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ORIGINAL ARTICLE

Thiazide Use Is Associated With Reduced Risk for Incident Lower Extremity Fractures in Men With Spinal Cord Injury

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Abstract

Objective: To determine the association between thiazide use and lower extremity fractures in patients who are men with a spinal cord injury (SCI).

Design: Cohort study from fiscal years 2002 to 2007.

Setting: Medical centers.

Participants: Men (N=6969) with an SCI from the Veterans Affairs (VA) Spinal Cord Dysfunction (SCD) Registry, including 1433 users of thiazides and 5536 nonusers of thiazides.

Intervention: Thiazide use versus nonuse.

Main Outcome Measure: Incident lower extremity fractures.

Results: Among the men, 21% in the VA SCD Registry (fiscal years 2002−2007) included in these analyses used thiazide diuretics. There were 832 incident lower extremity fractures over the time period of this study: 110 fractures (7.7%) in 1433 thiazide users and 722 fractures (13%) in 5536 nonusers of thiazides. In unadjusted and adjusted models alike, thiazide use was associated with at least a one-quarter risk reduction in lower extremity fracture at any given point in time (unadjusted: hazard ratio (HR)=.75; 95% confidence interval (CI), .59−.94; adjusted: HR=.74; 95% CI, .58−.95).

Conclusions: Thiazide use is common in men with SCI and is associated with a decreased likelihood for lower extremity fractures.

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Traumatic spinal cord injury (SCI) affects between 12.1 and 57.8 individuals per 1 million people annually on a worldwide basis.[1] Substantial sublesional bone loss occurs after SCI,[2] and these patients are at risk for osteoporotic fractures.[3-5] However, there is no consensus regarding the best pharmacotherapeutic agents or rehabilitative strategies to prevent or treat osteoporosis in patients with SCI.[6,7] Most importantly, to date, no intervention[3-5,8] has been shown to prevent fractures in this population.

The absence or decrease of lower limb weight bearing in patients with SCI clearly plays a major role in SCI-related osteoporosis.[9] However, the pathophysiology of SCI-related osteoporosis is complex and differs from senile or simple disuse osteoporosis.[10] Increased renal elimination and reduced intestinal absorption of calcium occur in SCI-related osteoporosis.[10]

In persons without SCI, thiazide diuretics decrease calcium excretion, and higher calcium excretion is associated with lower bone mineral density.[11] Additionally, in observational studies in

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patients without SCI, thiazide use has been associated with lower rates of hip fractures.[12] However, the relation of thiazide use to osteoporosis in persons with SCI has not been studied, to our knowledge. We hypothesized that thiazide use might be associated with fewer fractures in patients with SCI because negative calcium balance is a component of SCI-related bone loss.[10]

The objective of this study was to determine whether thiazide use was associated with a lower risk for fractures among men with SCI.

Methods

All men included in the Veterans Affairs (VA) Spinal Cord Dysfunction (SCD) Registry from fiscal year (FY) 2002 to FY 2007 with a traumatic SCI of at least 2 years duration were eligible for the analyses. The VA SCD Registry is a clinical administrative database maintained by individual VA medical centers to track the population of veterans with SCI followed by each center, and these data are aggregated at a national level.[13] The date of onset of SCI was obtained from the VA SCD Registry data; of those with a missing date of onset, only those with at least 2 years of SCI care documented were included. Trauma was defined as acts of violence, falls, sports activity, and motor vehicular etiologies, as per the VA SCD Registry data. Diagnoses were determined using the VA Medical Statistical Analysis System (SAS) Inpatient Datasets and the Outpatient Care File.

Lower extremity fractures that occurred between FY 2002 and FY 2007 were defined using *International Statistical Classification of Diseases, 9th revision* (ICD-9) codes for fractures of the lower extremity, including femoral neck (820.xx), intertrochanteric (820.21, 820.31), subtrochanteric (820.22, 820.32), pelvis (808.xx), femur (820.xx, 821.xx), patella (822.xx), and tibia/fibula (823.xx). Only incident fractures were included. A fracture was considered an incident (ie, new episode of fracture and not coding of follow-up care for a prior fracture) if there were no encounters with the same 3-digit ICD-9 fracture code within a 120-day time period prior to the fracture.[14]

The study was approved by the VA Institutional Review Boards at the investigators' sites, and the study procedures were done in accord with the ethical standards of the VA Institutional Review Boards.

Thiazide use

Thiazide use was defined as any use prior to the incident fracture within FY 2002 to FY 2007 captured from the VA Decision Support System pharmacy prescription database.[15] Duration of thiazide use prior to the incident fracture was categorized as <6 months, 6 months to ≤1 year, 1 to ≤2 years, 2 to ≤3 years, and >3 years of use.[16] History of hypertension (uncomplicated and complicated) was obtained from the VA SCD Registry data and the SAS Medical Datasets.

Covariates

Age, race, duration, level, and completeness of SCI were obtained from the VA SCD Registry data and the SAS Medical Datasets. To adjust for differences in comorbidities in the thiazide users and nonusers, which might explain differences in fracture rates, Charlson comorbidity indices were also calculated per individual. Indices were calculated from comorbidities present 1 year prior to study entry (FY 2002) or 2 years prior to study entry for those missing health care utilization the first year prior and were aggregated into a single Charlson comorbidity index. The Charlson index component hemiplegia/tetraplegia was excluded from the aggregate index, and the level of SCI (paraplegia/tetraplegia, as previously indicated) was explicitly included in the analyses as a separate explanatory variable. For those missing health care utilization within 2 years of the study start (n = 125), the median imputation of Charlson comorbidity indices was explored for these individuals.

Medication use that may be associated with fracture risk (including heparin,[17] corticosteroids,[18] loop diuretics,[19] opioids,[20] proton pump inhibitors,[21] selective serotonin reuptake inhibitors [SSRIs],[22] anticonvulsants, benzodiazepines [BZDs],[23] thiazolidinediones,[24] calcium and vitamin D supplements[25]), prescribed at any time between FY 2002 and FY 2007, was included as a covariate. Patient medication usage was identified from the VA pharmacy dispensing data and was represented similar to thiazide use as a dichotomous time-dependent variable per 6-month time interval from patient entry into the study. We excluded those who were already taking a pharmacologic therapy for osteoporosis (teriparatide, bisphosphonates, calcitonin) from the primary analyses.[25] The time period for the covariate selection (other than the Charlson comorbidity index and medication use) was the first encounter during the study period.

Statistical analysis

From the 7447 men in the VA SCD Registry from 2002 to 2007, we excluded 478 who had received pharmacologic therapy for osteoporosis. This left 6969 men who were included in all analyses. These 6969 men included 1433 users of thiazides and 5536 nonusers of thiazides.

Fracture risk was analyzed using time-to-event analysis, including thiazide use as a dichotomous time-dependent variable, per 6-month time intervals. The event of interest was the first lower extremity fracture in the study period. Endpoints were censored for death, 6 months with no utilization from last known VA encounter, or end of study period (2010), as appropriate.

Univariate analyses of baseline characteristics for thiazide users compared with nonusers included chi-square tests for categorical variables and *t* tests for continuous variables. Associations between lower extremity incident fractures and potential confounding variables were investigated via multivariate Cox regression models. We chose to include all variables regardless of statistical significance in the final fully adjusted model because a priori all were thought to be of clinical significance.

List of abbreviations:

BZD	**benzodiazepine**
CI	**confidence interval**
FY	**fiscal year**
HR	**hazard ratio**
ICD-9	***International Statistical Classification of Diseases, 9th revision***
SAS	**Statistical Analysis System**
SCD	**Spinal Cord Dysfunction**
SCI	**spinal cord injury**
SSRI	**selective serotonin reuptake inhibitor**
VA	**Veterans Affairs**