Cognitive Impairment, Drug Use, and the Risk of Hip Fracture in Persons over 75 Years Old: A Community-based Prospective Study

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The authors examined the effects of cognitive function, as assessed by the Mini-Mental State Examination, and drug use on the incidence of hip fracture in a community-based Swedish population of 1,608 subjects who were aged ≥75 years on October 1, 1987, and who had not had a hip fracture. During the 7,123.8 person-year follow-up, 134 first hip fractures were identified. The Cox proportional hazards model was used to estimate the relative risk of developing hip fracture, taking into account several potential confounders. Compared with those without cognitive impairment, subjects with mild impairment (Mini-Mental State Examination scores 18–23) had a relative risk of 2.04 (95% confidence interval (CI) 1.29–3.24), and subjects with moderate-severe impairment (Mini-Mental State Examination score <18) had a relative risk of 2.09 (95% CI 1.17–3.72). Subjects using opioid analgesics (97% took propoxyphene) had a relative risk of 2.01 (95% CI 1.19–3.40). Taking potassium supplements (99% took potassium chloride) was related to a reduced risk of hip fracture (relative risk = 0.55, 95% CI 0.31–0.98), while diuretics did not have an independent impact. In summary, the results show that cognitive impairment and use of propoxyphene are associated with increased risk of hip fracture. The observed protection of potassium chloride merits further attention. The limitation of the study was that the assessment of drug use was made only at baseline. Am J Epidemiol 1998;148:887–92.

cognition; hip fractures; potassium; propoxyphene

The incidence of hip fracture increases sharply after the age of 70 years (1). It is still unclear which factors are mainly responsible for this exponential increase. It is well known that osteoporosis is one underlying cause of hip fracture (1, 2). However, bone density is already below the fracture threshold for most elderly (3), and more than 90 percent of hip fractures are the result of a fall (1, 4). Therefore, prevention of falls may be the most promising way to prevent fractures (1), particularly considering the difficulty and cost of prevention and treatment of osteoporosis (5). Cognitive impairment is a risk factor for falling (6, 7), and it may also affect bone density in indirect ways (8, 9). As cognitive impairment is common in the very elderly (10), it is important to know to what extent cognitive impairment may contribute to the occurrence of hip fracture in this age group. Such knowledge may help in future preventive strategies.

Elderly people are more prone to an adverse reaction to drugs, because of pharmacokinetic changes that may increase the level and duration of action of many drugs and because of pharmacodynamic changes that often lead to increased sensitivity to drugs (11). In addition, elderly people use more medicines than younger people. For example, 8 percent of the Swedish population who are aged more than 75 years consume 18 percent of the medicines (12). Several drugs have been implicated as risk factors for hip fracture, but few prospective studies have been performed to support these links. Some of the drugs that have been shown in case-control studies to increase the risk of hip fracture are psychotropics (13, 14), cyclic antidepressants (15), long elimination half-life benzodiazepines (16), and opioid analgesics (17). Some of the drug groups that may decrease the risk of hip fracture include estrogens (1), vitamin D3 and calcium (1), and thiazide diuretics (18).

We conducted a prospective study on risk factors for hip fracture in a geographically defined cohort of people aged 75 years and older, examining especially the possible effects of cognitive function and drug use on the incidence of hip fracture.

MATERIALS AND METHODS

Study population

All inhabitants of the Kungsholmen district of Stockholm who were aged 75 years and older on...
October 1, 1987, were invited to participate in a comprehensive survey about aging and health (19). The main purpose of the survey was to screen for dementia and create a base for longitudinal observation of age-related disorders. Of the eligible subjects, 1,810 (77 percent) were interviewed between October 1987 and April 1989, and 1,608 subjects who had not had a hip fracture were included in this study. The follow-up for hip fracture was performed through December 31, 1993.

Baseline data collection

Cognitive function was assessed by the Mini-Mental State Examination (20). It is a brief cognitive test that is commonly used for screening dementia (21). It measures several domains of cognitive function, yielding a possible total score from 0 (worst) to 30 (best) points. A score of less than 24 was considered as cognitive impairment, with 18–23 as mild impairment and less than 18 as moderate-severe impairment (22–24). Functional limitation was assessed according to the Katz index of independence in activities of daily living (25). The subjects were asked questions regarding their ability to bathe, dress, toilet, transfer, maintain continence, and feed. Any dependent performance in any item of these activities was recorded as limitation in the activities of daily living.

Information on drug use was collected for the 2 weeks preceding the interview (26). All drug use variables were treated as dichotomous; that is, subjects were considered to be taking a drug if the drug had been used at any time in the 2 weeks before the interview regardless of the information about drug use before or after these 2 weeks. Both prescription drug use and nonprescription drug use were asked about, and drug containers or prescription forms were inspected to check this information. If medication was administered by caregivers or health care personnel, they were asked about the participant drug use, and medical records were consulted. The data of drug use were classified according to the Anatomical Therapeutic Chemical classification system (27).

Institutions included nursing homes, homes for the elderly, long-term wards, and mental hospitals. A simple question was asked about visual problems (yes or no). When the subject was unable to provide reliable information, as assessed by the response to the first few items of the questionnaire and to all items of the Mini-Mental State Examination, a proxy respondent (relative, caregiver, or other) was required. Data on 8 percent of the subjects were obtained from the proxy.

Ascertainment of cases

We identified hip fracture cases (International Classification of Diseases, Ninth Revision (ICD-9), code 820) through the computerized inpatient register system, which included identification number, name, address, hospitals, dates of admission and discharge, and diagnoses for each patient. This system covers all hospitals in the Stockholm area and was started in 1969. There are no private hospitals that treat patients with hip fracture in this area. A previous study has estimated that less than 2 percent of hip fracture cases may not be recorded in the registry before 1981 (28). The incident date was considered to be the date of first admission due to hip fracture. The medical records were reviewed, and the diagnoses were verified. We did not exclude the cases of hip fracture with pathologic origin. However, we did adjust for the history of tumor in the analyses. Deaths were noted through the Swedish national civil registration and regular contacts with the subjects or their relatives. History of stroke (ICD-9 codes 430–438) or tumor (ICD-9 codes 140–239) was traced using the same data source.

Analysis

The follow-up time was determined from the date of baseline interview to the date of death, or the first hip fracture event, or December 31, 1993. Incidence rates were calculated by dividing the number of events by the number of person-years of follow-up according to sex and entry age. We used the Cox proportional hazards model to examine the univariate and multivariate effect of each potential risk factor for hip fracture. The effect was expressed as the relative risk, which would be considered significant if the 95 percent confidence interval does not overlap 1. Each group of drugs used by more than 10 persons was examined, but the results of only the drugs reported to be related to hip fracture in the literature are presented.

RESULTS

The mean age at entry was 82 (range, 75–101) years. During the 7,123.8 person-year follow-up, 134 first hip fractures were identified, giving the overall incidence of 18.8 per 1,000 person-years. The incidence of hip fracture increased with age and female sex (table 1). The mean follow-up interval was 4.4 years, with a maximum of 6.3 years.

Cognitive function and covariables

Both mild and moderate-severe cognitive impairment were associated with increased risk of hip fracture (table 2). There was a linear trend between increase in the Mini-Mental State Examination score (as a continuous variable) and decrease in the risk of hip fracture (adjusted relative risk (RR) = 0.96, 95 percent confidence interval (CI) 0.93–0.99). A history of any...
risk of developing hip fracture (table 3). Taking nonopioid analgesics or nonsteroidal anti-inflammatory products was not significantly related to the occurrence of hip fracture. Controlling for these two variables did not modify the effect of opioid analgesics. No significant interaction between the use of opioid analgesics and cognitive impairment was observed.

Taking potassium supplements (99 percent took potassium chloride) or nonthiazide diuretics was related to significantly reduced risk of hip fracture, while taking thiazide diuretics was not related to the occurrence of hip fracture (table 3). About 48 percent (205 of 431) of the subjects receiving nonthiazide diuretics were taking potassium preparations, but only 18 percent (30 of 165) of the subjects taking thiazide diuretics also used potassium preparations. As compared with those not taking diuretics and potassium preparations, subjects receiving both diuretics and potassium preparations had a significantly reduced risk of hip fracture (adjusted RR = 0.53, 95 percent CI 0.29–0.98), and subjects receiving potassium-sparing diuretics had a relative risk of 0.74 (95 percent CI 0.42–1.31), while subjects taking non-potassium-sparing diuretics but not taking potassium preparations had a relative risk of 1.10 (95 percent CI 0.66–1.85).

Among the 209 subjects who used benzodiazepines, 55 took long elimination half-life benzodiazepines (16). The relative risk was not significant for benzodiazepines as a whole (table 3) or for long half-life benzodiazepines. No significant relation was found for use of neuroleptics or taking hypnotic and sedative drugs.

Few people took insulin, calcium, estrogen preparations, or antidepressants. No significant results were obtained for these drugs (table 3).

A forward stepwise Cox model

We used a forward stepwise Cox model to document five major predictors of hip fracture (table 4). Age in years (RR = 1.09), female sex (RR = 2.35), a history of tumor (RR = 1.80), cognitive impairment (mild: RR = 2.04; moderate-severe: RR = 2.09), and use of opioid analgesics (RR = 2.01) were associated with a significantly increased risk of hip fracture, while the use of potassium supplements (RR = 0.55) was related to a significantly reduced risk of hip fracture. However, limitation in the activities of daily living and use of nonthiazide diuretics were not statistically entered into the final model.

Additional analyses

We did not include body mass index in the Cox models because of incomplete information. However, we did compare the mean values in several groups.


<table>
<thead>
<tr>
<th>Drug use</th>
<th>ATC* code</th>
<th>% (n= 1,608)</th>
<th>Relative risk†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin preparations</td>
<td>A10A</td>
<td>0.6</td>
<td>1.28 (0.17–9.56)†</td>
</tr>
<tr>
<td>Oral antidiabetics</td>
<td>A10B</td>
<td>3.2</td>
<td>0.90 (0.33–2.47)</td>
</tr>
<tr>
<td>Calcium preparations</td>
<td>A12A</td>
<td>1.5</td>
<td>0.52 (0.07–3.72)</td>
</tr>
<tr>
<td>Potassium preparations</td>
<td>A12B</td>
<td>14.7</td>
<td>0.56 (0.31–0.99)</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>C03A</td>
<td>10.3</td>
<td>1.10 (0.65–1.87)</td>
</tr>
<tr>
<td>Nonthiazide diuretics</td>
<td>C03B, C, D, E</td>
<td>26.8</td>
<td>0.65 (0.42–0.99)</td>
</tr>
<tr>
<td>Estrogens</td>
<td>G03C§</td>
<td>2.5</td>
<td>0.21 (0.03–1.53)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>D07, H02</td>
<td>5.3</td>
<td>0.55 (0.20–1.50)</td>
</tr>
<tr>
<td>Nonsteroidal antiinflammatory products</td>
<td>M01A</td>
<td>7.8</td>
<td>1.25 (0.69–2.27)</td>
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<tr>
<td>Opioid analgesics</td>
<td>N02A#</td>
<td>6.8</td>
<td>1.79 (1.05–3.05)</td>
</tr>
<tr>
<td>Nonopioid analgesics</td>
<td>N02B, C</td>
<td>16.8</td>
<td>0.86 (0.54–1.37)</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>N05A</td>
<td>5.2</td>
<td>0.86 (0.40–1.84)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>N05BA</td>
<td>13.0</td>
<td>1.41 (0.90–2.19)</td>
</tr>
<tr>
<td>Hypnotics and sedatives</td>
<td>N05C</td>
<td>25.4</td>
<td>1.15 (0.76–1.69)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>N06A</td>
<td>1.4</td>
<td>1.75 (0.65–4.93)</td>
</tr>
</tbody>
</table>

* ATC, Anatomical Therapeutic Chemical classification system.
† Adjusted for all other variables listed in table 2.
‡ Numbers in parentheses, 95% confidence interval.
§ Only included women.
# Ninety-seven % took propoxyphene.


<table>
<thead>
<tr>
<th>Variable</th>
<th>ATC* code</th>
<th>Relative risk†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (each 1-year increment)</td>
<td>1.09 (1.06–1.13)‡</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>2.35 (1.37–4.03)</td>
<td></td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>2.04 (1.29–3.24)</td>
<td></td>
</tr>
<tr>
<td>Mild§</td>
<td>2.09 (1.17–3.72)</td>
<td></td>
</tr>
<tr>
<td>Moderate-severe¶</td>
<td>1.80 (1.17–2.77)</td>
<td></td>
</tr>
<tr>
<td>History of tumor</td>
<td>A12B</td>
<td>0.55 (0.31–0.99)</td>
</tr>
<tr>
<td>Potassium preparations</td>
<td>N02A#</td>
<td>2.01 (1.19–3.40)</td>
</tr>
</tbody>
</table>

* ATC, Anatomical Therapeutic Chemical classification system.
† Determined by Cox proportional hazards model using a forward stepwise procedure.
‡ Numbers in parentheses, 95% confidence interval.
§ Mini-Mental State Examination score 18–23.
¶ Mini-Mental State Examination score less than 18.
# Ninety-seven % took propoxyphene.

Subjects with cognitive impairment had a lower body mass index than did those without cognitive impairment. Subjects taking opioid analgesics and nonthiazide diuretics had a higher body mass index than did the corresponding reference groups. No significant difference of body mass index and serum potassium was found between those taking and not taking potassium supplements.

DISCUSSION

Cognitive impairment as a risk factor for hip fracture

In this large geographically defined cohort of people aged 75 years and over, subjects with cognitive impairment at baseline had a twofold higher risk of developing hip fracture than did those without cognitive impairment, when several other factors were taken into account. Cognitive impairment is related to hip fracture probably through increasing the risk of falls or the risk of serious sequelae of a fall (6), although not all studies have found that cognitive impairment is related to the risk of falls (29). Cognitive impairment may also indirectly affect bone density. Bone mass may decrease more rapidly in subjects with cognitive impairment because of lower weight (30) and malnutrition (31). It has been reported that calcium absorption is decreased in women with dementia (8). A recent study also suggests that vitamin D deficiency in women with mild dementia may alter the quality of bone and therefore increase the risk of fractures (9).

Opioid analgesics and the risk of hip fracture

Our data support the previous finding from a large case-control study that use of opioid analgesics (codeine and propoxyphene) may increase the risk of hip fracture (17). We found that use of opioid analgesics (propoxyphene) was associated with an 80 percent increased risk of hip fracture after adjustment for several other factors including functional status. The result may not be explained as the confounding effect of body mass index because subjects taking opioid analgesics had a higher body mass index than did those not taking opioid analgesics, and body mass index may inversely associate with hip fracture (32, 33). It seems that the result cannot be the outcome of such conditions as tumor and arthritis, which result in
the pain for which the relevant drugs were used, since the use of nonopioid analgesics or nonsteroidal anti-inflammatory products was not significantly related to the occurrence of hip fracture, and even direct adjustment for these two drug groups and history of tumor did not modify the effect of opioid analgesics. We did not include arthritis in the analyses because our data source may significantly underestimate the prevalence of arthritis. However, there is no evidence that arthritis may independently increase the risk of hip fracture (1), and also, hospitalization for arthritis was unrelated to hip fracture in this population. Even so, caution is necessary when interpreting the results, because the assessment of drug use was made only at baseline as discussed later.

**Thiazide diuretics, potassium supplements, and the risk of hip fracture**

Many (18, 34), but not all (35, 36), studies have shown that thiazide diuretics may protect against hip fracture, possibly through decreasing the urinary excretion of calcium (37) and thereby increasing the bone density (38). However, we did not observe this protection by use of thiazide diuretics. In contrast, we did find that nonthiazide diuretic agents decreased the risk of hip fracture, but the effect was fully explained by the use of potassium supplements that was independently related to a 45 percent reduced risk of hip fracture. One study that has measured the use of thiazide diuretics and bone density simultaneously has shown that the small effect of thiazide diuretics on bone density cannot account for the protective trend of thiazide diuretics for hip fracture (36). No previous studies have considered the use of potassium supplements in the analyses. There is a possibility that variation in the use of potassium supplements may explain the inconsistent results about the benefit of thiazide diuretics (18, 34–36). However, subjects taking potassium supplements may differ in many aspects from those not taking potassium supplements. It is possible that our results have been biased by other factors that we did not measure and also by the single measurement of drug use. Nevertheless, it is necessary to reexamine the effect of thiazide diuretics on the risk of hip fracture in other populations, taking into account the use of potassium supplements.

**Other risk factors for hip fracture**

In accordance with previous studies (1, 39–41), our univariate analyses showed that a history of tumor, visual problems, and limitation in the activities of daily living were related to increased risk of hip fracture. However, the effects of visual problems and limitation in the activities of daily living were explained mainly by other variables, such as age, sex, and cognitive impairment. Although we did not obtain significant results for the use of insulin, calcium, estrogen preparations, antidepressants, or long half-life benzodiazepines, all relative risks for these variables are in the same direction as those of previous studies (1, 15, 16). Use of hypnotic and sedative drugs was not related to the occurrence of hip fracture, which is similar to the results of a recent study (42).

**Limitations of the study**

The major limitation of our study is that only baseline information was collected. Drug use may change frequently in elderly people. Although such assessment of exposure generally decreases the power to detect a given association, we cannot rule out the possibility that the misclassification of drug use has already biased our results. This should be considered when interpreting the results. However, on the other hand, our results about the use of opioid analgesics and potassium supplements may reflect the strong relation between the use of these two groups of drugs and hip fracture, and they may also suggest that these drugs were used chronically in this population. In addition, we may also have significantly underestimated the effect of cognitive impairment, as a proportion of the subjects who were cognitively intact at baseline would become cognitively impaired during the follow-up period.

There are potential confounders that were not included in our study. We did not measure bone density. However, we believe that both cognitive impairment and the use of opioid analgesics increase the risk of hip fracture mainly through increasing the risk of falls, although the independent effect of cognitive function on the risk of falls has not been consistently confirmed (29). Body mass index may be inversely associated with hip fracture (32, 33). Comparison of body mass indices between those using and not using opioid analgesics and potassium supplements suggests that body mass index cannot explain the effect of opioid analgesics and potassium supplements.

**Conclusions**

The incidence of hip fracture is high among very old Swedish people. The risk of hip fracture in this population can be predicted by a brief cognitive test, such as the Mini-Mental State Examination (20). In our prospective study, we found that use of opioid analgesics (propoxyphene) increases the risk of hip fracture, probably by increasing the risk of falls (17). The finding that taking potassium supplements (potassium...
chloride) is related to a 45 percent reduced risk of hip fracture deserves further evaluation.

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