be verified in larger studies in the future.

Conclusions

Patients with stage 4 and 5 CKD initiating hemodialysis appear to be at increased risk for developing dyslipidemia and the MetS from the first year of initiation of renal replacement therapy. The increase in the incidence of hyperlipidemia/dyslipidemia is coupled with a progressive decrease in the need for antihypertensive medications.

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