Plasma urea in hypertensive patients

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The annual increase in plasma urea was measured in 253 hypertensive patients. On average there was a significant increase in plasma urea with time which did not depend on the sex of the patient or the type of hypertension. It did, however, depend on the initial level of plasma urea. A table giving the upper limits for expected annual increment may prove useful in clinical assessment.

The relation between plasma urea and presenting blood pressure and age was examined in 1217 patients seen at the Hammersmith Hospital hypertension clinic from 1952 to 1967. The plasma urea was significantly related to both age and diastolic and systolic blood pressure. It was higher in men than in women up to 60 years of age, but not above that age, and it increased with presenting mean blood pressure in both sexes, but the increase was greater in men. There was a quadratic relation between age and plasma urea in both men and women. In both sexes the plasma urea increased between the ages of 60 and 80.

A pathological lesion in a kidney may increase blood pressure by several mechanisms; conversely in essential hypertension the kidneys may be morphologically normal but renal function may be impaired. It is generally accepted that hypertension itself can damage the renal microvasculature and up to a third of treated hypertensives who die may die from renal failure (Breckenridge, Dollery, and Parry, 1970). There has been no reduction in deaths from hypertensive renal disease in the United Kingdom (Registrar General, 1973), but the mortality from both hypertensive heart failure and malignant hypertension has been falling.

For these reasons the clinician is interested in the factors influencing renal function in the hypertensive patient. Long-term assessment of renal function in a hypertensive patient usually relies on repeated measurements of plasma urea or creatinine. This paper examines the plasma urea concentrations in hypertensive patients seen at a clinic and the annual increment in plasma urea during follow-up. By considering confidence limits for these increases a clinician may assess the change in renal function of his patients.

The annual increment in plasma urea does not correlate well with blood pressure control during treatment (Bulpitt, 1974), and this article examines

the relation between plasma urea before treatment and the patient's presenting blood pressure, age, and sex.

Patients and methods

Patients studied

Group 1 The case records were examined of all patients attending the Hammersmith Hospital hypertension clinic during a three-month period between November 1970 and January 1971. Of these patients 253 who had attended for at least 5 years and had had at least 4 measurements of plasma urea were selected. The information recorded included sex, age, diagnosis, hypotensive treatment given, and plasma urea measurements with dates. Any in-hospital measurements after a surgical operation were omitted.

Of the 253 patients, 77 had been diagnosed as having hypertension which might be 'secondary' to a renal lesion; 23 of these patients had chronic pyelonephritis, 6 renal calculi, 6 renal artery stenosis, 10 only a single kidney, and the remainder a variety of renal lesions. Their average follow-up was 7 years during which a mean of 12 plasma urea estimations were made.

Group 2 The relation between the pretreatment blood pressure and the plasma urea on presentation

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TABLE 1 *Average plasma urea (mmol/l) and annual increment (mmol/l per year) according to the type of hypertension and sex for group 1*

Measurement	Men			Women			
	Essential hypertension	'Secondary' hypertension	Significance of between-diagnoses difference	Essential hypertension	'Secondary' hypertension	Significance of between-diagnoses difference	Significance of between-sex difference for essential hypertension
Average log plasma urea	0.803	0.853	P<0.05	0.744	0.755	NS	P<0.001
Number	86	33		90	44		
Annual increase in log urea							
(a) mean	0.0065	0.0068	NS	0.0074	0.0068	NS	NS
(b) Percentage with a positive increase	72.1	75.8	NS	62.7	77.3	NS	NS
Number	86	33		90	44		

Conversion SI to traditional units: Plasma urea 1 mmol/l $\approx$ 6.0 mg/100 ml.

was determined in 1294 patients referred to the Hammersmith Hospital hypertension clinic from 1952 to 1967 inclusive. A computer file was available, including age, sex, presenting blood pressure, and plasma urea. Seventy-seven patients were excluded as they were taking potent hypotensive drugs, leaving 614 men and 603 women. The computer record did not include details of diuretic therapy or diagnoses.

Group 3 This group consisted of 283 patients attending for follow-up during 1973 who presented originally while not receiving any treatment and had a diagnosis of essential hypertension.

Biochemical methods

All biochemical measurements were made in the Department of Chemical Pathology, at the Royal Postgraduate Medical School. The plasma urea was measured by the diacetyl monoxime method, using an autoanalyser after 1958.

Statistical methods

The biochemical data were examined for statistical normality. Plasma urea (in mmol/l) had a log-normal distribution and was converted to a normal distribution by taking the logarithm of each observation. Many patients in group 1 had had more than one measurement in a year, and the averages (arithmetic means) of the transformed plasma ureas were calculated for each patient and each year together with the corresponding average dates. From these data the average log urea and age were computed for the period of follow-up and the an-

nual increment in plasma urea was computed by a least squares regression of the yearly averages on time. Theoretical confidence limits for the observed data were computed by the standard method (Armitage, 1971).

In groups 2 and 3 independent effects on plasma urea of age and blood pressure were computed for the two sexes by standard multiple regression techniques. The mean blood pressure was calculated as the diastolic pressure plus a third of the pulse pressure.

Results

Table 1 shows the average log urea during follow-up in group 1 and the average log urea increment according to sex and the type of hypertension. The average log urea was higher in men than women and in men with 'secondary' hypertension compared with those thought to have essential hypertension. Between 63 and 77 per cent of the patients had a positive increase in log urea during the follow-up period. The average annual increment in urea was 0.007 log mmol/l per year. It did not differ significantly between the groups but was significantly different from zero ($P < 0.0001$). The 90 per cent confidence limits for a single estimate were -0.02 and $+0.03$ log mmol/l per year in both men and women. Five per cent of patients would, therefore, be expected to have an annual log increment greater than $+0.03$. The annual increase in untransformed plasma urea increased with the starting plasma urea concentration. Taking a logarithmic transformation of plasma urea resulted in an annual increment in log urea independent of the urea concentration achieved.

Table 2 lists the annual increments in plasma urea which would be expected to be exceeded by 5 per cent of a hypertensive population according to the initial plasma urea.

Table 3 shows the average results for group 2. Both plasma urea and diastolic pressure were higher in men. In this sample the plasma urea varied between 1.7 mmol/l and 79.2 mmol/l, age between 12 and 84 years, and mean blood pressure between 93 and 233 mmHg (12.4 and 31.0 kPa).

Tables 4 and 5 show the average log urea for both men and women in group 2 according to age and presenting mean blood pressure. In men the average log urea fell between the fourth and sixth decades rising again in the seventh decade. In women over 40 there was a rise with age, accelerating from the fifth to the seventh decade. In both sexes the plasma urea increased with the mean blood pressure.

The best correlation between blood pressure and log urea was with diastolic blood pressure in men and mean blood pressure in women. The correlation between mean blood pressure and log urea was also good in men, and mean blood pressure was used to predict log urea in both sexes. The following relation between urea, age, and mean blood pressure was found in men:

$$Y = 0.8326 - 0.016240A + 0.000149A^2 + 0.002676M \quad (1)$$

Where Y is log plasma urea in log mmol/l, A is age in years, M is mean blood pressure in mmHg.

($n=614$, $R^2=0.094$, square of age partial regression coefficient being significant at the 1% level, and age and mean blood pressure coefficients at the 0.1% level).

Similarly, in women:

$$Y = 0.6830 - 0.008873A + 0.000113A^2 + 0.001446M \quad (2)$$

($n=603$, $R^2=0.056$, the partial regression coefficient for age being significant at the 1% level and those for the square of age and mean blood pressure at the 0.5% and 0.1% level, respectively).

The prediction equations explained only 9 per cent of the variation in plasma urea in men and 6 per cent in women.

Comparing the sexes, Tables 4 and 5 show that a higher average log plasma urea in men is present in the younger age groups and is not noticeable above the age of 60. Similarly, the difference between the average log plasma urea in men and the average in women is more pronounced at a presenting mean blood pressure greater than 170 mmHg (22.6 kPa), than at lower presenting pressures.

The effect of blood pressure level on log urea

TABLE 2 Annual increment in plasma urea in mmol/l per year exceeded by theoretical 5 per cent of hypertensive patients and according to initial plasma urea

Initial plasma urea (mmol/l)	Upper limit for annual increment (mmol/l per year)
2	0.14
4	0.28
8	0.57
16	1.14

Conversion SI to traditional units: Plasma urea, 1 mmol/l $\approx$ 6 mg/100 ml.

concentration was more pronounced in men than in women, the partial regression coefficients (standardized for age) of log urea on mean blood pressure for the sexes being significantly different at the 5 per cent level. The increase in plasma urea with age was similar in the two sexes only after the sixth decade.

The relation between plasma urea and blood pressure was similar when the analysis was confined to patients presenting with essential hypertension and not receiving any treatment (group 3). On average a rise of 1 mmHg (0.1 kPa) mean pressure was associated with a 0.0020 log mmol/l rise in plasma urea in men and a 0.0011 log mmol/l rise in women.

Discussion

Increase in plasma urea with time or age

Equations (1) and (2) indicate that, pressure remaining constant, an increase in age of between 40 and 80 years would give an annual increase in log urea of 0.002 in hypertensive men and 0.005 in hypertensive women. (Increase in untransformed

TABLE 3 Details of patients presenting to clinic between years 1952 and 1967, and not receiving potent hypotensive drugs (group 2)

	Men	Women	Significance of difference
Number	614	603	—
Average			
Plasma urea (mmol/l)	8.23	6.68	$P < 0.001$
Log plasma urea	0.832	0.759	$P < 0.001$
Systolic pressure (mmHg)	211.56	211.44	NS
Diastolic pressure (mmHg)	127.20	122.19	$P < 0.001$
Age (y)	48.12	49.00	NS

Conversion SI to traditional units: Plasma urea, 1 mmol/l $\approx$ 6 mg/100 ml.

TABLE 4 Average log plasma urea in mmol/l for males in 28 groups subdivided according to presenting mean blood pressure and age

Age (y)	Mean blood pressure (mmHg)							All pressures
	≤130	~140	~150	~160	~170	~180	>180	
40	0.743 (36)	0.774 (30)	0.867 (20)	0.832 (9)	0.943 (25)	1.159 (14)	0.953 (20)	0.868 (154)
~50	0.723 (20)	0.832 (17)	0.796 (23)	0.774 (35)	0.810 (29)	0.853 (23)	1.051 (19)	0.825 (168)
~60	0.765 (24)	0.765 (32)	0.780 (35)	0.872 (39)	0.843 (32)	0.847 (25)	0.829 (28)	0.816 (215)
>60	0.845 (6)	0.787 (10)	0.787 (15)	0.769 (17)	0.821 (14)	0.900 (9)	0.967 (6)	0.821 (77)
All ages	0.752 (86)	0.783 (89)	0.803 (98)	0.817 (100)	0.855 (100)	0.921 (68)	0.932 (73)	0.832 (614)

Figures in parentheses are numbers contributing to each average. Plasma urea increases with level of presenting blood pressure (group 2). Conversion from traditional to SI units: 1 mmHg ≈ 0.133 kPa.

urea 0.03 mmol/l per year for an initial plasma urea of 6.3 mmol/l in men and an increase of 0.06 mmol/l per year for an initial urea of 5.5 mmol/l in women.) The hypertensive patients, when treated, had an average increase of +0.007 per annum (0.1 mmol/l per year for an initial urea of 6.0 mmol/l). The greater rise in plasma urea per annum during follow-up is possibly the result of treatment as it is recognized that diuretics and adrenergic neurone-blocking drugs increase plasma urea (Dinon, Kim, and Vander Veer, 1958; Bulpitt, 1974). However, we are comparing the results from cross-sectional and longitudinal studies. Early death from renal failure ensures that a patient is not included in a longitudinal study and the average increase of +0.007 must be an underestimate. Similarly the failure of a patient to survive to a certain age prevents his inclusion in a cross-sectional study, and patients with a high plasma urea will be poorly represented in the older decades. The average increments of +0.002 to 0.005 are presumably also underestimated.

Many cross-sectional studies have found normal subjects to have a rise in plasma urea with age. Taking a logarithmic transformation of the urea values reported in these studies, there have been

reports of a greater rise in log plasma urea in women, 0.002 per annum, as opposed to 0.001 for men (Campbell *et al.*, 1968); similarly 0.002 per annum for women and no significant increase in men (Roberts, 1967), and rises in log urea of 0.002 (Keating *et al.*, 1969), and 0.001 per annum (Josephson and Dahlberg, 1952) for both men and women.

The use of different techniques in determining plasma urea makes it difficult to compare the absolute values of plasma urea in this study with those in 'normal' populations. However, the average plasma urea for men in this study with essential hypertension (6.3 mmol/l) was at the upper limit of the 'normal' range accepted by many laboratories, and the corresponding average for women with essential hypertension was 5.5 mmol/l. An average of 5.3 to 5.8 mmol/l and 4.0 to 5.3 mmol/l would be expected for men and women, respectively (Mackay and Mackay, 1927; Campbell *et al.*, 1968; Josephson and Dahlberg, 1952). The average plasma urea and annual increment in plasma urea are, therefore, increased in hypertensive patients, especially as the quoted increases in log urea per year of age in normal subjects were not adjusted for increases in blood pressure with age.

TABLE 5 Average log plasma urea in mmol/l for females in 28 groups subdivided according to presenting mean blood pressure and age

Age (y)	Mean blood pressure (mmHg)							All pressures
	≤130	~140	~150	~160	~170	~180	>180	
40	0.695 (45)	0.704 (31)	0.674 (23)	0.821 (24)	0.788 (14)	0.774 (14)	0.758 (9)	0.725 (165)
~50	0.705 (22)	0.713 (21)	0.707 (21)	0.813 (17)	0.673 (25)	0.792 (17)	0.874 (11)	0.740 (135)
~60	0.732 (19)	0.733 (33)	0.753 (33)	0.791 (27)	0.753 (23)	0.737 (22)	0.800 (16)	0.763 (178)
>60	0.804 (19)	0.843 (15)	0.761 (23)	0.733 (23)	0.837 (25)	0.835 (14)	0.903 (12)	0.819 (125)
All ages	0.719 (105)	0.738 (100)	0.723 (102)	0.803 (88)	0.762 (93)	0.791 (67)	0.836 (48)	0.759 (603)

Figures in parentheses are number contributing to each average. Plasma urea increases with both age and presenting mean blood pressure (group 2). Conversion from traditional to SI units: 1 mmHg ≈ 0.133 kPa.

FIG. 1 Relation between urea (log mmol/l) and presenting mean blood pressure for both sexes and after standardizing for age 50 years. All 1217 patients presented between the years 1952 and 1967. Conversion: SI to traditional units—Urea: 1 mmol/l $\approx$ 6.0 mg/100 ml.

FIG. 2 Relation between urea (log mmol/l) and age at presentation for both sexes and after standardizing for mean blood pressure of 150 mmHg (20.0 kPa). All 1217 patients presenting between the years 1952 and 1967.

Relation between plasma urea and presenting blood pressure

The blood pressure was important in determining the concentration of plasma urea on presentation to the clinic—the higher the untreated blood pressure the higher the plasma urea. The blood pressure in untreated patients may be raised as a consequence of renal dysfunction, whereas the blood pressure during treatment may well be more related to the hypotensive drugs given than to renal function. This might explain the presence of a correlation between plasma urea and blood pressure in untreated patients, whereas treated patients did not show a significant positive correlation (Bulpitt, 1974).

Interestingly, the presenting blood pressure was more closely related to the plasma urea in men than in women. The plasma urea increased, on average, by 0.04 mmol/l in men and 0.02 mmol/l in women for every 1 mm increment of presenting mean blood pressure.

The difference between the sexes in the relation both between age and plasma urea and mean pressure and urea may be related to the duration of hypertension. The two sexes have similar blood pressures at the ages of 5 to 8 (Beresford and Holland, 1973) but male subjects have an increase in pressure between the ages of 10 and 20, after which systolic, and to some extent diastolic, pressure remain fairly constant until the age of about 50 (Miall and Lovell, 1967). Women show a consistent rise in both diastolic and systolic pressure from childhood resulting in higher levels than men after the age of 40. These cross-sectional studies have been confirmed to some extent by longitudinal studies. Johnson, Karunas, and Epstein (1973) reported increases in systolic pressure for males aged 10 to 19 and 55 to 74 which were not so striking in females.

A longer exposure to a high pressure may explain the larger regression coefficient in men when log urea is regressed on pressure. This is supported by Fig. 1 where log urea is plotted against mean blood pressure according to equations (1) and (2) and for patients aged 50 years. The log urea is similar for the two sexes when the mean pressure is near normal and the patients cannot have been exposed to high pressures for any length of time.

In Fig. 2 log urea is plotted against age for a mean pressure of 150 mmHg (20.0 kPa). Over the age of 60 both men and women hypertensive patients may have been exposed equally to hypertension for many years and the log urea is similar for the two sexes. Below the age of 50 men may have been exposed to a high pressure for a relatively long interval and their plasma urea concentrations are greater.

The results for group 3 indicate that the relation between plasma urea and presenting blood pressure was not due to either diuretic therapy or the inclusion in group 2 of some patients with 'secondary' hypertension, the increases in plasma urea with mean pressure being similar for both groups 2 and 3. As group 2 was larger and less affected by non-survival, only the results for this group are presented in detail (equations (1) and (2)).

The relation between mean blood pressure and log urea may be a causal relation, a high pressure causing a deterioration in renal function. If the duration of raised pressure is important the between-sex differences in these relations may be explained, and possibly renal function may be preserved by the earlier detection and treatment of hypertension. The alternative hypothesis is that changes in renal function raise blood pressure. While receiving treatment any deterioration in renal function can be compared with the upper limits for annual increment shown in Table 2.

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References

- Armitage, P. (1971). *Statistical Methods in Medical Research*, p. 164. Blackwell, Oxford.
- Beresford, S. A. A., and Holland, W. W. (1973). Levels of blood pressure in children: a family study. *Proceedings of the Royal Society of Medicine*, **66**, 1009.
- Breckenridge, A., Dollery, C. T., and Parry, E. H. O. (1970). Prognosis of treated hypertension. Changes in life expectancy and causes of death between 1952 and 1967. *Quarterly Journal of Medicine*, **39**, 411.
- Bulpitt, C. J. (1974). Blood urea changes in hypertensive patients according to therapy given, blood pressure control, and serum potassium level. *British Heart Journal*, **36**, 383.
- Campbell, H., Greene, W. J. W., Keyser, J. W., Waters, W. E., Weddell, J. M., and Withey, J. L. (1968). Pilot survey of haemoglobin and plasma urea concentration in a random sample of adults in Wales, 1965-66. *British Journal of Preventive and Social Medicine*, **22**, 41.
- Dinon, L. R., Kim, Y. S., and Vander Veer, J. B. (1958). Clinical experience with chlorothiazide (Diuril), with particular emphasis on untoward responses. A report of 121 cases studied over a 15 month period. *American Journal of the Medical Sciences*, **236**, 533.
- Johnson, B. C., Karunas, T. M., and Epstein, F. H. (1973). Longitudinal change in blood pressure in individuals, families and social groups. *Clinical Science and Molecular Medicine*, **45**, 35S.
- Josephson, B., and Dahlborg, G. (1952). Variation in the cell-content and chemical composition of the human blood due to age, sex and season. *Scandinavian Journal of Clinical and Laboratory Investigation*, **4**, 216.
- Keating, F. R., Jones, J. D., Elveback, L. R., and Randall, R. V. (1969). The relation of age and sex to distribution of values in healthy adults of serum calcium, inorganic phosphorus, magnesium, alkaline phosphatase, total proteins, albumin and blood urea. *Journal of Laboratory and Clinical Medicine*, **73**, 825.
- Mackay, E. M., and Mackay, L. L. (1927). The concentration of urea in the blood of normal individuals. *Journal of Clinical Investigations*, **4**, 295.
- Miall, W. E., and Lovell, H. G. (1967). Relation between change of blood pressure and age. *British Medical Journal*, **2**, 660.
- Registrar General (1973). *Statistical Review of England and Wales for the Year 1971*. Her Majesty's Stationery Office, London.
- Roberts, L. B. (1967). The normal ranges with statistical analysis for seventeen blood constituents. *Clinica Chimica Acta*, **16**, 69.

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