Hypertensive retinal changes, a screening tool to predict microalbuminuria in hypertensive patients: a cross-sectional study

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Abstract

Background. Studies have shown that hypertensive retinal changes (HRC) have a moderate accuracy in predicting microalbuminuria (MA) in elderly hypertensive patients (age >65 years). This study is an effort to identify a similar relationship in hypertensive patients aged <65 years.

Methods. Eight hundred and seventy consecutive hypertensive patients (males, 460; females, 410) aged 18–65 years were assessed for their demographic characteristics and other laboratory variables. Patients with diabetes mellitus, metabolic syndrome and overt nephropathy were excluded. Optic fundi were assessed for HRC after pupillary dilatation, which were photographed. MA (albumin–creatinine ratio) was measured as an average of two non-consecutive overnight spot urine samples.

Results. Mean age was 45 ± 13.4 years. Prevalence of MA and HRC was 36.7 and 38%, respectively. MA showed a strong association with HRC (P < 0.0001). Logistic regression identified the association between MA, duration of hypertension (HTN) (P = 0.016), smoking (P = 0.012) and elevated high-sensitivity C-reactive protein (hsCRP) (P = 0.032). HRC were associated with duration of HTN (P = 0.021) and smoking (P < 0.0001). Tests of accuracy for HRC as a predictor of MA showed sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test and likelihood ratio of a negative test of 78%, 86%, 76%, 87%, 5.2 and 0.26, respectively. Area under the receiver operating characteristic curve was 81%. Similarly, the individual grades of HRC had a moderate predictive accuracy. Higher grades had higher predictive accuracy. Inter- and intra-observer correlation in interpreting HRC was acceptable.

Conclusions. HRC of any grade have moderate accuracy in predicting MA and hence can be used as a cost-effective

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screening tool to predict MA especially in a resource-poor setting.

Keywords: albuminuria; clinical hypertension; clinical nephrology; chronic inflammation; microalbuminuria

Introduction

Hypertensive nephropathy constitutes a major cause of end-stage renal disease (ESRD) [1]. A recent study from India observed an 18% prevalence of hypertensive nephropathy among patients with chronic renal failure [2]. In South India, hypertensive nephropathy ranks fourth (11%) among the causes of ESRD, preceded only by chronic glomerulonephritis (17.4%), chronic interstitial nephritis (20.4%) and diabetic nephropathy (29.6%) [3].

With hypertensive nephropathy becoming highly prevalent, evaluation for microalbuminuria (MA) becomes essential in the management of patients with hypertension (HTN) as it is not only an early marker of hypertensive nephropathy, but also an independent risk factor for morbidity and mortality in these patients [4,5]. However, the laboratory tests, including dip sticks, used in the diagnosis of MA are not readily available to most primary care physicians working in rural India, inhabited by 70% of the country’s population [3].

This prompted us to search for a clinical tool to predict early nephropathy, which is readily available to the clinician. In our earlier study, we showed that hypertensive retinal changes (HRC) had a moderate accuracy in predicting MA among elderly hypertensive patients (aged >65 years) from South India [6]. With this concept in mind, our present study attempts to identify a similar relationship between HRC and MA among a cohort of hypertensive patients (aged <65 years) from a similar ethnic background. If such a relationship can be established, then HRC may be used as a cost-effective screening tool to predict MA and hence will prove to be clinically useful in this resource-poor setting. Also, in our previous study, the important aspect of intra- and inter-observer correlation (reproducibility) in interpreting HRC was not assessed [6]. This has been assessed in the present study.

Materials and methods

The study period spanned over 5 years (April 2004 to March 2009). From a total of 1040 consecutive patients who attended the outpatient HTN clinic of our teaching hospital, a tertiary care referral centre in South India during this study period, 133 patients with the following features were excluded, in view of their potential confounding effect on the above association between retinopathy and nephropathy:

1. diabetes mellitus and pre-diabetes as defined by the American Diabetes Association [7];
2. metabolic syndrome as defined by the NCEP ATP III guidelines [8];
3. patients taking angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers;
4. presence of overt nephropathy (creatinine >1.5 mg/dl);
5. presence of overt proteinuria [albumin–creatinine ratio (ACR) >3000mg/g];
6. secondary forms of HTN as per standard diagnostic guidelines [9];
7. active infection as observed by the treating physician;
8. age >65 years.

Twenty-four patients were excluded as they had MA only in the first spot urine sample and the second urine sample was determined to be negative for MA. A further 13 patients were excluded because they refused to give informed consent for the study. Consequently, 870 consecutive hypertensive patients, aged between 18 to 65 years (range, 30–61 years; median, 46 years), formed the final study cohort. All study patients were from a low socioeconomic status. The study patients were predominantly from a rural background (from 12 villages for which our institution serves as referral centre). The average per capita income of our study patients was approximately 30 US dollars per month. Informed consent was obtained from all patients. The study was approved by the hospital’s ethics committee.

Method of patient evaluation

Patients were questioned about their age, smoking status and duration of treatment by the principal investigator. Two office blood pressure recordings were taken 30 min apart as per standard method and then similarly repeated on the second visit (usually after 2 weeks) [9]. The average of all these readings was taken as the final blood pressure of the patient [9]. Blood pressure severity was classified according to the Joint National Committee (JNC) VII classification [9]. A normal blood pressure was defined as a systolic pressure (SP) <120 mmHg and a diastolic pressure (DP) <90 mmHg. Furthermore, pre-HTN, stage I and stage II HTN were defined as a SP/DP of 120–139/80–89, 140–159/90–99 and >160/100 mmHg, respectively. Body mass index (BMI) was calculated for all the study patients and obesity was defined as a BMI >30 kg/m² [10]. MA was measured as an average of two non-consecutive overnight spot urine samples for ACR using a quantitative assay (DCA 2000, Bayer Diagnostics Europe, Dublin, Ireland) with a coefficient of variation of 2.8% [11,12]. MA was diagnosed if the ACR ranged between 30 and 300 mg/g of creatinine [13]. Only patients who had MA in both the spot urine samples were included. Patients who tested positive for MA in the first spot urine sample but tested negative for MA in the second sample were excluded. This being a cross-sectional study, further follow-up was not possible. For this reason, patients with one sample positive and one negative were excluded as these patients could not be followed up to see if MA was persistent. Patients who tested negative for MA in the first spot urine sample itself were also excluded. Plasma levels of high-sensitivity C-reactive protein (hsCRP) were assessed using a validated high-sensitivity assay (Dade Behring N high-sensitivity CRP assay, Marburg, Germany), with a coefficient of variation of 3.6%. Fasting blood sugar, glycosylated haemoglobin (HbA1C) and serum creatinine were measured for all the patients. A standard 12-lead electrocardiogram (ECG) was taken for all patients and Romhilt and Estees criteria were used to classify left ventricular hypertrophy (LVH) [14]. Estimated glomerular filtration rate (eGFR) was calculated for all the study patients using the Modified Diet in Renal Disease formula [15].

Retinal examination for HRC

After adequate pupillary dilatation using tropicamide dilating drops, optic fundi were photographed using the Zeiss f450 plus fundus camera for all the study patients. Each optic fundus was assessed for HRC. The changes were reported according to the Keith–Wagener–Barker classification of hypertensive retinopathy [16]. Grade I consists of ‘mild’ generalized retinal arteriolar narrowing; grade 2 consists of ‘more severe’ generalized narrowing, focal areas of arteriolar narrowing and arteriovenous (AV) nicking; grade 3 consists of grade 1 and 2 signs plus the presence of retinal haemorrhages, microaneurysms, hard exudates and cotton wool spots; grade 4 consists of signs of the preceding three grades plus optic disc swelling and macular oedema [16]. The fundus photograph was interpreted by the primary ophthalmologist involved in the study. He was blinded about the demographic and laboratory details (including ACR) of the study patients.
**Methods to assess inter- and intra-observer correlation in interpreting HRC**

To assess intra-observer correlation in interpreting HRC, all fundus photographs were reinterpreted by the same primary ophthalmologist, totally blinded about the previous interpretation results, after a 1-month period. Then, correlation was calculated comparing the present and the previous findings. A second ophthalmologist, totally blinded regarding the findings of the primary ophthalmologist and the patient characteristics, was asked to interpret all fundus photographs. These findings were correlated to those of the primary ophthalmologist (initial findings).

**Methods to assess the correlation in interpreting HRC by the internist and the primary ophthalmologist**

An internist who has had training in interpreting HRC assessed all study patients after pupillary dilatation with a direct ophthalmoscope (Welch-Allyn, Ref 13010). He was blinded regarding the findings of the primary ophthalmologist and the patient characteristics. His findings were correlated with the initial findings of the primary ophthalmologist.

**Statistical analysis**

Baseline characteristics of the study patients were expressed as mean ± SD and percentage. Student's t-test and chi-square test were used to analyse differences in baseline characteristics between (i) patients with or without MA and (ii) patients with or without HRC. Chi-square test was used to analyse the association between MA and HRC. Associations between patient characteristics (age, gender, smoking status, duration of HTN, severity of HTN, BMI, levels of HsCRP and ECG changes of LVH), MA and HRC were analysed using multiple logistic regression. Retinopathy, as a predictor of MA, was evaluated using sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratio of a positive and negative test using standard epidemiological methods [17]. Receiver operating characteristics (ROC) curve and area under the curve were calculated using standard methods [17]. Similarly, likelihood ratio of a positive test (LR+) and likelihood ratio of a negative test (LR−) were calculated for individual stages of HRC. Pearson's correlation was used to assess intra- and inter-observer correlation in interpreting HRC. Similarly, correlation between the internist and the primary ophthalmologist was calculated. A P-value of <0.05 was considered statistically significant. Statistical analyses were performed using the SPSS Windows version 15.0 software (SPSS Inc., Chicago, IL).

**Results**

**Baseline characteristics of the study population**

Baseline characteristics of the study population (n = 870) is shown in Table 1. Mean age of the study population was 45 ± 13.4 years, with males marginally outnumbering the female patients. Twenty-one percent were obese and a relatively small proportion (15.6%) had LVH in ECG. The mean fasting blood sugar, HbA1C, serum creatinine and eGFR were 89 ± 7.99 mg/dl, 4.5 ± 0.68, 0.9 ± 0.31 mg/dl and 97 ± 4.79 ml/min, respectively. None of the study patients had an eGFR <90 ml/min. The prevalence of MA in the study cohort was 36.7% and the prevalence of retinopathy was 38%. Analysis of baseline differences between microalbuminuric and normoalbuminuric patients using the t-test showed no difference in age, sex, JNC class, LVH, mean systolic blood pressure, mean diastolic blood pressure, mean serum creatinine, mean eGFR, mean fasting blood sugar and mean HbA1C between groups, while the microalbuminuric group had significantly more smokers, were more obese, had a longer duration of HTN and had higher HsCRP compared to the normoalbuminuric group (Table 2). Analysis for differences between patients with or without retinopathy showed no difference in age, sex, JNC class, HsCRP, LVH, duration of HTN, mean systolic blood pressure, mean diastolic blood pressure, mean serum creatinine, mean eGFR, mean fasting blood sugar and mean HbA1C between groups, while the retinopathy group had significantly more smokers and obese individuals (Table 2).

**Association between MA and HRC**

Among patients with MA (n = 320), there was coexistent HRC in 250 (78.1%) patients, while among patients with normal urinary albumin excretion (n = 550), HRC was present in 80 (14.5%) patients (Table 1). Chi-square analysis showed a strong association between presence of MA and HRC (P < 0.0001).
Associations of MA and HRC with demographic and other laboratory variables

Multiple logistic regression identified the association between MA, duration of HTN ($P = 0.016$), smoking ($P = 0.012$) and elevated HsCRP ($P = 0.032$) (Table 3). HRC were associated with duration of HTN ($P = 0.021$) and smoking ($P < 0.0001$) (Table 3).

Table 2. Comparison between patients with or without MA and with or without HRC

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients with MA</th>
<th>Patients without MA</th>
<th>$P$-value</th>
<th>Patients with HRC</th>
<th>Patients without HRC</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47 ± 11.6</td>
<td>43 ± 12.7</td>
<td>0.231</td>
<td>46 ± 9.11</td>
<td>44 ± 10.7</td>
<td>0.315</td>
</tr>
<tr>
<td>Males</td>
<td>172</td>
<td>288</td>
<td></td>
<td>187</td>
<td>273</td>
<td>0.117</td>
</tr>
<tr>
<td>Females</td>
<td>148</td>
<td>262</td>
<td></td>
<td>172</td>
<td>267</td>
<td>0.284</td>
</tr>
<tr>
<td>Smokers</td>
<td>182</td>
<td>138</td>
<td>0.021</td>
<td>200</td>
<td>130</td>
<td>0.013</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>26 ± 5.21</td>
<td>23 ± 3.7</td>
<td>0.033</td>
<td>27 ± 4.12</td>
<td>23 ± 2.1</td>
<td>0.037</td>
</tr>
<tr>
<td>Obesity</td>
<td>103</td>
<td>80</td>
<td>0.027</td>
<td>120</td>
<td>63</td>
<td>0.009</td>
</tr>
<tr>
<td>HTN duration (years)</td>
<td>9.5 ± 2.91</td>
<td>7.9 ± 3.81</td>
<td>0.042</td>
<td>8.9 ± 4.71</td>
<td>9.2 ± 3.31</td>
<td>0.241</td>
</tr>
<tr>
<td>Mean systolic BP</td>
<td>140 ± 16.9</td>
<td>145 ± 12.2</td>
<td>0.077</td>
<td>138 ± 15.6</td>
<td>141 ± 13.44</td>
<td>0.711</td>
</tr>
<tr>
<td>Mean diastolic BP</td>
<td>94 ± 10.77</td>
<td>90 ± 12.57</td>
<td>0.365</td>
<td>93 ± 9.47</td>
<td>89 ± 10.44</td>
<td>0.061</td>
</tr>
</tbody>
</table>

Table 3. Logistic regression analysis to identify the associations of MA and HRC

<table>
<thead>
<tr>
<th>Variables</th>
<th>MA</th>
<th>OR</th>
<th>CI</th>
<th>P-value</th>
<th>HRC</th>
<th>OR</th>
<th>CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.371</td>
<td>0.219</td>
<td>1.462</td>
<td>0.135</td>
<td>0.943</td>
<td>0.337</td>
<td>1.052</td>
<td>0.263</td>
</tr>
<tr>
<td>Gender</td>
<td>1.265</td>
<td>0.352</td>
<td>1.701</td>
<td>0.251</td>
<td>0.918</td>
<td>0.279</td>
<td>1.283</td>
<td>0.146</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.451</td>
<td>1.073</td>
<td>2.316</td>
<td>0.012</td>
<td>4.271</td>
<td>2.172</td>
<td>6.831</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HbA1C</td>
<td>1.365</td>
<td>1.421</td>
<td>1.783</td>
<td>0.016</td>
<td>2.531</td>
<td>1.317</td>
<td>4.5</td>
<td>0.029</td>
</tr>
<tr>
<td>LVH</td>
<td>0.218</td>
<td>0.167</td>
<td>2.428</td>
<td>0.162</td>
<td>1.014</td>
<td>0.102</td>
<td>3.162</td>
<td>0.290</td>
</tr>
<tr>
<td>HsCRP</td>
<td>3.296</td>
<td>1.329</td>
<td>4.563</td>
<td>0.032</td>
<td>1.165</td>
<td>0.133</td>
<td>2.156</td>
<td>0.302</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.837</td>
<td>0.511</td>
<td>1.127</td>
<td>0.406</td>
<td>1.440</td>
<td>0.291</td>
<td>2.368</td>
<td>0.320</td>
</tr>
</tbody>
</table>

MA, microalbuminuria; HRC, hypertensive retinal changes; BMI, body mass index (in kilograms per square metre); Obesity, BMI >30 kg/m²; BP, blood pressure (in millimetres of mercury); JNC, Joint National Committee; HTN, hypertension; LVH, left ventricular hypertrophy; HsCRP, high-sensitivity C-reactive protein; HbA1C, glycosylated haemoglobin; eGFR, estimated glomerular filtration rate.

Table 4. Predictive accuracy of each grade of hypertensive retinopathy

<table>
<thead>
<tr>
<th>Grade of retinopathy</th>
<th>MA ($n$)</th>
<th>LR+</th>
<th>LR−</th>
</tr>
</thead>
<tbody>
<tr>
<td>I ($n = 76$)</td>
<td>52</td>
<td>3.68</td>
<td>0.88</td>
</tr>
<tr>
<td>II ($n = 145$)</td>
<td>120</td>
<td>7</td>
<td>0.68</td>
</tr>
<tr>
<td>III ($n = 105$)</td>
<td>78</td>
<td>4.7</td>
<td>0.79</td>
</tr>
</tbody>
</table>

LR, likelihood ratio; n, number of patients.

HRC as a screening tool to predict MA

Evaluation of retinopathy (HRC) as a screening tool to predict MA showed a sensitivity, specificity, positive predictive value, negative predictive value, LR+ and LR− of 78%, 86%, 76%, 87%, 5.2 and 0.26, respectively, when collectively analysed with all stages of HRC taken together. Area under the ROC curve was 81%. The predictive accuracy of individual stages of hypertensive retinopathy in predicting MA is shown in Table 4. Grades II and III have higher predictive accuracy when compared to grade I.

Reproducibility of HRC

The intra-observer and inter-observer correlation in identifying the different stages of HRC is depicted in Table 5. Intra-observer correlation varied between 0.76 for grade I HRC and 1 for grade IV HRC. Inter-observer correlation varied from 0.70 for grade I HRC to 1 for grade IV HRC.
The correlation between HRC interpreted from fundus photography by the primary ophthalmologist to the HRC interpreted by an internist using a direct ophthalmoscope varied from 0.61 for grade I HRC to 1 for grade IV HRC (Table 5).

Table 5. Measures of intra- and inter-observer reproducibility of HRC

<table>
<thead>
<tr>
<th>HRC stages</th>
<th>Intra-observer correlation (fundus photographs)</th>
<th>Inter-observer correlation (fundus photographs)</th>
<th>Correlation with internist’s observation (direct ophthalmoscopy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>0.76</td>
<td>0.70</td>
<td>0.61</td>
</tr>
<tr>
<td>Grade II</td>
<td>0.84</td>
<td>0.78</td>
<td>0.67</td>
</tr>
<tr>
<td>Grade III</td>
<td>0.91</td>
<td>0.89</td>
<td>0.71</td>
</tr>
<tr>
<td>Grade IV</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

All values represent significant correlations ($P < 0.05$).

Discussion

In this study, we observed a high prevalence (36.7%) of MA in a cohort of hypertensive patients (aged <65 years) who were free from diabetes and overt nephropathy. The prevalence of MA in hypertensive patients varied between 6.7 and 40% [18–20]. The MAGIC study [20] has reported a very low prevalence of MA (6.7%) among untreated patients (males, 49 ± 0.6 years; females, 52 ± 0.6 years) with mild to moderate HTN. The methodology of their study was similar to our study where patients with comorbid conditions were excluded. Even then, we observed a higher prevalence of MA. In our previous study involving elderly hypertensive patients (aged >65 years) from a similar ethnic background, MA was prevalent in 39.4% of the study cohort [6]. The reason for this high prevalence of MA is not clear. It is possible that the prevalence of MA among South Indian hypertensive patients might be higher when compared to the rest of the world, probably due to the effect of ethnicity on MA [21]. However, this observation needs validation in further studies.

Duration of HTN, smoking and elevated HsCRP were associated with MA in our study population (Table 3). Furthermore, smokers and patients with longer duration of HTN had nearly 1.5-fold odds of having MA, whereas patients with elevated HsCRP had 4-fold odds of having MA (Table 3). In our previous study as well, duration of HTN had nearly 1.5-fold odds of having MA; whereas duration of HTN that has higher influence on MA and HRC. Also, in both our studies, the duration of HTN has been consistently associated with both MA and HRC [6]. Hence, it is possible that, more than age, it is the duration of HTN that has higher influence on MA and HRC. However, this hypothesis needs validation in future studies.

Observations are again conflicting with regard to the association between retinopathy and MA among hypertensive patients. Our present study and our previous study have consistently observed a strong association between MA and retinopathy in our South Indian hypertensive patients [6]. In the ETODH study [30], no association between MA and retinopathy was observed, but retinopathy was associated with macrovascular markers of target organ damage. Cuspidi et al. [32] also identified no significant difference between severity of retinopathy and different albumin excretion rates. A systematic review by Born et al. [29] states that, ‘data on association between hypertensive retinopathy and MA are inconsistent’. However, they were unable to pool the data from the MAGIC study [20] and Saitoh et al. [33], both showing a strong association between hypertensive retinopathy and MA due to marked heterogeneity. Since the studies done on the association between retinopathy and MA in hypertensive patients are complicated by significant heterogeneity, an extensive systematic review on this topic is still not possible.

Our analysis on accuracy of retinal changes in predicting MA showed interesting findings. We would like to emphasize the fact that, when a screening or diagnostic test is assessed for its predictive accuracy, the variations in the prevalence of the disease or the complication of the disease should be taken into consideration [17]. When the prevalence of the disease or the complication of disease varies
shown to be associated with higher levels of past, current and future blood pressure and obesity and to predict the incidence of diabetes, coronary heart disease, stroke and vascular diseases in other parts of the body [36–39]. Hence, patients with HRC are not only at risk for MA and CKD but also are at risk for all the above-mentioned cardiovascular diseases. Hence, patients detected to have HRC may be initiated on measures for intensive blood pressure control and may be counselled regarding work-up for other cardiovascular risk factors. Further optimal blood pressure control has been associated with regression of both HRC and hypertensive nephropathy [40].

Limitations

Our study has the following limitations: a cross-sectional study design with lack of follow-up to see if these observations remain valid over time, with treatment and with blood pressure control, exclusion of patients with other risk factors like diabetes, metabolic syndrome and overt nephropathy which are known risk factors for MA and retinopathy limits the generalization of the study findings. But our study objective was to identify a clinical tool to predict nephropathy at the stage of MA before overt nephropathy or overt proteinuria occurs. This was the reason for excluding these patients. Furthermore, the application of our study findings to day-to-day clinical practice relies on the ability of physicians to interpret HRC. Reasonable physician training in interpreting HRC is required before this concept could be put to clinical use. For a purported screening study, more than one internist should really be used and inter-observer variability should be judged on these individuals. However, we used only one internist in our study. This is another limitation of our study.

Conclusion

We conclude that prevalence of MA (36.7%) and HRC (38%) is quite high compared to other studies. No new information was observed regarding the associations of MA or HRC. HRC of any grade have a moderate accuracy in predicting MA and hence can be used as a screening tool to predict MA. The higher the severity of HRC, the higher is its predictive accuracy. Any physician with knowledge in the interpretation of HRC may use this to predict MA in a resource-poor setting.

Conflict of interest statement. None declared.

References

Hypertensive retinal changes


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