Published in final edited form as:
Clin Breast Cancer. 2010 June ; 10(3): 224–229. doi:10.3816/CBC.2010.n.030.

Effects of a Structured Weight-Bearing Exercise Program on Bone Metabolism Among Breast Cancer Survivors: A Feasibility Trial

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Abstract

Purpose—Treatments for breast cancer, specifically hormonal therapy, accelerate bone loss (BL) among breast cancer survivors, leading to osteoporosis and an increase in fracture risk. Tai Chi Chuan (TCC) is a moderate form of weight-bearing exercise, equivalent to walking, and it has been shown to improve aerobic capacity and strength among breast cancer survivors and might also be effective in slowing bone loss in breast cancer survivors. This pilot study compared the influence of TCC with that of standard support therapy (ST; exercise control) on BL biomarkers among breast cancer survivors.

Patients and Methods—Randomly assigned breast cancer survivors (N = 16; median age, 53 years; < 30 months after treatment) completed 12 weeks (3 times per week, 60 minutes per session) of TCC or ST. Serum levels of *N*-telopeptides of type I collagen (NTx), a marker of bone resorption, and bone-specific alkaline phosphatase (BSAP), a marker of bone formation, were determined according to enzyme-linked immunosorbent assay at baseline and after the intervention.

Results—Using analysis of covariance, survivors in the TCC group experienced a greater increase in levels of bone formation (BSAP [μg/L]: before, 8.3; after, 10.2; change, 1.9 μg/L and 22.4%), compared with survivors in ST (BSAP [μg/L]: before, 7.6; after, 8.1; change, 0.5 μg/L [6.3%]). Survivors in the TCC group also experienced a significant decrease in bone resorption (NTx [nanomoles bone collagen equivalent; nmBCE]: before, 17.6; after, 11.1; change, −6.5 nmBCE; −36.9%), whereas women in the ST group did not (NTx [nmBCE]: before, 20.8; after, 18.8; change, −2.0 nmBCE; −9.6%).

Conclusion—This pilot study suggests that weight-bearing exercise exerts positive effects on BL, through increased bone formation and decreased bone resorption. Further examinations of the influence of TCC on bone health are warranted.

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Disclosures

The authors have no relevant relationships to disclose.

Introduction

Breast cancer is the most frequently diagnosed cancer among women in the United States, with an estimated 182,460 new cases in 2008 alone.[1] Advances in cancer screening and treatment have drastically increased the odds of survival during the past 25 years.[2] With this increased life expectancy, breast cancer survivors face new health issues stemming from the treatments for their cancer that were not relevant a few decades ago. For example, secondary osteopenia and osteoporosis, ie, bone loss that is not a direct result of aging but arises from cancer treatment, are major health problems for many breast cancer survivors.[3] However, no clinical guidelines for the management of cancer treatment-induced bone loss exist.[4]

Cancer treatment–induced bone loss affects both premenopausal and postmenopausal breast cancer patients. Chemotherapy has a direct effect on bone health. Breast cancer patients who receive chemotherapy have a significantly lower bone mineral density (BMD) than breast cancer patients who do not receive chemotherapy.[5] Chemotherapy also exerts an indirect effect on the skeleton through its effects on the ovaries.[6] Premenopausal women who experience ovarian failure as a result of chemotherapy lose up to 7.6% of BMD annually, compared with < 1% for a healthy premenopausal woman. The increase in bone loss among postmenopausal women with breast cancer is primarily attributed to the effects of treatment, namely aromatase inhibitors (AIs) and chemotherapy. In recent years, AIs have been favored among postmenopausal women over tamoxifen because of increased survival and decreased rates of recurrence.[7,8] Rates of BMD loss for postmenopausal breast cancer patients receiving AI therapy are significantly greater than for postmenopausal breast cancer patients receiving tamoxifen or a placebo treatment.[7–11] On average, postmenopausal breast cancer patients receiving AI therapy tend to lose about 2.6% of their BMD annually, which is more than double the rate of healthy postmenopausal women.[12] Research clearly demonstrates that as a result of these life-saving treatments, the bone density of women diagnosed with breast cancer is poorer than the bone density among women of the same age without cancer.

Predictably, BMD loss has led to an increased fracture rate among breast cancer patients. Large, randomized trials of adjuvant hormonal therapy found that those receiving AI were significantly more likely to suffer a fracture than those who did not receive AI.[7,10,13,14] Increased fracture risk is not confined solely to those receiving AI. After 5 years of follow-up, those who reported a history of breast cancer in the Women's Health Initiative had a 31% increase in risk of any clinical fracture, compared with women who reported no history of cancer ($P < .05$).[15] Kanis et al reported that breast cancer survivors were nearly 5 times more likely to suffer a vertebral fracture than healthy control patients ($P < .05$), whereas breast cancer patients with soft-tissue metastases but no bone metastases were almost 23 times more likely to suffer a vertebral fracture.[16] The increase in fracture risk can reduce the quality of life for breast cancer survivors.

This decline in BMD and the resultant fractures constitute a major problem for breast cancer survivors because they can interfere with activities of daily living and quality of life. Fractures resulting from osteoporosis have rapidly become a major cause of disability and a public health priority.[17] Hip fractures are a major indicator of bone health because their occurrence is closely related to diminished BMD.[17] Up to 25% of those who suffer a hip fracture die within 1 year.[18] More than 20% of those who experience a hip fracture require long-term care in a nursing facility.[19] Those who suffer a hip fracture usually lose the ability to perform daily functions such as climbing stairs, getting dressed, and taking a shower.[20] Because of the increasing number of breast cancer survivors and their increased fracture risk, the issue of a decline in quality of life becomes a significant public health issue.

Weight-bearing exercise slows the rate of bone loss across the general population.[21,22] Tai Chi Chuan (TCC) is a traditional Chinese martial art that combines slow, circular, fluid movements with deep breathing and relaxation.[23,24] Because of its presumed health benefits, safety, and low cost, TCC has become increasingly popular among cancer survivors.[25] Tai Chi Chuan may be ideal for preserving bone health in breast cancer survivors because it provides a low-impact form of weight-bearing exercise that is slow and gentle, and improves balance.[23,26] Observational studies found that those who regularly practiced TCC had a higher BMD than age-matched counterparts who did not practice TCC.[27,28] A few clinical trials used TCC as an intervention to improve bone health in postmenopausal women. One trial demonstrated a significant 2.6-fold to 3.6-fold retardation of bone loss ($P < .01$) for those in the TCC arm, compared with those who maintained a sedentary lifestyle.[29] Another trial found that those assigned to the TCC arm maintained BMD better than the control group, but the results were not statistically significant.[23] In another trial, the effects of TCC were measured according to bone-metabolism biomarkers.[30] Six weeks of TCC led to a significant increase in bone-specific alkaline phosphatase (a biomarker of bone formation) compared with the control arm. Recently, cancer patients used TCC as a form of weight-bearing exercise (although it is often considered complementary and alternative medicine) to help manage side effects from cancer treatments.[31,32] No clinical trials, to the best of our knowledge, have examined TCC in relation to bone health among women who were diagnosed with breast cancer.

This study sought to examine the effects of TCC on bone health, as defined by bone-metabolism biomarkers, among breast cancer survivors. The change in bone markers over the course of the intervention was calculated and compared between the exercize and control groups. In addition, changes in growth-factor and inflammatory-marker levels were correlated with the change in bone markers, to investigate the underlying biologic mechanism of bone metabolism.

Patients and Methods

Participants

The methods for this study were previously described.[33,34] Women who had been diagnosed with breast cancer and had previously completed treatment were recruited through mass mailings, advertising material posted throughout the community, and physician referrals. After expressing interest in this trial, potential subjects were contacted by the principal investigators, briefly screened for eligibility, and given the details of the intervention (eg, length of study, study design, randomization, assessment methods, and details of TCC classes). Potential participants were required to meet several criteria for inclusion: (1) female sex; (2) a primary diagnosis of breast cancer at stages 0-IIIB; (3) treatment completed more than 1 month previously, but less than 30 months before enrollment; (4) no drainage tubes or catheters; (5) no participation in moderate or vigorous physical activity more than once a week; (6) physician’s permission for aerobic fitness testing and exercise; (7) physical ability to participate in an exercise regimen; and (8) no clinical diagnosis of any mental disorder, as defined by the use of psychotropic drugs and self-report. Approval from our Institutional Review Board was obtained before acquiring written consent and enrolling participants.

Design and Procedures

A repeated-measures experimental design was used to compare the effects of TCC with standard support therapy (ST) on bone metabolism among women who had completed treatment for breast cancer within the past 30 months. Participants were randomly assigned to either the TCC exercise group or the ST exercise control group for a period of 12 weeks.

Both groups met for 60 minutes three times a week in separate classrooms in the same building at the same time of day for the duration of the trial. Randomization was achieved by flipping a coin, and group assignment was concealed from participants until the completion of all baseline assessments. All baseline assessments were completed 2 days before initiating the intervention. Adherence and compliance in the trial were monitored through attendance records compiled by the group instructor and personal records kept by each participant. The ST group sessions were facilitated by a trained counselor and exercise psychology graduate student, who led the participants in an open-ended format. The ST sessions placed special emphasis on behavioral coping strategies, cohort support, and group unity. Participants in the ST arm were sedentary upon study entry and were instructed not to change their pattern of physical activity in any manner for the duration of the intervention. According to self-reported data, 80% (n = 8) of participants in the ST arm did not change their level of physical activity, whereas 20% (n = 2) did so and initiated an intensified walking program.

The TCC group was led by an American College of Sports Medicine–certified health and fitness instructor. The instructor was extensively trained in Yang-style TCC and had more than 6 years of TCC teaching experience in a variety of populations (eg, healthy older individuals, frail individuals, and younger individuals). At the start of a session, participants performed 10 minutes of warm-up exercises, stretches, and Chi Kung (stationary TCC fundamentals). The participants then performed TCC for approximately 40 minutes and learned a 15-move, short-form sequence of Yang-style TCC. The 15 moves used in this intervention comprise the first 15 moves of the traditional 104-move, long-form, Yang-style TCC. The 15-move short form of Yang-style TCC is typically used to instruct novice TCC students and instills the fundamentals and principles of the long form. In the final 10 minutes of the session, participants were instructed to perform regulatory breathing, imagery, and meditation as part of the cool-down, and to enhance their TCC skills. All participants completed a series of self-reported questionnaires (concerning demographics and health-related quality of life) and a succession of functional capacity tests (eg, a 6-minute walk test, bioelectrical impedance, and handgrip dynamometry test) to assess aerobic capacity, flexibility, muscular strength, and body composition at baseline and after 12 weeks. Participants received no formal assignments to perform at home, but they were encouraged to practice TCC and the behavioral coping strategies they learned during the intervention. Participants in the TCC group were instructed not to begin any other physical exercise programs and not to change their normal daily physical activity during the course of the study. One hundred percent (n = 7) of the women completing the TCC intervention adhered to this requirement.

Measures

Demographics and Related Medical Information—Demographic information was self-reported and included a participant's age, height, weight, partner status, race, employment status, education, and household income. In addition, body mass index was calculated for each participant (weight [kg]/height [m^2]). Relevant medical information was extracted from medical records at time of entry into the trial, including stage of disease and type of treatment received.

Bone Health—Bone metabolism is a key element in maintaining proper bone health. Cells called osteoclasts attach to bones and remove old bone through a process called resorption. This study used cross-linked *N*-telopeptides of type I collagen (NTx) to assess bone resorption. As a bone marker, NTx responds to exercise intervention more rapidly than bone densitometry and independently predicts fracture risk.[35,36] After bone resorption, bone-forming cells called osteoblasts fill the area with a material called osteoid, which will

become fully mineralized bone. To measure bone formation, this study used bone-specific alkaline phosphatase (BSAP), a byproduct of osteoblast activity, that independently predicts fracture risk.[37] Fasting-state blood samples were collected in plain red-top tubes both before and after the intervention. Blood samples were allowed to clot for ≥ 30 minutes and were then centrifuged. Serum samples were then aliquoted and stored at −80°C. Serum samples were shipped to a central reference laboratory and tested simultaneously to avoid interassay variation. All serum assays were performed at first thaw, using commercial kits from ARUP Laboratories at the University of Utah (Salt Lake City). Serum NTx levels were determined using an enzyme-linked immunosorbent assay and a specific monoclonal antibody for NTx (osteomark serum NTx). The intra-assay and interassay coefficients of variation for the NTx assay are 4.6% and 6.9%, respectively. Serum BSAP levels were determined by a chemiluminescent immunoassay. The intra-assay and interassay coefficients of variation for the BSAP assay are 2.3% and 5.6%, respectively.

To investigate the balance between bone formation and bone resorption, we used the formula proposed by Eastell et al to calculate a bone remodeling index (BRI).[38] The formula is: $\Delta Z_{BSAP} - \Delta Z_{NTx}$, where $Z_{BSAP} = (BSAP_{Observed} - BSAP_{\mu \text{ at baseline}})/\sigma$ at baseline, and $Z_{NTx} = (NTx_{Observed} - NTx_{\mu \text{ at baseline}})/\sigma$ at baseline. A positive number for the BRI indicates a net bone gain, ie, resorption decreased and formation increased over the course of the intervention. A negative number for the BRI indicates net bone loss, ie, resorption increased and formation decreased over the course of the intervention.

Growth Factors and Cytokines—Serum concentrations of total insulin-like growth factor (IGF)-1, free IGF-1, insulin-like growth factor-binding protein (IGFBP)-1, and IGFBP-3 were measured using an immunoradiometric assay with commercial kits from Diagnostic Systems Laboratories, Inc (Webster, TX). Serum cytokines (interleukin [IL]-2, IL-6, IL-8, IL-1b, and interferon [IFN]-γ2) were measured using enzyme-linked immunoassays.

Fitness Outcomes and Body Composition—Aerobic capacity was estimated before and after the intervention, using a 6-minute walk-test protocol in which participants were instructed to walk as far as they could for 6 minutes. The total distance walked was recorded and used as a measure of aerobic capacity. Muscular strength was estimated using a handgrip dynamometer, which measured maximum grip strength before and after the intervention. Participants were allowed 6 attempts (3 with each hand), and the mean of the attempts was used as a measure of body strength. Body composition was assessed using bioelectrical impedance analysis (BIA) both before and after the intervention. Using BIA, we were able to calculate the amount of body fat and lean muscle mass. The results regarding fitness outcomes and body composition were previously reported.[34]

Statistical Analysis

Data analyses were performed using SPSS, version 16.0. Descriptive statistics for participants' demographics and baseline calculated values included percentages for categorical variables and means for continuous variables. To determine whether a difference existed in levels before and after the intervention of NTx, BSAP, and BRI within each group, a paired *t* test was used. To determine the difference in values before and after the intervention between the exercise and control groups for NTx, BSAP, and BRI, an analysis of covariance (ANCOVA) with repeated measures was performed. In addition to treatment assignment, baseline percentage of body fat and use of hormonal therapy were included in the model because these variables can influence rates of bone turnover. Significance was assigned at $P \leq .05$.

Because this is a pilot study, additional post hoc analyses were performed. Pearson correlates were calculated to measure the correlation between bone biomarkers, serum cytokines, fitness outcomes, and body composition. These analyses may provide insights into possible biologic mechanisms, and aid in the design of future trials involving TCC.

Results

More than 70 women expressed an interest in participating in this trial. The principal investigator contacted potential participants, and 35 met the inclusion criteria. Thirty-one breast cancer survivors agreed to participate, 21 participants (68%) successfully completed the trial, and 16 participants had evaluable blood samples before and after the intervention, whereas the other 5 participants had an inadequate amount of serum to complete the bone-biomarker tests. Participants failed to complete the study for a variety of reasons: side effects of treatment, work and family commitments, joining a gym, and dissatisfaction with their group assignment. Those who expressed dissatisfaction with their group assignment were all in the ST exercise control group and had a desire to participate in the TCC group.

Table 1 displays the baseline characteristics of participants according to group assignment. Participants ranged in age from 43 to 78 years, with a mean age of 53 years. No significant differences were evident between groups in age, marital status, education, ethnicity, or income ($P > .05$). In addition, no differences existed between groups regarding primary treatment and adjuvant endocrine therapy. Participants did not differ in aerobic capacity or body composition, as assessed by the 6-minute walk test, BRI, and percentage of body fat.

Table 2 displays the changes in bone biomarkers from baseline to follow-up according to group assignment. We constructed ANCOVA models, adjusting for baseline body-fat percentage and adjuvant endocrine therapy, to determine mean differences between groups. A greater, though not statistically significant, increase in bone formation was evident in the TCC group versus the ST group (BSAP, TCC = 1.9 vs. ST = 0.5; $P = .17$). The TCC group exhibited a greater, nonsignificant decline in bone resorption than the ST group (NTx, TCC = −6.5 vs. ST = −2.0; $P = .14$). A BRI was created, using levels of bone resorption and formation to reflect the balance between the removal of older bone and building of newer bone. Whereas bone remodeling remained virtually unchanged throughout the course of the study for the ST group, bone metabolism increased in the TCC group (BRI, TCC = 1.6 vs. ST = 0.2; $P = .04$).

Table 3 lists the Pearson correlation coefficients between changes in bone biomarkers and changes in cytokine and growth-factor levels. The change in bone formation was positively correlated with changes in IL-6, and negatively correlated with changes in IGFBP-1 and IL-2. The change in bone resorption was negatively correlated with changes in IGFBP-3 and IL-6, and positively correlated with changes in IGFBP-1 and IL-8. Changes in the BRI were negatively correlated with IGFBP-1 and IL-8, and positively correlated with IL-6.

Discussion

The results of this pilot study suggest that TCC could be an effective intervention for preserving bone health among women diagnosed with breast cancer. The TCC group demonstrated an increase in bone formation, a decrease in bone resorption, and a net gain in bone metabolism. The results of this study are consistent with the results of other studies demonstrating that TCC might help maintain BMD in the general population.[29,30] Changes in these bone markers were correlated with growth factors and cytokines. These correlations provide a biologic rationale for the positive effect of TCC on bone health, possibly through a reduction in inflammation, hence promoting bone formation. High-impact exercises such as

weight-lifting, running, and jumping help preserve bone health but might not be suitable for cancer patients.[39,40] Conversely, TCC is a low-impact exercise that uses slow, circular, fluid motions that are ideal for maintaining bone health in patients receiving treatment for breast cancer.

Our results also indicate that changes in bone markers were correlated with growth factors and cytokines that were implicated in bone remodeling.[36] Insulin-like growth factor-binding protein-1 is an established marker for osteoporosis, with high levels indicating excessive bone resorption.[41] In this trial, levels of IGFBP-1 decreased as levels of bone formation and metabolism increased. The inflammation-modulator IL-6 is defined as a "myokine," ie, a cytokine that is released in large quantities by muscle fibers during exercise.[42] In bone metabolism, IL-6 functions as an anti-inflammatory cytokine and enhances bone formation.[43] We found a strong correlation between IL-6 levels and both bone formation and metabolism. Interleukin-2 is a proinflammatory cytokine that tends to push the bone-metabolism scale toward resorption by increasing osteoclast formation through various mechanisms.[44,45] Interleukin-2 stimulates INF-γ, another proinflammatory cytokine, which, in turn, promotes the formation of osteoclasts.[46,47] In this trial, declining IL-2 levels were correlated with increasing bone formation and metabolism levels. Because multiple effects on bone metabolism for IL-2, IL-6, and IGRBP-1 were reported in the literature, their role remains unclear.

The positive results of this study must be interpreted with caution because of certain limitations. The most notable limitation of this study is its small sample size, which significantly limited statistical power and an ability to detect statistical differences between the two interventions. Because of the smaller, homogeneous population, the results cannot be generalized to other populations. Exercise contamination was a concern in this study, but only 20% of the ST group reported increasing their level of exercise, and 100% of the TCC reported that their only exercise involved the intervention. Furthermore, the study duration was only 12 weeks, whereas many exercise trials are of longer duration. Because the study lasted only 12 weeks, it had to rely on biomarkers of bone health rather than BMD. Although bone biomarkers were shown to predict fracture risk, BMD is considered a better predictor of fractures. Because blood samples were not collected months or years after completion of the trial, we cannot tell if the women in the TCC group maintained the benefits to bone health after they stopped the intervention. Lastly, because the study was not blinded, these benefits may have been attributable to the effects of patient expectancy, although this is not likely with the biologic outcomes in use.

Despite these limitations, this trial had a number of strengths. It was randomized, and participants at baseline did not differ in terms of bone markers, body composition, previous treatments, or socioeconomic variables. The trial collected blood at the beginning and end of the intervention, making it possible to determine the change in bone markers over the course of the intervention. Moreover, data on growth factors and cytokines were collected. The subsequent correlation found between bone markers and these growth factors and cytokines supported the biologic plausibility of TCC as an effective intervention for preserving bone health in breast cancer patients.

Conclusion

The positive results of this pilot study provide preliminary evidence that TCC could be an effective intervention for decreasing bone resorption and increasing bone formation and metabolism among women treated for breast cancer. The osteoporosis and fractures resulting from breast cancer treatment have become serious health concerns for breast cancer survivors, increasing their mortality and decreasing their quality of life. Tai Chi

Chuan could provide a safe and accepted form of exercise for the maintenance of bone mineral density, with or without pharmaceutical therapies. However, we urge caution in interpreting these results, based on such a small group of participants. Large-scale, randomized trials of longer duration are needed to confirm these findings and expand on the results of this pilot trial. Further research is required to determine the amount of TCC needed to elicit optimal effects on bone health and to determine if TCC can prevent fractures.

Acknowledgments

This work was supported by National Cancer Institute grant 1R25-CA102618-01A1 and the Sally Schindel Cone Foundation.

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Table 1

Baseline Characteristics of Participants

Characteristic	Tai Chi Chuan (n = 7)	Control Group (n = 9)	*P* Value
Mean Age, Years	53.8	52.6	.78
Ethnicity, %			
White	100	100	.99
Marital Status, %			
Married	57	44	.61
Not married	43	56	
Education, %			
Some college or less	28.6	33.3	.84
College graduate or more	71.4	66.7	
Income, %			
$40,000 or less	28.6	22.2	.77
Greater than $40,000	71.4	77.8	
Occupation, %			
Homemaker/retired	28.6	44.4	.52
Employed outside home	71.4	55.6	
Primary/Local Treatment, %			
Mastectomy	57	33.3	.34
Breast-conserving surgery	43	66.7	
Adjuvant Endocrine Therapy, %			
Yes	42.9	66.7	.34
No	57.1	33.3	
6-Minute Walk Test, Distance in Meters	618	624	.85
Body Mass Index, kg/m^2	25.8	24.2	.55
Body Composition, % Fat Mass	39.9	41.1	.68

Table 2

Change in Bone Biomarkers From Baseline to Follow-up Between Groups

Time Point	Tai Chi Chuan Group	Control Group	*P* Value Between Groups
BSAP, μg/L			
Baseline	8.34 ± 0.8	7.64 ± 0.7	
12 Weeks	10.21 ± 1.1	8.12 ± 1.1	.17
Change	1.87	0.48	
NTx, nmBCE			
Baseline	17.6 ± 3.7	20.8 ± 3.3	
12 Weeks	11.1 ± 2.9	18.8 ± 2.5	.14
Change	−6.5	−2.0	
Bone Remodeling Index			
Baseline	0.37 ± 0.6	0.10 ± 0.5	
12 Weeks	2.00 ± 0.6	0.33 ± 0.6	.04
Change	1.63	0.23	

Data are given as least-squares mean ± SE, adjusted for % body fat and adjuvant endocrine therapy.

Abbreviations: BSAP = bone-specific alkaline phosphatase; nmBCE = nanomoles bone collagen equivalent; NTx = *N*-telopeptides of type I collagen

Table 3

Pearson Correlation Coefficients in Bone Biomarkers and Changes in Cytokines and Growth Factors

Factor	Pearson Correlation					
	Change in BSAP (Bone Formation)	*P* Value	Change in NTx (Bone Resorption)	*P* Value	Change in Bone Remodeling Index	*P* Value
IGFBP-1 Change	−0.54	.05	0.26	.34	−0.43	.14
IGFBP-3 Change	−0.10	.75	−0.27	.32	0.19	.53
Cortisol Change	−0.36	.23	−0.07	.79	−0.22	.48
IL-2 Change	−0.50	.08	−0.05	.84	−0.35	.24
IL-6 Change	0.76	.00	−0.20	.45	0.69	.01
IL-8 Change	−0.01	.97	0.23	.39	−0.03	.93

Abbreviations: BSAP = bone-specific alkaline phosphatase; IGFBP = insulin-like growth factor binding protein; IL = interleukin; NTx = *N*-telopeptides of type I collagen