UNIVERSIDAD DE CANTABRIA

GRADO EN MEDICINA

TRABAJO FIN DE GRADO

Trabecular Bone Score (TBS). Reference values in males of our region.

Índice Óseo Trabecular (TBS). Valores de referencia en varones de nuestra región.

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Santander, Junio 2019

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1. Abstract

Introduction: Trabecular Bone Score (TBS) is a textural index that provides information about the quality of bone microarchitecture and has shown usefulness predicting fracture risk.

Objectives: a) To describe TBS values in men of 50 years and older of our region, b) assess whether the TBS measurement decreases with age; c) to determine if there is an association between TBS and the presence of densitometric osteoporosis, d) analyze their relationship with bone mineral density (BMD) values in lumbar spine (LS-BMD), femoral neck (FN-BMD) and total hip (TH-BMD), e) assess the correlation of the TBS with bone quantitative ultrasounds (QUS), f) to evaluate the relationship of the TBS with serum concentrations of 25(OH)D, PTH and bone remodeling markers (PINP and CTX).

Patients and methods: We studied 863 men aged 50-91 years (65 ± 9) included in a population-based study of osteoporosis screening and other bone metabolic diseases (the Camargo cohort study). BMD was measured by DXA (Hologic QDR 4500). TBS was evaluated using TBS iNsight® v2.1 (Med-Imaps, Pessac, France). TBS results were also analyzed after stratifying the participants according to the values of BMD in the spine and hip (normal, osteopenia, and osteoporosis). The study was approved by the local Ethics Committee.

Results: The mean values of TBS and BMD were as follows: TBS; 1.355 ± 0.128; LS- BMD: 1.021 ± 0.159 g/cm^2; FN-BMD: 0.819 ± 0.122 g/cm^2; TH-BMD: 0.977 ± 0.130 g/cm^2. Men with densitometric osteoporosis showed a lower TBS value than men with osteopenia or with normal BMD (Table). TBS values were inversely related to age (r=-0.157, p <0.0001) and body mass index (r = -0.494, p <0.0001), whereas they did directly with LS-BMD (r =0.350; p <0.001), FN-BMD (r = 0.125; p <0.001) and TH-BMD (r = 0.150; p <0.001). An association was observed between TBS and QUS, although the association was weak and lower than that found between TBS and BMD at lumbar spine. The relationship between TBS and PTH was negative (r = -0.080; p<0.019), and between TBS and 25(OH)D was positive (r = 0.177; p<0.001). However, no association was found between TBS and bone turnover markers.

Classification	*Normal*	*Osteopenia*	*Osteoporosis*
TBS	1.394±0.121*	1.331±0.120*	1.266±0.118

* p <0.001 compared to men with osteoporosis

Conclusions: TBS values of adult males from our area are similar to those described in other countries. TBS measurement decreases with age, due to TBS is negatively correlated with age, in our population. TBS is lower in patients with densitometric osteoporosis than in those with osteopenia or normal BMD. Although the TBS and BMD values are significantly correlated, the degree of relationship is poor. A weak association was observed between TBS and QUS, suggesting that both techniques capture different aspects of bone microarchitecture. The weak association with 25(OH)D, PTH, and the absence of association with bone remodeling markers may be due to the fact that TBS assesses a specific part of the skeleton, as trabecular bone; whilst the three serum factors are related to the whole skeleton.

2. Resumen

Introducción: el índice trabecular óseo (TBS) es un índice de textura que proporciona información sobre la calidad de la microarquitectura ósea y ha demostrado su utilidad para predecir el riesgo de fractura.

Objetivos: a) Describir los valores de TBS en hombres de 50 años o más de nuestra región, b) evaluar si la medición de TBS disminuye con la edad; c) para determinar si existe una asociación entre el TBS y la presencia de osteoporosis densitométrica, d) analizar su relación con los valores de densidad mineral ósea en la columna lumbar, el cuello femoral y la cadera, e) evaluar la correlación de la TBS con ultrasonidos óseos cuantitativos (QUS), f) evaluar la relación de la TBS con concentraciones séricas de 25 (OH) D, PTH y marcadores de remodelación ósea (PINP y CTX).

Pacientes y métodos: Hemos estudiado a 863 hombres de 50 a 91 años (65 ± 9) incluidos en un estudio poblacional de detección de osteoporosis y otras enfermedades metabólicas óseas (el estudio de cohorte de Camargo). La DMO se midió por DXA (Hologic QDR 4500). TBS se evaluó utilizando TBS iNsight® v2.1 (Med-Imaps, Pessac, Francia). Los resultados de TBS también se analizaron después de estratificar a los participantes según los valores de DMO en la columna vertebral y la cadera (normal, osteopenia y osteoporosis). El estudio fue aprobado por el Comité de Ética local.

Resultados: Los valores medios de TBS y DMO fueron los siguientes: TBS; 1.355 ± 0.128; Columna lumbar- DMO: 1.021 ± 0.159 g / cm2; Cuello femoral-DMO: 0,819 ± 0,122 g / cm2; Cadera-DMO: 0.977 ± 0.130 g / cm2. Los hombres con osteoporosis densitométrica mostraron un valor de TBS más bajo que los hombres con osteopenia o con DMO normal (Tabla). Los valores de TBS se relacionaron inversamente con la edad ($r = -0.157$, $p < 0.0001$) y el índice de masa corporal ($r = -0.494$, $p < 0.0001$), mientras que lo hicieron directamente con CL-DMO ($r = 0.350$; $p < 0.001$), CF-DMO ($r = 0.125$; $p < 0.001$) y C-DMO ($r = 0.150$; $p < 0.001$). Se observó una asociación entre TBS y QUS, aunque la asociación fue débil e inferior a la encontrada entre TBS y DMO en la columna lumbar. La relación entre TBS y PTH fue negativa ($r = -0.080$; $p < 0.019$), y entre TBS y 25 (OH) D fue positiva ($r = 0.177$; $p < 0.001$). Sin embargo, no se encontró asociación entre TBS y marcadores de recambio óseo.

Clasificación	*Normal*	*Osteopenia*	*Osteoporosis*
TBS	1.394±0.121*	1.331±0.120*	1.266±0.118

* $p < 0.001$ comparado con hombres con osteoporosis.

Conclusiones: los valores de TBS de hombres adultos de nuestra área son similares a los descritos en otros países. La medición de TBS disminuye con la edad, debido a que TBS se correlaciona negativamente con la edad, en nuestra población. El TBS es menor en pacientes con osteoporosis densitométrica que en aquellos con osteopenia o DMO normal. Aunque los valores de TBS y DMO están significativamente correlacionados, el grado de relación es bajo. Se observó una asociación débil entre TBS y QUS, lo que sugiere que ambas técnicas capturan diferentes aspectos de la microarquitectura ósea. La asociación débil con 25 (OH) D, PTH y la ausencia de asociación con marcadores de remodelación ósea, puede deberse al hecho de que el TBS evalúa una parte específica del esqueleto, como es el hueso trabecular; mientras que los tres factores séricos están relacionados con todo el esqueleto.

3. Introduction

Osteoporosis a systemic bone disease, characterized by a decrease in bone mineral density and deterioration of the microarchitecture of bone, which increases the bone fragility and the risk of fragility fractures.

Classically, this disease has been postmenopausal women however it is increasingly recognized a significant health burden in men as well. Men also experience higher mortality and morbidity from osteoporotic fractures as compared to women.[1]

Although bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) is a major determinant of bone strength and fracture risk, it is well known that over 50% of fractures occur in patients with DXA values that are not classified as "osteoporotic". This observation means that factors other than BMD influence bone strength and fracture risk, including microarchitectural deterioration of bone tissue as implied from the conceptual definition of osteoporosis. Additional skeletal and extraskeletal factors such as bone geometry, microdamage, mineralization, bone turnover, age, family history, and fall risk contribute to the overall fracture risk. [2]

The trabecular bone score (TBS) is a measure that can be obtained from a bone densitometry image, provided by some dual-energy X-ray absorptiometry (DXA) densitometers. The score is related to the bone microarchitecture and provides additional information to conventional densitometry on bone texture.

Globally, one in three women and one in five men over the age of 50 will experience a fracture due to osteoporosis with a subsequent decrease in quality of life and an excess mortality rate for hip fractures >20% in the first year.[3] By 2050, the worldwide incidence of hip fracture in women is projected to increase by 240%; and in men by 310%.[4]

Osteoporosis represents a major health and societal burden in men, as well as in women. However, only a minority of men are screened and treated for osteoporosis and fracture prevention, even after the first fracture.[5]

3.1. Osteoporosis diagnosis

The gold standard to diagnose osteoporosis is based on the analysis of images by dual-energy X-ray absorptiometry (DXA), that provides information about the bone mineral density (BMD).
DXA is used to asses mineral content of the entire skeleton, and especially, the most vulnerable to fracture. Bone mineral content is the amount of mineral in the specific site scanned and, when divided by the area measured, can be used to derive a value for BMD.
Using these measurements, we can calculate T-score, that describes the patient's BMD in terms of the number of SDs by which it differs from the mean peak value in young, healthy persons of the same sex.

The World Health Organization (WHO) considers osteoporosis diagnosis when the T-score is at least minus 2.5 SD, in the lumbar spine, total hip, femoral neck; or radius, being measured when the lumbar spine and hip cannot be measured.

Classification	*T-score*
Normal	< -1.0 SD
Osteopenia	≥ -1.0 SD and < 2.5 SD
Osteoporosis	≥ -2.5 SD
Severe osteoporosis	≥ -2.5 SD + fragility fracture

Table 1. World Health Organization criteria for the classification of patients with bone mineral density measured by dual-energy X-ray absorptiometry.[2]

Nevertheless, osteoporosis also can be clinically diagnosed, in a patient with a fragility fracture with lack of other metabolic bone diseases. Also, tools as the clinical fracture risk assessment (FRAX®) are useful in patients with osteopenia and increased fracture risk. [7]

3.2. Trabecular Bone Score (TBS). Definition

The Trabecular Bone Score (TBS) is a texture index that evaluates pixel gray-level variations in DXA images of the lumbar spine. This tool has been developed in order to assess bone microarchitecture; because it is a determinant key of bone strength, that cannot be measured by DXA. It works by using the TBS iNsight software, that transforms the 2D images obtained in the DXA of the lumbar spine, in 3D images using mathematical calculations.

It is strongly related to the number of trabeculae and their connectivity, and negatively to the space between the trabeculae. A high TBS means that the bone microarchitecture is dense, well connected, with small spaces between trabeculae. In contrast, a low value means that the microarchitecture of the bone is incomplete and poorly connected, with wide spaces between trabeculae.

Therefore, despite being derived from standard DXA images, the information contained in TBS is independent and complementary to the information provided by BMD and the FRAX® tool.[8]

3.3. Technique and interpretation of TBS

The measurement is performed by a software tool that is installed on existing DXA scanners, as GE Lunar and Hologic devices, and calculate the TBS automatically at the same time that the DXA is done. In addition, it allows doing retrospective analysis, of the previous results of each patient. [9]

In order to understand the development of TBS we should consider the following issues:
A healthy patient has a well-structured trabecular bone at the vertebral level. This means that his trabecular structure is dense; with high connectivity, high trabecular number, and small spaces between trabeculae. If we project this structure onto a plane, we obtain a homogeneous image containing a large number of pixel value variations, but the amplitudes of these variations are small

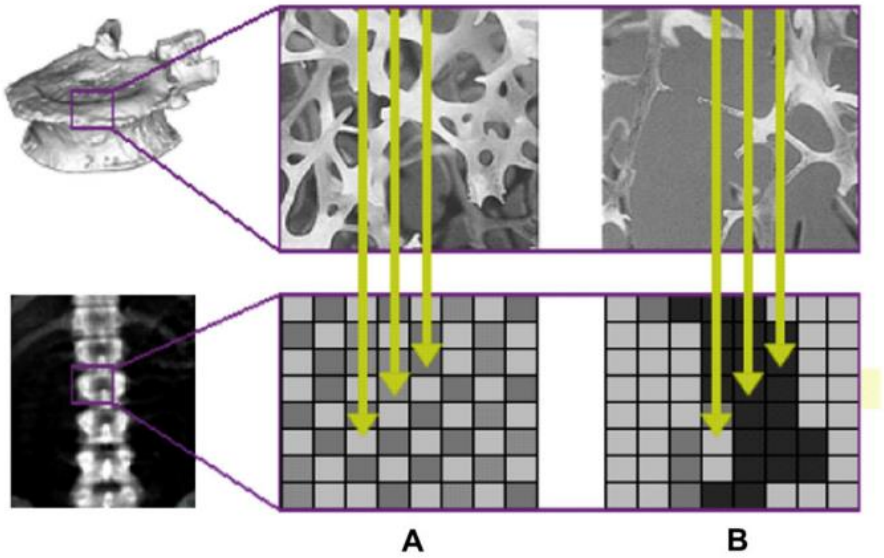

Figure 1. Healthy (A) vs altered (B) trabecular structures.

In Contrast, an osteoporotic patient has an altered trabecular bone structure. This indicates that his trabecular structure is porous; with low connectivity, low trabecular number, and wide spaces between trabeculae. If we project this structure onto a plane, we obtain an image containing a low number of pixel value variations, but the amplitudes of these variations are high (Fig. A1B).

TBS allows us to estimate a 3D structure from the existing variations on the 2D projected images by calculating the variogram. It is calculated as the sum of the squared gray-level differences between pixels at a specific distance.
TBS is a black-box algorithm using the variogram after its log-log transformation. TBS is calculated as the slope of the log-log transformation of this variogram. This slope characterizes the rate of gray-level amplitude variations into the trabecular bone.[10]

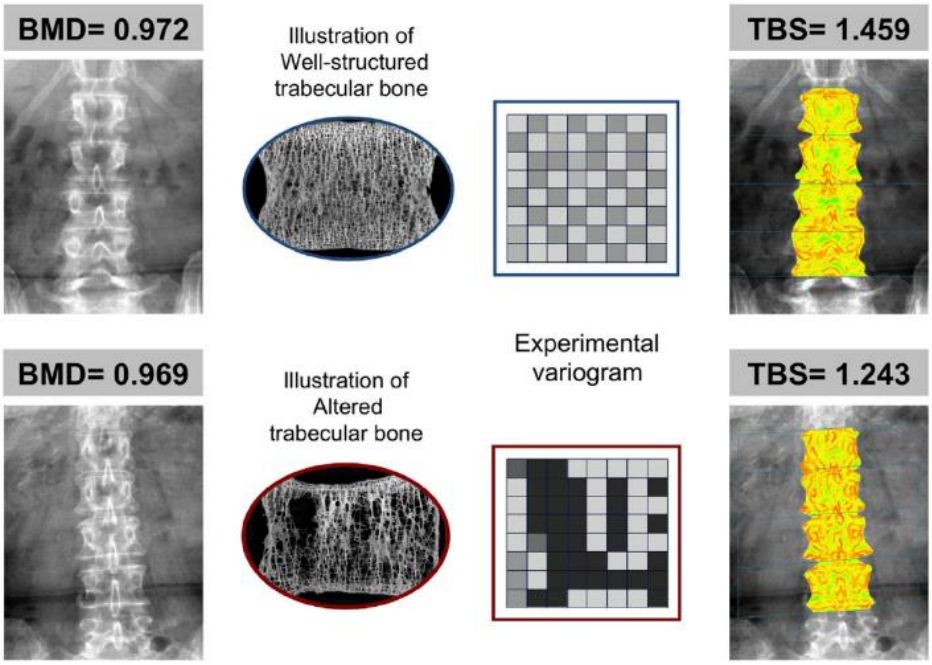

Figure 2. The experimental variogram of the gray variation and the TBS value obtained from a DXA image.

Upper panel is an example of a patient with a high TBS value and a good bone microarchitecture, which presents a high number of trabeculae, little separated and with high connectivity. In the experimental variogram, there is a gray scale variation of each pixel, if we compare with those around it, although of low amplitude.
Lowe panel, is another patient who presents a low TBS and a deteriorated bone microarchitecture, with smaller number of trabeculae and less connectivity to each other. There is smaller variation of grays between pixels, but of greater amplitude.

Both examples have a similar BMD with different trabecular involvement, this is because the first patient has thicker trabeculae in his vertebra despite having less density of these. This shows that TBS is an independent index of BMD and that vertebrae characterized densitometrically as osteoporotic can have very different TBS values.
Low thresholds are considered, with degraded bone microarchitecture, values for TBS below 1200 and considered normal above 1350, between 1200 and 1350 it is considered partially degraded, both in men and women.

Interpretation TBS values

Normal microarchitecture	TBS ≥ 1,350
Partially deteriorated	≥ 1200 TBS and < 1,350 TBS
Degraded microarchitecture	≤ 1,200 TBS

Table 2. Interpretation TBS values in women and men.

3.4. Applications of TBS

Although osteoporosis is considered a disease of women, 25% of the individuals with osteoporosis are men. BMD measurement by DXA is the gold standard used to diagnose osteoporosis and assess fracture risk. Nevertheless, BMD does not take into account alterations of microarchitecture. TBS is an index of bone microarchitecture that has shown efficiency as a fracture-risk assessment tool. Specially, the risk of vertebral fracture, femur and global fragility in women and men over 50 years.

Furthermore, TBS has shown sensitivity as an assessment of fracture risk in diabetic patients, as well as, patients in treatment with glucocorticoids, endocrinology patients that suffer from hypo and hyperparathyroidism, and also, patients with osteoarthritis.

Patients with type 2 diabetes (DM2) have a higher BMD and an increased risk of fragility fractures. Although in DM2 the risk of fracture is increased in relation to the non-diabetic population, baseline BMD values were higher in DM2 than in non-diabetics, while those in TBS were significantly lower in both men and women. In these studies, TBS in the lumbar spine was able to predict the appearance of fragility fractures both in diabetics and in patients without diabetes. In addition, the predictive capacity was higher than that of BMD in diabetic patients and TBS was inversely associated with hemoglobin A1c (HbA1c).

Glucocorticoids (GC) produce a fast bone loss and an increased risk of fracture that cannot be completely explained by changes in BMD. Several studies demonstrated that chronic GC therapy decrease the TBS rate, and this measure has more sensitivity than the DXA, in these patients. Moreover, this decrease in TBS rate was stronger in males than in women.

In primary hyperparathyroidism (PHPT), vertebral fractures are independent of BMD and may depend on decreased bone quality. Two small independent studies found that TBS was lower in patients with PHPT than in controls. TBS rate after parathyroidectomy was without changes, although, the patients treated with parathyroid hormone during 18 months, experimented a significant increase of TBS rate.

TBS has become a tool for predicting the risk of fractures and making decisions about the start of treatment, nevertheless, there are other factors that influence in bone resistance, such as age, sex, body mass index, smoking, intake of alcohol or personal history of osteoporotic fracture.

This risk factors can be assessed by FRAX^{TM}; a tool that evaluates the 10-year probability of suffering a hip fracture or a major osteoporotic fracture (clinical vertebral, hip, forearm and humerus). The calculation can be done including or not the results of the densitometry. The odds can be calculated for several European countries. Although the intervention thresholds in our country are not yet defined, the threshold for each age is established at a level of risk equivalent to that associated with a previous fracture and increases with age.

There are numerous studies that have shown that TBS is related to the risk of fracture. In 2015, McCloskey E, et al, published a meta-analysis that included men and women, from independent

international cohorts and including different ethnic groups, conducted with the objective of observing whether TBS predicted fracture risk independently of FRAX and examining the performance of a FRAX adjusted to TBS.

In the study, it is observed that the TBS predicts the risk of osteoporotic fractures in both sexes and in any type of fracture, independently of the BMD and the FRAX. In addition, the determination of the TBS improved the risk prediction of the FRAX tool.
Therefore, the determination of TBS has recently been incorporated into the factors used by the FRAX tool to calculate the risk of osteoporotic fracture, which seems to improve the predictive capacity.[11]

3.5. Limitations of TBS

As all clinical tools, TBS is associated with several limitations, both technical and clinical. Between technical limitations, we can stand out the inherent to the acquisition process, such as image noise, which contributes to degradation in resolution. It was found that noise addition reduced TBS mean values, irrespective of the pixel size considered; because it affects the experimental variogram used to calculate the TBS. Moreover, DXA scanners must be maintained within normal operating parameters and controlling causes of extraneous noise; due to this alteration degrade the image resolution, increasing TBS. Therefore, the results of TBS may not be comparable in different DXA devices. [12]
As a clinical limitation, we can outline the adjustment in TBS for the BMI, that is optimized for BMI ranges from 15 to 34 kg/m^2. In consequence, the assessment of TBS is not validated in patients with a BMI beyond these limits; owing to the increase in the thickness of the soft tissue degrade the resolution and reduce the average values of the TBS obtained.
The use of TBS in patients with significant scoliosis is also controversial, however, what constitutes 'significant' scoliosis is not clearly defined. [13]

3.6. TBS as control of response to treatments.

One of the treatments most frequently used in osteoporosis are antiresorptive drugs, that increases the mineralization and fills the remodeling space, nevertheless, it does not improve the trabecular microstructure. Therefore, TBS is not good in the response assessment of antiresorptive drugs.

Meanwhile, in therapy with outperforming drugs, the changes in TBS are more striking than with antiresorptive.

There are no studies that have shown that change in TBS is associated with a change in fracture risk. According to this, the International Society for Clinical Densitometry (ISCD) has recommended not to use TBS for monitoring therapy with antiresorptive.
The TBS provides a complementary and independent value to the BMD measurements, so it is not expected that the response to skeletal changes by an antiosteoporotic treatment will be similar.[14]

4. Hypothesis and objectives

In 2006, a study was started in order to recruit a cohort of postmenopausal women and men 50 years old and older from our region (The Camargo cohort). This is a prospective, community-based study designed to assess the prevalence of bone metabolic diseases and the risk factors of osteoporosis and fragility fractures in postmenopausal women and men 50 years of age or older treated in a health center of Cantabria, the Camargo Health Center. During these years, more than 3000 people have been recruited and their follow-up has begun. The assessment of the data obtained in our Cohort has allowed us to know the prevalence (cross-sectional study) in our environment of different disorders of bone and mineral metabolism. Moreover, we have studied the prevalence of osteoporosis risk factors. Once the recruitment phase was completed, the follow-up of this cohort (prospective study) allowed us to know the incidence in our environment of mineral metabolism disorders. The possibility of incorporating the measurement of the TBS to the people included in the Cohort could help us to know what are the reference values of the healthy population of both sexes in our region. It will also allow expanding the information on the capacity of the TBS to evaluate the involvement of the trabecular structure in the different alterations of the bone metabolism (osteoporosis, hypovitaminosis D, primary hyperparathyroidism, etc). Finally, the combination of BMD measurements along with those of TBS and the assessment of the clinical risk factors of the people in our cohort will allow us to add information about the usefulness of TBS in the stratification of fracture risk. Therefore, these are our objectives:

3.1. Objectives

- Describe the TBS values in men of 50 years or older in our region.
- Assess whether the TBS measurement decreases with age.
- To determine if there is an association between TBS and the presence of densitometric osteoporosis.
- Analyze the relationship of the TBS with BMD values in the lumbar, femoral neck and total hip.
- Asses the correlation of the TBS with bone quantitative ultrasound (QUS).
- To evaluate the relationship of the TBS with serum concentrations of 25(OH)D, PTH and bone remodeling markers (PINP and CTX).

5. Methodology and work plan

4.1. Design

A cross-sectional study with the baseline data of males included in the cohort that has already been recruited (The Camargo cohort).

4.2. Subjects of study

The study population consists of 863 men aged 50 or more years recruited during 2006-2010 in the Health Center of the City of Camargo (Cantabria, Spain), "The Camargo cohort".

4.3. Variables

4.3.1. Variables description

4.3.1.1. A structured clinical history is available, which has allowed us to collect the demographic, anthropometric and clinical variables -including the main risk factors for osteoporosis- (Annex I). We have expanded the clinical history model, allowing for the most relevant clinical aspects in the assessment and follow-up of these people (death and its cause, falls, new fractures and their location, changes in treatment, etc.).

4.3.1.2. We also have baseline routine analytical data and some of the parameters of mineral metabolism such as serum concentrations of 25OHD, PTHi, and those of P1NP and Cross-Laps, (CTX), as markers of formation and resorption, respectively.

- Baseline routine analytical data include: Basic blood count and biochemistry including glycemia, urea, creatinine, bilirubin, AST, ALT, GGT, calcium, phosphorus, albumin, alkaline phosphatase, and TSH (HUMV Central Laboratory).

- Specific parameters of bone metabolism include: Serum concentrations of 25-hydroxyvitamin D (25OHD), parathormone (intact-PTHi- molecule), pro-amino terminal propeptide of type 1 (P1NP) and carboxy-terminal telopeptide of the alpha 1 chain of collagen type 1 (CTX). They were determined by a fully automated Roche electrochemiluminescence system (Elecsys 2010, Roche Diagnostics, GmbH, Mannheim, Germany). The detection limit of serum 25 OHD was 4 ng/ml, its intraassay coefficient of variation (CV) 5%, and its interassay CV 7.5%. Regarding intact PTH, the detection limit was 6 pg/ml, with a normal range of 15-65 pg/ml. Intraassay and interassay CV were 3.4% and 5.9%, respectively. The P1NP limit of detection was 5 ng/ml, its reference range 15-78 ng/ml, and its intraassay and interassay CV 3.9% and 4.1%, respectively. Intraassay and interassay CV for β-CTX were 4.2% and 4.7%, also respectively, the detection limit was 0.01 ng/ml, and its reference range 0.112-1.018 ng/ml.[16,17.]

4.3.1.3. Bone mineral density assessment

BMD was measured by DXA (Hologic QDR 4500, Bedford, MA, USA) at the lumbar spine (LS), femoral neck (FN), and total hip (TH). Results were expressed in grams per square centimeter and as T-score (defined as the number of standard deviations [SDs] below the mean value of young women). In vivo precision was 0.4-1.5% at the different measurement sites. Quality control was performed according to the usual standards.[16]

4.3.1.4. Trabecular Bone Score (TBS).

Spine TBS measurements were performed using the TBS software installed on our densitometer (TBS iNsight® v2.1, Med-Imaps, Pessac, France). The TBS was calculated on the basis of the raw data acquired in the DXA scan, assessing the same vertebrae on which the LS-BMD was measured.[25] As a rule, the measurement of BMD in LS was performed in L1-L4, with the exception of those cases in which the morphology of a vertebra advised its exclusion.

4.3.1.5. Quantitative ultrasound

Heel bone ultrasonography (QUS) measurements were performed in all the subjects using the Sahara Clinical Sonometer (Hologic, Bedford, MA, USA). The Sahara device measured both broadband ultrasound attenuation (BUA) (dB/MHz) and speed of sound (SOS) (m/s) at a fixed region of interest in the right mid-calcaneous. The BUA and SOS results are combined to provide the "quantitative ultrasound index" (QUI) using the formula: QUI = 0.41 * (BUA + SOS) – 571. The European reference population has been described elsewhere[18,19], and yields similar results to the application of normative values from Spanish women for the same QUS device. Quality controls were performed daily by scanning manufacturer-provided phantoms prior to scanning the subjects. In-vivo short-term precision was 4.9% for BUA, 0.4% for SOS, and 3.4% for QUI; in vitro precision was 0.4% for SOS and 2.7% for BUA. One single investigator performed all QUS measurements.

4.3.1.6. Association between TBS and the presence of densitometric osteoporosis.

The results of the TBS were also analyzed after stratifying the participants according to the values of BMD in the spine and hip (normal, osteopenia and osteoporosis).

4.4. Statistical analysis

The statistical analysis of the data was carried out using the SPSS 22.0 package. A descriptive analysis of the sample was carried out. The quantitative variables were expressed as mean ± standard deviation or median (interquartile range) as appropriate. The qualitative variables were expressed as number and percentage. Correlations between study variables were analyzed by the Pearson coefficient as appropriate. To assess if there were differences between the TBS in the different groups (osteoporosis, low bone mass or Normal) an Analysis of the Variance (ANOVA) was performed, while to evaluate the relationship between TBS and BMI, age, etc., the Pearson Correlation was used.

4.5. Ethical aspects

The people included in this study belong to the Camargo Cohort. The study of this Cohort has been approved by the Committee of Ethics and Clinical Research of Cantabria and all the people included in the study have read and signed the mandatory informed consent (Annex II).

6. Results

Initially a total of 1003 men with were included in the study, although 115 were excluded because they did not have adequate images of lumbar BMD or TBS after the treatment period, and 25 because they presented a BMI less than 15 kg / m2 or greater than 37 kg / m2.

Table 3 shows the baseline characteristics of the study population.

	N	Mean	SD
Age (years)	863	64.53	8.77
Weight (kg)	861	82.04	11.66
Height (cm)	861	1.68	0.06
IMC (kg/m^2)	861	28.96	3.51
Waist perimeter (cm)	805	101.61	9.68
Wingspan (cm)	850	172.48	8.76
Glucose (mg/dl)	859	102.86	27.94
Urea (mg/dl)	202	43.56	12.66
Creatinine (mg/dl)	859	1.05	0.23
Cholesterol (mg/dl)	858	209.21	39.34
HDL (mg/dl)	833	51.94	13.21
LDL (mg/dl)	828	133.61	33.72
Triglycerides (mg/dl)	835	120.46	78.73
Alkaline Phosphatase (U/L)	853	67.32	20.57
Total protein (g/ml)	830	7.193	0.41
Albumin (g/dl)	708	4.45	0.30
Calcium (mg/dl)	848	9.51	0.36
Phosphorus (mg/dl)	804	3.05	0.48
PCR (mg/L)	815	0.47	1.01
T4L (ng/dl)	798	1.16	0.17
TSH (uU/ml)	835	1.61	1.15
PTHi (pg/ml)	863	55.37	22.92
25-OHD (ng/ml)	862	22.81	8.15
CTX (ng/ml)	863	0.299	0.177
P1NP (ng/ml)	863	37.72	17.17

Table 3. Baseline characteristics of the population (n=863).
25OHD: 25-hydroxyvitamin D; PTH intact parathyroid hormone; CTX: C-terminal telopeptide of type I collagen; P1NP: Aminoterminal propeptide of type I collagen.

Table 4 summarize bone mineral density (BMD), quantitative ultrasound (QUS), and trabecular bone score (TBS).

	N	Mean	SD
Lumbar BMD (g/cm^2)	863	1.021	0.159
Lumbar T	863	-0.83	1.45
lumbar Z	848	-0.04	1.50
BMD femoral neck (g/cm^2)	853	0.819	0.122
Femoral neck T	853	-0.80	0.90
Femoral neck Z (g/cm^2)	839	0.28	0.91
Total hip BMD (g/cm^2)	853	0.977	0.130
Total hip T	853	-0.35	0.85
Total hip Z	839	0.23	0.87
QUI/Stiffness	783	97.55	30.48
T	782	-0.26	1.82
SOS (m/sec)	763	1553.22	48.40
BUA (dB/MHz)	763	79.14	25.79
BMDe (g/cm^2)	779	0.54	0.18
TBS	863	1.355	0.128

Table 4. Bone mineral density (BMD), quantitative ultrasound (QUS), and trabecular bone score (TBS) in men.

BMD. LS: Bone mineral density at the lumbar spine; BMD: Bone mineral density; QUI: Quantitative ultrasound index; SOS: Speed of sound; BUA: Broadband ultrasound attenuation.

A total of 863 men aged 50-92 years (64,53 ± 8,77 years) were included in the study included in a population-based study of osteoporosis screening and other metabolic bone diseases (the Camargo cohort) have been studied. The BMI, expressed in kg / m2 is 28,96; and the waist perimeter average, expressed in cm is 101,61. According to the analytical data, blood calcium levels of 9,51 mg/dl stand out. Regarding the reference values of bone densitometry, it should be noted that the average value in the patients studied in the cohort is in the lumbar spine is 1,021, in the femoral neck it is 0,819 and in the total hip, it is 0,977.

Four hundred and forty-three men (51.33%) had a TBS >1.350, which is considered to be normal; 315 (36.5%) a TBS between 1.200 and 1.350, consistent with partially degraded microarchitecture; and 105 (12.16%) a TBS <1.200. which defines degraded microarchitecture.

The values (Mean ± SD) of the Trabecular Bone Score (TBS), grouped into patients with osteoporosis, osteopenia and without bone disease, are shown in table 5.

TBS	N	Mean	SD
OP	105	1.266	0.118
Osteopenia	315	1.331	0.120
Normal	443	1.394	0.121
Total	863	1.355	0.128

Table 5. TBS values.

The present work shows that. in a cohort of Spanish men (Camargo Cohort), constituted for the study of risk factors of osteoporotic fracture, the average TBS is located in degraded microarchitecture values and is related to several clinical and anthropometric factors such as age, weight, height, BMD, history of fragility fracture or the presence of DM2.

		Age	BMI	PTHi	25-OHD	P1NP	CTX	BMD.LS	BMD.FN	BMD.TH	SOS	BUA
TBS	**r**	-0.157	-0.494	-0.080	0.177	0.009	0.049	0.350	0.125	0.150	0.141	0.112
	p	0.000	0.000	0.019	0.000	0.784	0.155	0.000	0.000	0.000	0.000	0.002
		863	861	863	862	863	863	863	853	853	763	763

Table 6. Correlations.
BMI: Body mass index; PTH intact parathyroid hormone; 25OHD: 25-hydroxyvitamin D; P1NP: Aminoterminal propeptide of type I collagen; CTX: C-terminal telopeptide of type I collagen; BMD. LS: Bone mineral density at the lumbar spine. BMD. FN: Bone mineral density at the femoral neck. BMD. TH: Bone mineral density at the total hip; SOS: Speed of sound; BUA: Broadband ultrasound attenuation.

As presented in table 6, weakly significant negative correlations were obtained between TBS and age (r=-0.157, p<0.0001), as well as, BMI (r=-0.494, p<0.0001) and PTHi (r=-0.080, p<0.019). Nevertheless, there is a positive correlation between TBS and 25-OHD (r=0.177, p<0.0001) and BMD in the three localizations studied. We can stand out lumbar BMD, that is strongly associated with higher correlation than femoral neck and total hip.
Furthermore, P1NP (r= 0.009, p<0.784) and CTX (r= 0.049, p<0.155), can be considered independent valors of TBS, due to their p valor are increased, whereas a significant positive correlation was obtained SOS (r=0.141, p<0.0001) and BUA (r=0.112, p<0,002).

Analyzing the values of the data proposed in the previous tables, we can conclude that in the study of the Camargo Cohort in men, although the densitometric and TBS indices show that there is a statistically significant correlation between the decrease in bone mass and microarchitecture with the aging process, the TBS values are lower in patients with osteoporosis than in patients with osteopenia or normal bone mass; and that both densitometry and TBS seem to be very useful for the diagnostic and follow-up techniques for loss of bone mass. The relationship between both tests

does not seem to have good results when comparing them, so that although the TBS does a more in-depth study of the bone microarchitecture, and that the data exposed on these appear to have a high degree of reliability, bone densitometry continues to have a greater significance in terms of the diagnosis and monitoring of osteoporosis.

7. Discussion

TBS is a textural index that evaluates pixel gray-level variations in the lumbar spine DXA image, providing an indirect index of trabecular microarchitecture. It has shown efficiency as a fracture-risk assessment tool, due to lower TBS values are associated with increased risk of osteoporosis fracture, especially in those with densiometric values of normality and osteopenia.
In addition, the information contained in TBS is independent and complementary to the information provided by BMD and the FRAX tool. This allows a better prediction of future fractures and guiding decisions regarding treatment initiation, particularly for patients with FRAX probabilities around an intervention threshold.[11]

In this study, a total of 863 men, of 50 years old or older, were included in order to analyze the TBS values. One hundred and five of these patients (12.16%) had a TBS lower than 1.200, that defined as osteoporosis, with degraded microarchitecture; 315 (36.5%) had osteopenia, with a TBS between 1.200 and 1.350; and 443 (51.33%) men had normal TBS values, that is over 1.350.

In our population, TBS values are similar to those reported in other population-based studies as NHANES 2005-2008 study, Looker et al.[20]. In this study, they examined demographic patterns and body size relationship in TBS and lumbar spine BMD of US adults. They found mean TBS values in non-Hispanic white men over 60 years were 1.301; meanwhile, in our study, the mean TBS values were 1.355.

The correlation coefficients of the relationship between TBS and BMD ranged from 0.150, at the TH; to 0.350, at the LS. However, the relationship between TBS and the QUS parameters was significant but weak. This is due to both parameters share the common characteristic of being related to bone microstructure.
Nevertheless, bone microarchitecture has to be determined by different aspects, as the disposition of the trabeculae, the arrangement of the lamellae or collagen organization; and it is conceivable that TBS and QUS are influenced by these microarchitecture elements in different ways. In any case, beyond the microarchitecture, TBS is determined to a large extent by bone mass, an expression of which is its better relationship with the result of the densitometric study.

We have found a negative correlation between TBS and age, indicating that TBS values decrease with age (data not shown). We also found that TBS was positively correlated with serum levels of 25(OH)D, and negatively with PTH. Low serum 25(OH) D concentrations are associated with increased PTH levels, high bone turnover and a weakened bone architecture.[14] These modifications occur secondary to the preferential effect of vitamin D and PTH on cortical rather than trabecular

bone.[15] This favored relationship with cortical bone may explain the weak relationship between vitamin D, PTH and TBS that we observed in our study, since TBS is assessed at the spine, which is a skeletal site fundamentally consisting of trabecular bone.

Bone remodeling markers, are also related to bone microstructure, because they define the rate of turnover; however, the correlation between TBS and bone remodeling markers, as P1NP and CTX, are not significant. This may also be due to the fact that TBS assesses a very specific area of the skeleton, while the markers represent the global turnover of the whole skeleton.

Regarding this study, it has strengths and limitations. Among the first ones, we can stand out that all the participants were carefully studied from the mineral and bone metabolism point of view. Additionally, participants with BMI lower than 15 kg/m^2 or greater than 37 kg/m^2 were also excluded. Finally, all samples were obtained at the same time of day and in a fasting state, and all BMD and TBS measurements were performed with the same device; in order to minimize biological variability. Our study has limitations, those inherent in a cohort study that analyzes the results of a new technique transversely, and there may be selection bias or basal and longitudinal information that influence the results.

8. **Conclusions**

1) TBS values of adult males from our area are similar to those described in other countries.
2) TBS measurement decreases with age, due to TBS is negatively correlated with age, in our population.
3) TBS is lower in patients with densitometric osteoporosis than in those with osteopenia or normal BMD.
4) Although the TBS and BMD values are significantly correlated, the degree of relationship is poor.
5) A weak association was observed between TBS and QUS, suggesting that both techniques capture different aspects of bone microarchitecture.
6) The weak association with 25(OH)D, PTH, and the absence of association with bone remodeling markers may be due to the fact that TBS assesses a specific part of the skeleton, as trabecular bone; whilst the three serum factors are related to the whole skeleton.

9. **Bibliography**

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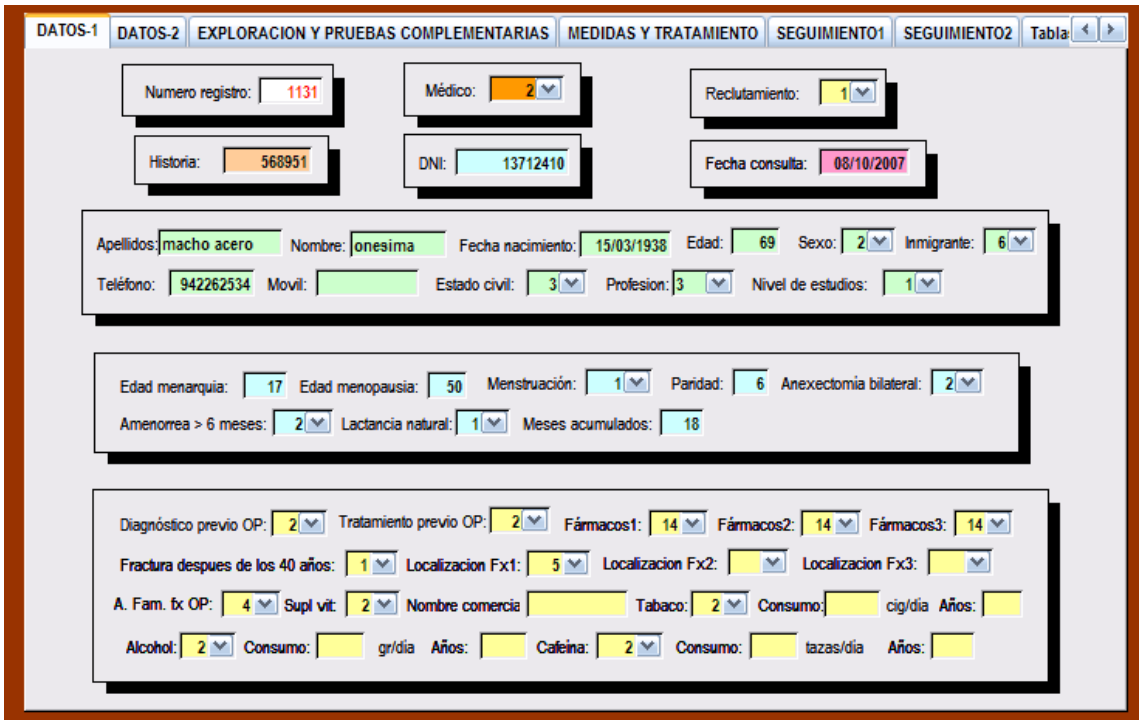
ANEX I


DATOS-1
DATOS-2
EXPLORACION Y PRUEBAS COMPLEMENTARIAS
MEDIDAS Y TRATAMIENTO
SEGUIMIENTO1
SEGUIMIENTO2
Tabla
Numero registro: 1131
Médico: 2
Reclutamiento: 1
Historia: 568951
DNI: 13712410
Fecha consulta: 08/10/2007
Apellidos: macho acero
Nombre: onesima
Fecha nacimiento: 15/03/1938
Edad: 69
Sexo: 2
Inmigrante: 6
Teléfono: 942262534
Movil:
Estado civil: 3
Profesion: 3
Nivel de estudios: 1
Edad menarquia: 17
Edad menopausia: 50
Menstruación: 1
Paridad: 6
Anexectomia bilateral: 2
Amenorrea > 6 meses: 2
Lactancia natural: 1
Meses acumulados: 18
Diagnóstico previo OP: 2
Tratamiento previo OP: 2
Fármacos1: 14
Fármacos2: 14
Fármacos3: 14
Fractura despues de los 40 años: 1
Localizacion Fx1: 5
Localizacion Fx2:
Localizacion Fx3:
A. Fam. fx OP: 4
Supl vit: 2
Nombre comercia
Tabaco: 2
Consumo:
cig/dia
Años:
Alcohol: 2
Consumo:
gr/dia
Años:
Cafeina: 2
Consumo:
tazas/dia
Años:


DATOS-1
DATOS-2
EXPLORACION Y PRUEBAS COMPLEMENTARIAS
MEDIDAS Y TRATAMIENTO
SEGUIMIENTO1
SEGUIMIENTO2
Tabla
Ejercicio:
Disminucion agudeza visual: 2
Cataras: 2
Hipoacusia: 2
Caidas ultimo año: 2
Capacidad de levantarse silla: 1
Lácteos en dieta: 3 raciones/dia
Cantidad: 550 mg/dl
MEDICACION CON INFLUENCIA ÓSEA
Esteroides: 5
Antiepilepticos: 2
Inmunosupresores: 2
Tiazidas: 3
H tiroideas: 2
Anticoagulantes: 2
BZD: 1
IRSS: 2
Antiarritmicos: 2
Betabloqueantes: 2
Estatinas: 2
Insulina: 2
ADO: 2
Diureticos no tiazidas: 3
IBPs:
Calcio: 2
Vitamina D: 2
Bisfosfonatos: 2
Raloxifeno: 2
Tibolona: 2
Calcitonina: 2
THS: 2
Estroncio: 2
PTH: 2
Tiempo de uso de antiresortivos (meses):
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Diabetes: 2
HTA: 1
Dislipemia: 2
C. Isquemica: 2
I. renal crónica: 2
EPOC: 2
Br cronica 1
Hepatopatia cronica: 2
Neoplasia: 2
ACVA: 2
Parkinson: 2
Demencia: 2
Artrosis: 1
Protesis:
Urolitiasis: 2
Hipogonadismo (varón):
Hiperparatiroidismo primario: 2
Artromialgias: 2
Conectivopatias: 2
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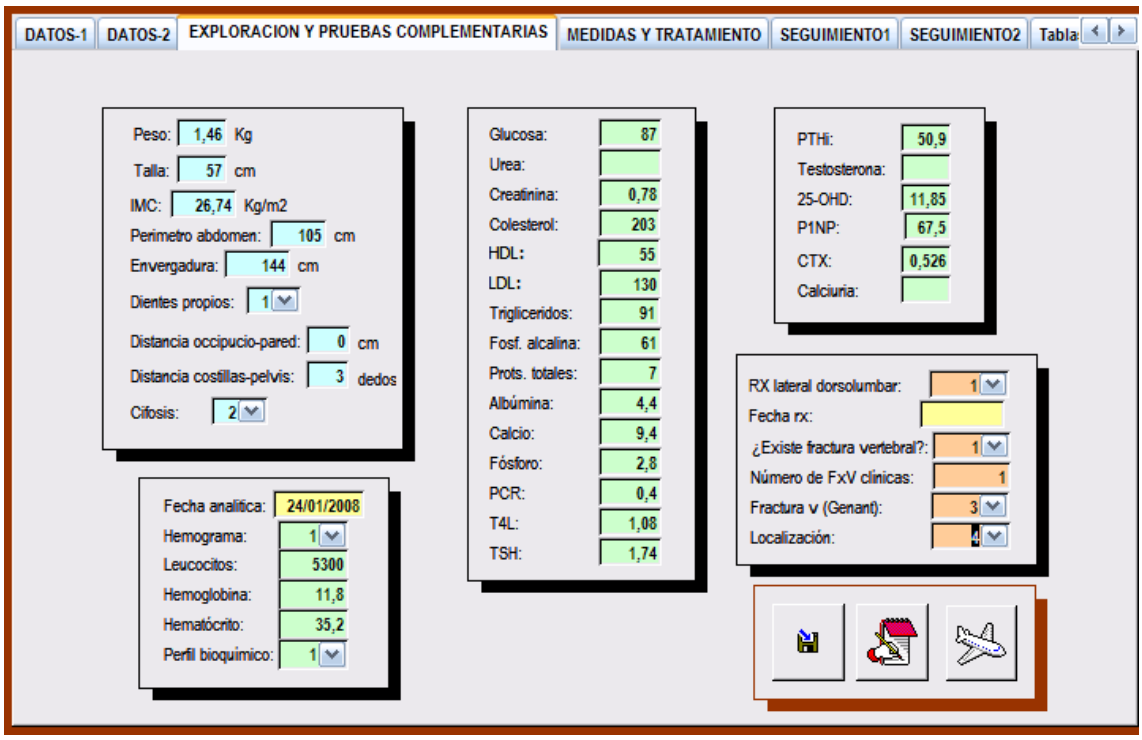
Fibromialgia: 2


DATOS-1
DATOS-2
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SEGUIMIENTO1
SEGUIMIENTO2
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Dientes propios: 1
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Distancia costillas-pelvis: 3 dedos
Cifosis: 2
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Perfil bioquimico: 1
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LDL: 130
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Calcio: 9,4
Fósforo: 2,8
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T4L: 1,08
TSH: 1,74
PTHi: 50,9
Testosterona:
25-OHD: 11,85
P1NP: 67,5
CTX: 0,526
Calciuria:
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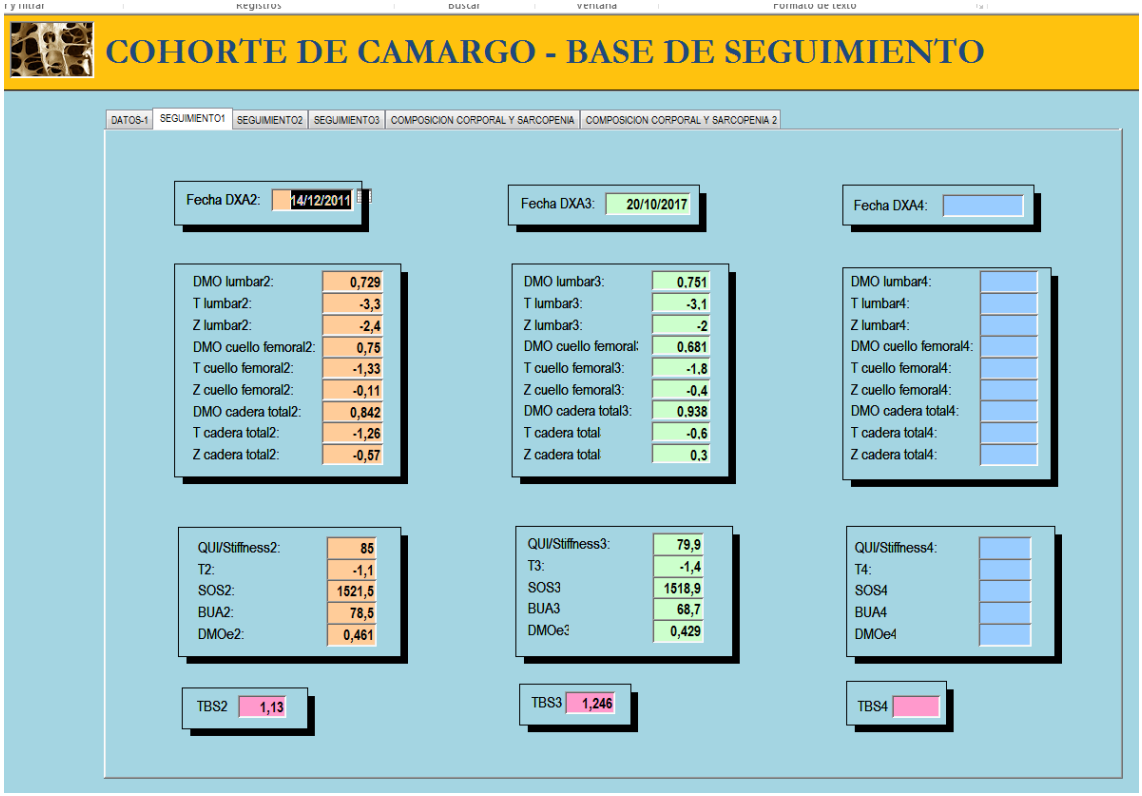
COHORTE DE CAMARGO - BASE DE SEGUIMIENTO
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SEGUIMIENTO2
SEGUIMIENTO3
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COMPOSICION CORPORAL Y SARCOPENIA 2
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T lumbar2: -3,3
Z lumbar2: -2,4
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Z cuello femoral2: -0,11
DMO cadera total2: 0,842
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QUI/Stiffness2: 85
T2: -1,1
SOS2: 1521,5
BUA2: 78,5
DMOe2: 0,461
TBS2 1,13
Fecha DXA3: 20/10/2017
DMO lumbar3: 0,751
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Z lumbar3: -2
DMO cuello femoral: 0,681
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DMO cadera total3: 0,938
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QUI/Stiffness3: 79,9
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SOS3 1518,9
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DMO cuello femoral4:
T cuello femoral4:
Z cuello femoral4:
DMO cadera total4:
T cadera total4:
Z cadera total4:
QUI/Stiffness4:
T4:
SOS4
BUA4
DMOe4
TBS4

ANEX II

CONSENTIMIENTO INFORMADO

TÍTULO DEL ESTUDIO: Estudio del metabolismo óseo y mineral de la población femenina postmenopáusica y masculina mayor de 50 años atendida por un Centro de Salud en Cantabria. La cohorte Camargo.

INVESTIGADOR PRINCIPAL: José M. Olmos Martínez

CENTRO: Hospital Universitario Marqués de Valdecilla. IDIVAL. Universidad de Cantabria.

D./Dña._____

(Nombre y apellidos del paciente en MAYÚSCULAS)

He leído y comprendido la hoja de información que se me ha entregado sobre el estudio arriba indicado.

He recibido suficiente información sobre el estudio.

He realizado todas las preguntas que he precisado sobre el estudio.

He hablado con el Dr./Dra. …….. con quien he clarificado las posibles dudas.

Comprendo que mi participación es voluntaria.

Comprendo que puedo retirarme del estudio:

- Cuando quiera
- Sin dar explicaciones
- Sin que repercuta en mis cuidados médicos

Comprendo que la información personal que aporto será confidencial y no se mostrará a nadie sin mi consentimiento.

Comprendo que mi participación en el estudio implica autorizar …

Y presto libremente mi conformidad para participar en el estudio.

Firma del investigador Firma del paciente

Fecha _____

(la fecha debe estar cumplimentada de puño y letra por el paciente)

REVOCACIÓN DEL CONSENTIMIENTO:

Yo, D./Dña. _____
retiro el consentimiento otorgado para mi participación en el estudio arriba citado.

Fecha y firma:

HOJA DE INFORMACIÓN AL PACIENTE

TÍTULO DEL ESTUDIO: Estudio del metabolismo óseo y mineral de la población femenina postmenopáusica y masculina mayor de 50 años atendida por un Centro de Salud en Cantabria. La cohorte Camargo.

INVESTIGADOR PRINCIPAL: José M. Olmos Martínez.

CENTRO: Hospital Universitario Marqués de Valdecilla. IDIVAL. Universidad de Cantabria.

INTRODUCCIÓN

Nos dirigimos a usted para informarle sobre un estudio de investigación en el que se le invita a participar. El estudio ha sido aprobado por el Comité Ético de Investigación Clínica correspondiente y respeta la normativa vigente.

Nuestra intención es proporcionarle información adecuada y suficiente para que pueda evaluar y juzgar si quiere o no participar en el estudio. Para ello lea con atención esta hoja informativa con atención y luego podrá preguntar cualquier duda que le surja relativa al estudio. Además, puede consultar con cualquier persona que considere oportuno.

PARTICIPACIÓN VOLUNTARIA

Debe saber que su participación en este estudio es voluntaria y puede decidir no participar. En caso de que decida participar en el estudio puede cambiar su decisión y retirar su consentimiento en cualquier momento, sin que por ello se altere la relación con su médico y sin que se produzca perjuicio alguno en su tratamiento.

DESCRIPCIÓN GENERAL DEL ESTUDIO

Metodología:

Los trastornos del metabolismo óseo y mineral (osteoporosis, enfermedad de Paget y déficit de vitamina D) son procesos frecuentes que producen un debilitamiento de la resistencia de los huesos, aumentando el peligro de tener una fractura.

En la mayoría de las ocasiones no dan síntomas antes de la fractura y por ello es importante diagnosticarlos precozmente. Para ello, además del preceptivo reconocimiento médico, disponemos de métodos auxiliares como son algunas determinaciones analíticas, la radiología y la densitometría. Con estas técnicas podemos detectar la presencia de estos trastornos antes de que aparezcan los síntomas y nos hacemos una idea aproximada de cuál es el riesgo de fractura.

Hace algo más de seis años aceptó usted participar en este estudio. Como recordará, el estudio en

el que le propusimos participar consistió en acudir a su Centro de Salud para ser valorado por su médico de familia y, posteriormente, realizar unas determinaciones analíticas (se le extrajeron unos 30 cc de sangre), se realizó una radiografía de la columna y se midió la densidad mineral ósea por DEXA. **También se obtuvo una muestra de 5 ml de sangre que se utilizó para extraer su DNA que se almacenó a -80ºC en el laboratorio del Departamento de Medicina y Psiquiatría de la Universidad de Cantabria siendo el responsable de las mismas el Dr. José A. Riancho Moral. Estas muestras se han utilizado para determinar si existe una predisposición genética a desarrollar alguna enfermedad ósea metabólica como la osteoporosis. El material genético no utilizado en el presente estudio se almacenará para estudios posteriores, siempre relacionados con la osteoporosis y otras enfermedades óseas metabólicas.** E**n** caso de revelarse información relevante para su salud, usted tiene derecho a ser informado, aunque también puede indicar que no quieren recibir esta información.

El estudio actual es un estudio observacional prospectivo, que pretende continuar el seguimiento ya iniciado hace algunos años. Para ello, tendrá que acudir en una ocasión cada tres o cuatro años al Departamento de Medicina Interna para realizarle una serie de preguntas acerca de su salud (caídas, posibles fracturas, tratamiento actual, etc.). Además, al igual que en la visita inicial, se obtendrá una muestra de sangre para llevar a cabo una serie de determinaciones analíticas (se le extraerán unos 30 cc de sangre, que es el equivalente a dos cucharadas soperas) y se realizará una radiografía lateral de columna dorsal y lumbar y se volverá a medir la densidad mineral ósea mediante densitometría. En esta ocasión, analizaremos además el Trabecular Bone Score (TBS) a partir de los resultados de la primera densitometría, con los datos almacenados en el densitómetro, sin necesidad de que tenga usted que repetir esta prueba para este menester. También se valorará la velocidad habitual de la marcha y se evaluará la fuerza muscular de prensión con ayuda de un dinamómetro. La duración aproximada para llevar a cabo todas estas pruebas será de unos 30-40 minutos.

Las pruebas que se le van a realizar son las mismas que se le hacen a un paciente en el que se quiera descartar la existencia de un trastorno del metabolismo óseo y mineral (osteoporosis, enfermedad de Paget o deficiencia de vitamina D) o de sarcopenia (pérdida de masa y fuerza muscular). No implican ningún peligro y no interferirán con sus otros problemas de salud ni con su plan de tratamiento habitual. Y nos van a ayudar a estudiar su metabolismo mineral óseo y a orientarle sobre si precisa o no alguna medida de prevención o un tratamiento.

BENEFICIOS Y RIESGOS DERIVADOS DE SU PARTICIPACIÓN EN EL ESTUDIO

Beneficios de la participación en el estudio.

Se espera mejorar el conocimiento científico relativo a las enfermedades metabólicas óseas y puede que otros pacientes se beneficien en el futuro. Es posible que usted no reciba ningún beneficio directo en su salud por su participación en este estudio.

Riesgos de la participación en el estudio.

Se trata de un estudio observacional por lo que no se llevará a cabo ninguna intervención terapéutica, salvo las que se derivaran de la posible detección de alguna enfermedad metabólica ósea (osteoporosis, deficiencia en vitamina D, etc.) no conocida previamente.

Las muestras de sangre se obtendrán mediante venopunción de forma similar a lo que sucede cuando se realiza un análisis rutinario de sangre.

Tendrá que acudir a las visitas previstas en el estudio (una vez cada tres o cuatro años) y someterse a las pruebas complementarias previstas en el protocolo del estudio.

Si su médico del estudio considera que seguir participando puede suponer un riesgo para su salud puede retirarle del mismo aún sin su consentimiento.

CIRCUITO DE MUESTRAS BIOLÓGICAS

Este estudio cumple la normativa vigente de la Ley 14/2007 de investigación biomédica en cuanto a la protección de los derechos de los pacientes que quieran libremente participar y el manejo de muestras biológicas.

La muestra obtenida de sangre supondrá de una cantidad de unos 30 cc y serán sometidas a las siguientes pruebas: Centrifugación para obtener el suero. Determinación de analítica rutinaria (Perfil de Medicina Interna incluyendo Fosforo y PCR, determinación de parathormona (PTHi), vitamina D (25OHD) y marcadores de la remodelación ósea (PINP y CTX).

Durante el estudio las muestras se conservarán en congeladores a -20ºC (hasta un máximo de 2 meses) y posteriormente a -80ºC en el congelador situado en la planta baja del edificio del Instituto de Investigación Marqués de Valdecilla (IDIVAL)) y se mantendrán hasta la finalización de la muestra.

Si hay restos sobrantes de las muestras se donarán al Biobanco del IDIVAL.

CONFIDENCIALIDAD

Todos los datos de carácter personal se tratarán de acuerdo con lo dispuesto en la Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal y el Real Decreto 1720/2007, de 21 de diciembre, por el que se aprueba el Reglamento que la desarrolla.

Los datos recogidos para el estudio estarán identificados mediante un código de forma que no sea posible la identificación del paciente. Sólo el investigador y personas autorizadas relacionadas con el estudio tendrán acceso a dicho código y se comprometen a usar esta información exclusivamente para los fines planteados en el estudio. Los miembros del Comité Ético de Investigación Clínica o Autoridades Sanitarias pueden tener acceso a esta información en cumplimiento de requisitos legales. Se preservará la confidencialidad de estos datos y no podrán ser relacionados con usted, incluso aunque los resultados del estudio sean publicados.

DATOS DE CONTACTO

Si tiene dudas en cualquier momento puede contactar con el médico del estudio:

Dr. José M. Olmos_____

Tfno.: 942-202513 (Desde las 09:00 hasta las 14:00h) _____