Correlates of target organ damage among black patients with arterial hypertension.

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Résumé

Objectif: évaluer la prévalence et les déterminants de l'atteinte des organes cibles chez les patients porteurs d'une hypertension artérielle essentielle.

Méthodes: la présente analyse transversale porte sur 100 patients noirs (53 hommes et 47 femmes, âge moyen 49 ± 10 ans, IMC 27 ± 5 kg/m², PAS 155 ± 19 mmHg, PAD 101 ± 11 mmHg) porteurs d'une hypertension artérielle essentielle, recrutés de manière consécutive dans une étude cas-témoins sur les lipides et les lipoprotéines aux Cliniques Universitaires de Kinshasa. L'évaluation de l'atteinte des organes cibles (TOD) a été faite sur base de l'examen clinique, des tests biologiques et de l'électrocardiogramme. L'atteinte des organes cibles était définie par la présence de la maladie rénale chronique, l'hypertrophie ventriculaire gauche et/ou la rétinopathie hypertensive. La comparaison entre groupes a été faite, selon le cas, à l'aide des tests t de Student, non paramétrique de Mann Whitney ou Chi carré. La régression logistique a été utilisée pour évaluer les déterminants indépendants du risque d'atteinte des organes cibles (TOD).

Résultats: l'atteinte d'au-moins un organe cible a été observée chez 79 patients (79%) ; l'atteinte de 1, 2 ou 3 organes a été observée, respectivement, .chez 27 (27%), 31 (31%) et 21 patients (21%). Le rein était l'organe le plus souvent atteint chez les patients avec atteinte d'un seul organe cible ; le rein et la rétine étaient la combinaison d'atteinte la plus fréquemment observée chez les patients avec atteinte de 2 organes cibles. L'obésité a émergé comme le seul facteur de prédiction du risque de TOD avec paradoxalement un effet protecteur [0R 0.19 95% CI 0.052 – 0.738; p = 0.001].

Conclusion: l'atteinte des organes cibles est fréquente dans la présente série d'hypertendus et les expose à un risque cardiovasculaire élevé. L'effet protecteur paradoxal de l'obésité pourrait traduire le phénomène d'épidémiologie inverse observé dans les affections chroniques.

Mots clé: atteinte organes cibles, déterminants, hypertension essentielle

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Summary

Objective: to investigate the prevalence and correlates of target organ damage (TOD) among Black patients with essential hypertension (EHT).

Methods: cross sectional analysis for the presence of multiple TOD of data from 100 consecutive uncomplicated hypertensive patients (53 men and 47 women, mean age 49 ± 10 years, BMI 27 ± 5 kg/m², SBP 155 ± 19 mmHg, DBP 101 ± 11 mmHg) attending the University of Kinshasa hypertension outpatient clinic and enrolled in a case-control study of lipids and lipoproteins. Target organ damage was defined as the presence of either renal dysfunction, left ventricular hypertrophy (LVH) or hypertensive retinopathy. Renal dysfunction was defined as creatinine < 60 mL/min and classified according to NKF-K/DOQI guidelines. Electro-cardiographic LVH was defined according to Cornell Voltage index as R wave > 13 mm in aVL lead. Hypertenive retinopathy was defined according to Keith and Wegener. Multiple TOD was defined as the concomitant presence in the same patient of the three TOD. Student t test, Mann Whitney U, Chi square tests and logistic regression analysis were used as appropriate.

Results: Overall, 79 patients (79%) had at least the damage of one end-organ. The involvement of 1, 2 or 3 end-organs was observed in 27 (27%), 31 (31%) and 21 patients (21%), respectively. The kidney was most frequently involved in patients with one end-organ damage. Kidney and retina damage was the combination of end-organs most frequently encountered in patients with damage of two end-organs. Obesity has appeared as the only determinant of the risk of having TOD with a paradoxical protective effect [0R 0.19 95% CI 0.052 – 0.738; p = 0.001] in comparison with patients with normal BMI.

Conclusion: TOD is common among the present case series and could expose them to high risk for CVD. The paradoxical protective effect of obesity could translate the phenomenon of reverse epidemiology of traditional risk factors observed in chronic diseases. Identification and management of TOD and associated risk factors should be encouraged in these patients.

Key words: Target organ damage, prevalence, correlates, African blacks, hypertension

Introduction

In patients with essential hypertension (EHT), accurate cardiovascular (CV) risk estimation is a prerequisite for devising cost-effective therapeutic strategies (1). In fact, the burden of risk may influence the identification of target blood pressure (BP) and may be useful for establishing the need for specific drugs (1). Within this context, the presence of target organ damage (TOD) has an important impact on CV risk (1). Indeed, after being exposed to risk factors for variable periods of time, a larger number of patients progresses through an asymptomatic phase that is characterized by the presence of subclinical organ damage: left ventricular hypertrophy (LVH), mild renal dysfunction and peripheral atherosclerosis (1). This asymptomatic phase often precedes and predicts the occurrence of majors CV events (1). Nowadays, patients who are at this preclinical stage can be easily identified and, with appropriate aggressive multifactorial treatment, not only the occurrence of major events can be prevented but the regression of organ damage can also be obtained (1). As different signs of TOD cluster in part, different tests should therefore be performed in the same patient to maximize the sensitivity of the diagnostic process with reference to economic resources (1).

In the Democratic Republic of the Congo (DRC), the prevalence of hypertension in the general population has increased in the past two decade from 10 to 27.6% in Kinshasa (2, 3). Hypertension is associated with multiple risk factors (4, 5). Despite of the growing evidence of the impact of multiple TOD on hypertension related-CV risk and treatment choice and intensity (1), little is known about TOD and its correlates in hypertensive patients. Therefore, the aim of the present study was to determine the clinical correlates of TOD among patients with essential hypertension attending Hypertension outpatient clinic at the University of Kinshasa Hospital.

Material and methods

Cross sectional analysis for the presence of target organ damage (TOD) and associated risk factors of data from 100 consecutive black patients with essential hypertension enrolled in a case-control study of lipid and non lipid risk factors, described in details elsewhere (8). Available lifestyle data included self reported physical activity and smoking habits. Data were also available for the duration of hypertension and current antihypertensive medication. Measures of adiposity included body mass index (BMI) and waist circumference. All patients had the following measurements made after 12 h fasting: total cholesterol (TC), high density lipoprotein-cholesterol (LDL-c), triglycerides, glucose, uric acid, fibrinogen, and creatinine. Low density lipoprotein-cholesterol (LDL-c) and creat-inine clearance (CrCl) were calculated according to Friedewald (6) and Cockroft and Gault (7) equations, respectively. Target organ damage (TOD) was defined as the presence of either chronic kidney disease (CKD), left ventricular hypertrophy (LVH) or hypertensive retinopathy. CKD was defined as creatinine clearance (CrCl) < 60 mL/min according to NKF-K/DOQI guidelines (8) and stratified as initial (NKF-K/DOQI stages 1-3) and advanced (NKF-K/DOQI stage 4) involvement. Electro-cardiographic left ventricular hypertrophy (ECG-LVH) was defined according to Cornell voltage index as R wave in lead aVL ≥ 13 mm (9). Hypertensive retinopathy was classified according to Keith, Baker

and Wegener (10) and stratified as initial (stages 1-2) and advanced (stage 3) involvement. Metabolic syndrome (MS) was defined according to NCEP-ATP III criteria (11). Hyperfibrinogenemia was defined as plasma fibrinogen levels above 3.5 g/L (12). All patients gave informed consent and Kinshasa School of Medicine research and Kinshasa School of Public Health ethic committees approved data collection.

Data were expressed as mean ± standard deviation (SD) or relative frequency in percent. The distribution of duration of hypertension and triglycerides being positively skewed, non parametric test (Mann Whitney) was used for these variables. Chi square and Student t tests were used for the comparison of categorical and continuous variables normally distributed, respectively. Multiple logistic regression analysis was used to evaluate the independent contribution of selected variables in the risk of having TOD. P value ≤ 0.5 defined statistical significance. All statistical analyses were performed with SPSS for Windows version 10.0 at the Department of Epidemiology and Biostatistics of the Kinshasa School of Public Health.

Results

Clinical and biological characteristics of the whole group are summarized in tables 1 and 2.

Table 1. Clinical characteristics of the whole group and hypertensives with and without target organ damage

Characteristic	Whole group (n = 100)	Without (n = 21)	With (n = 79)
Gender: M/F	53/47	14/7	39/40
Age, years	49 ± 10	40 ± 8	49 ± 10
DHT, months	66 ± 72	33 ± 61	74 ± 73**
Treatment, %	50	38	53
BMI, Kg/m^2	27 ± 5	29 ± 5	26 ± 4***
WHR	0.93 ± 0.07	0.87 ± 0.08	0.90 ± 0.07
SBP, mmHg	155 ± 19	156 ± 26	155 ± 16
DBP, mmHg	101 ± 10	105 ± 9	100 ± 9
PP, mm Hg	54 ± 14	51 ± 19	51 ± 12
Heart rate, b/min	79 ± 11	81 ± 11	78 ± 10

Data are expressed as mean ± SD or relative frequency in percent.
Abbreviations: M, male F, female DHT, duration of hypertension BMI, body mass index WHR, waist to hip ratio SBP, systolic blood pressure DBP, diastolic blood pressure PP, pulse pressure b, beat *p ≤ 0.05 **p ≤ 0.01 ***p ≤ 0.001

Table 2. Biological characteristics of the whole group and hypertensives with and without target organ damage

Characteristic	Whole group (n = 100)	Without (n = 21)	With (n = 79)
TC, mmol/L	5.01 ± 1.49	5.11 ± 1.31	5.01 ± 1.52
LDL-c, mmol/L	3.36 ± 1.31	3.33 ± 1.21	3.33 ± 1.20
HDL-c, mmol/L	1.27 ± 0.38	1.39 ± 0.51	1.24 ± 0.33
TG, mmol/L	1.07 ± 0.67	1.17 ± 1.16	1.03 ± 0.45
Glucose, mmol/L	5.05 ± 0.77	5.05 ± 0.88	5.05 ± 0.77
Uric acid, mmol/L	393 ± 112	393 ± 101	392 ± 118
Fibrinogen, g/L	2.80 ± 0.80	2.89 ± 0.53	2.78 ± 0.86
Creatinine, µmol/L	97 ± 26	103 ± 29	102 ± 26
CrCl, mL/min	81 ± 34	84 ± 34	82 ± 29

Data are expressed as mean ± SD
Abbreviations: TC, total cholesterol LDL-c, low-density lipoprotein-cholesterol male
HDL-c, high-density lipoprotein-cholesterol TG, triglycerides CCl, creatinine clearance
*p ≤ 0.05 **p ≤ 0.01 ***p ≤ 0.001

A total of 100 consecutive hypertensive patients (47 women) were examined. Their mean age was 49 ± 10 years and average levels of BMI and BP were 27 ± 5 Kg/m² and 155 ± 19/101 ± 10 mmHg, respectively. Fifty patients (50%) were receiving antihypertensive medication as mono-therapy (n = 27) or combined therapy (two drugs, n = 27; three drugs, n = 3); treatment consisted of calcium channel blockers, diuretics, angiotensin converting enzyme inhibitors, central acting drugs and beta blockers in 42%, 30%, 24%, 24% and 16% of patients, respectively.

Overall, 79 patients (79%, 7 men) had at least one TOD (Table 1). The involvement of 1, 2 or 3 end-organs was observed in 27 (27%), 31 (31%) and 21 patients (21%), respectively (Table 3). The kidney was most frequently affected in patients with one end-organ damage. In patients with two end-organs damage, the combination of kidney and retina damage was most frequently encountered. Twenty one patients (21%) had all the three end-organs damaged.

Table 3. Distribution of hypertensive patients according to the number of end-organs involved

Number of organ involved	N	%
0	21	21
1	27	27
Kidneys	19	19
Retina	5	5
Heart	3	3
2	31	31
Heart + Retina	17	17
Heart + Kidneys	8	8
Kidneys + Retina	6	6
3	21	21

Data are expressed as absolute frequency and relative frequency (%)

Table 4 summarizes the distribution of patients according to the severity of end-organ damage. LVH, hypertensive retinopathy and renal dysfunction were observed in 49 (49%), 49 (49%) and 55 patients, respectively. The majority of patients with retinopathy (n = 41) and renal dysfunction (n = 42) were at preclinical stages of retinal (Keith & Wegener stages I and II) and renal (NKF-K/DQOI CKD stages 2 and 3) involvement, respectively.

Table 4. Distribution of hypertensive patients according to end-organ involved and severity of damage

Target organ damage	N	%
LVH	49	49
CKD	55	55
Initial involvement	41	41
Advanced involvement	14	14
Retinopathy	49	49
Initial involvement	42	42
Advanced involvement	7	7

Data are expressed as absolute frequency and relative frequency (%)
Abbreviations: LVH, left ventricular hypertrophy; CKD, chronic kidney disease: initial (NKF-K/DQOI CKD stage 1-3) and advanced (NKF-K/DQOI CKD stage 4) Retinopathy: initial (Keith, Baker and Wegener stage 1-2) and advanced initial (Keith, Baker and Wegener stage 3) involvement

In univariate analysis (Table 5), patients with TOD had longer duration hypertension (74 ± 73 vs 33 ± 61 months; $p \leq 0.01$) and lower levels of BMI (26 ± 4 vs 29 ± 5 Kg/m²; $p \leq 0.001$) in comparison with patients with normal BMI. The two groups were similar for other variables considered in the present analysis. In multivariate analysis (Table 4), the strength of the association persisted only for BMI. However, the risk of having TOD was paradoxically lower [0R 0.19 95% CI 0.052 – 0.738; p = 0.001] in obese patients in comparison with those having normal BMI.

Table 5. Independent predictors of the risk of TOD in hypertensive patients in multiple logistic regression analysis

Variable	B	SE	P value	0R [95 CI]
Constant	2.140	0.520	0.001	8.50
BMI < 25 Kg/m²			0.05	1
BMI 25-30 Kg/m²	-0.818	0.662	0.21	0.44 [0.121-1.614]
BMI ≥ 30 Kg/m²	-1.629	0.676	0.001	0.19 [0.052-9.738]

Abbreviations: B, regression coefficient SE, standard error OR, odds ratio CI, confidence interval BMI, body mass index.

Discussion

The main observations of the present study are as follow: first, TOD is common among the study case series; second, the use of CG formula in obese subject may have overestimated CrCl, hiddening CKD. Third, the majority of patient with TOD were yet at preclinical stages; fourth, patients with TOD had a longer duration of hypertension; fifth; obesity has appeared as the only predictor of the risk of TOD but with an apparent paradoxical protective effect.

However, a full interpretation of the results of the present analysis is handicapped by some limitations. First, the cross sectional design precludes clear establishment of a causal relationship between TOD and associated risk factors. second, the sample size could not allow sufficient power to detect additional associations thrid, the relation between TOD and its correlates could be attenuated by a regression dilution since only a single measurement of biological variables was performed. Furthermore, electrocardiographic LVH known to be less sensitive than echocardiographic LVH was used to define LVH (13). Nevertheless, the results of the present study provide some insights on the frequency of TOD in hypertensive patients and the possible role of obesity as a risk factor of TOD.

In accordance with previous reports (14-19), the present study has shown that TOD is common among black patients with hypertension. The presence of TOD, mainly mild renal dysfunction and LVH, could expose these patients to increased CV risk (20). Indeed, an association between mild renal dysfunction and several CV risk factors, such as BP load, dyslipidaemia, endothelial dysfunction, insulin resistance, salt sensitivity, increased renin-angiotensin system (RAS) activity, has been widely demonstrated in hypertensive patients (1). Furthermore, mild renal dysfunction is associated with signs of subclinical extrarenal organ damage such as LVH (especially concentric) and carotid wall thickness (1, 20). Patients with mild renal dysfunction had an almost 20-fold greater risk for having both LVH and carotid wall abnormalities (1). The presence of TOD is also of therapeutic importance. Indeed, current guidelines on management of hypertension (21, 22) recommend more aggressive treatment of patients with TOD, a marker of high CV risk, with 2 or more drugs (23). Unfortunately, most patients in the present case series were still on monotherapy despite of the presence of multiple TOD. Therefore, adjustment of treatment regimen is needed in these patients in order to reduce CV risk

The majority of patients with TOD were at preclinical stages of end-organ involvement. In our setting with limited

access to dialysis facilities, this observation is of utmost importance with reference to CKD and its progression (24). Indeed, appropriate aggressive mutlifactorial treatment of patients at the preclinical stages of TOD has been reported not only to prevent the occurrence of major CV events but also to obtain the regression of end-organ damage or, at least, to slow its progression (1). There is evidence that the regression of LVH parallels the regression of albuminuria and is related to it, to some degree regardless of BP changes (1).

Patients with TOD had a longer duration of hypertension that could translate the negative impact of aging on the cardiovascular structure and function (25). Indeed, vascular remodelling of aging process is similar to that of high BP and is characterized by vascular wall hypertrophy, fibrosis and dysfunction (26, 27). Resulting arterial wall stiffness is associated with elevated systolic and pulse pressure (28), well-known independent predictor of LVH and CV events (29). Aging has been also reported to contribute to CV risk through the clustering of multiple risk factors (28, 30, 31).

In univariate and multivariate analyses, obesity has appeared as an independent predictor of TOD. Obesity has been reported to induce CV and renal damage either directly (32, 33) or indirectly as a component of the metabolic syndrome (34). Insulin resistance/ hyperinsulinemia is thought to contribute substantially to CV and renal damage induced by excessive weight. Insulin resitance/hyperinsulinemia can activate sympathetic nervous (SNS) and renin angiotensin aldosterone (RAAS) systems (32-34). In addition to hemo-dynamic changes, activation of RAAS can stimulate endothelial NAD(P)H-oxidase with production of free radicals and subsequent endothelial dysfunction (32-34). Despite these deleterious effects of obesity on CV and renal structure and function, obesity in the present study appears to be paradoxically protective. A similar paradoxical protective effect of excessive weight has already been reported by Kovesdy *et al.* (35); they found a paradoxical association between BMI and all cause mortality in men with CKD not yet on dialysis. Low BMI levels have also been reported in Nigerian hypertensive patients with CKD (36). This apparent paradox is thought to rely upon the growing phenomenon of "reverse epidemiology" of traditional risk factors seen in chronic diseases such as cardiac and renal diseases (37). Time differentials competing risk factors with over nutrition acting as a long term killer but short term protective versus undernutrition as a short term killer as well as malnutrition-inflammation complex syndrome (MICS) have been evoked as potential explanatory mechanisms of this phenomenon (38).

Conclusion

The present study has shown that TOD is common among the present case series. Obesity, the central component of the metabolic syndrome, has appeared as the main determinant of the risk of TOD with paradoxically a protective effect that needs to be clarified. Interventions aimed at identifying and managing TOD and its correlates should be encouraged in hypertensive patients.

Author's contributions

LFB conceived of the study and participated in the study design, data acquisition and statistical analysis. MJR participated in the study design and statistical analysis. KKP contributed to study design and statistical analysis.

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