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Discriminatory Ability of Calcaneal Quantitative Ultrasound in the Assessment of Bone Status in Patients with Inflammatory Bowel Disease

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ABSTRACT

A high incidence of bone disease in patients with inflammatory bowel disease (IBD) requires frequent monitoring of skeletal status, and for that reason evaluation of radiation free technology is an issue of interest. Our objective was to appraise the parameters of calcaneal quantitative ultrasound (QUS): broadband ultrasound attenuation (BUA), speed of sound (SOS) and stiffness index (QUI), and establish their t-score values to investigate discriminatory ability of QUS in IBD patients with metabolic bone disease.

The study included 126 patients (Crohn's disease n=94, and ulcerative colitis n=32), and 228 age- and sex-matched healthy volunteers. Bone status was evaluated on the same day by calcaneal QUS and dual-energy x-ray absorptiometry (DXA) at spine (L1-L4) and total hip.

All QUS measurements were lower in patients compared with healthy controls (BUA $p<0.001$; SOS $p<0.001$; QUI $p<0.001$) and correlated significantly but inversely with disease duration ($r=-0.3$, $p=0.002$). There was no difference with respect to type of disease (Crohn's disease or ulcerative colitis) or corticosteroid therapy. All three QUS t-scores were significantly lower in patients who had previously sustained fragile fractures (n=28) than in those without fracture in their history (n=98) (t-scores*:* BUA -2.0 *vs.* -1.3, $p=0.008$; SOS -2.1 *vs.* -1.4, $p=0.02$: QUI -2.3 *vs.* -1.5, $p=0.009$). Axial DXA was not significantly different between the fracture and non-fracture patients (-1.7 *vs.* -1.2, $p=0.1$), whereas total hip DXA showed a discriminatory power between the two (-1.6 *vs.* -0.7, $p=0.001$). Patients with t-score <-1.0 scanned by DXA were classified as bone disease. The sensitivity of QUS to identify bone disease was 93% and specificity 63%. The sensitivity of QUS to detect osteopenia was 84% and 72% for osteoporosis. Alternatively, less negative QUS t-score cut-off ≤ -1.8 identified 83% of osteoporosis at lumbar spine and 100% at total hip. All three QUS variables had t-scores less than -1.8 when osteoporosis was detected at both spine and hip. However, the subgroup of IBD patients with QUI t-score cut-off ≤-1.8 still included 26% of individuals with normal bone status.

Calcaneal QUS measurements may identify patients with inflammatory bowel disease at a higher risk of fracture, independently of DXA

measurements. However, QUS showed poor agreement with bone status scanned by DXA and a low discriminatory power between osteopenia and osteoporosis.

KEY WORDS

Inflammatory bowel disease; Metabolic bone disease; Calcaneal quantitative ultrasound; Dual-energy x-ray absorptiometry; Specificity; Sensitivity

INTRODUCTION

Metabolic bone disease is an established complication in patients with inflammatory bowel disease (IBD) (Bernstein et al. 2003; Harpavat et al. 2004; Kirchgatterer et al. 2002; Lichtenstein 2003; Schoon et al. 2000; Schulte 2004). Bone lesions ranging from variable osteopenia to osteoporosis with a consequential increased risk of bone fractures have been described in both Crohn's disease and ulcerative colitis (Schoon et al. 2000). The etiology of bone changes in IBD is rather complex. It is known that skeletal system may be affected by chronic remittent inflammation *per se* and corticosteroid medications used in the treatment of disease, or by genetic susceptibility to bone loss (Schulte 2004). Bone mineral density (BMD) at the femoral neck and lumbar spine is a critical parameter to measure bone mass and fracture risk. Dual-energy x-ray absorptiometry (DXA) is the current gold standard technique for measuring BMD. Studies using DXA, published to date, report that 40%-50% of patients with IBD have osteopenia and as many as 30% of individuals have osteoporosis (Kirchgatterer et al. 2002; Lichtenstein 2003). Generally, osteopenia and osteoporosis are more frequently seen in patients with Crohn's disease than in patients with ulcerative colitis (Lichtenstein 2003).

Quantitative ultrasound (QUS) is an alternative technology for monitoring skeletal status. It is a non-invasive technique that may be useful in assessing bone structure as well as bone mass. QUS has the advantages of being radiation-free and using relatively inexpensive, portable devices. The two ultrasound variables currently measured are broadband ultrasound attenuation (BUA) and speed of sound (SOS). *In vitro* studies of cancellous bone specimens have demonstrated BUA to be associated with trabecular bone structure, while SOS parameters depend more on elasticity and density (Bouxsein and Radloff 1997). QUS technology is suitable for recurrent measurements and monitoring of bone status at peripheral sites, such as the calcaneus, phalanges and tibia (Cook et al. 2005). QUS technique has been shown to be a good predictor of fracture risk in postmenopausal women, independent of DXA (Knapp et al 2001). Calcaneal QUS has also been

demonstrated to discriminate low bone density in patients with rheumatoid arthritis and to detect bone changes in corticosteroid users (Maricic 2004).

Only a few previous studies referred QUS data in IBD patients, with controversial results. QUS was found to be useful as a screening tool for metabolic bone disease in four studies (Fries et al. 1998; Hartman et al. 2004; Javaid et al. 2001; Zadik et al. 2005) but not in another five (Jahnsen et al. 1999; Levine et al. 2002; Robinson et al. 1998; Schwartz et al. 2005; von Tirpitz et al. 2003). As in IBD patients bone pathology is developing since young age and may progress over a shorter period of time than in postmenopausal osteoporosis, monitoring of bone status by DXA should be performed frequently. That is why the evaluation of an alternative, radiation frees technology, remains an issue of interest. Therefore, the aim of the present study was first to establish t-score values for individual QUS parameters; BUA, SOS and QUI-stiffness index were converted into t-scores to reflect the number of standard deviations below the mean of reference values in the control population**.** Namely, all reports referring to QUS data in IBD patients provided and analyzed solely crude values for QUS variables. In the present study, bone status was first classified by use of QUS t-scores, and then we investigated whether the data obtained by QUS could serve as an alternative or complementary option to those established by DXA.

SUBJECTS and METHODS

Subjects and study design

A total of 126 patients with inflammatory bowel disease (Crohn's disease n=94, and ulcerative colitis n=32) diagnosed according to conventional clinical, radiological, endoscopic, and histological criteria were recruited. Baseline characteristics of patients are shown in Table 1. Clinical data were collected from hospital records. None of the patients had a history of treatment with any medication affecting bone density other than corticosteroids, prior to the study. Moreover, the patients were not treated with vitamin D and calcium supplements. Data on corticosteroid use were categorized into two groups: never used, and corticosteroid therapy (≥ 8 mg prednison/day) over 3 months. Duration of disease and body mass index (BMI) were calculated. Twenty-eight patients (9 with osteoporosis and 19 with osteopenia) reported a history of fragile fractures. In order to obtain a control group of healthy individuals age- and sex-matched to the study group of IBD patients, we selected 228 healthy volunteers (median age 33.5, range 21-45 years) receiving no medication nor suffering from conditions affecting bone density or from any known disease. The local reference population was recruited from general practitioners, hospital personnel and their friends. The investigation was designed and carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000. The Hospital Ethics Committee approved the study protocol, and informed written consent was obtained from each subject before entering the study.

Bone status measurements

Bone mineral density (BMD) of lumbar spine (L1-L4) and total hip (femoral neck and trochanter) was measured by the absorptiometric technique (DXA) using a Delphi W (S/N 700483) instrument (Hologic, Inc., Waltham, MA, USA). BMD measurements were converted into t-scores reflecting the number of standard deviations below the mean for a young healthy population, and z-scores reflecting the number of standard deviations below the mean for age-matched controls (database gathered by Hologic). According to the WHO

guidelines, osteopenia was defined as a t-score between -1 and -2.5, and osteoporosis as a t-score less than -2.5.

Calcaneal structure was measured in all subjects on the left heel using the Sahara bone sonometer (Hologic, Inc., Waltham, MA, USA). The measurements included broadband ultrasound attenuation (BUA), speed of sound (SOS), BMD with t-score, and stiffness index (QUI). BUA (dB/MHz) is a parameter that describes the energy loss of an ultrasound wave as it passes through the os calcis. SOS denotes the speed of sound expressed in m/s, which is the passing distance of a sound wave divided by transit time. QUI is a mathematical index and provides a linear combination of BUA and SOS. The Hologic manufacturer's reference data for Sahara QUS parameters BUA, SOS and QUI, and related t-scores were not available. Therefore, reference values for BUA, SOS, QUI (mean±SD), and related individual t-scores were calculated from our own reference group of healthy volunteers, using the formula: T-score = (individual measurement – mean of reference)/SD of reference (Cook et al. 2005). The *in vivo* precision of BUA and SOS were estimated by repeat measurements on the left heel with repositioning. Coefficients of variation in 30 healthy subjects were 2.7% for BUA and 0.4% for SOS, which is consistent with literature data. However, precision was poorer in the high-risk group of 30 IBD patients; coefficient of variation was 17.3% for repeat BUA measurement and 0.9% for SOS. All measurements were done on the same day, in identical conditions, and by the same operator.

Statistical analysis

Analysis of data was performed using the StatSoft statistical package. Results for continuous variables are given as mean±SD or range, and for non-continuous variables as frequency and percentage. Comparison for differences among variables was tested by ANOVA and nonparametric Mann Whitney U-test, Kruskal-Wallis ANOVA or Wilcoxon matched pair test when appropriate. Bivariate correlation was examined by Spearman, and multiple stepwise regression analysis was used for association among variables. Patients with t-score <-1.0 scanned by DXA were classified as “bone disease” and those with DXA t-score >-1.0 as “normal”. Results obtained by QUS

technique relative to DXA diagnosis were expressed by 2*2 contingency table and their validity assessment was calculated. Precision was assessed by determination of coefficient of variation.

RESULTS

Calcaneal QUS measurements

Crude values of the QUS parameters of BUA, SOS and QUI for all study patients and reference population are shown in Table 2. Reference values for BUA t-scores, SOS t-scores and QUI t-scores were calculated from the local reference population of 228 healthy volunteers that were age-and sex-matched to the study group of IBD patients. All three calcaneal t-scores were significantly lower in patients compared with healthy volunteers (BUA $p<0.001$; SOS $p<0.001$; QUI $p<0.001$). ANOVA analysis of calcaneal QUS variables showed no significant differences between patients with Crohn's disease (n=94) and ulcerative colitis (n=32) (BUA p=0.27; SOS p=0.82; QUI p=0.62). There were no differences in t-scores measured by DXA at lumbar spine (p=0.68) and total hip (p=0.061) between the the two groups of IBD patients. Additionally, corticosteroid treatment lasting for more than 3 months in lifetime was analyzed as a categorized variable. QUS t-scores were lower in corticosteroid users (n=77) than in patients free from corticosteroid therapy (n=49), however, the difference did not reach statistical significance (t-scores: BUA -1.6 *vs.* -1.3, p=0.24; SOS -1.7 *vs.* -1.4, p=0.14; QUI -1.8 *vs.* -1.5, p=0.19). Corticosteroid therapy was associated with lower DXA t-scores in corticosteroid users, however, without statistical significance (spine: -1.02 *vs* -1.49, p=0.101; total hip: -0.74 *vs* -1.04, p=0.16). When age, disease duration and body mass index were taken into account, stepwise multiple regression analysis indicated that disease duration significantly predicted QUS variables ($p<0.01$). All study parameters of calcaneal QUS showed a significant inverse correlation with disease duration (r=-0.3, p=0.002) (Fig. 1). Twenty-three percent of IBD patients reported previous fractures in their history. All three calcaneal t-scores were significantly lower in patients who had previously sustained fragile fractures (n=28) than in those without fracture in their history (n=98) (t-scores*:* BUA -2.0 *vs.* -1.3, p=0.008; SOS -2.1 *vs.* -1.4, p=0.02: QUI -2.3 *vs.* -1.5, p=0.009) (Fig. 2). Axial DXA was not significantly different between the fracture and non-fracture patients (-1.7 *vs.* -1.2, p=0.1), whereas total hip DXA showed a discriminatory power between the two (-1.6 *vs.* -0.7, p=0.001).

DXA* versus *QUS measurements

According to the WHO guidelines (WHO Study Group Report 1994) based on the results produced by DXA at lumbar spine and total hip, study patients (n=92) were divided into three subgroups: normal bone status (n=38; 41%), osteopenia (n=36; 39%) and osteoporosis (n=18; 20%) detected at least at one measurement site. In these patients, t-scores for calcaneal QUS-stiffness index (a combination of BUA and SOS) identified 28 (30%) subjects with normal bone status, whereas bone changes were detected as osteopenia in 45 (49%) and as osteoporosis in 19 (21%) patients. Osteoporosis scanned by DXA was confirmed by QUS parameters in 13/18 cases, and detected as osteopenia in 5/18 cases. However, none of the osteoporosis cases scanned by DXA was falsely detected by calcaneal QUS as normal bone status. Yet, the analysis of sensitivity and specificity as measures of test validity revealed a greater discrepancy. All patients with t-score <-1.0 scanned by DXA were classified as bone disease. The sensitivity of QUS-index to identify bone disease was 93% and specificity 63%. The calculated positive predictive value of QUS was 78%, and negative predictive value 86%. The sensitivity of QUS to detect osteopenia properly was 84% and for osteoporosis only 72%. Kappa statistica showed moderate agreement between QUS and DXA (κ=0,58 $SE_{(\kappa)}$=0,15 z=3,9)

In another attempt to use QUS measurements for assessment of skeletal status in IBD patients, a less negative QUS t-score cut-off ≤ -1.8 was chosen, as suggested by Frost *et al*. (2000). Thus, QUI t-score ≤ -1.8 identified 83% of cases with osteoporosis, 56% with osteopenia and 26% with normal bone status scanned by DXA. As DXA results for osteoporosis compared between different skeletal sites vary, we analyzed agreement between QUI and DXA at L1-L4 spine and separately between QUI and total hip. QUI t-score ≤ -1.8 identified 100% of hip osteoporosis and 83% of lumbar spine osteoporosis. When osteoporosis was detected by DXA at both spine and hip, all three QUS variables had t-scores less than -1.8: BUA -3.0 (range -4.3 to -2.2), SOS -2.6 (range -3.2 to -1.85) and QUI -3.0 (range -3.7 to -2.2).

DISCUSSION

In recent years, a high incidence of metabolic bone disease in patients with inflammatory bowel disease has been recognized as a problem and preventive screening has been recommended (Papaionnou et al. 2001; Valentine and Sninsky 1999). The present study investigated the general ability of calcaneal QUS parameters to discriminate IBD patients according to bone status. The study population of IBD patients included 41% of patients with normal bone status, 39% of patients with osteopenia and 20% of patients with osteoporosis. The criterion for establishing metabolic bone disease was the finding of BMD produced by lumbar spine and/or total hip DXA. In order to make QUS data comparable with the parameters of classical densitometry, each individual QUS parameter was converted into t-score. Normative values for BUA t-scores, SOS t-scores and QUI t-scores were calculated from our own reference group of 228 healthy volunteers.

There were several strengths of calcaneal QUS measurements. First, all QUS t-scores (BUA, SOS and QUI) discriminated IBD patients from healthy age- and sex-matched controls. Second, there were significant differences in the mean values of calcaneal QUS between fracture and non-fracture patients. Third, none of osteoporosis cases was falsely detected by calcaneal QUS as normal bone status. Finally, all QUS parameters showed a significant inverse correlation with disease duration. Despite all these facts, the sensitivity (93%), specificity (63%) and positive predictive value (78%) of calcaneal QUS measurements failed to support QUS as a valuable method in discriminating IBD patients with bone disease. Our observations are comparable to some previously published studies evaluating clinical value of calcaneal QUS measurements in IBD patients. Schwartz et al (2005) compared QUS and DXA in 124 IBD patients, 62% of them with DXA t-score ≤-1.0, and found that calcaneal QUS sensitivity and specificity were too low to be clinically useful. In a study reported by Jansen et al (1999) the correlation between calcaneal QUS and DXA measurements ranged from 0.50 to 0.67, yet the agreement between measurements in individual patients was poor. In our study, the 93% sensitivity implied 7% of patients with established bone disease to be classified as false negative, whereas 63% specificity indicated

as many as 37% of subjects with normal bone status to be classified as false positive. We should point out that the patients classified as false positive had calcaneal QUS parameters indicative of variable osteopenia. The fact that QUS failed to differentiate osteoporosis from osteopenia (in 28% of cases) appears to be of major clinical relevance, as this differentiation is a *condicio sine qua non* for the introduction of treatment with highly potent antiresorptive agents. Frost et al (2000) consider that WHO criteria (t-score ≤-2.5) for diagnosing osteoporosis in postmenopausal women cannot be applied to calcaneal QUS. The QUS parameters BUA and SOS do not measure bone mineral content, whereas WHO classification is based on bone mineral density. Therefore, these authors suggest a less negative t-score threshold of -1.8 for QUS as a tool to compare QUS and DXA. This approach was alternatively used in our study, and QUI t-score cut-off ≤-1.8 identified 83% of osteoporosis at lumbar spine and 100% at total hip. All three QUS variables had t-scores less than -1.8 when osteoporosis was detected at both spine and hip. However, the subgroup of IBD patients with QUI t-score cut-off ≤-1.8 still included 26% of individuals with normal bone status. The problem of how to use QUS results in the assessment of bone status was the subject of a review recently published by Nayak *et al.* (2006). The authors summarized data currently available in the literature, and using meta-analysis concluded that QUS results at the commonly used thresholds did not definitely exclude or confirm DXA established osteoporosis.

Because of the high incidence of metabolic bone disease, IBD patients are at a high risk of bone fractures. However, the measurement of bone mineral density *per se* failed to prove as a reliable predictive parameter of fracture risk in this patient population (Stockbrugger 2002, Lee 2000). In our study group, 23% of patients reported a history of fragile fractures, and all QUS measurements were significantly lower in patients who had previously sustained at least one bone fracture. Similar findings are reported by Jahnsen *et al.* (1999) who observed significant between-group difference in SOS but not in BUA. In our study group, QUS and DXA differed in the ability to distinguish fracture from non-fracture patients with IBD. Thus, axial DXA was not significantly different between the fracture and non-fracture patients, whereas total hip DXA showed greater discriminatory potential. The objective

of bone status assessment is to identify patients at risk of fracture, where QUS seems to provide some elements related to bone microarchitecture or elasticity rather than bone mineral content. For example, QUS technique has been shown to be a good predictor of fracture risk in postmenopausal women, independent of DXA (Knapp et al 2001); therefore, we consider this method being worthy of additional evaluation.

A limitation of this study was the absence of long-term longitudinal QUS measurements, which would be necessary for comprehensive evaluation of the technique. This is supported by Zadik *et a*l. (2005), who detected an early deterioration in bone quality by the follow-up of QUS measurements in a population of adolescents with active Crohn's disease. Comprehensive evaluation of the potential value of QUS technique in daily clinical practice requires additional clinical investigations in which medical treatment efficacy will be monitored by QUS parameters. To date, there are no study reports on using QUS as a criterion for therapy introduction.

In conclusion, our results suggest that calcaneal QUS measurements may identify patients with inflammatory bowel disease at a high risk of fracture, independently of DXA measurements. However, calcaneal QUS cannot successfully discriminate osteoporosis from osteopenia, which is necessary for the choice of an efficacious therapeutic option. The results of presented study suggest that data obtained by QUS cannot be considered a valuable alternative to DXA but may be used as a complementary option to classical densitometry due to QUS ability to predict fracture risk. Additional prospective studies in patients with inflammatory bowel disease are necessary to evaluate whether QUS can be used to monitor bone disease progression in parallel with therapeutic efficacy.

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LIST of TABLE CAPTIONS

Table 1

Baseline Patient Characteristics

Patients	
N (men/women)	126 (63/63)
Age (yr.)	34.9±12
Patients with inflammatory bowel disease	
Crohn's disease (n)	94
Ulcerative colitis (n)	32
Disease duration (years) (median; range)	6 (0.1-26)
Body mass index (kg/m^2) (mean, SD)	21.6±5
Corticosteroid use > 3 months	
No	49
Yes	77

Table 2

Calcaneal Quantitative Ultrasound Parameters in Patients with Inflammatory Bowel Disease and Reference Population

	Patients	Reference population	p-level
n	126	228	
Age (yr.)	34.9±12	32.5 ± 8	0.32
BUA (dB/MHz)	66.7±16	88.7±13.8	0.00041
BUA t-score	-1.4±1.1		
SOS (m/s)	1529.7 ±31	1570±25	0.000001
SOS t-score	-1.7±1.2		
QUI- index	83.61±18	108.5±14.5	0.000001
QUI t-score	-1.69±1.2		

BUA= broadband ultrasound attenuation; SOS=speed of sound; QUI=stiffness index, and t-scores; all expressed as mean±SD
Individual t-scores for BUA, SOS and QUI were calculated by mean (±SD) of reference population

LEGEND to FIGURES

Figure 1.

Correlation between calcaneal quantitative ultrasound parameters and disease duration in 126 patients with inflammatory bowel disease. A significant negative correlation was found with broadband ultrasound attenuation /BUA/ (r=-0.3 p=0.002), speed of sound /SOS/ (r=-0.35 p=0.001), and stiffness index /QUI/ (r=-0.33 p=0.001).

Figure 2.

T-scores of calcaneal quantitative ultrasound: BUA (broadband ultrasound attenuation), SOS (speed of sound) and QUI (stiffness index) in patients with inflammatory bowel disease with at least one fragile fracture (n=28) and with no fractures (n=98) in history. All three calcaneal t-scores were significantly lower in patients who had sustained fractures from non-fracture patients: BUA t-score p=0.008; SOS t-score p=0.02: QUI t-score p=0.001.

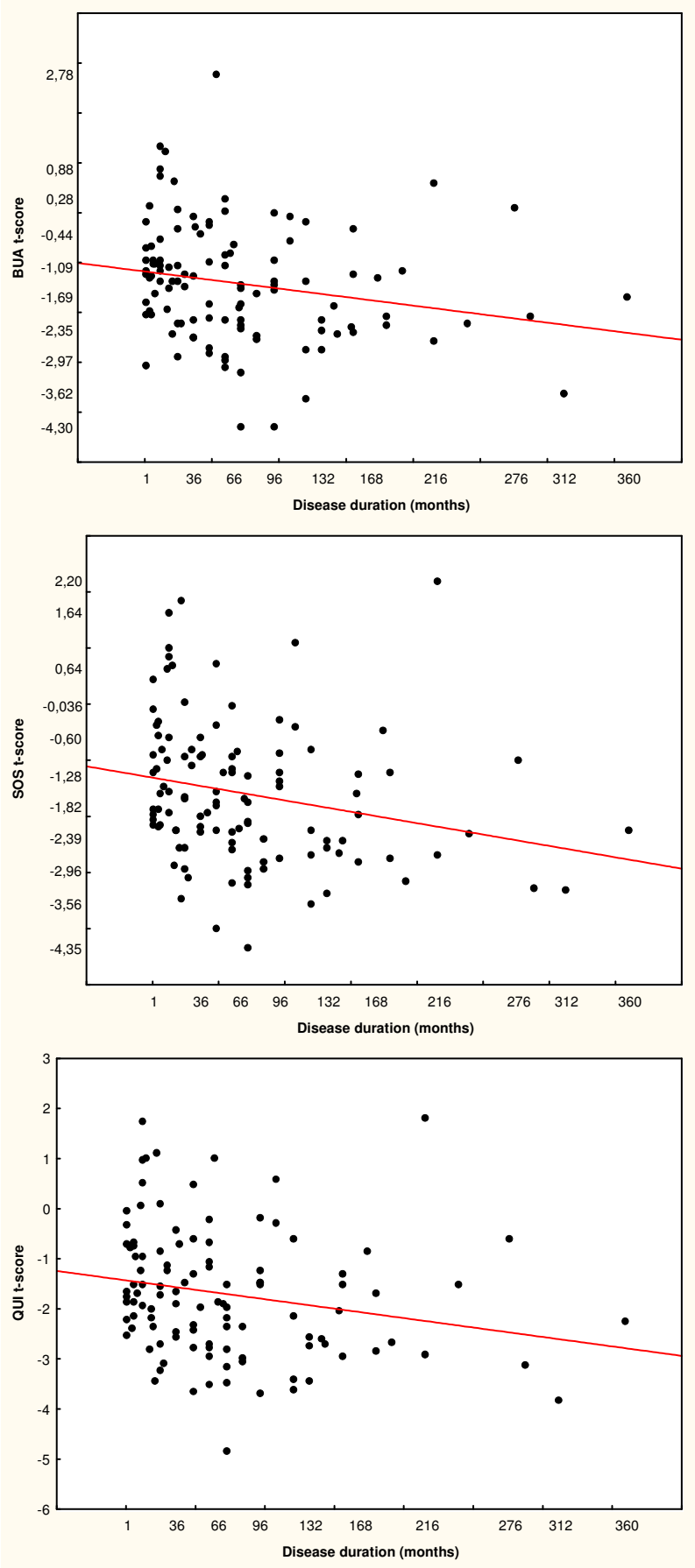
BUA t-score
2,78
0,88
0,28
-0,44
-1,09
-1,69
-2,35
-2,97
-3,62
-4,30
1
36
66
96
132
168
216
276
312
360
Disease duration (months)
SOS t-score
2,20
1,64
0,64
-0,036
-0,60
-1,28
-1,82
-2,39
-2,96
-3,56
-4,35
1
36
66
96
132
168
216
276
312
360
Disease duration (months)
QUI t-score
3
2
1
0
-1
-2
-3
-4
-5
-6
1
36
66
96
132
168
216
276
312
360
Disease duration (months)

Figure 1

Figure 2