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HOMOCYSTEINEMIA IN HYPERTENSIVE PATIENTS WITH RENAL TARGET ORGAN DAMAGE (MILD RENAL DYSFUNCTION)

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Abstract
The prevalence of high plasmatic levels of homocysteine in hypertensive patients with mild renal dysfunction (MRD) defined by 2003 European Hypertension Society Guidelines (men plasmatic creatinine between 1.3 and 1.5; women plasmatic creatinine between 1.2 and 1.4 mg/dl) has not been previously reported. To evaluate this item 18 MRD patients were recruited (54% males, mean age 59.2 ± 17.3 years, mean plasmatic creatinine 1.30 ± 0.12 mg/dl). They were compared with a control group of hypertensives with normal renal function (n = 87, 42,9% males, mean age 53.6 ± 12.3 years, mean plasmatic creatinine 0.83 ± 0.21 mg/dl) and a group of 29 chronic renal failure patients (51.7% males, mean age 56.9 ± 15.0 years, mean plasmatic creatinine 2.39 ± 0.95 mg/dl). Age and sex differences are not significant, plasmatic creatinine levels are different among three groups ($p < 0.001$, t student test). Basal homocysteine levels of CRF (19.3 ± 7.1 μmol/l) were higher than those of control group (11,0 ± 4,3 μmol/l) and MRD patients (14.8 ± 5.5 μmol/l; $p = 0.027$ vs. CRF and $p = 0.007$ vs. control, Mann-Whitney test). Mean creatinine clearance was 30.3 ± 11.5 ml/min for CRF group, significantly lower than MRD patients creatinine clearance (54.5 ± 9.4 ml/min, $p < 0.001$, t student test) and control ones (88,9 ± 18,9 ml/min, $p < 0.001$, t student test). Hypertensive patients with mild renal dysfunction showed higher and pathological levels of homocysteinemia as compared with controls, this finding might be related to the higher cardiovascular risk described in this group of patients.
Key words: Homocysteinemia. Renal dysfunction. Hypertension

INTRODUCTION

Several studies have demonstrated that hyperhomocysteinemia is a risk factor for premature cardiovascular disease [1, 2] independent of other classic risk factors, such as smoking, hypercholesterolemia, arterial hypertension and diabetes [3]. Hyperhomocysteinemia has a high prevalence in the end stage-renal disease patients, which may contribute to the very high cardiovascular risk of this patients [4]. Homocysteine levels are closely related to plasmatic creatinine [5] and even small increments in plasmatic creatinine concentration produce higher homocysteine levels and frequently pathological blood homocysteine values [6].

Chronic renal failure is another important risk factor not only for premature atherosclerosis but also for its rapid progression, because the risk of cardiovascular and peripheral vascular disease is associated with the metabolic abnormalities involved in uraemia [7]. Recently the European Society of Cardiology- European Hypertension Society Clinical Guidelines have stated that slight elevation of serum creatinine concentration (either 107-124 μmol/l, 1.2-1.4 mg/dl, for women; or 115-133 μmol/l, 1.3-1.5 mg/dl, for men) should be taken as a sign of target organ damage, and higher creatinine concentrations regarded as an associated clinical condition to arterial hypertension [8]. Thus, these Guidelines have taken down the classical normality values of creatinine to a better classification of hypertensive patients.

In recent years, a large body of information has confirmed that, as soon as renal function exhibits even minor derangements, a rise in cardiovascular risk occurs with a continuous relationship between decreasing renal function, up to the development of end-stage renal disease and increasing cardiovascular risk [9, 10]. Recently published guidelines have recognized the relevance of detecting chronic kidney disease, which relies on the finding of slight elevations in serum creatinine, a diminished value of creatinine clearance) and/or the presence of albuminuria [11, 12]. The aim of this study was to assess the risk associated to hyperhomocysteinemia in a group of hypertensive patients with mild renal dysfunction (MRD) (target organ disease stage).

DESIGN AND METHODS

PATIENTS AND CONTROLS

Eighteen patients with MRD were studied. They were 10 males and 8 females, mean age 59.2 ± 17.3 years. Eighty-seven hypertensive controls were selected and recruited in the outpatient clinic after renal disease or failure was excluded (38 men and 49 women, mean age 53.6 ± 12.3 years, differences are not significant). A third group of 29 chronic renal failure patients (plas-

matic creatinine ≥1.5 for males and ≥1.3 for females) were selected to compare the results. They were 15 males and 14 females, mean age 56.9 ± 15.0 years. These age and sex differences are not significant. Patients were classified according to K/DOQI stages of chronic renal disease [13].

Determination of Total Plasma Homocysteine

Total fasting plasma homocysteine were measured on samples drawn at the time of the study by fluorescence polarization inmunoanalysis. All forms of plasma homocysteine are determined in this analysis, including reduced (homocysteine) and oxidized (homocystine, homocysteine-cysteine mixed disulfide and protein bound homocysteine mixed disulfide) forms. These forms are collectively referred as total plasma homocysteine. A total plasma homocysteine level of 10.4 μmol/l for men and 11.4 μmol/l for women was used as threshold value to diagnosis hyperhomocysteinemia.

Glomerular filtration rate was estimated using the abbreviated Modification of Diet in Renal Disease equations [14] for every sex. Only caucasic patients were included in the study, so this parameter was not included in calculation.

Statistical Analysis

Results are expressed as mean ± 1 standard deviation. Kolmogorof-Lilliefors Test showed that plasmatic homocysteine levels did not follow a normal distribution so these values were been compared using Man-Whitney test for non-paired data. Other continuous values have been compared through non-paired Student "t" test. The chi square test was used to challenge discrete data. All statistical tests were two-sided. P values lower than 0.05 were considered as significant. Analysis was developed with the statistical package G-Stat.

Results

Basal total blood homocysteine levels of CRF patients (19.3 ± 7.1 μmol/l) near doubled those of control ones (11.0 ± 4.3 μmol/l, $p < 0.0001$, Mann-Whitney test). MRD patients showed lower total blood homocysteine concentrations than CRF patients (14.8 ± 5.5 μmol/l, $p = 0.026$) but higher than those of the control group ($p = 0.045$) (see Fig. 1). Two thirds ($n = 6$) of MRD patients showed pathological homocysteinemia values. Just two patients (6.9%) of the CRF group have normal blood homocysteine levels and 43 (48%) control group ones have non-pathological blood homocysteine concentrations ($p < 0.0001$, chi square test) (these frequencies are plotted in Fig. 2).

Mean plasmatic creatinine concentration of MRD patients was (1.30 ± 0.12 mg/dl). It was higher than the creatinine of control group ones (0.83 ± 0.21 mg/dl, $p < 0.0001$ vs. MRD patients, Student t test). CRF patients have the highest plasmatic creatinine levels (2.39 ± 0.95 mg/dl, $p = 0.0002$ vs. MRD group).

Glomerular filtration rate was lowest in CRF group (mean 30.3 ± 11.3 ml/min/1.73 m², $p < 0.0001$ vs. MRD group, t Student test). It was lower for MRD group (53.8 ± 8.7 ml/min/1.73 m²) than for control group (88.9 ± 18.7 ml/min/1.73 m², $p < 0.0001$).

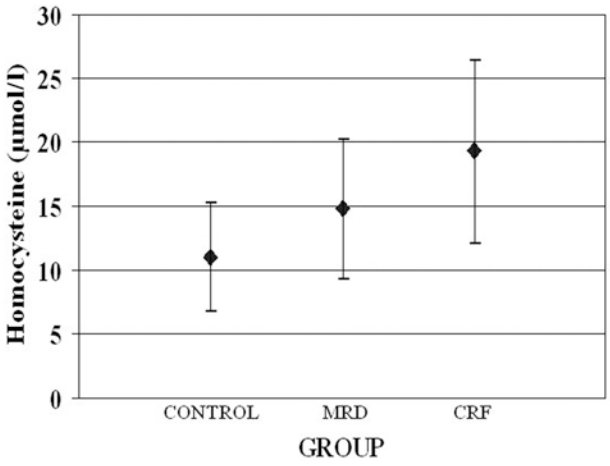

Fig. 1. Plasmatic homocysteine levels were significantly higher in MRD patients when compared to controls (see significance in the text).

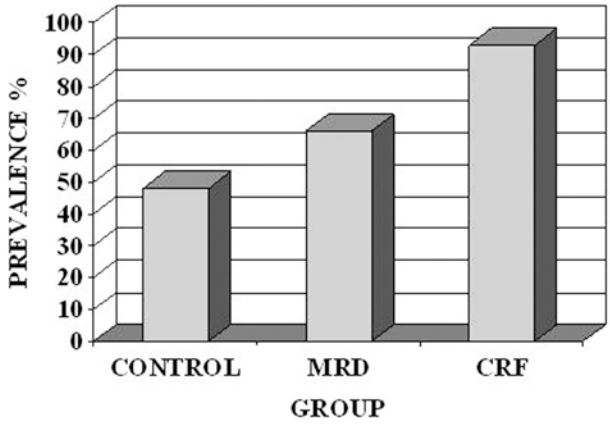

Fig. 2. Prevalence of hyperhomocysteinemia was also increased n MRD group (pathological total blood homocysteine levels) ($p < 0.0001$ chi square test).

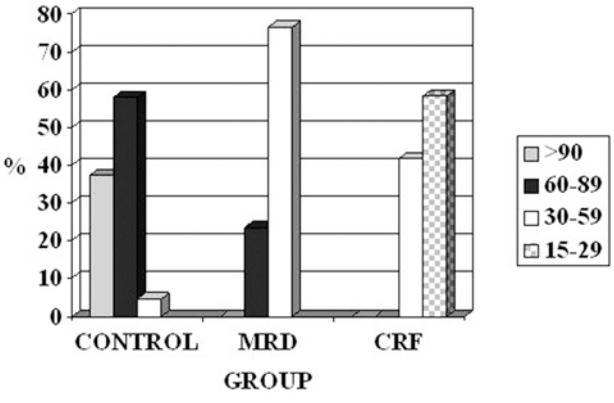

Fig. 3. Renal dysfunction measured by MDRD formulation was deeper than expected since creatinine figures were within the accepted normality range.

Most patients of control group were in chronic kidney disease stages I and II (95.4%). MRD patients were in stage II (n = 4) or III (n = 14) of K/DOQI classification and CRF patients were in either stage III (n = 15) or stage IV (n = 14) chronic kidney disease ($p < 0.0001$, chi square test) (Fig. 3).

Discussion

Recently the European Society of Cardiology- European Hypertension Society Clinical Guidelines have stated that slight elevation of serum creatinine concentration (either 107-124 μmol/l, 1.2-1.4 mg/dl, for women; or 115-133 μmol/l, 1.3-1.5 mg/dl, for men) should be taken as a sign of target organ damage, and higher creatinine concentrations regarded as an associated clinical condition to arterial hypertension [9]. Thus, these Guidelines have taken down the classical normality values of creatinine to a better classification of hypertensive patients.

This change has been made more in the ground of associated cardiovascular risk than in order to detect hidden chronic kidney disease and it is related to cumulated experience pointing at an increased cardiovascular risk within this range of plasmatic creatinine concentrations. The Hypertension Detection and Follow-up Program trial was the first to show that the presence of elevated serum creatinine values (≥1.7 mg/dl) at baseline was a very potent predictor for all-cause mortality within 5-8 years [15]. Data from the Hypertension Optimal Treatment (HOT) study showed that serum creatinine levels above 1.5 mg/dl were accompanied by an adjusted relative risk of 2.05 for major cardiovascular events and 3.24 for cardiovascular mortality [16]. Another analysis of HOT data indicated an elevated cardiovascular risk in hypertensive patients with serum creatinine above 1.3 mg/dl [17].

In the same way, the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) Study, followed up patients with hypertension and with normal pretreatment creatinine levels (men <1.5 mg/dL; women <1.4 mg/dL) to evaluate the incidence of cardiovascular events. The event rate increased progressively from the first to the fourth sex-specific quartiles of creatinine distribution (1.5, 2.3, 2.3, and 3.5 per 100 patient-years respectively); thus, in this study a serum creatinine value within the reference range was a predictor of cardiovascular morbidity in patients with essential hypertension. The observed excess risk was 1.30 for a 0.23-mg/dL increase in creatinine concentration [18].

The causes of this increment in vascular mortality are multiple, but concentrations of homocysteine rise in chronic renal failure and this increase in amino acid levels are reported to be associated with atherosclerotic disease both in uremic patients [8, 9] and those ones with normal renal function [1-7]. Although most of studies on uremic patients have been performed among patients undergoing chronic haemodialysis or peritoneal dialysis [8, 19, 20] a high prevalence of homocysteinemia in patients suffering mild chronic renal failure (creatinine clearance from 40 to 80 ml/min) has been reported [6]. In this way the subjects with small increments of plasmatic creatinine within the accepted range of normality shows a higher prevalence of hyperhomocysteinemia when compared to hypertensive patients with lower

Some studies in end-stage renal failure and in diabetic patients have shown that the glomerular filtration rate is a strong determinant of plasma homocysteine and cysteine concentrations [21-23]. It has been reported that homocysteine plasma concentrations increased about four-fold in patients on renal replacement therapy, being the mean increase 36 μmoles/L [24]. There is also a strong correlation between homocysteine concentrations and circulating creatinine concentrations, even in individuals with normal creatinine concentrations [9-11]. Cystatin C, another surrogate of renal function, is an independent marker of total blood homocysteine level. Cystatin C alone determined over half of the variability in total homocysteine levels in coronary artery disease patients. Thus it could be expected that even small increments of creatinine within the reference range may be accompanied by to raised concentrations of total blood homocysteine and this hypothesis has been confirmed by these results: Patients which plasmatic creatinine is in the range of renal target organ disease as defined by the clinical guidelines have increased blood homocysteine levels.

The most common measure used to assess overall kidney function is the plasmatic creatinine concentration. Interpretation of this index is complicated, as it is inversely proportional to the glomerular filtration rate and varies between individuals based on differences in age, sex and muscle mass. Furthermore, serum creatinine concentration is affected by factors other than glomerular filtration rate, such as tubular secretion, generation and extra renal excretion of creatinine. Thus, using plasmatic creatinine concentrations to determine an absolute level of kidney function, including distinguishing normal from abnormal function in the individual patient, is inherently difficult [25]. To avoid these pitfalls the K/DOQI guidelines recommended estimation of glomerular filtration rate by using prediction equations based on serum creatinine determinations [4]. The K/DOQI guidelines advise that chronic kidney disease can be defined and appropriately managed by a staging approach that relies on estimating the severity of kidney damage based on the degree of proteinuria and impaired kidney function, this latter assessed as a decrease in the glomerular filtration rate. These guidelines defines fives stages for chronic renal disease from I (glomerular filtration rate >90 ml/min) to V (<15 ml/min). Using this classification most of patients with renal target organ disease (slight increments of plasmatic creatinine within the currently accepted reference range) have indeed moderate renal failure (stage III from 30 to 60 ml/min of glomerular filtration rate). Thus, this group of patients should be considered as truly renal patients and treated as this situation deserve.

Resuming, this study shows time a high prevalence of homocysteinemia in patients with very slightly increments of plasmatic creatinine within the range of renal target organ disease defined by the 2003 European Cardiology Society-European Hypertension Society Clinical Guidelines. This finding may be related to the higher cardiovascular morbimortality found in this group of patients.

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