Serum Potassium, Cigarette Smoking, and Mortality in Middle-aged Men

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The relation between serum potassium level and all-cause mortality was examined in a prospective study of 7,636 middle-aged British men followed for 11.5 years (1978–1991). Men being treated for hypertension had a significantly lower mean (± standard error) potassium level than men not in treatment (4.24 ± 0.03 mmol/liter vs. 4.32 ± 0.01 mmol/liter; p < 0.01). During the follow-up period of 11.5 years, after exclusion of the 374 men under antihypertensive treatment, there were 771 deaths from all causes in the remaining 7,262 men. A low potassium level (<3.7 mmol/liter) was not associated with increased mortality. Elevated potassium levels (≥5.2 mmol/liter) were associated with a significant increase in mortality, particularly noncardiovascular deaths, even after adjustment for potentially confounding factors. However, serum potassium was strongly related to smoking, and the increased risk of mortality associated with elevated potassium was seen only among current smokers. In current smokers with raised potassium levels (≥5.2 mmol/liter) compared with smokers with levels under 5.2 mmol/liter, the relative risks of mortality were 1.7 (95% confidence interval (CI) 1.2–2.5) for deaths from all causes, 1.8 (95% CI 1.0–3.2) for all cancer deaths, and 2.5 (95% CI 1.1–5.6) for lung cancer deaths. In the 374 men receiving regular antihypertensive treatment, a low potassium level was not associated with excess mortality; those with raised potassium levels had excess risks for both cardiovascular and noncardiovascular deaths. The findings suggest that either raised potassium levels in association with smoking have an influence on the risk of death from noncardiovascular disease, particularly lung cancer, or a raised serum potassium level is a marker for some other risk factor associated with smoking. The prognostic and therapeutic implications of these observations warrant further exploration. Am J Epidemiol 1997;145:598–606.

There has been concern about the potential harm caused by diuretic-induced hypokalemia. Several investigators have reported associations with ventricular dysrythmia (1–4), and the relation between ventricular dysrythmia and coronary heart disease death is well recognized (5). In a longitudinal study of patients being treated for hypertension at the Glasgow Blood Pressure Clinic, potassium concentrations showed no consistent relation with ischemic heart disease mortality rates; all-cause mortality appeared to be lower in patients with hypokalemia and was increased in those with higher potassium levels (6). The observation that increased potassium might be related to higher mortality is supported by a study of hospital inpatients which found increased mortality among patients with raised potassium levels (≥6.0 mmol/liter) (7). The long-term relation between potassium levels and mortality has yet to be examined in a general population sample including both normotensive and hypertensive subjects, subjects receiving and not receiving antihypertensive treatment, and subjects with and without evidence of ischemic heart disease. In this report, we describe the relation between serum potassium level at screening and all-cause mortality in a longitudinal study of middle-aged British men.

MATERIALS AND METHODS

The British Regional Heart Study is a large prospective study of cardiovascular disease in 7,735 men aged 40–59 years. The men were selected from the age/sex registers of one group general practice in each of 24 towns in England, Wales, and Scotland (response rate = 78 percent). The criteria for selecting the towns, general practices, and subjects, as well as the methods of data collection, have been reported previously (8). In 1978–1980, research nurses administered to each man a standard questionnaire which included questions on smoking habits, alcohol intake, physical activity, and medical history. Several physical measurements were made, and blood samples (nonfasting) were taken throughout the day between 8:30 a.m. and
Serum Potassium, Cigarette Smoking, and Mortality

Serum cadmium concentration has been shown to be strongly associated with smoking status in this cohort (13, 14). Mean cadmium levels increased progressively and significantly with increasing numbers of cigarettes smoked per day. In the analyses, “nonsmokers” included both never smokers (1,819 men) and ex-cigarette smokers (2,715 men). Data on smoking were not available for 15 men.

Preexisting disease and medication use

The men were asked whether a doctor had ever told them that they had angina or myocardial infarction (heart attack, coronary thrombosis), stroke, or a number of other disorders. They were also asked about any medications regularly used, including antihypertensive drugs. Men on diuretics who did not recall a diagnosis of hypertension or cardiovascular disease were not included in the group of antihypertensive drug users. The World Health Organization (Rose) chest pain questionnaire (15) was administered to all men at the initial examination, and a three-orthogonal-lead electrocardiogram was recorded at rest.

Follow-up

All men were followed for all-cause mortality and cardiovascular disease morbidity for 11.5 years. Information on deaths was collected through the established “tagging” procedures provided by the National Health Service registers in Southport (England and Wales) and Edinburgh (Scotland) (16). The only death certificates which were fully explored were those relating to cardiovascular disease. This was done routinely as each quarterly batch of death certificates was received from the National Health Service registries. If it appeared that coding for cardiovascular disease was not appropriate, or if cardiovascular disease was not the attributed code when it might have been, the findings were explored by correspondence to the certifying doctor and the relevant hospital.

Statistical methods

Cox proportional hazards modeling was used to estimate relative risks adjusted for age, social class, smoking, alcohol intake, body mass index, physical activity, diabetes mellitus, blood glucose, preexisting ischemic heart disease, heart rate, forced expiratory volume in 1 second (FEV₁), and systolic blood pressure (17). Relative risks for the six potassium groups were obtained by fitting potassium as five dummy variables (for the six potassium groups; see table 3). Tests for trend were carried out with potassium values fitted in their original continuous form. Age, body mass index, blood glucose, cholesterol, FEV₁, and

Smoking

The men were classified according to their current cigarette smoking status: never smokers, ex-smokers, and current smokers at four levels (1–19, 20, 21–39, and ≥40 cigarettes/day). Those who had ever smoked only pipes or cigars were grouped with never smokers. Ex-cigarette smokers who were currently pipe or cigar smokers were classified as ex-smokers. Measurements of serum cadmium, a strong biologic marker of smoking, were available for validation of smoking status.

Blood samples for assessment of biochemical and hematologic variables were drawn into five separate Vacutainer tubes (Becton Dickinson, Rutherford, New Jersey) using a Velcro tourniquet (Velcro USA, Inc., Manchester, Ohio) on the upper arm. Serum separation tubes were stood upright for 30 minutes and then spun for 10 minutes. All biochemical samples were stood vertically at 4°C and dispatched overnight to the Wolfson Research Laboratories, Queen Elizabeth Hospital, Birmingham, England, where estimations were completed by noon of the following day. Thirteen biochemical measurements, including potassium level, were made on each serum sample using a Technicon SMA 12/60 autoanalyzer (Technicon Instruments Corporation, Tarrytown, New York).

The London School of Hygiene and Tropical Medicine sphygmomanometer was used to measure blood pressure twice in succession, with the subject seated and the arm supported on a cushion. The mean of the two readings was used in the analysis, and all blood pressure readings were adjusted for observer variation within each town (9). Classification methods for alcohol consumption, occupation (social class), body mass index (weight (kg)/height (m)²), and heart rate have been reported elsewhere (8, 10). Obesity was defined as a body mass index ≥ 28, the top 20 percent of the distribution in these men. Heavy alcohol drinking was defined as consumption of more than six alcoholic drinks daily or on most days (one drink = 8–10 g alcohol). The men were asked to indicate their usual pattern of physical activity, under the headings of regular walking or cycling, recreational (weekend) activity, and active physical exercise. A physical activity (exercise) score was derived for each man based on the frequency and type (intensity) of physical activity. Full details on the derivation of the score have been given elsewhere (11). The men were grouped into six broad categories based on their total score: inactive, and occasional, light, moderate, moderately vigorous, and vigorous activity. A resting electrocardiogram was recorded at the end of the examination, and heart rate was determined from this tracing (12).
systolic blood pressure were fitted as continuous variables. Smoking was fitted as four dummy variables for the five smoking categories (never, former, light, moderate, and heavy smoking) or as a 0/1 variable (non-smokers vs. smokers). Physical activity was fitted as five dummy variables for the six activity groups (inactive, occasional, light, moderate, moderately vigorous, and vigorous), social class as two dummy variables for the three socioeconomic groups (manual labor, nonmanual labor, and Armed Forces), and alcohol as four dummy variables for the five alcohol consumption groups (none, occasional, light, moderate, and heavy).

RESULTS

Data on serum potassium were available for 7,636 men—98.7 percent of the study population. The mean serum potassium level was 4.32 mmol/liter (standard deviation 0.41; range, 2.8–6.0 mmol/liter). Diuretic treatment of hypertension is known to lower potassium levels, and men on antihypertensive drugs (n = 374 men) had lower potassium levels (4.24 ± 0.03 (standard error) vs. 4.32 ± 0.01; p < 0.01). All men under antihypertensive treatment were excluded from the initial analyses, leaving 7,262 men.

Figure 1 shows the distribution of potassium values in the 7,262 men. One hundred and seventy-six men had values below 3.7 mmol/liter, a level generally regarded as hypokalemia, and only 17 men had potassium values below 3.5 mmol/liter. Because of the interest in men with low and high levels of potassium, the men were divided into seven groups based on absolute potassium levels: <3.7 (n = 176), 3.7–3.9 (n = 1,060), 4.0–4.2 (n = 2,156), 4.3–4.5 (n = 2,017), 4.6–4.8 (n = 1,103), 4.9–5.1 (n = 499), and ≥5.2 (n = 251) mmol/liter.

All-cause mortality

During the follow-up period of 11.5 years, among the 7,262 men who were not under antihypertensive treatment, there were 771 deaths from all causes (8.1/1,000 person-years), including 370 cardiovascular disease deaths (304 due to ischemic heart disease, 29 to stroke, and 37 to other cardiovascular causes) and 401 noncardiovascular deaths, 282 of which resulted from cancer. Figure 2 shows the relation between the seven potassium categories and crude mortality rates per 1,000 person-years for deaths from all causes and from cardiovascular and noncardiovascular causes. Mortality from all causes increased with increasing potassium level, with a marked increase at 5.2 mmol/liter and above (test for trend: p < 0.0001). The increase was largely due to a significant increase in noncardiovascular mortality (test for trend: p < 0.0001). Mortality from cardiovascular causes increased slightly with increasing levels of potassium, and a test for trend yield a p value of 0.04.

Cancer and other non-cardiovascular disease mortality

Table 1 shows the death rates for non-cardiovascular disease mortality separately for cancer and other noncardiovascular causes. Mortality rates from cancer increased slightly with increasing potassium levels and were mark-
TABLE 1. Mortality rates per 1,000 person-years of observation for deaths due to cancer and other non-cardiovascular disease (CVD) causes during 11.5 years of follow-up, by serum potassium level: British Regional Heart Study, 1978–1991

<table>
<thead>
<tr>
<th>Serum potassium (mmol/liter)</th>
<th>All cancers (n = 282)</th>
<th>Lung cancer (n = 96)</th>
<th>Digestive tract cancers (n = 85)</th>
<th>Other cancers (n = 98)</th>
<th>All (n = 119)</th>
<th>Respiratory disease (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.7</td>
<td>2.5 (5)*</td>
<td>1.5 (3)</td>
<td>1.0 (2)</td>
<td>0</td>
<td>0.5 (1)</td>
<td>0.7 (1)</td>
</tr>
<tr>
<td>3.7–3.9</td>
<td>3.0 (36)</td>
<td>1.5 (18)</td>
<td>0.8 (9)</td>
<td>0.8 (9)</td>
<td>1.0 (12)</td>
<td>0.5 (8)</td>
</tr>
<tr>
<td>4.0–4.2</td>
<td>3.4 (80)</td>
<td>1.0 (25)</td>
<td>0.9 (21)</td>
<td>1.4 (34)</td>
<td>1.3 (31)</td>
<td>0.5 (10)</td>
</tr>
<tr>
<td>4.3–4.5</td>
<td>3.4 (76)</td>
<td>1.2 (22)</td>
<td>0.9 (22)</td>
<td>1.3 (28)</td>
<td>1.4 (30)</td>
<td>0.5 (11)</td>
</tr>
<tr>
<td>4.6–4.8</td>
<td>4.2 (50)</td>
<td>1.2 (14)</td>
<td>1.6 (19)</td>
<td>1.4 (17)</td>
<td>2.2 (27)</td>
<td>1.3 (16)</td>
</tr>
<tr>
<td>4.9–5.1</td>
<td>3.5 (19)</td>
<td>0.9 (5)</td>
<td>1.6 (9)</td>
<td>0.9 (5)</td>
<td>1.5 (8)</td>
<td>0.5 (3)</td>
</tr>
<tr>
<td>5.2</td>
<td>6.0 (16)</td>
<td>3.0 (8)</td>
<td>1.1 (3)</td>
<td>1.8 (5)</td>
<td>3.7 (10)</td>
<td>1.1 (3)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, number of deaths.

Edly increased only at levels ≥ 5.2 mmol/liter (test for trend: p = 0.05), largely because of an excess of lung cancer. For noncancer noncardiovascular deaths, the mortality rate tended to increase with increasing serum potassium level and was most sharply increased at levels ≥ 5.2 (test for trend: p < 0.0001). There were 10 deaths in this group, three of which were due to respiratory causes and three to endocrinologic causes. None of these deaths had cardiac arrhythmia or renal failure listed on the death certificate.

Risk factors for mortality

The relation between serum potassium and known risk factors for mortality was examined in the men not receiving antihypertensive treatment.

Personal characteristics. There was a tendency for potassium levels to increase with age (p = 0.01) (table 2). Smoking and alcohol intake were strongly and positively associated with increased potassium levels (p < 0.0001). There was also a dose-response relationship with cigarette smoking; mean potassium levels increased with increasing numbers of cigarettes smoked per day. Body mass index showed an inverse association with potassium level (p < 0.001). Manual workers had slightly higher levels of potassium than nonmanual workers (p < 0.01). On the other hand, physical activity showed a small but significant inverse relation with potassium level (p = 0.04).

Preexisting disease. No association was seen with a history of diabetes, stroke, or ischemic heart disease or with the presence of ischemic heart disease on the World Health Organization (Rose) questionnaire or electrocardiogram.

Biologic factors. Serum potassium was inversely related to systolic blood pressure (r = −0.06), FEV₁ (r = −0.08), heart rate (r = −0.09), and blood...
glucose \((r = -0.10)\); all of these relations were statistically significant \((p < 0.001)\). A weak but significant association was seen with blood cholesterol \((r = 0.03)\).

**Adjustment for mortality risk factors**

Since men in the lower two potassium concentration groups had similar mortality rates (figure 1), the two groups were combined and used as the reference group \(<4.0 \text{ mmol/liter}\). Table 3 shows the relation between serum potassium and mortality after adjustment for age and then, in addition, for the risk factors listed above, namely social class, smoking, alcohol intake, body mass index, physical activity, cholesterol, FEV\(_1\), heart rate, and blood glucose. Adjustment for these factors reduced the increased relative risks seen, but there still remained a significant positive association with total mortality, with risk significantly increased relative to the reference group at levels \(\geq 5.2 \text{ mmol/liter}\) (relative risk \((RR) = 1.7, 95\text{ percent confidence interval (CI)} \ 1.1-2.6\)). For cardiovascular mortality, risk was lowest in the men with levels below 4 mmol/liter, but there was little difference between the other groups, and a test for linear trend was not significant. Cancer mortality remained raised in men with levels \(\geq 5.2 \text{ mmol/liter}\) \((RR = 1.6, 95\text{ percent CI} \ 0.9-2.9)\) compared with those with levels under 4.0 mmol/liter, but the difference was not statistically significant. A significant positive association was seen with other noncardiovascular deaths, with markedly raised mortality at levels \(\geq 5.2 \text{ mmol/liter}\) \((RR = 2.4, 95\text{ percent CI} \ 1.0-5.9)\) compared with those with levels below 4.0 mmol/liter.

Further adjustment for preexisting ischemic heart disease and history of diabetes made little difference in the relations seen. The positive relations between serum potassium and all-cause mortality, cancer death, and other noncardiovascular death persisted after exclusion of men with preexisting ischemic heart disease.

**Early death**

To assess whether the increased mortality seen in those with serum potassium levels \(\geq 5.2 \text{ mmol/liter}\) was associated with underlying subclinical illness which itself influenced potassium concentrations, we examined the potassium-mortality relations after excluding deaths occurring during the first 5 years of follow-up. The significant positive association with total mortality persisted. The increased risk for other noncancer, noncardiovascular mortality associated with potassium levels \(\leq 5.2 \text{ mmol/liter}\) was slightly attenuated, from 2.4 to 2.0 (95 percent CI 0.6–6.2). Men with potassium levels \(\geq 5.2 \text{ mmol/liter}\) still showed increased mortality from cancer, albeit nonsignificant \((RR = 1.7, 95\text{ percent CI} \ 0.9-3.8)\). For

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**TABLE 3.** Adjusted relative risk (RR) of mortality from all causes, cardiovascular disease (CVD), cancer, and other non-CVD causes, by serum potassium level: British Regional Heart Study, 1978–1991

<table>
<thead>
<tr>
<th>Serum potassium (mmol/liter)</th>
<th>Total mortality</th>
<th>CVD deaths</th>
<th>Cancer deaths</th>
<th>Other non-CVD deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age-adjusted RR</td>
<td>Adjusted† RR</td>
<td>(95% CI)</td>
<td>Age-adjusted RR</td>
</tr>
<tr>
<td>&lt;4.0* (1,236)†</td>
<td>1.0</td>
<td>1.0</td>
<td>(0.9–1.6)</td>
<td>1.0</td>
</tr>
<tr>
<td>4.0–4.2 (2,156)</td>
<td>1.3</td>
<td>1.2</td>
<td>(1.0–1.6)</td>
<td>1.5</td>
</tr>
<tr>
<td>4.3–4.5 (2,017)</td>
<td>1.4</td>
<td>1.2</td>
<td>(1.0–1.8)</td>
<td>1.5</td>
</tr>
<tr>
<td>4.6–4.8 (1,103)</td>
<td>1.5</td>
<td>1.4</td>
<td>(0.8–1.4)</td>
<td>1.4</td>
</tr>
<tr>
<td>4.9–5.1 (498)</td>
<td>1.4</td>
<td>1.4</td>
<td>(1.2–1.7)</td>
<td>1.4</td>
</tr>
<tr>
<td>5.2 (251)</td>
<td>2.0</td>
<td>1.7</td>
<td>(1.2–2.6)</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Test for trend (p-value)

- Total mortality: <0.0001
- CVD deaths: 0.02
- Cancer deaths: 0.09
- Other non-CVD deaths: 0.08
- Cancer deaths: NS
- Other non-CVD deaths: NS

* Reference category.
† Numbers in parentheses, number of deaths.
‡ Adjusted for age, social class, smoking, alcohol intake, body mass index, physical activity, systolic blood pressure, cholesterol, forced expiratory volume in 1 second, heart rate, and blood glucose.
§ CI, confidence interval; NS, not significant.

cardiovascular mortality, the increased risk of 1.5 was attenuated to 1.3.

**Smoking, serum potassium level, and total mortality**

Smoking showed a strong association with serum potassium. The proportion of current smokers increased progressively with increasing potassium levels: 27 percent, 33 percent, 39 percent, 42 percent, 44 percent, 55 percent, and 61 percent for the seven potassium groups, respectively. We therefore examined the all-cause mortality pattern separately for current smokers and nonsmokers (figure 3), adjusting for age, social class, alcohol intake, body mass index, physical activity, systolic blood pressure, cholesterol, FEV\textsubscript{1}, heart rate, blood glucose, preexisting ischemic heart disease, and diabetes. In nonsmokers, mortality tended to increase with increasing potassium levels up to 4.6 mmol/liter, beyond which risk was similar to that for persons with levels less than 4.0 mmol/liter. The lack of association seen in the higher serum potassium group may be associated with small numbers of subjects, since only 96 nonsmoking men had levels ≥ 5.2 mmol/liter. Among current smokers, men with potassium levels ≥ 5.2 mmol/liter showed nearly a twofold increase in risk of total mortality (RR = 1.7, 95 percent CI 1.2–2.5) compared with all smokers with levels less than 5.2 mmol/liter. Hyperkalemic smokers had only a slightly higher prevalence of heavy smoking (≥21 cigarettes/day) than nonhyperkalemic smokers (40 percent vs. 35 percent), and adjustment for the number of cigarettes smoked per day made little difference in the increased risk. The number of nonsmokers with levels ≥ 5.2 mmol/liter was small, and a test for interaction made to assess whether the relation between raised potassium and all-cause mortality differed by smoking status yielded a p value of 0.09.

In current smokers, hyperkalemia was associated with a significant increase in the risk of deaths due to cancer (RR = 1.8, 95 percent CI 1.0–3.2) and other noncardiovascular causes (RR = 2.5, 95 percent CI 1.1–5.6) in comparison with those with levels under 5.2 mmol/liter. This was seen even after further adjustment for number of cigarettes smoked per day. For cardiovascular mortality, hyperkalemia was associated with a nonsignificant 1.3-fold increase in risk. Among nonsmokers, no association was seen between hyperkalemia and mortality from any cause.

**Smoking, hyperkalemia, and noncardiovascular mortality**

As an illustration of the combined effects of smoking and hyperkalemia on mortality due to noncardiovascular causes, table 4 shows the adjusted relative risks for mortality in hyperkalemic men (≥5.2 mmol/liter) by current smoking status (nonsmoking men with potassium levels less than 5.2 mmol/liter were used as the reference group). In the nonsmokers, as indicated above, there was no increase in mortality from any cause in hyperkalemic men. Compared with nonsmokers with potassium levels less than 5.2 mmol/liter, current smokers with levels less than 5.2 mmol/liter showed a significant 1.6-fold increase in risk of cancer death and a threefold increase in risk of lung cancer death. In smokers with potassium levels ≥ 5.2 mmol/liter, the risk of death due to all cancers increased to threefold, and for lung cancer the risk was sixfold. Current smokers with potassium levels less than 5.2 mmol/liter showed only a small increase in other noncardiovascular deaths compared with nonsmokers with potassium levels less than 5.2 mmol/liter, but smokers with levels less than 5.2 mmol/liter showed nearly a threefold increase in risk. The significantly increased risks of death due to cancer and other noncardiovascular mortality were seen even when early deaths (<5 years of follow-up) were excluded.

**Men in antihypertensive treatment**

There were 374 men receiving antihypertensive therapy. Among these men, there were 112 deaths...
TABLE 4. Adjusted* relative risk (RR) of mortality from all causes, cancer, and other noncardiovascular disease (CVD) causes in smokers and nonsmokers with elevated (>5.2 mmol/liter) serum potassium levels: British Regional Heart Study, 1978-1991

<table>
<thead>
<tr>
<th>Serum potassium (mmol/liter)</th>
<th>Nonsmokers</th>
<th>Smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 4,149</td>
<td>n = 154</td>
</tr>
<tr>
<td>&lt;5.2</td>
<td>2348</td>
<td>154</td>
</tr>
<tr>
<td>≥5.2</td>
<td>252</td>
<td>252</td>
</tr>
<tr>
<td>Total mortality</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>All cancer deaths</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Lung cancer deaths</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Other non-CVD deaths</td>
<td>1.0</td>
<td>1.4</td>
</tr>
<tr>
<td>RR</td>
<td>0.8</td>
<td>1.6</td>
</tr>
<tr>
<td>95% CI*</td>
<td>0.4-1.9</td>
<td>1.3-1.9</td>
</tr>
<tr>
<td>RR</td>
<td>0.3</td>
<td>1.6</td>
</tr>
<tr>
<td>95% CI*</td>
<td>0.05-2.5</td>
<td>1.2-2.1</td>
</tr>
<tr>
<td>RR</td>
<td>0</td>
<td>3.1</td>
</tr>
<tr>
<td>95% CI*</td>
<td>1.9-5.0</td>
<td>1.8-5.6</td>
</tr>
<tr>
<td>RR</td>
<td>1.4</td>
<td>3.1</td>
</tr>
<tr>
<td>95% CI*</td>
<td>0.9-1.9</td>
<td>2.7-15.8</td>
</tr>
</tbody>
</table>

* Adjusted for age, social class, smoking, alcohol intake, body mass index, physical activity, systolic blood pressure, preexisting ischemic heart disease, history of diabetes, cholesterol, forced expiratory volume in 1 second, heart rate, and blood glucose.
† Reference category.
‡ CI, confidence interval.

from all causes—a mortality rate of 30.2/1,000 person-years, over three times the rate observed in the rest of the study population. In these men, 86 deaths were attributed to cardiovascular causes. Figure 4 shows the mortality rates for all-cause, cardiovascular, and noncardiovascular deaths in each of the seven potassium groups. No excess deaths were seen in persons with low potassium levels. Although the number of men with potassium levels ≥ 5.2 mmol/liter was small, these men had high mortality rates from both cardiovascular and noncardiovascular causes. The all-cause mortality rates tended to increase with increasing potassium levels, even after adjustment for the other risk factors (test for trend: p = 0.03).

DISCUSSION

It is generally recognized that severe hypokalemia and severe hyperkalemia are life-threatening events (18, 19). Mild hypokalemia is a common consequence of diuretic treatment, and diuretic-induced hypokalemia has been linked to cardiac arrhythmia (1-4). There has been concern that mild hypokalemia may increase mortality, but in this cohort of middle-aged men there was no evidence that a low potassium level (<3.7 mmol/liter) was associated with increased risk of mortality either with or without hypertensive treatment. This is consistent with the earlier report from the Glasgow Blood Pressure Clinic Study of treated hypertensives (6). In the present study, mortality was significantly increased only in the small group of men with potassium levels ≥ 5.2 mmol/liter, affecting approximately 2.5 percent of the study population. This effect was seen even after adjustment for smoking and a wide range of confounding factors in multivariate analysis, and was due largely to a significant increase in noncardiovascular mortality.

In the MRC Mild Hypertension Trial, a high serum potassium level at entry into the trial was significantly associated with all-cause mortality and with coronary events (20). Other evidence for the effect of hyperkalemia on mortality has been confined to patients admitted to hospital in whom hyperkalemia (≥6.0 mmol/liter on one occasion and ≥5.5 mmol/liter subsequently) was more marked and often associated with the presence of other clinical diseases, particularly impaired renal function (7). In the present study, the range of potassium values associated with increased mortality was 5.2-6.0 mmol/liter, levels regarded as just beyond the normal clinical range. Evidence of
renal impairment (blood urea ≥10 mmol/liter) in our study was uncommon, and none of the men with a raised potassium level (≥5.2 mmol/liter) had evidence of renal impairment.

Smoking and hyperkalemia

The strong relation observed here between smoking and potassium is particularly important, and although the relation was statistically independent of cigarette smoking in multivariate analysis, there was evidence of an interaction with cigarette smoking. The increased risk of noncardiovascular mortality seen for both cancer and other causes in hyperkalemic men was present only among smokers. The association between smoking and potassium is not well documented, but smoking appears to have been one of the strongest determinants of potassium levels in this study. A dose-response relationship was seen with increasing numbers of cigarettes smoked per day, and ex-smokers showed only slightly higher levels than those who had never smoked, indicating that the effect of smoking on serum potassium level is reversible. Nearly two thirds of the hyperkalemic men (≥5.2 mmol/liter) were current smokers, and these men showed a markedly increased risk of mortality from cancer, particularly lung cancer.

In a 1-year follow-up study of hyperkalemic patients in hospital (7), it was also observed that cancer diagnoses occurred more commonly in the hyperkalemic men than in controls. This raises the possibility that severe lung pathology, particularly cancer, raises the serum potassium level. It is unlikely that the increased risk of cancer death is due to a preclinical cancer’s raising the potassium level, since the relation was even stronger when early deaths (<5 years of follow-up) were excluded from analysis.

The potassium-mortality relation might be thought to reflect smoking intensity. However, cadmium concentration, which is a strong marker of smoking and which was seen to increase with increasing potassium level, did not show any relation with mortality in smokers, unlike the case for potassium. Although the prevalence of heavier smoking increased slightly with increasing potassium level and this is consistent with the increase in cadmium concentration, the significantly increased risk of mortality was seen even after adjustment for number of cigarettes smoked per day. Furthermore, in men not receiving antihypertensive treatment, the potassium-mortality relation was seen only for noncardiovascular deaths and was only evident in men with potassium levels ≥5.2 mmol/liter. If elevated potassium was merely reflecting smoking intensity, one might have expected to see a more "linear" relation, and a relation with cardiovascular mortality as well.

These findings suggest that the increased risk among hyperkalemic smokers is not merely reflecting smoking intensity. We are left with the possibilities that 1) smoking-induced hyperkalemia has adverse effects, 2) hyperkalemia may be a marker for some other effect of cigarette smoking on mortality, or 3) hyperkalemia could be a marker for some other problem or behavior commonly found among smokers.

Men receiving antihypertensive treatment

The known influence of antihypertensive drugs in lowering potassium levels was also seen in this study. Only 5 percent of the men in this study reported undergoing antihypertensive treatment, and the majority of these men reported being on beta-blockers. Our study was not designed to examine in detail the influence of hypokalemia among men in treatment, but there was no evidence that low potassium in this group of men was associated with increased risk. Potassium levels ≥5.2 mmol/liter were also shown to be associated with markedly increased mortality from all causes in these men.

Artifacts of measurement

Potassium level in this study was measured using serum samples. Artifacts can occur with measurements made in this way, since potassium leaks from cells into the serum during coagulation of blood. The process occurs after the blood sample is taken, and it is prevented by the addition of heparin (21). It leads to levels of potassium which are higher in serum than in plasma (22), and the extent of this difference is a measure of the magnitude of the leak. When the leakage is large, the condition is referred to as "pseudohyperkalemia" (21, 23). Also contributing to a difference of potassium in serum and plasma is a decline of potassium in samples of anticoagulated blood awaiting centrifugation and separation of plasma (24). Pseudohyperkalemia is usually seen among patients with serious illness—myeloproliferative disorders, renal failure, and thrombocytosis (7, 21, 23, 25). It is unlikely that an artifact of this sort explains the increased mortality observed here in the subjects with high serum potassium, since none of them had advanced disease at the time of blood sampling and the relation between potassium and risk persisted when deaths occurring within the first 5 years of follow-up were excluded from the analysis.

A second possibility is that cigarette smoking increases the leakage of potassium from cells. Coagulation mechanisms are certainly altered by smoking
(26), but there are few reports on the relation between smoking and potassium leakage from cells. However, in the Renfrew Study (27), where potassium was measured in plasma samples that were centrifuged within 2 hours of venipuncture, mean plasma potassium was significantly higher in smokers than in nonsmokers (4.18 mmol/liter vs. 4.07 mmol/liter), and, as in the present study, a dose-response gradient of smoking against plasma potassium was seen (D. Hole, D. G. Beevers, and V. Hawthorne, personal communication, 1995). The similarity between these observations and ours makes it very unlikely that our findings are explained by a greater artifactual leak of potassium from cells in cigarette smokers.

Conclusion

In this prospective study of middle-aged British men, there was no evidence that a low serum potassium level is associated with increased mortality in men either receiving or not receiving antihypertensive treatment. Serum potassium levels $\geq 5.2$ mmol/liter in the presence of cigarette smoking were associated with a significant increase in mortality, particularly noncardiovascular deaths, even after adjustment for potentially confounding factors. These findings suggest that raised potassium levels in association with smoking have an influence on the risk of death from noncardiovascular disease, particularly lung cancer. Another possibility is that the relation with potassium is indirect and that potassium is a marker for some other risk factor associated with cigarette smoking. The prognostic and therapeutic implications of these observations warrant further exploration.

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