events and protection against the evolution of quinine resistance by limiting unsupervised quinine therapy in the community.

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SCREENING FOR PRIMARY ALDOSTERONISM — NORMAL RANGES FOR ALDOSTERONE AND RENIN IN THREE SOUTH AFRICAN POPULATION GROUPS

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Objective. To establish normal ranges for plasma aldosterone, renin and aldosterone/renin (A/R) ratio in South African normotensives under typical outpatient conditions, and to estimate the prevalence of primary aldosteronism (PA) among hypertensives in primary care settings.

Design and methods. One hundred and thirty-six normotensive subjects and 154 sex- and age-matched hypertensives at three primary care clinics had measurements of blood pressure, plasma creatinine, K^+, aldosterone, plasma renin activity, and spot urine for urinary Na^+/creatinine ratio. Medication was not withdrawn before testing.

Results. Mean plasma renin activity in black normotensive subjects (0.95 ± 1.25 ng/ml/h, mean ± standard deviation (SD)) was significantly lower than in white (2.09 ± 1.12 ng/ml/h; $P < 0.0001$) and coloured (1.81 ± 1.86 ng/ml/h, $P = 0.013$) normotensives. Mean plasma aldosterone in black normotensives (306 ± 147 pmol/l) was also significantly lower than in white (506 ± 324 pmol/l, $P = 0.0002$) and coloured (418 ± 304 pmol/l, $P = 0.0148$) normotensives. In hypertensives, there were no significant differences in renin or aldosterone levels between the three population groups. Urinary Na^+/creatinine ratios, an index of Na^+ intake, were not significantly different in the three population groups. None of the normotensives had an A/R ratio ≥ 1 000 plus aldosterone ≥ 750, while 7.1% of hypertensives exceeded these levels, suggesting that they are appropriate criteria for screening for PA.

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Conclusions. A large fraction of black normotensive subjects had low renin and aldosterone levels compared with whites, suggesting a salt-retaining tendency in black subjects. These results have important implications for the interpretation of plasma renin and aldosterone levels in hypertensive patients. In primary care settings, 7.1% of hypertensives had biochemical results indicating the need for investigation of PA.

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Although primary aldosteronism (PA) was previously considered to be a rare cause of hypertension, several recent studies, reviewed by Vallotton,[1] indicate that the prevalence of PA is actually much higher, ranging from 1.5% to 12% of hypertensives.[2-5] PA is now diagnosed more frequently as a result of several factors, including the recognition that hypokalaemia is not a good screening test,[1,6] the wider availability of aldosterone and renin assays, and the use of the casual aldosterone/renin (A/R) ratio as a screening test.[3,7,8] This shift in perspective has clinical relevance as PA is potentially curable by unilateral adrenalectomy, is effectively treated with spironolactone, and may not respond well to standard therapy.

The aims of the present study were to establish reference ranges for plasma renin, aldosterone and A/R ratio, and to estimate the prevalence of biochemical PA in hypertensives seen at primary care centres. In view of the fact that ethnic differences in sodium homeostasis and in the renin-aldosterone system have previously been proposed to have importance in the pathogenesis of hypertension,[9-15] a second aim was to clarify whether ethnic differences exist in renin or aldosterone levels, or in the prevalence of PA in South African patients.

Published reference ranges for plasma renin and aldosterone in normotensives have invariably been obtained under controlled conditions of posture (i.e. supine or ambulant) and in many cases under controlled salt intake. These normal ranges are not directly applicable to patients in primary care settings, under variable conditions of posture and salt intake. In addition, mean renin levels have been reported to be lower in black subjects than in whites living in the United Kingdom,[10] raising the concern that a high A/R ratio alone may be an inappropriate screen for PA in black population groups. It was therefore necessary to first establish normal ranges for the A/R ratio in normotensives under primary care clinic conditions, in order to estimate the prevalence of PA in hypertensives.

METHODS

Hypertensive patients, and sex- and age-matched normotensives attending community health centres at three different locations, were divided into ethnic categories. (Patients originated in three source populations which were classified by the previous apartheid legislation into black, coloured and white 'race' groups. Residential segregation in terms of this classification was also strictly enforced before 1994. Since that time there has been limited transformation in residential arrangements, and the three clinics were located in areas where the predominant population was one of these three populations.) The normotensives were patients whose blood pressure (BP) was 140/90 mmHg or less attending the same clinics for medical problems unrelated to hypertension. Subjects had their BP recorded in the sitting position after 5 minutes of rest. After 10 minutes blood was drawn for creatinine, potassium, aldosterone and plasma renin activity, and a spot urine sample was obtained for urinary Na^+/creatinine ratio as an estimate of daily sodium intake.[16,17] The hypertensive patients remained on their usual hypotensive medication. Patients taking spironolactone were excluded from the study.

Plasma renin activity was measured using the Incstar GammaCoat kit (Incstar Corporation, Stillwater, Minn.), and plasma aldosterone using the DPC Coat-a-count kit (Diagnostic Products Corporation, Los Angeles, Calif.). The A/R ratio was calculated from plasma aldosterone in pmol/l and plasma renin activity in ng/ml/h.

Data were analysed using Stata version 6.[18] For normally distributed data, means were compared with two-tailed Student's *t*-tests. Non-normally distributed data were analysed using the Kruskal-Wallis equality of populations rank test and the Mann-Whitney two-sample test statistic.

RESULTS

Table I shows the ages and BPs of normotensive and hypertensive subjects in each of the three ethnic groups. Mean plasma aldosterone, renin, A/R ratios and urinary Na^+/creatinine ratios are shown in Table II. Plasma aldosterone levels plotted against plasma renin activity for normotensives and hypertensives are shown in Figs 1 and 2 respectively.

There were highly significant ethnic differences in the distribution of plasma renin and aldosterone values among normotensives. Mean plasma renin activity was lower in black normotensives compared with whites and coloureds. The majority of black subjects (70%) had a plasma renin less than 1 ng/ml/h, while this was present in only 16% of whites.

Mean plasma aldosterone was also significantly lower in black normotensives than in whites and coloureds. Only 9% of blacks had a plasma aldosterone greater than 500 pmol/l, while this was present in 34% of whites.

The mean A/R ratio was significantly higher in black normotensives compared with whites. An A/R ratio ≥ 1 000, which has previously been used as a criterion for diagnosis of PA, was present in a large fraction of black (32%) and coloured

Table I. Age and blood pressures in normotensive and hypertensive subjects (mean ± standard deviation)

Category	N	Age (yrs)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Normotensive				
Black	46	55.5 ± 12.7	128 ± 11.2	80 ± 10.4
Coloured	46	55.0 ± 7.6	130 ± 11.0	82 ± 7.6*
White	44	53.4 ± 12.3	126 ± 11.5	78 ± 5.5
Hypertensive				
Black	56	56 ± 11.0	145 ± 18.2†	93 ± 9.2‡
Coloured	47	56 ± 7.7	155 ± 17.3§	93 ± 13.1¶
White	51	56 ± 10.4	144 ± 14.9	88 ± 7.7

* Coloured v. white: $P = 0.0087$.
† Black v. coloured: $P = 0.0072$.
‡ Black v. white: $P = 0.0045$.
§ Coloured v. white: $P = 0.0012$.
¶ Coloured v. white: $P = 0.042$.

Table II. Mean plasma renin activity, plasma aldosterone, and A/R ratio in normotensive and hypertensive subjects (mean ± standard deviation). Pairwise comparisons of data were performed using two-sample Wilcoxon rank-sum (Mann-Whitney) tests

Category	Renin (ng/ml/h)	Aldosterone (pmol/l)	A/R ratio	Urine Na^+/Cr
Normotensive				
Black	0.95 ± 1.25*†	306 ± 147‡§	1 050¶ ± 1 205	15.5 ± 11.7
Coloured	1.81 ± 1.86	418 ± 304	1 017 ± 1 638	12.9 ± 8.4
White	2.09 ± 1.12	506 ± 324	306 ± 240	11.8 ± 7.8
Hypertensive				
Black	2.93 ± 4.40	600 ± 470	609 ± 605	13.2 ± 17.1
Coloured	1.81 ± 2.07	594 ± 401	1 361 ± 1 938	14.9 ± 11.1
White	3.69 ± 7.01	577 ± 442	962 ± 1 599	11.7 ± 6.9

* Renin: black v. coloured normotensives: $P = 0.0001$.
† Renin: black v. white normotensives: $P = 0.013$.
‡ Aldosterone: black v. white normotensives: $P = 0.0002$.
§ Aldosterone: black v. coloured normotensives: $P = 0.0148$.
¶ A/R ratio: black v. white normotensives: $P = 0.0003$.

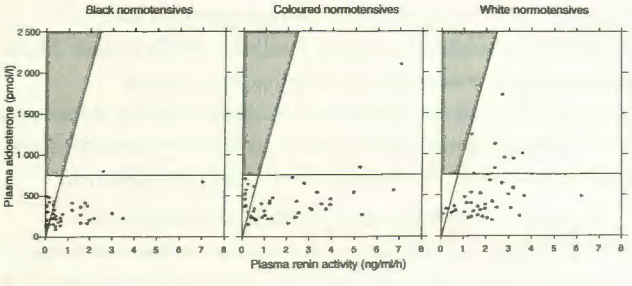

Fig. 1. Plasma aldosterone plotted against renin in normotensives. The diagonal line indicates an A/R ratio = 1 000. The shaded area represents a positive screening test for primary aldosteronism.

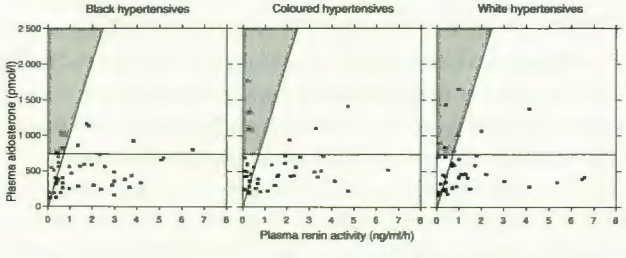

Fig. 2. Plasma aldosterone plotted against renin in hypertensives. The diagonal line indicates an A/R ratio = 1 000. The shaded area represents a positive screening test for primary aldosteronism.

(19.5%) normotensives, compared with only 4.2% of whites.

Mean sodium intake, estimated by urinary Na^+/creatinine ratio, was somewhat higher in blacks than whites (in both normotensives and hypertensives), but these differences were not statistically significant (Table II). While a higher Na^+ intake is expected to result in a lower renin level, the distribution of renin levels plotted against Na^+/creatinine ratio (Fig. 3) suggested that renin levels tended to be lower in black subjects over the entire range of Na^+ intakes. This was confirmed by stratifying normotensives into three groups defined by tertiles with low, medium or high urinary Na^+/creatinine ratios, which showed that renin levels were significantly lower in black subjects than in whites, irrespective of Na^+ intake (Table III).

In contrast to the normotensives, there were no significant ethnic differences in renin, aldosterone or A/R ratios in the

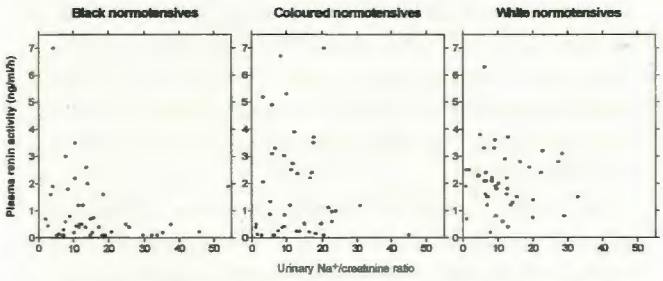

Fig. 3. Plasma renin activity plotted against urinary Na⁺/creatinine ratio in normotensives.

hypertensives (Fig. 2 and Table II). The profiles of antihypertensive drug usage are shown in Table IV.

Table IV. Percentages of hypertensive patients taking various classes of hypotensive drugs according to population group

Hypotensive drugs	Hypertensive patients		
Drug class	Black	Coloured	White
Diuretics	89.8	87.2	42.3
β blockers	1.7	27.6	34.6
Ca^{++} channel blockers	6.7	14.8	17.3
ACE inhibitors	10.2	29.7	46.1
Centrally acting agents	49.1	40.4	1.9
α–blockers	0	0	13.8

ACE = angiotensin converting enzyme.

Discussion

In a recent study[19] we found that 8% of patients at a tertiary hypertension clinic had biochemical results strongly indicative of PA (aldosterone ≥ 1 000 plus A/R ratio ≥ 1 000), and a further 24% had results compatible with PA. Of these patients with biochemical PA, 10% had definite adrenal masses on computed tomography (CT) scan, and a further 6% had probable adrenal masses. Because it was unclear whether this high prevalence of PA was the result of referral bias, the present study was undertaken to investigate the prevalence of biochemical PA among hypertensives in primary care settings. In order to do this, it was first necessary to establish reference ranges for plasma renin and aldosterone in normotensives.

Ethnic differences in sodium homeostasis and in the renin-aldosterone system have previously been reported, and have been proposed to be relevant to the pathogenesis of hypertension.[10] Blacks in the USA have been reported to have a higher incidence of PA[9] and low-renin hypertension.[11,12] Low-renin hypertension has also been found to be prevalent in Zimbabwean blacks.[13,14,20] Recently, variants of the epithelial sodium channel have been found associated with particular ethnic groups.[15,21] For these reasons, we opted to analyse the renin and aldosterone values according to ethnic group.

The present study reveals highly significant differences in plasma renin activity, aldosterone and A/R ratio between the three ethnic groups among normotensives. Both plasma renin and aldosterone levels were significantly lower in the black group than in whites and coloureds. Because of their low renin values, a high proportion of normotensive black subjects (32%)

Table III. Stratification of normotensives into low, medium and high sodium intake tertiles. Cut-off points for stratification by urinary sodium/creatinine ratio were chosen to optimise the statistical power of the analysis. Means were compared using two-sample Wilcoxon rank-sum (Mann-Whitney) tests. Significant ($P < 0.05$) differences are indicated by superscripts

	Urinary Na⁺/Cr ratio (3 tertiles)		
	Low	Medium	High
Urinary Na⁺/Cr ratio range	< 8.3	≥ 8.3 and < 14.6	≥ 14.6 and < 36
Black normotensives			
N	13	14	15
Mean renin (ng/ml/h)	1.24*	1.27	0.37†‡
Mean aldosterone (pmol/l)	331§	329	280
Coloured normotensives			
N	14	14	17
Mean renin (ng/ml/h)	1.59	2.41	1.59
Mean aldosterone (pmol/l)	408	379	453
White normotensives			
N	17	16	11
Mean renin (ng/ml/h)	2.23	1.96	2.08
Mean aldosterone (pmol/l)	545	427	558

* Black v. white: $P = 0.0082$.
† Black v. white: $P = 0.0001$.
‡ Black v. coloured: $P = 0.0018$.
§ Black v. white: $P = 0.0061$.

and to a lesser extent normotensive coloured subjects (19.1%) had an A/R ratio ≥ 1 000, compared with only 4.2% of whites.

In previous studies of predominantly white population groups, a high A/R ratio has often been used as a sole criterion for diagnosing PA, with varying cut-off points for diagnosis of PA. A/R ratios greater than 1 385,[22] 1 390,[23] 950,[8] 831,[24] 1 100[25] and 555[26] have been used as cut-off points (expressed in the same units as the present study). In addition to the A/R ratio, Young[26] required an absolute aldosterone level greater than 416 pmol/l for diagnosis of PA.

The present data show that a high A/R ratio cannot be used as the sole criterion for screening for PA in black and coloured patients, as the high prevalence of low renin levels in normotensives would lead to an unacceptably high false-positive rate. It is necessary to include an additional criterion in order to exclude the large number of low-renin patients who do not have PA. An elevated plasma aldosterone level would serve this purpose, but our previous results,[19] as well as other data,[2] have shown that many proven cases of PA do not have an unequivocally elevated aldosterone level. As there is an overlap in aldosterone levels between PA and low-renin essential hypertension, any aldosterone level chosen as a cut-off point will inevitably be a compromise between sensitivity (pick-up of cases of PA) and specificity (false-positives due to low-renin hypertension). No normotensives in our series had A/R ratios > 1 000 plus aldosterone > 750, suggesting these criteria as reasonable cut-off points for screening for PA.

To determine whether the lower renin and aldosterone levels in black normotensives were the result of higher Na^+ intakes, we estimated sodium intake by the Na^+/creatinine ratio in a spot urine sample, which has previously been shown to correlate well with 24-hour sodium excretion.[16,17] Mean Na^+/creatinine ratios were higher (though not statistically significantly) in black subjects, but this was not a major factor contributing to their lower renin levels, as stratifying the subjects into groups with low, medium or high salt intake showed that black subjects had lower renin levels across the full range of salt intakes.

In considering possible reasons for the lower renin and aldosterone levels in black normotensives, the most direct hypothesis is that the low-renin state is secondary to, and compensates for, a relative tendency to retain sodium. A sodium-retaining tendency could be mediated by differences at many points in the complex control loops governing sodium homeostasis.

Mutations in the β- or α-subunits of the epithelial sodium channel (ENa^+_C) have been identified as the cause of Liddle's syndrome, a rare cause of hypertension with low renin and aldosterone levels.[27-30] While the Liddle's mutations are rare, a polymorphic variant of the βENa^+_C, which has altered function *in vitro*,[31] is present in 6% of African Americans[15] and is reported to be associated with hypertension in blacks in London.[21] The prevalence of epithelial sodium channel mutations in South African populations in unknown. Differences in the secretion or action of dopamine,[12,32] atrial natriuretic peptide[33,34] and renal prostaglandins[14] have all been proposed as possible mechanisms for salt retention in low-renin hypertension.

If the sodium-retention hypothesis is correct, it follows that the black normotensive subjects may have normal BP because they have successfully decreased their renin secretion in response to a salt-retaining tendency. Conversely, the higher renin and aldosterone levels observed in black hypertensives (compared with normotensives) may reflect an inappropriate level of renin and aldosterone secretion in the face of the putative sodium-retaining tendency, and may therefore be a causative factor in these patients' hypertension. However, it is very likely that the renin and aldosterone levels in the hypertensives in the present study have been markedly altered by the use of antihypertensive drugs (Table IV). Diuretics, used by 90% of black hypertensives, are known to increase renin and aldosterone, and are therefore likely to be a significant factor contributing to the higher levels of renin and aldosterone seen in black hypertensives compared with normotensives. Beta-blockers suppress renin secretion, while angiotensin-converting enzyme (ACE) inhibitors increase it, and it is therefore not possible to speculate on the overall effect of combinations of these drugs in the white hypertensives.

Of the 154 hypertensives, 7.1% (11 patients: 3 black, 3 coloured, 5 white) fulfilled the criteria for PA derived from normotensive data as described above (A/R ≥ 1 000 plus aldosterone ≥ 750). This is clearly a first approximation, and the true prevalence of PA in the primary care setting will require further testing after withdrawal of hypotensive drugs, as we have proposed.[35]

In summary, we have established normal ranges for plasma aldosterone, renin and A/R ratio in South African normotensives under outpatient conditions. Screening of hypertensives in primary care settings indicated that 7.1% require definitive investigation for PA.

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OCCUPATIONAL LUNG DISEASES AMONG FORMER GOLDMINERS IN TWO LABOUR SENDING AREAS

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Objectives. To compare and contrast the prevalence of pneumoconiosis in two groups of former migrant mineworkers in southern Africa, and to examine the effectiveness of the South African compensation system for occupational lung diseases.

Design. Comparison of two cross-sectional studies and follow-up data on compensation results.

Setting. The village of Thamaga, Botswana and the rural area of Libode, Eastern Cape, South Africa.

Subjects. Two hundred and thirty-four former underground mineworkers in Thamaga, and 238 in Libode.

Main outcome measures. Prevalence and severity of pneumoconiosis, prevalence of radiological signs of tuberculosis (TB), Medical Bureau for Occupational Diseases (MBOD) certification committee decisions, and compensation results.

Results. Prevalence of pneumoconiosis ≥ 2/1 was 15.4% in Libode and 13.6% in Thamaga. Significantly more Libode than Thamaga subjects (51.1% versus 29.0%) reported past TB treatment. Radiological signs of pulmonary TB were also more prevalent in Libode (33.3% v. 23.9%). Twenty-six per cent of Libode men and 16.1% of Thamaga men were certified with compensable disease. Libode payments were finalised within 30 months, whereas Thamaga cases only began receiving payments 52 months after medical

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