Higher BMC and areal BMD in children and grandchildren of individuals with hip or knee replacement

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Introduction

Epidemiological studies have reported an association between osteoarthritis (OA) and areal bone mineral density (aBMD), with the majority of studies finding higher aBMD in individuals with OA compared to controls [1–4]. However, some studies have found no association or an inverse association [5,6]. The etiology of this relationship remains unclear, and several hypotheses have been put forth.

One possibility is that OA is primarily a disease of bone, and that stiffer bone (higher aBMD) is less deformable, leading to increased mechanical stress on cartilage during impact loading [7]. Another possibility is that the relationship between OA and osteoporosis is an indirect one, being a result of common confounders such as body weight or activity levels. For example, greater body weight could lead to increased cartilage damage, as well as increased aBMD. However, some investigators have reported a significant relationship between OA and aBMD even after controlling for these potential confounders [2,3].

Naganathan et al. compared aBMD in daughters of mothers with OA [8] and Jones et al. reported a greater bone size in children of individuals with OA [9]. Naganathan and coworkers speculated that high peak aBMD may be responsible, in part, for the development of OA. The daughter's mean age was 31 years, and it is possible that similarities in lifestyle between the mothers and daughters could have been responsible for the observed relationships.

The Hutterites are an Anabaptist religious group who believes in isolated communal living and self-sufficiency through technologically advanced agricultural based rural lifestyle. Because they live a

Abstract

The relationship between aBMD and osteoarthritis (OA) remains unclear. We compared aBMD, BMC and bone size among children and grandchildren of Hutterites with hip or knee replacement (n = 23 each) to children and grandchildren of age- and sex-matched controls (178 children and 267 grandchildren). There were no differences in anthropometric measures or activity levels between case and control probands, but femoral neck (FN) and spine (LS) aBMD and Z-scores were greater in cases than controls (0.89 vs. 0.80 g/cm²; 1.15 vs. 1.03 g/cm²; 1.5 vs. 0.8; 2.4 vs. 1.2; all p < 0.05), Hip, FN and LS aBMD (1.05 vs. 0.97, 0.92 vs. 0.84, 1.15 vs. 1.03 g/cm²), BMC (34.1 vs. 32.0, 4.58 vs. 4.27, 69.5 vs. 62.4 g) and Z-scores (1.0 vs. 0.4; 0.9 vs. 0.2; 1.3 vs. 0.2) were greater in daughters of cases than controls (hip BMC p = 0.06, others p < 0.05); there were no differences between sons. Grandchildren (aged 8–39 years) were categorized as growing (premenarcheal or male ≤14 years) or not growing (≥2 years post-menarcheal or males ≥18 years); 33 were not classified. Post-menarcheal, but not premenarcheal, granddaughters of cases had greater hip, FN and LS aBMD Z-scores (0.7 vs. −0.1; 0.6 vs. −0.1; 0.8 vs. −0.3); greater hip and spine aBMD (1.03 vs. 0.95, 1.10 vs. 0.98 g/cm²); greater femoral neck and spine BMC (4.77 vs. 4.21, 66.7 vs. 55.4 g); and greater spine bone area (60.7 vs. 56.6 cm²) compared to granddaughters of controls (all, p < 0.05), which remained significant when height, weight, and age were included as covariates. Growing grandsons of cases were taller and heavier than control grandsons, and a greater hip aBMD among grandsons of cases (0.88 vs. 0.76 g/cm²) was the only bone difference that remained significant after taking into account body size differences. Grandsons who were not growing had greater spine bone area (1.19 vs. 1.08 cm²) if their grandparent had OA compared to grandsons whose grandparents did not have OA. We speculate that there is a genetic basis for OA that leads to early differences in growth patterns among boys and greater peak bone mass and aBMD among girls.
communal lifestyle, potential confounding factors such as access to health care, would theoretically be more similar. We are currently conducting a longitudinal study of bone health among rural populations and noted that several of the Hutterite participants had hip and knee replacements, with an underlying diagnosis of OA. The objective of the current study was to compare aBMD, BMC and bone size among participating Hutterites with and without hip and knee replacements for OA, as well as the aBMD, BMC and bone size of their children and grandchildren for whom we also had bone measurements. This would allow us to determine whether children and grandchildren of OA subjects have higher aBMD or larger bone size prior to the development of OA, which would support the theory that changes in bone precede the development of OA.

Methods

Cases and controls

The South Dakota Rural Bone Health Study is a longitudinal study of bone health among rural populations aged 20–66 years, of which approximately one-third of the subjects are Hutterite (n = 586) [10]. In addition to SDRBHS participants, we obtained similar study measurements on an additional 402 Hutterites, 325 aged 8–19 years of age and 34 older than 66 years. These 988 Hutterites were all residents of one of 17 colonies located in eastern South Dakota that participated in the SDRBHS.

Study records of participating Hutterite subjects were queried to identify any individual with either a previous joint replacement at the time of enrollment or any individual having a joint replacement once they were enrolled in the study. Twenty-three individuals with hip or knee replacement were identified: 10 had single knee replacements, 5 had a single hip replacement, 3 had two knees replaced, 2 had both a knee and a hip replaced, 2 had both hips and 1 knee replaced, and 1 had both knees and a hip replaced. Medical records confirming the diagnosis of OA were obtained for nineteen of the individuals with joint replacement. Among those with medical records, there were no cases of hip or knee replacement for any reason other than OA. Two of the four cases for whom we did not have medical records passed away prior to obtaining a medical records release; the other two individuals were taking prescribed medication for arthritis. The 23 study subjects came from 17 families; one family with four sibs, one family with three sibs, one family with two sibs and 14 families with one individual with a joint replacement. Sex- and age-matched Hutterite controls were obtained by identifying a study participant closest in age to the proband case who did not have a parent or grandparent in the analyses.

Comparisons between proband cases and controls were done using Student’s t-test, chi-square, and analysis of covariance. Analyses for children and grandchildren were stratified by sex and comparison of bone outcomes was done with and without adjusting for age, height, and weight. In the instances where there were grandchildren of two cases (n = 8) or two controls (n = 4, growth status classified in 3), analyses were completed including the grandchild in the dataset only once. In the 25 instances (growth status classified in 20) where the grandchild was both a grandchild of a control and a case, the grandchild was only included as a grandchild of the case.

Results

As expected based on the selection of controls, the sex distribution and mean ages were similar among cases and controls (Table 1). There were no differences between proband cases and controls in weight, height, BMI or activity levels; among females the age at menarche and menopause were similar. Femoral neck and spine aBMD (Table 1) and Z-scores (Fig. 1) were greater in cases compared to controls. Spine (p = 0.02), but not femoral neck (p = 0.06), aBMD remained significantly greater when age, sex, height and weight were included as covariates.
The children of cases and controls had a mean age of 36 years and anthropometric measurements and activity levels were similar between cases and controls for both sons and daughters (Tables 2 and 3). There was no difference in the sex distribution between cases and controls for both sons and daughters (Tables 2 and 3). Anthropometric measurements and activity levels were similar between cases and controls in any bone measure (Table 2). Daughters of cases had greater hip, femoral neck and spine aBMD, BMC and bone area than growing control grandsons when just age was included in the analysis. However, when weight and height were included, only hip aBMD was greater in growing grandsons of cases than in controls, suggesting that bone differences at the femoral neck and spine were due to body size differences. There were no anthropometric differences between grandsons of cases and controls who were not growing (Table 2), yet spine aBMD was slightly greater in grandsons of cases than in controls even after controlling for age, weight and height (p = 0.03).

Granddaughters of cases who were still growing had similar age, weight, and BMI but were slightly taller compared to granddaughters of controls (Table 3). However, height Z-scores were similar and differences in mean heights did not remain significant when age was included in the analyses indicating that height differences were due to the small age differences between the two groups. Growing granddaughters of cases had greater femoral neck and spine BMC and bone area than granddaughters of controls, but the majority of these differences were no longer significant when age, weight, and height were included in the analysis. Only a greater spine bone area among growing granddaughters of cases compared to controls remained significant when covariates were taken into account in the analysis (p = 0.01) (Table 3). Granddaughters who were not growing were slightly heavier and taller, had less time in moderate plus vigorous activity, had lower grip strength, and had greater hip, femoral neck and spine aBMD if their grandparent was a case than if their grandparent was a control (Figs. 2 and 3). Hip and spine aBMD, femoral neck and spine BMC, and spine bone area among granddaughters of cases remained significantly greater than granddaughters of controls after including covariates.

Similar results were obtained if the cases without medical confirmation of OA and their matched controls, as well as their children and grandchildren, were omitted from the above analyses.

Discussion

We are unaware of any study that has investigated differences in aBMD Z-scores and anthropometric measurements among grandchildren of individuals with history of hip or knee replacement. We observed greater aBMD, which remained statistically significant after adjusting for age, weight, and height at some bone sites among grandchildren who were no longer growing if their grandparent had a hip or knee replacements compared to grandchildren of grandparents without a hip or knee replacement. These aBMD differences were not apparent among younger grandchildren who were still growing.

We used aBMD measurements from grandchildren of individuals with joint replacements is consistent with the study by Naganathan and coworkers who found higher hip and femoral aBMD in 60 daughters of women with hand OA compared to daughters of women without OA (mean age of 34 years) [8]. In this study, 124 women aged 50–75 years were randomly selected from a defined population (North Sydney Health Area) and were invited to participate in a study of osteoporosis and OA. The daughters of these women also were invited to participate. Naganathan and coworkers found no difference in age,

![Fig. 1. Mean hip, femoral neck, and spine aBMD Z-scores of Hutterites with history of hip or knee replacement and sex- and age-matched controls. Cases had significantly greater aBMD Z-scores than controls at the femoral neck and spine.](image-url)
Tables 2 and 3 present anthropometric and bone measurements for various generations within the proband's family. The data are means ± SEM, and statistical tests such as t-tests and ANOVA were used to compare means between different groups. Significant differences are noted by asterisks in the tables. The results suggest that certain factors, such as age, weight, and height, may influence bone density and anthropometric measurements over generations, with some patterns consistent across family members.

For a detailed understanding, please refer to the full text for a comprehensive analysis of the findings.
The cases in a population-based case–control study by Jones et al. were individuals who had undergone knee replacement for primary OA at any hospital in the capital city of Southern Tasmania (Australia) between 1996 and 2000. The controls were randomly selected individuals from Southern Tasmania who had no personal or family history of knee osteoarthritis. The offspring had a mean age of 45 years, which is slightly older than the children of our cases. Jones et al. reported greater weight, BMI and knee pain, and lower strength measures among the 188 children of OA cases compared to controls. They also investigated cartilage volume and medial tibial bone area in these offspring and found similar cartilage volume, but larger tibial bone area among the daughters of individuals with knee replacements. We did not observe a greater body size among the children of our cases compared to controls as Jones et al. reported [9], but we did find that differences in bone measures were limited to the daughters and older granddaughters with few differences among the grandsons. Jones et al. also reported sex differences, with daughters of cases having larger medial tibial bone area than controls.

The finding of lower strength measures among the older granddaughters of individuals with joint replacement is consistent with sex-specific findings of decreased strength among offspring of cases compared to controls, which theoretically should lead to decreased cartilage volume. Despite the lower activity levels and strength measures, which are typically associated with decreased aBMD, we still observed a greater aBMD among the granddaughters of cases compared to the granddaughters of controls.

The results of the current study support the speculation that higher aBMD observed in individuals with OA may be due to genetic factors that lead to early rapid growth among boys and higher peak bone mass among girls. Not only were bone differences observed in children, but also grandchildren of individuals with history of joint replacement from OA. One may expect that observed bone differences between children of cases and controls would be stronger than bone differences between grandchildren if genetic factors leading to high aBMD were a factor in the pathogenesis of OA. However, bone differences between grandchildren may be more apparent than differences among children due to a longer period of time that environmental exposures may influence bone in the children compared to the grandchildren.

Osteoarthritis in older individuals affects women two to three times more often than it affects men and our findings among sons and grandsons were markedly different than the findings among daughters and granddaughters. We found that the growing grandsons of cases were taller and heavier than grandsons of controls with a greater hip aBMD that remained significant even after taking into account body size differences. It is interesting to note that there were no body size differences between grandsons of cases and controls who were no longer growing or between the sons. We speculate based on these results that an increased growth rate early in life, or a gene or combination of genes common to both early growth velocity and OA combination of genes common to both early growth velocity and OA among males may be associated with joint replacement as an older adult. There are several genes that are reported to be associated with both growth and OA. Associations between OA and IGF-1 genotype have been previously reported [14], as well as associations with procollagen type II (COL2A1) and the vitamin D receptor gene (VDR) [15–17]. However, the influence of some of these genes, at least the IGF-1 gene, on OA have not been found to be sex-specific [15].

Our findings of higher hip, femoral neck, and spine aBMD Z-scores among daughters and post-menarcheal granddaughters of subjects with joint replacement are consistent with sex-specific differences in aBMD among individuals with OA and their offspring. Even
controlling for covariates, significant differences in the majority of bone measures of granddaughters who were no longer growing were observed and were similar to those differences seen in the daughters. The observation that bone differences were apparent in granddaughters who were at least 2 years post-menarcheal, but not in premenarcheal granddaughters, suggests a possible role of estrogen in the pathogenesis of high aBMD and OA.

The prevalence of OA among women and the development of OA symptoms around the time of menopause have lead to the speculation, as early as the 1920s, that OA was a hormonally mediated disease [18]. Results from observational cohort studies are inconsistent, with some investigators finding estrogen use to protect against OA, while others find no relationship [1,19]. Randomized trials of estrogen therapy and OA have been completed, but the results are inconclusive [20,21]. Estrogen receptors (ER-alpha and ER-beta) are expressed in both chondrocytes and bone and polymorphisms in the ERs have been shown to be associated with OA [22,23]. Bergink and coworkers suggested that there may be a greater sensitivity of ER-alpha haplotype allele PX individuals to estrogen compared with those without the PX allele [23]. This increased sensitivity may lead to increased stimulation of local bone formation and greater susceptibility to osteophyte formation, thereby explaining the association with both OA and high aBMD. The findings of high aBMD among the daughters and postmenarcheal granddaughters of individuals with hip or knee replacements is consistent with the speculation of Bergink and coworkers.

There are several limitations to the current study. First, we defined our cases on the history of joint replacement. The diagnosis of OA was confirmed by obtaining medical records for the majority of cases (83%) and omitting the cases without confirmed OA, along with their matched controls, and their children and grandchildren, did not change the results. The presence of OA, however, was not ruled out in the controls. Since access to healthcare is uniform in this population it is assumed that individuals with joint replacement had severe OA, whereas the controls, even if they had OA, were less severe cases. If some of the controls actually had OA we would expect their aBMD and that of their children and grandchildren to be more similar to cases. Second, the data are cross-sectional and we did not compare growth velocities of grandchildren of cases and controls. Obtaining longitudinal growth and bone measures on this cohort will provide us with the data to determine whether longitudinal changes are different between grandchildren of cases and controls. Although we had sufficient power to detect numerous differences between children and grandchildren of cases and controls, it is possible that we did not have sufficient sample size to detect other differences that may exist. Selection bias is often a problem in retrospective case–control studies when the controls are not from the same population as the cases. In the current analyses, the controls came from the same Hutterite colonies as the cases; the only difference was that they had not had a joint replacement. Due to the communal way of life, access to medical care is similar among all Hutterites, so there should not be a bias in who is receiving needed joint replacements and who is not.

In summary, we observed differences in growth parameters and bone measurements in children and grandchildren of individuals with joint replacement compared to children and grandchildren of sex- and age-matched controls. Body size differences were apparent among growing grandsons, while post-menarcheal bone differences among granddaughters and daughters were observed. These findings support a genetic basis for OA that leads to early differences in growth patterns among boys and greater bone mass and aBMD among girls.

Conflict of interest
All authors have no conflicts of interest.

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