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Original Article

The Relationship of Serum Serotonin Levels to the Rate of Bone Loss and Fractures in Men

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Abstract

Recent genetic studies in rodents have revealed that circulating serotonin plays a key role in regulating bone formation and skeletal mass. However, the reported effects of circulating serotonin on bone mass in humans have been conflicting. We determined whether circulating serotonin levels influenced the rate of bone loss and fractures in men. We assessed the effect of serum serotonin on bone loss rate in a population-based cohort of 202 ambulatory men aged 56–70 years who were followed up for a median duration of 3.7 years. Serum serotonin levels were assayed, and the Timed Up and Go Test (TUGT) was performed, at baseline. Dual-energy X-ray absorptiometry was performed both at baseline and during follow-up. Fracture prevalence was assessed using questionnaires. The serotonin levels were inversely associated with the lumbar spine bone mineral density ($r = -0.174$, $p = 0.028$) at baseline. No association was evident between the bone mineral densities of the femoral neck or total hip and serotonin level. The annual rates of bone loss from the lumbar spine, the femoral neck, and the total hip were 0.01%, 0.46%, and 0.46%, respectively. The baseline serum serotonin level did not predict the bone loss rate in any skeletal site. Lower limb disability evident upon TUGT at baseline predicted bone loss from the total hip. No significant difference of serotonin level was observed between subjects with and without fractures. The serum serotonin level was not associated with the rate of bone loss in elderly men. Thus, the circulating serotonin level does not reliably predict bone loss.

Key Words: Bone loss; fractures; Korean; serotonin.

Introduction

Recent genetic studies in rodents have revealed that circulating serotonin (5-hydrxytryptamine, 5-HT) plays a key role in regulating both bone formation and skeletal mass *(1,2)*. Further support for an important role of serotonin in bone metabolism has come from studies on patients treated with selective serotonin reuptake inhibitors (SSRIs), which increase extracellular serotonin levels *(3,4)*. In the study of osteoporotic fractures, SSRIs, but not tricyclic antidepressants (TCA), increased hip bone loss *(3)*. Similarly, SSRIs, but not other antidepressants, were associated with reduced bone mineral density (BMD) in multiple skeletal sites of men *(4)*. However, increased levels of depression, and falls, may have confounded the SSRI data. Reports on the effects of depression and fractures on BMD have been conflicting *(5,6)*.

Mödder et al found that the serum serotonin level and the lumbar spine BMD tended to be negatively associated in postmenopausal women *(7)*. Kim et al reported that the plasma serotonin levels of 80 postmenopausal women did not correlate with the BMDs of the lumbar spine or proximal femur *(8)*. Wang et al recently found that the serum serotonin level of postmenopausal women was positively correlated with both the femoral and lumbar spine BMDs *(9)*, unlike what was noted in other studies. The observed positive association between bone density and serum

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serotonin level in postmenopausal women suggests that higher levels of serum serotonin may be beneficial in terms of bone preservation, whereas lower levels may be detrimental *(9)*. The among-study differences render interpretation of the role played by circulating serotonin in bone metabolism difficult. Thus, further population-based studies are required. Estrogen can affect the serotonergic neurotransmitter system by modulating all of serotonin synthesis, release, degradation, and receptor activation *(10)*. Two earlier studies *(7,9)* revealed that statistical significance (between serum serotonin level and BMD loss) was evident only in postmenopausal women, suggesting that estrogen may confound the relationship between circulating serotonin level and bone metabolism. Thus, in the present study, we focused on healthy men to more precisely analyze the effect of serotonin on bone density. We explored whether the circulating serotonin level influenced the rate of bone loss and fractures in an elderly population-based cohort of 180 healthy (ambulatory) men aged 56–70 years who were followed up for a median duration of 3.7 years.

Materials and Methods

Subjects

The Chungju Metabolic Disease Cohort study is an ongoing community-based evaluation of metabolic diseases including diabetes, metabolic syndrome, and osteoporosis in a population aged ≥40 years living in the rural hinterland of the city of Chungju, Korea. The first phase of the study was conducted in 2003–2006. A total of 334 districts were selected by stratified random cluster sampling and 11,718 subjects were enrolled. All were followed up at 4-year intervals in the second phase of the study (2007–2010) (the successful follow-up rate was 58%). The third phase of the study is ongoing (2011–2014). Of men who attended all follow-up appointments during the second phase (2008–2009), we excluded those with underlying diabetes mellitus, thyroid disease, cardiovascular disease, hepatitis, liver cirrhosis, any malignancy, chronic kidney disease, and rheumatoid arthritis, as well as those who had been treated for osteoporosis for over 1 month and those who had suffered stroke or who had undergone gastrectomy. All included men were aged 56–70 years. A total of 287 subjects were consecutively enrolled and serum serotonin levels were assayed in baseline blood samples. In prospective analysis, all subjects who had attended all scheduled follow-up visits in both the second phase (2008–2009; these data served as baseline data for the present analysis) and third phase of the study (2011–2014; these data were the follow-up data) were included (n = 202). The institutional review board of The Catholic University of Korea approved the study (Approval Nos. KCMC070T076 and KC13OISI0427) and written informed consent was obtained from all participants. Certain study protocols (including anthropometry) have been described in previous reports *(11,12)*.

Bone Densitometry

The BMDs of the lumbar spine (lumbar vertebrae L1–L4), the total hip, and the femoral neck were measured via dual-energy X-ray absorptiometry (Hologic QDR 4500, Waltham, MA) both at baseline and at all follow-up visits. The coefficients of variation (CVs; the CV is a measure of precision) were 1.36% for the lumbar spine and 1.5% for the total hip. The lumbar BMDs of subjects with scoliosis or lumbar osteophytes were excluded from the analysis. The annual change in BMD was calculated as follows: annual change (%) = [BMD at follow-up minus BMD at baseline] ÷ BMD at baseline ÷ follow-up time × 100.

Serum Serotonin Measurement

Serum serotonin levels were measured via a competitive enzyme-linked immunosorbent assay (Immuno-Biological Laboratories GmbH, Hamburg, Germany). The intra- and inter-assay CVs were 3.8% and 6.0%, respectively. All samples were collected between April 2008 and September 2009 after subjects had fasted for at least 12 h. Sera were divided into 0.5-mL aliquots and immediately frozen at −80°C until assayed. Samples were thawed immediately prior to assay of serotonin levels and were not re-frozen.

Physical Performance (the Timed Up and Go Test)

In the Timed Up and Go Test (TUGT), a subject is initially seated on an armless chair of standard height. When commanded to "go," the subject stands, walks 3 m, turns, walks back to the chair, and returns to the seated position. This sequence is timed *(13,14)*. The test is repeated twice, and the shortest time was recorded.

Assessment of Fractures

The fracture history, which includes age at the time of fracture, fracture location, and fracture cause, was obtained from each participant. We considered a fracture history positive if the participant had a fracture since the age of 50. We only considered prevalent fractures that occurred with minimal or no trauma (fall from standing height or less). All fractures that were considered non-osteoporotic (fractures due to an accident or cancer, and all fractures of the fingers, faces, skull, and toes) were excluded (n = 53). Subjects with missing data on prevalent fracture were excluded (n = 3).

Statistical Analysis

Data are presented as mean ± standard deviations unless stated otherwise. If necessary, logarithmic transformation was performed to attain a normal distribution. Pearson's correlation coefficients between serum serotonin levels and various other parameters were calculated. Repeated measures analysis was used to compare BMDs at baseline and at follow-up. Multiple linear regression was used to identify factors associated with the baseline BMD and the rate