

# Creatinine clearance and subclinical target organ damage in primary hypertension

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## Abstract

**Introduction:** Despite the widely recognized dangers of uncontrolled hypertension, the disease remains inadequately treated in the majority of patients. This may be, in large part, because of the asymptomatic nature of the disease for the first 15 to 20 years, even as it progressively damages the cardiovascular system. Therefore, assessment of hypertension related subclinical target-organ damage represents a key diagnostic procedure for the risk stratification of hypertensive patients.

**Methods:** A prospective case control study of 40 cases (hypertensive patients with CCR<60) and 40 controls (hypertensive patients with CCR>60) was conducted in Tribhuvan University Teaching Hospital (TUTH). Renal function was estimated by the Cockcroft-Gault formula. Left ventricular hypertrophy was determined by echocardiography. Retinal vascular changes were evaluated by direct ophthalmoscopy. Microalbumin in urine was measured from spot morning sample.

**Results:** The prevalence of Left ventricular hypertrophy (LVH), microalbuminuria and retinopathy in cases and control group was 55% VS 20% (P=.001), 50% VS 20% (P=.004) and 92.5% VS 52.5% (P=.001). Patients with microalbuminuria showed prevalence of LVH, CCR<60 and retinopathy as 78.57%, 71.43% and 100% respectively. There was high prevalence of grade I and grade II retinopathy in patients with low CCR

**Conclusions:** Results show that a reduction in creatinine clearance and/or presence of microalbuminuria is a marker of subclinical organ damage in patients with primary hypertension and normal serum creatinine irrespective of BP load and other traditional risk factors.

*Keywords:* Creatinine clearance, primary hypertension, subclinical, target organ damage.

## Introduction

As the population grows older and more obese, the incidence of hypertension continues to increase, not only in developed societies but also in developing societies.<sup>1</sup> At the same time, despite the widely recognized dangers of uncontrolled hypertension, the disease remains inadequately treated in the majority of patients.<sup>2</sup>

Asymptomatic patients are often unwilling to alter life style or take medication to forestall some far-off, poorly perceived danger, particularly when they are made uncomfortable in

the process. Therefore, assessment of hypertension related subclinical target-organ damage represents a key diagnostic procedure for the stratification of hypertensive patients according to their cardiovascular risk profile. Recent Guidelines jointly issued by the European Society of Hypertension and the European Society of Cardiology (ESH-ESC) have emphasized the rationale, indications and therapeutic implications of this evaluation.<sup>3</sup>

Optimizing the diagnostic approach to the detection of target organ damage is of the utmost importance for a rationale and cost-effective allocation of economic resources.

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Although extensive diagnostic workup can lead to the identification of a larger number of patients at risk, routine Ultra sonogram evaluation of target organ damage may be too expensive and impractical to be applied on a large scale. The development of new, integrated, and low-cost tools to identify patients at higher risk may therefore prove to be very helpful in clinical practice.

This study is expected to help in improving the level of compliance in otherwise asymptomatic hypertensive patients by creating awareness regarding subclinical organ damage. This study is also expected to promote determination of Creatinine clearance rate (CCR) and microalbuminuria as routine procedure in evaluation of hypertensive patients, as these tests are easily available and less costly.

**Methods**

This is a prospective case control study conducted in department of internal medicine, Tribhuvan University Teaching Hospital, which is a tertiary care hospital in Nepal. We included diagnosed case of primary hypertension with normal serum creatinine. Patients with CCR<60 were taken as cases and patients with CCR>60 as controls. All the included patients were divided into 2 groups, each containing 40 patients.

Hypertensive patients with overt organ damage, diabetes mellitus (DM), and severe obesity were excluded from study. Renal function was estimated by means of the serum creatinine level using the Cockcroft-Gault formula. This value was adjusted for body surface area (BSA). Left ventricular hypertrophy was determined by electrocardiography (Romhilt-Estes criteria) and echocardiography (Troy formula). Retinal vascular changes were evaluated by direct ophthalmoscopy. Microalbumin in urine was measured from spot morning sample after excluding other possible causes of microalbuminuria. All analysis was performed using statistical software (SPSS v 11.5).

**Results**

Among the study patients male to female ratio was 0.77:1. The mean age in control group was 53.70±9.72 years, while in case group it was 64.03±8.50 years. The mean duration of hypertension in control patients was 4.78± 2.03 and that in case was 7.08±3.54. The mean CCR in control patients was 76.96±11.50 ml/min per 1.73 m<sup>2</sup> and in case group it was 53.49±5.30 ml/min per 1.73 m<sup>2</sup>. The prevalence of left ventricular hypertrophy, microalbuminuria and retinopathy was significantly higher in patients with CCR<60 (Table 1).

**Table 1:** Prevalence of Target organ damage (TOD) in study patients according to creatinine clearance rate

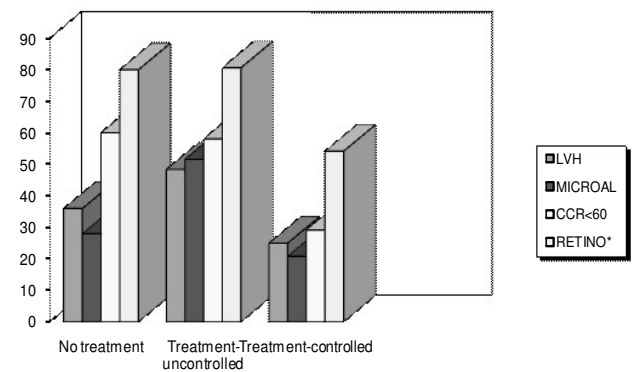
| Patients with CCR | LVH    |    | LVDD   |    | MICROAL |    | RETINO |    |
|-------------------|--------|----|--------|----|---------|----|--------|----|
|                   | Freq.  | %  | Freq.  | %  | Freq.   | %  | Freq.  | %  |
| ≥60n=40           | 8      | 20 | 8      | 20 | 8       | 20 | 21     | 53 |
| ≤60n=40           | 22     | 55 | 11     | 28 | 20      | 50 | 37     | 93 |
| r value           | -0.361 |    | -0.314 |    |         |    |        |    |
| pvalue            | 0.001  |    | NS     |    | 0.004   |    | 0.001  |    |

Similarly, left ventricular hypertrophy, decreased in renal function and retinopathy all were significantly higher in patients with microalbuminuria (Table 2).

**Table 2:** Prevalence of TOD in patients with microalbuminuria

| Microal    | LVH   |    | CCR<60 |    | Retino |     |
|------------|-------|----|--------|----|--------|-----|
|            | Freq. | %  | Freq.  | %  | Freq.  | %   |
| (+) (n=28) | 22    | 79 | 20     | 71 | 28     | 100 |
| (-) (n=52) | 8     | 15 | 20     | 38 | 30     | 58  |
| r value    | 0.677 |    | -0.314 |    |        |     |
| p value    | 0.000 |    | 0.004  |    | 0.001  |     |

Among 80 study patients, 55 patients (68.75%) were on antihypertensive medications. 75% of control patients were on antihypertensive medication while the percentage of cases that were on antihypertensive medication was 62.5. BP was controlled only in 28% of cases who were on antihypertensive medication. BP was relatively better managed in control group, where it was controlled in 56.67% of treated patients. Left ventricular hypertrophy, decreased in renal function, microalbuminuria and retinopathy all were significantly higher in patients who were not on treatment and who were on treatment but BP was not controlled (Fig. 1).



**Fig. 1:** Prevalence of TOD according to treatment groups

## Discussion

This study demonstrates that mild reduction in creatinine clearance rate is associated with subclinical end-organ damage, namely, LVH, retinal vascular changes and microalbumin, in a population with primary hypertension and normal serum creatinine levels.

These data are relevant to previous reports, which showed an association between mild renal dysfunction and adverse cardiovascular prognosis in hypertensive patients. In the 'Hypertension Detection and Follow-up Program trial', a linear relation between serum creatinine and cardiovascular mortality was observed over a 5-year follow-up, with a 2 times higher risk of mortality in patients with serum creatinine >1.7 mg/dl at baseline.<sup>4</sup>

More recently, in the *HOT* study a slight increase in serum creatinine was associated with a 3.2 times greater incidence of fatal events, regardless of common cardiovascular risk factors.<sup>5</sup> Similar findings have also been reported by using creatinine clearance as an estimate of the GFR in patients with isolated systolic hypertension and in those with concomitant cardiovascular risk factors participating in the *HOPE* study.<sup>6,7</sup>

Among the quantitative markers of target organ damage (TOD), the prognostic significance of echocardiographically confirmed LVH in hypertension is well established.<sup>8</sup> LVH is widely considered as "the hemoglobin A1C of blood pressure" since it is an objective measure of both the severity and duration of the elevation in BP.<sup>9</sup>

The prevalence of LVH was 20% in patients with CCR < 60 and 55% in patients with CCR < 60 (p= .001). This value is slightly lower than that shown by *Giovanna Leoncini* et al (42% VS 71%, p= 0.0001).<sup>10</sup> *Cesare Cuspidi* et al showed 22% prevalence of LVH.<sup>11</sup> The prevalence of LVDD in patients not having LVH was 20% in patients with CCR < 60 and 27.5% in patients with CCR < 60. *Fagard R et al* found evidence of asymptomatic LVDD in 33% of patients who did not have LVH.<sup>12</sup>

There was positive significant correlation between LVH and microalbuminuria (r= .677, p= .000), duration of hypertension (r= .352, p= .001), smoking (r= .452, p= .000) and uncontrolled BP (r= .314, p= .019). There is negative significant correlation between LVH and CCR (r= -0.361, p=001).

Similarly, the prevalence of microalbuminuria in this study is 20% in control group and 50% in cases (p= .005). Though these values are higher than that shown by *Giovanna Leoncini* et al, it is consistent with that shown by *Hsegholm A et al* and *Bigazzi R et al*. In their study, the prevalence of

microalbuminuria was in the range of 25% to 40% in primary hypertensive patients selected from a hypertension clinic.<sup>10-14</sup>

Patients with microalbuminuria showed higher prevalence of LVH (78.57% vs 15.38%, p= .000). It was more strongly correlated with LVH than the correlation between CCR and LVH (r= 0.677 VS r= -0.361). *Cesare Cuspidi et al* showed positive significant correlation between microalbuminuria and left ventricular mass (r= 0.20, p < 0.03).<sup>11</sup>

In this study, we found negative significant correlation between microalbuminuria and CCR (r= -0.314, p=.004). This finding is consistent with results observed by *De La Sierra et al* who showed a serum creatinine >88 pmol/L (odds ratio: 3.08; CI 95%: 1.39-6.84) was independently associated with increased urinary albumin excretion.<sup>16</sup> *Cesare Cuspidi et al* showed different grade of retinopathy in 80.5% of patients.<sup>11</sup> *G. MULÈ et al* showed higher prevalence of hypertensive retinopathy in patients with HTN and metabolic syndrome (87.7% vs. 48.4%; P < 0.00001).<sup>15</sup>

In this study we found 92.5% retinopathy of different grade in patients with CCR < 60 and 52.5% retinopathy in patients with CCR e" 60 (p=.001). Its prevalence was also significantly higher in smokers (p=.011), in patients with microalbuminuria (p=.001), in patients with uncontrolled BP (p=.035) and in patients with longer duration of HTN (P=.023).

## Conclusions

A reduction in creatinine clearance is a marker of sub-clinical organ damage in patients with primary hypertension and normal serum creatinine irrespective of BP load and other traditional risk factors. Thus, due to the ready availability and low cost, this test can be routinely performed not only to assess renal function but also to obtain a more sensitive evaluation of cardiovascular damage in hypertensive patients.

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