

Relationship between renal size and blood pressure profile in patients with autosomal dominant polycystic kidney disease without renal failure

L. Sans Atxer¹, A. Roca-Cusachs², R. Torra³, F. Calero³, P. Arias⁴, J. Ballarin³, P. Fernández-Llama³

¹ Nephrology Department. Hospital del Mar. Barcelona, Spain

² Internal Medicine Department. Hypertension Unit. Hospital de la Santa Creu i Sant Pau. Universitat Autònoma de Barcelona, Spain

³ Nephrology Department. Fundació Puigvert. Department of Medicine (Universitat Autònoma de Barcelona). REDinREN. Instituto de Investigación Carlos III, Spain

⁴ Nursing Department. Fundació Puigvert. Barcelona, Spain

Nefrologia 2010;30(5):567-72

10.3265/Nefrologia.pre2010.May.10418

ABSTRACT

Background: Enlargement of renal size plays an important role in the development of hypertension in patients with autosomal dominant polycystic kidney disease (ADPKD) and normal renal function. **Methods:** A 24h blood pressure monitoring (ABPM) and a renal ecography have been performed in 37 patients with ADPKD and estimated glomerular filtration rate >60 ml/min/1,73 m² to study the relationship between renal size and an altered blood pressure profile in prehypertension stages. **Results:** 13 patients had normal blood pressure, 11 were diagnosed of masked hypertension, 4 had white coat hypertension and 9 had hypertension. We have found in the normotensive group with a dipper blood pressure profile a positive and statistically significant relationship between renal size and diastolic blood pressure variability. **Conclusions:** ABPM helps to make an early diagnosis of hypertension and to identify those patients with masked hypertension. This study suggests a relationship between renal size and a blood pressure profile linked to a major cardiovascular risk in normotensive patients with ADPKD

Key words: Autosomal dominant polycystic kidney disease. Renal size. Ambulatory monitoring of blood pressure. Blood pressure profile. Blood pressure variability

Relación entre el tamaño renal y el perfil de presión arterial en pacientes con poliquistosis renal autosómica dominante sin insuficiencia renal

RESUMEN

Antecedentes: El aumento del tamaño renal desempeña un papel importante en el desarrollo de la hipertensión arterial (HTA) en pacientes con poliquistosis renal autosómica dominante (PQRAD) con función renal normal. **Material y métodos:** Se han practicado a 37 pacientes con PQRAD, filtrado glomerular estimado (FGe) por MDRD >60 ml/min/1,73 m² y supuestamente normotensos, una monitorización de la presión arterial (MAPA) y una ecografía renovesical para investigar la posible relación entre el aumento del tamaño renal y un perfil patológico de presión arterial (PA) en estadios de prehipertensión. **Resultados:** 13 pacientes resultaron ser normotensos, 11 presentaron HTA enmascarada, cuatro tuvieron HTA de bata blanca y nueve, HTA verdadera. Se ha observado en los pacientes normotensos con patrón reductor de la PA una correlación positiva y estadísticamente significativa entre el tamaño renal y la variabilidad de la presión arterial diastólica (PAD). **Conclusiones:** La MAPA permite realizar un diagnóstico precoz de la HTA e identificar a pacientes con hipertensión enmascarada. Este trabajo sugiere que en pacientes normotensos con PQRAD existe una posible relación entre el tamaño renal y un perfil de PA con mayor riesgo cardiovascular.

Palabras clave: Poliquistosis renal autosómica dominante. Tamaño renal. Monitorización ambulatoria de la presión arterial. Perfil circadiano de la presión arterial

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disease characterised by the presence of bilateral renal cysts that progressively increase in number and size.¹ It

Correspondence: Laia Sans Atxer
Servicio de Nefrología.
Hospital del Mar. Barcelona. Spain.
lsans@hospitaldelmar.cat

is the most common genetic disease affecting the kidneys and leads to terminal kidney failure as patients get into their 40s and 50s.^{2,3}

The leading cause of death in patients with polycystic kidney disease is cardiovascular disease, being arterial hypertension (AHT) its main determinant.⁴ Both hypertension and the increase in renal size secondary to the growth of cysts¹ is correlated with a progressive deterioration of renal function in ADPKD. The onset of hypertension in these patients is common and in approximately 60% of cases the diagnosis is performed before any renal function impairment appears. It seems that the increase in kidney size⁵⁻⁷ and the activity in the renin-angiotensin-aldosterone system⁸⁻¹⁰ are primarily responsible for the development of hypertension in these patients. Studies in patients with ADPKD and normal renal function have shown the presence of target organ damage (increased left ventricular mass)^{11,12} before developing AHT. This damage appears to be related more to the increase in systolic blood pressure (SBP) determined by ambulatory blood pressure monitoring (ABPM) than to the blood pressure (BP) measured at the clinic.¹²

Twenty-four hour ABPM adds additional information to the BP measurements in the clinic (BPc) as it reports on the circadian rhythm and the variability of the BP. Furthermore, it identifies patients with masked hypertension (normal clinic BP and high ambulatory BP) and isolated clinic hypertension (high BP readings in the clinic and normal ambulatory BP). A non-physiological BP profile (non-dipper nocturnal pattern), a greater BP variability (average of standard deviations over 24 hours greater than 18 mmHg for SBP or greater than 15mmHg for DBP) and the presence of masked or isolated clinic hypertension have been related to greater cardiovascular risk.¹³⁻¹⁷

Therefore, although hypertension is a key factor in cardiovascular morbidity and mortality in patients with polycystic disease, little is known about the pre-hypertensive stage. In addition, it is not known whether the increase in kidney size could be associated with a change in the BP profile and its variability. We therefore decided to evaluate the following points in patients with normotensive ADPKD *a priori* and with eGF by MDRD >60 mL/min/1.73m²:

1. Whether there are differences between the BPc and the ABPM readings.
2. The relationship between maximum kidney diameter and SBP, DBP and mean BP (MBP) over 24 hours, day and night, and pulse pressure (PP) obtained by 24-hour ABPM.
3. If there is a relationship between maximum kidney diameter and the variability of BP or the circadian BP pattern.

MATERIAL AND METHODS

We performed a transversal, observational study that included 37 patients with ADPKD from those who visited outpatient clinics, who were between the ages of 18 and 50 years, with eGF by MDRD >60 mL/min/1.73m² and who were normotensive (patients with home BP <135/85 mmHg and not receiving treatment for hypertension).

The following information was collected from these 37 patients:

1. Three readings of SBP and DBP with the OMRON 705 IT blood pressure monitor (Tokyo, Japan), following the standard for BPc readings of the European Society of Hypertension (ESH),¹⁸ using the average of three readings as the clinical BP value.
2. ABPM data (via the Dyasis Integra device) (Rueil-Malmaison, France).
 - SBP, DBP and MBP (DBP + 1/3 pulse pressure (PP) (PP = SBP – DBP) during the day, night and over 24 hours. Heart rate and 24-hour PP.
 - Percentage of nocturnal BP decrease with respect to the daytime SBP, DBP and MBP and quality of sleep on the ABPM date.
 - Load index (percentage of BP measurements above the established target BP) for SBP and DBP during the day, night and over 24 hours.
 - Typical or standard deviation of the average SBP and DBP during the day, night and over 24 hours. Maximum daytime, nighttime and 24-hour SBP and DBP.
3. Anthropometric data: weight, height, body surface area and body mass index.
4. Mean maximum diameter of both kidneys (in millimetres) by renal ultrasound performed by ultrasound specialists who are expert in renovesical ultrasound, using a single measure.

According to the ABPM readings and following the recommendation in the 2007 ESH Guidelines,¹⁸ patients are considered normotensive if they present a SBP <130 mmHg and a DBP <80 mmHg by ABPM over 24 hours.

The percentage of decrease in nocturnal MBP versus daytime MBP allows us to classify patients according to their BP profile:

1. Non-dipper pattern: nocturnal MBP decrease versus daytime MBP less than 10%.
2. Dipper pattern: nocturnal MBP decrease versus daytime MBP between 10 and 20%.

3. Riser pattern: nocturnal MBP higher than daytime MBP.
4. Extreme dipper pattern: nocturnal MBP decrease versus daytime MBP greater than 20%. The circadian profile was not assessed if the patient reported suffering from a bad night's sleep.

Considering the BP readings obtained from the ABPM and the BPc, we can classify the patients into four groups:

1. White coat AHT: patients with high BPc ($\geq 140/90$ mmHg) and BP by ABPM over 24 hours $< 130/80$ mmHg.
2. Masked AHT: patients with normal BPc ($< 140/90$ mmHg) and high BP by ABPM over 24 hours ($\geq 130/80$ mmHg).
3. True AHT: patients with high BPc and BP by ABPM over 24 hours.
4. True normotensives: patients with normal BPc and BP by ABPM over 24 hours.

The statistical analysis was carried out with the SPSS software. The results are expressed as the mean \pm standard deviation (SD) for the continuously distributed variables and as frequencies for the categorical variables.

Given the small sample size, the normal distribution of variables was studied using the Kolmogorov-Smirnov and Shapiro-Wilks tests. After verifying the normality of the variables, the Student's t-test was used to compare samples with two categories and ANOVA was used for those with three or more categories. For the non-parametric variables, the Mann-Whitney and Kruskal-Wallis tests were used depending on whether they had two or more categories.

To study the association between the mean maximum kidney diameter and the various data provided by the ABPM, the linear Pearson correlation coefficient was used. The distribution of categorical variables was analysed by means of the chi-squared test. A P less than 0.05 was considered statistically significant.

RESULTS

Blood pressure classification according to BP values obtained in the clinic and by ambulatory blood pressure monitoring

The 37 patients included were classified into four groups according to the BP obtained in the clinic and through 24-hour ABPM. Of these, 13 were true normotensives (35.1%), 9 were true hypertensives (24.3%), 4 patients had white coat hypertension (10.8%) and the remaining 11 (29.7%) had masked hypertension (Table 1).

Taking into account the average BP by ABPM over 24 hours and hypertension being diagnosed for a SBP ≥ 130 mmHg or a DBP ≥ 80 mmHg, 20 of the 37 patients (54%) initially selected as normotensives according to the home BP readings were diagnosed with AHT.

Relationship between kidney size and blood pressure characteristics

There is currently no standard of normality in relation to maximum kidney diameter in the general population but it is known that the maximum kidney diameter is correlated with height,¹⁹ which was coherent with our population ($r = 0.572$, $P = 0.016$). The mean maximum diameter was measured for both kidneys of each individual and was adjusted for height.

We had set out to only assess normotensive patients with ADPKD but because we had a significant percentage of hypertensive patients, we decided to study whether there was any relationship among the total available population (37 patients) between the various parameters obtained by the ABPM and the mean kidney diameter adjusted for height. This analysis revealed a statistically significant negative correlation between a greater kidney size and a lower PP ($r = -0.325$, $P = 0.05$) (Figure 1).

Subsequently and because this was the main objective of the paper, the results in the subset of 17 normotensive patients by ABPM over 24 hours were analysed. Table 2 and Table 3 contain the demographic characteristics, kidney size and BP

Table 1. Classification of BP according to measurements taken in the clinic and by ABPM

n = 37	Clinic BP $< 140/90$	Clinic BP $\geq 140/90$
BP by ABPM 24h $< 130/80$	Normotensive 13 (35.1%)	White coat AHT 4 (10.8%)
BP by ABPM 24h $\geq 130/80$	Masked AHT 11 (29.7%)	True AHT 9 (24.3%)

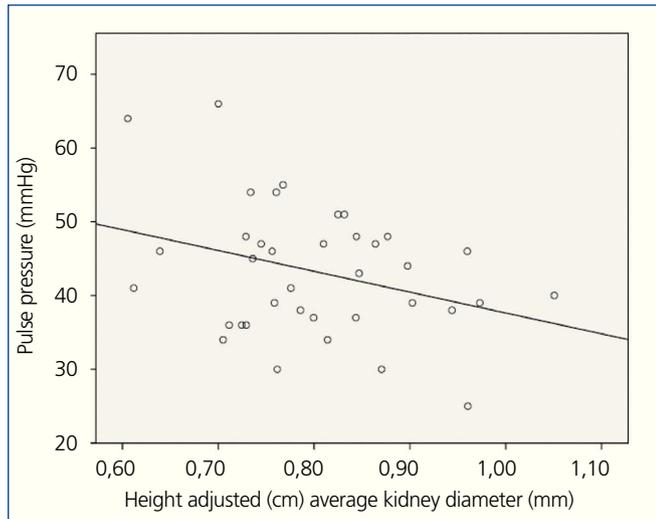


Figure 1. Linear regression line between height adjusted average renal diameter and pressure differential in the overall population ($n = 37$).

obtained in the clinic and by ABPM. When analysing the data from the group of the 17 normotensive patients, positive correlations were identified between average maximum kidney size adjusted for height and all parameters of ABPM with the exception of PP, without reaching statistical significance.

Kidney size, circadian profile and blood pressure variability

Clinically, the parameter used for assessing the BP pattern was the decrease in daytime to nighttime MBP. In the group of 17 normotensive patients, there were no statistically significant differences in the maximum renal diameter adjusted for height between patients with a non-dipper

pattern ($n = 6$), dipper pattern ($n = 8$) and extremely dipper pattern ($n = 3$) ($P = 0.662$) (Figure 2). None of the 17 patients reported a riser pattern.

Of the 17 normotensive patients, we decided to study those who had a physiological BP profile, maintaining 11 assessable patients with a dipper BP pattern.

In the group of 11 patients with dipper BP patterns according to the decrease in MBP, positive correlations were found, although not significant, between kidney size and all parameters (SBP, DBP, systolic and diastolic load index, SD of SBP and DBP) for daytime, nighttime and 24-hour BP readings by ABPM, where diastolic load index over 24 hours showed the greatest positive correlation ($P = 0.07$). The nocturnal decrease in BP for this group had a negative correlation, although not statistically significant, with the increase in kidney size.

Since, strictly speaking, a dipper pattern should present a nocturnal decrease in both SBP and DBP greater than 10%, we investigated in the 17 normotensive patients whether the absence of a nocturnal decrease in SBP and/or DBP was associated with a greater maximum renal diameter adjusted for height. No significant differences were found in kidney size among patients with or without a dipper BP pattern.

Applying this criterion of a nocturnal SBP and DBP decrease of $>10\%$ versus daytime to define the dipper pattern, only 6 of the 17 patients had a dipper pattern, all with a proper night's rest on the date of the ABPM. In these six patients, a trend was once again observed towards a positive correlation that approached statistical significance for the 24-hour mean DBP, the diastolic load index for day and night, with the 24-hour diastolic load index achieving statistical significance ($r = 0.875$, $P = 0.023$) (Table 4).

In the group of 11 patients without a dipper pattern of SBP and DBP, a positive and statistically significant correlation was observed ($r = 0.623$, $P = 0.04$) between the maximum kidney diameter adjusted for height and the standard deviation of DBP at night, which once again is a parameter that reflects the BP variability.

Table 2. Demographic and clinical characteristics of the normotensive population confirmed by 24-hour ABPM ($n = 17$)

Gender (men)	29.4 (%)
Age (years)	38.7 ± 10.4
Weight (kg)	65.8 ± 10.9
Height (cm)	168.0 ± 8.3
Body mass index (kg/m^2)	23.5 ± 3.2
Waist perimeter (cm)	76.7 ± 8.7
Mean renal diameter (mm)	133.8 ± 21.6
Height adjusted mean renal diameter (mm/cm)	0.795 ± 0.108
Mean clinic SBP (mmHg)	121.5 ± 12.3
Mean clinic DBP (mmHg)	84.2 ± 6.3

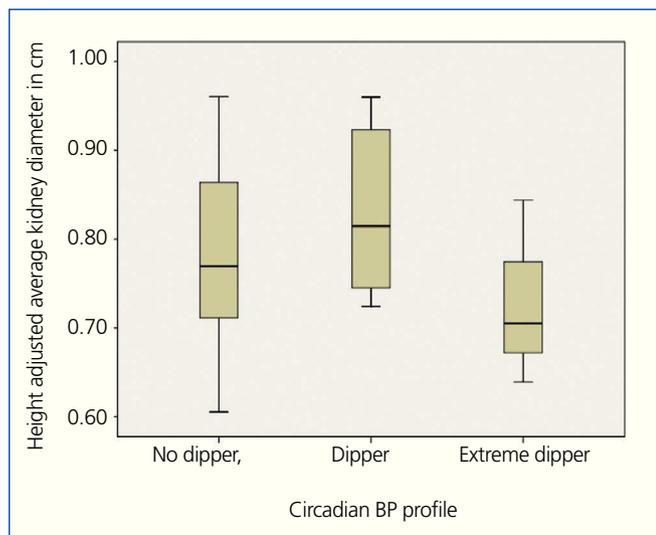
DISCUSSION

The ABPM study of this group of patients who reported correct home BP readings allowed us to diagnose some 54.1% of them as hypertensive. The patients were not trained to carry out a proper home blood pressure monitoring (HBPM), which would have helped diagnose hypertension in some of the patients who reported being normotensive at home.

An important aspect of this study is that 11 of the 37 patients selected (29.7%) would not have been diagnosed with

Table 3. BP readings by ABPM of the normotensive population (n = 17)

	24 hours	day	Night	Nocturnal decrease (%)
Mean SBP (mmHg)	113.9 ± 8.6	117.3 ± 10.6	103.2 ± 8.2	11.7 ± 7.2
Mean DBP (mmHg)	74.7 ± 3.2	77.8 ± 4.3	66.6 ± 6.1	14.1 ± 9.2
MBP (mmHg)	87.3 ± 4.5	90.4 ± 5.3	78.6 ± 6.6	12.9 ± 7.9
Systolic load index (%)	14.5 ± 15.1	16.0 ± 15.8	10.2 ± 19.4	
Diastolic load index (%)	36.1 ± 18.8	32.5 ± 20.3	51.9 ± 29.3	
SBP typical deviation (mmHg)	14.3 ± 7.4	8.8 ± 3.3	14.9 ± 6.9	
DBP typical deviation (mmHg)	10.9 ± 5.1	8.4 ± 2.6	11.7 ± 4.8	
Maximum SBP (mmHg)	163.8 ± 33.8	163.8 ± 33.8	119.2 ± 14.4	
Maximum DBP (mmHg)	110.4 ± 22.5	110.4 ± 22.5	82.6 ± 7.4	
Differential pressure (mmHg)	40.8 ± 8.9			

**Figure 2.** Height adjusted average renal diameter as a function of the circadian BP profile in the normotensive group (n = 17).

hypertension using only the clinical measurements, since they had masked AHT. Some studies have shown that patients with masked hypertension have more important subclinical organ damage than subjects with white coat hypertension or with grade I AHT, which causes this condition to carry a greater cardiovascular risk.¹⁵⁻¹⁷ Population studies have also shown a significant increase in mortality in this subset of the population, which might become comparable to the established AHT.¹⁸ The prevalence of masked AHT, according to the literature, varies between 6 and 26%. In the population studied, the prevalence of masked hypertension is very important and, if not detected and corrected, it can increase cardiovascular risk and the likelihood of developing target organs damages.

The existence of a statistically significant negative correlation between a greater maximum kidney diameter and a lower PP in the initial group of patients indirectly suggests an alteration of the DBP. The population studied was young, with an average age of approximately 38 years. As with our group, the general hypertensive young population is much more likely to have high DBP than SBP, which leads to a decrease in PP.

In the group of normotensive patients, no relationship was detected between kidney size and the alteration of the circadian BP cycle, although only a few patients were analysed. However, there remains a discernible trend towards a poorer BP profile associated with a poorer DBP to greater kidney diameter. This trend persists even in the group of normotensive patients with proper nocturnal decrease in MBP. The relationship between a greater diastolic load index over 24 hours to greater renal diameter in patients with dipper pattern of SBP and DBP is statistically significant. The load index (percentage of the BP readings by the ABPM that exceed the preset target BP) is one of the measures used for evaluating BP variability and it has been shown that an increased load index is related to greater target organ damage (left ventricular hypertrophy).²⁰ The trend towards increased diastolic load

Table 4. Study of the relationship between average renal diameter adjusted for height and the variability of BP in the group of normotensives with a dipper pattern of SBP and DBP (n = 6)

	r	P
24-hour diastolic load index	0.875	0.023
Daytime diastolic load index	0.783	0.065
Nocturnal diastolic load index	0.751	0.085

index as kidney size increases could ultimately be related to greater target organ involvement, which has been shown in some studies with this type of population.¹²

Given the importance of the results obtained in this study, it is necessary to expand the sample size to confirm the findings and to evaluate the possible relationship that these findings may have to subclinical involvement of target organs.

In conclusion, the single reading of BPC in patients with ADPKD and normal renal function leaves many hypertensive patients undiagnosed given the high prevalence of masked AHT. ABPM-assisted examination helps to identify these patients early on.

The analysis of the overall group of 37 patients, as well as the separate analysis of the group of normotensive patients, show a statistically significant relationship between greater renal size and a worse performance of DBP, as revealed by a lower PP in the former group and a greater variability in DBP in the latter group. This data shows a worse DBP profile as compared to SBP. These findings indicate that a relationship might exist along the entire evolution of the disease between renal growth and DBP alteration.

REFERENCES

1. Grantham JJ, Torres VE, Chapman AB, Guay-Woodford LM, Bae KT, King BF Jr, et al.; CRISP Investigators. Volume progression in polycystic kidney disease *N Engl J Med* 2006;18;354(20):2122-30.
2. Lawson CR, Doulton TW, MacGregor GA. Autosomal Dominant Polycystic Kidney Disease: Role of the Renin-Angiotensin System in Raised Blood Pressure in Progression of Renal and Cardiovascular Disease. *J Renin-Angiotensin-Aldosterone System* 2006;7:139-45.
3. Wang D, Strandgaard S. The pathogenesis of hypertension in autosomal dominant polycystic kidney disease. *J Hypertens* 1997;15(9):925-33.
4. Fick GM, Johnson AM, Hammond WS, Gabow PA. Causes of death in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 1995;5:2048-56.
5. Gabow PA, Chapman AB, Johnson AM, Tangel DJ, Duley IT, Kaehny WD, et al. Renal structure and hypertension in autosomal dominant polycystic kidney disease. *Kidney Int* 1990;38:1177-80.
6. Zeier M, Fehrenbach P, Geberth S, Mohring K, Waldherr R, Ritz E. Renal histology in polycystic kidney disease with incipient and advanced renal failure. *Kidney Int* 1992;42:1259-65.
7. Bennett WM, Elzinga L, Golper TA, Barry JM. Reduction of cyst volume for symptomatic management of autosomal dominant polycystic kidney disease. *J Urol* 1987;137:620-2.

8. Torres VE, Wilson DM, Burnett JC, Johnson CM, Offord KP. Effect of inhibition of converting enzyme on renal hemodynamics and sodium management in polycystic kidney disease. *Mayo Clin Proc* 1991;66:1010-7.
9. Watson MD, Macnicol AM, Allan PL, Wright AF. Effects of angiotensin converting enzyme inhibition in adult polycystic kidney disease. *Kidney Int* 1992;41:206-10.
10. Harrap SB, Davies DL, Macnicol AM, Dominiczak AF, Fraser R, Wright AF, et al. Renal, cardiovascular and hormonal characteristics of young adults with autosomal dominant polycystic kidney disease. *Kidney Int* 1991;40:501-8.
11. Cadnapaphornchai MA, McFann K, Strain JD, Masoumi A, Schrier RW. Increased left ventricular mass in children with autosomal dominant polycystic kidney disease and borderline hypertension. *Kidney Int* 2008;74(9):1192-6.
12. Valero FA, Martínez-Vea A, Bardají A, Gutiérrez C, García C, Richart C, et al. Ambulatory Blood Pressure and Left Ventricular Mass in Normotensive Patients with Autosomal Dominant Polycystic Kidney Disease. *J Am Soc Nephrol* 1999;10:1020-2.
13. Hernández del Rey R, Armario P, Martín-Baranera M, Sánchez P, Coca A, Pardell H. Afectación orgánica en hipertensos con efecto de bata blanca inversa. *Estudio Hospitalet. Hipertensión* 2000;17(extra):127.
14. Bjorklund K, Lind L, Zethelius B, Andrén B, Lithell H. Isolated ambulatory hypertension predicts cardiovascular morbidity in elderly men. *Circulation* 2003;107:1297-302.
15. Hernández del Rey R, Armario P, Martín-Baranera M, Sánchez P, Almendros MC, Coca A, et al. Cardiac damage in hypertensive patients with inverse white coat hypertension. *Hospitalet study. Blood Pressure* 2001;12:89-96.
16. Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, Hashimoto J, et al. Prognosis of masked hypertension and white coat hypertension detected by 24h ambulatory blood pressure monitoring: 10 year follow-up from the Ohasama study. *J Am Coll Cardiol* 2005;46:508-15.
17. Mancia G, Facchetti R, Bombelli M, Grassi G, Sega R. Long-term risk of mortality associated with selective and combined elevation in office, home, and ambulatory blood pressure. *Hypertension* 2006;47:846-53.
18. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007;25:1105-187.
19. Oyuela-Carrasco J, Rodríguez-Castellanos F, Kimura E, Delgado-Hernández R, Herrera-Félix JP. Longitud renal por ultrasonografía en población mexicana adulta. *Nefrología* 2009;29(1):30-4.
20. Sega R, Corrao G, Bombelli M, Beltrame L, Facchetti R, Grassi G, et al. Blood pressure variability and organ damage in a general population: results from the PAMELA study (Pressioni Arteriose Monitorate E Loro Associazioni). *Hypertension* 2002;39:710-4.