The review process has now been completed and I am pleased to report that the paper was accepted for publication on Jul 13, 2021. It is tentatively scheduled for publication in approximately four months from the date of acceptance.

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Focal bone marrow defects in the jawbone determined by ultrasonography – Validation of new trans alveolar ultrasound technique for measuring jawbone density in 210 patients

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Abstract

Ultrasound imaging of the jawbone is not currently used in dental medicine to determine bone density. Bone marrow defects in the human jawbone (BMDJ/FDOJ) are widely discussed in dentistry due to their role in implant failures and as sources of inflammation in various immune diseases. The use of through-transmission alveolar ultrasonography (TAU) to locate BMDJ/FDOJ was evaluated using a new TAU apparatus (TAU-n). The objective was to determine whether the readings displayed by TAU-n accurately indicate the clinical parameters to detect BMDJ/FDOJ. Three parameters were compared with TAU-n measurements: 2D-OPG, Hounsfield units (HU) using digital volume tomography and postoperatively measured levels of RANTES/CCL5 (R/C) expression in BMDJ/FDOJ samples. Based on the available clinical data, HU, R/C expression, and TAU-n color codes yielded consistent results with respect to bone mineral density. Thus, ultrasonography with TAU-n is a reliable and efficient diagnostic method to screen for BMDJ/FDOJ in dentistry.

Keywords: Bone marrow defects of the jaw, digital volume tomography, fatty-degenerative osteolysis/osteonecrosis of the jaw, orthopantomogram, RANTES/CCL5, TAU-n device, transalveolar ultrasonography.

Introduction

In the medical field, ultrasonography is widely used to image various types of soft tissues. In principle, images of structures in the body are generated by analyzing the reflection of ultrasound waves. To derive useful information concerning the status of the jawbone, different ultrasound techniques must be employed as the ultrasound waves are almost completely reflected at the bone/soft tissue interface. The *in vivo* measurement of ultrasound velocity in human cortical bone was introduced as a rapid, reliable, and noninvasive method which could be used to analyze the mechanical properties of bone (Greenfield et al., 1981). Cortical bone samples showed the highest values, followed by mixed bone samples and cancellous bone samples, with the latter showing the lowest values (Kumar et al., 2011). Thus, guided ultrasound waves are able to detect ischemic bone-marrow diseases, i.e., focal osteoporotic defects or cavitations in the jawbone (Al-Nawas et al., 2001). Intraoral equipment used in guided ultrasound must be minimized, however, as the area cannot be examined with commonly used ultrasound apparatus. Until now, ultrasound examinations have thus been of limited use in dental medicine, although they have been used to detect “focal” bone defects of the jawbone, (“focal osteoporotic marrow defects”), as described in previous scientific research (Kaufman and Einhorn, 1993; Lipani et al., 1982). The status of cancellous bone in the jaws may be of great clinical importance. Researchers have provided anatomical evidence that cancellous bone may be significantly degenerated, a phenomenon described as “ischemic osteonecrosis leading to cavitational lesions” (Bouquot et al., 1992).

The authors of the present study conducted an in-depth investigation of the tissue in such lesions, which appeared as clumps of fat within intact cortical bone. This tissue was in an ischemic, fatty-degenerative state. The observed bone marrow defects of the jaw (BMDJ) were thus defined as “fatty-degenerative osteolysis/osteonecrosis of the jawbone” (FDOJ). The clumps of fat found in the osteolytic jawbone are extremely biochemically active and produce specific cytokines in high amounts, the most notable of which is the chemokine RANTES (regulated on activation, normal T-cell expressed and secreted), or more recently known as CCL5 (chemokine ligand 5; R/C). This chronic R/C production may influence immunological patterns and exacerbate systemic immunological diseases (Lechner and Mayer, 2010; Lechner and von Baehr, 2013, 2015; Lechner et al., 2017a, 2017b). The status of cancellous bone in the jaw is of great importance with respect to dental implants and the success of implantology, according to previous publications by other authors (Klein et al., 2008; Lee et al., 2013). One of the most significant concerns associated with the treatment of this condition, however, is the fact that jawbone with fatty-degenerated bone marrow does not show signs of abnormal findings on X-ray examination (Lechner, 2014). Being virtually undetectable on any type of commonly used two-dimensional (2D) X-ray examination, the occurrence and phenomena of BMDJ/FDOJ remain widely unknown and are even denied. To overcome this challenge, the use of through-transmission alveolar ultrasonography (TAU) was evaluated using a new TAU apparatus (TAU-n) (CaviTAU® QINNO GmbH Argelsrieder Feld 11, 82234 Wessling Germany. International patent application No: PCT/EP2018/084199. CaviTAU® is approved by EU medical authorities according to MDD 93/42/EWG

Aim and Objectives

The aim of the present study was to evaluate BMDJ/FDOJ using TAU-n and to determine whether TAU-n measurements are practical and capable of promoting quality assurance when assessing BMDJ/FDOJ. Specifically, we aimed to answer the following questions: Are conventional radiographic techniques suitable to detect osteolytic bone marrow defects in the jaw (BMDJ/FDOJ), which may display local silent inflammation? Is a newly available ultrasound device (TAU-n) for the radiation-free measurement of bone density suitable to visualize the condition of BMDJ/FDOJ presented above?

Materials and Methods

Patient Selection

All 210 patients who were enrolled in this study were seeking to uncover the etiology of their respective systemic immunological diseases, specifically the possibility that BMDJ/FDOJ-induced “silent inflammation” of the jawbone may be involved in the pathogenesis of the disease. The samples and data were taken directly from daily clinical practice at the Clinic for Integrative Dentistry (Munich, Germany). Specifically, the data were obtained in the course of the patients’ routine medical care and were retrospectively evaluated. In cases that necessitated surgical treatment, samples of BMDJ/FDOJ were postoperatively evaluated to assess the level of R/C inflammatory markers. Radiographic examinations, namely 2D-OPG and DVT/CBCT, were assessed to determine bone density and provide the appropriate medical indication for the surgical treatment of BMDJ/FDOJ in these patients. This indication was supplemented by bone density measurements using TAU-n. The average age of the investigation group was 53,02 years; of these patients, there were 129 women and 81 men.

The clinical case studies presented here were performed as part of a case-control study and were deemed to be retrospective in nature. Approval was granted by the accredited forensic institute, IMD-Berlin, (DIN EN 15189/DIN EN 17025). All patients provided their written informed consent (as outlined in the PLOS consent form) to participate in this study. Patients taking bisphosphonates were excluded from the study. All patients reported that they were not taking vitamin D supplements.

Preoperative Methods to Determine Bone Marrow Defects in Jawbone (BMDJ/FDOJ)

Determining BMDJ/FDOJ with conventional 2D-OPGs

Panoramic radiographs are routinely used in clinical dentistry. This imaging technique is inexpensive and provides a general overview of the entire jaw and method of initial assessment of the condition of the jaw. The Orangedental PaX-i3D Duo 3D Multi X-ray unit used in this study displays a "relative bone density" measurement of the jawbone (rel-JBD) in the 2D-OGP Panoramix version. A red line shows the measuring range. Figure 1 presents the results of this rel-JBD measurement: the left image shows the relative density of an all-ceramic crown at 0.9. The right image shows the relative density of a healthy area of cancellous bone at 0.49.

Figure 1: Example of measurement of “relative bone density” using OPG.

Notes: The attenuation coefficients are displayed over the entire test section as a progression curve. In the present validation, only the mean values (MV) are used.

Measurement of relative jawbone density (rel-JBD) values with an Orangedental PaX-i3D Duo 3D Multi. Legend: Red lines mark the measuring range to display the "relative density" in the 2D-OPG.

Determining BMDJ/FDOJ with 3D-CBCT/DVT

Modern X-ray methods, like digital volume tomography (DVT), allow the clinician to perform a 3D assessment of the jawbone using Hounsfield units (HU), which are generally scientifically recognized as a bone density assessment tool. HU are used to describe the attenuation of X-ray radiation in tissues and this information is displayed in grayscale images. The HU scale ranges from –1,000 (attenuation coefficient of air) to –120 (fat), +300 to +400 (healthy cancellous bone), and +1,800 to +2,200 (cortical bone). Water is defined as 0 HU. Recently, methods to determine HU attenuation coefficients have become available (Norton and Gamble, 2001), as actual HU values can be derived using DVT (Misch, 1999; Swennen and Schutyser, 2006). Further investigations classified the density of cancellous bone in the jawbone into five categories, where the poorest jawbone density was below 150 HU (class 5). In this study, we used specific DVT equipment (Orangedental PaX-i3D Duo 3D Multi X-ray) with the appropriate software to evaluate the density of the jawbone in HU. In accordance with DIN 6868-57, the viewing monitors were set with a contrast of >40:1 and a brightness of at least 120 cd/m^2. The Orangedental PaX-i3D Duo 3D Multi X-ray machine used in this validation study showed the mean value of a randomly selected measurement path, with the maximum and minimum values presented as a progression curve (Figure 2).

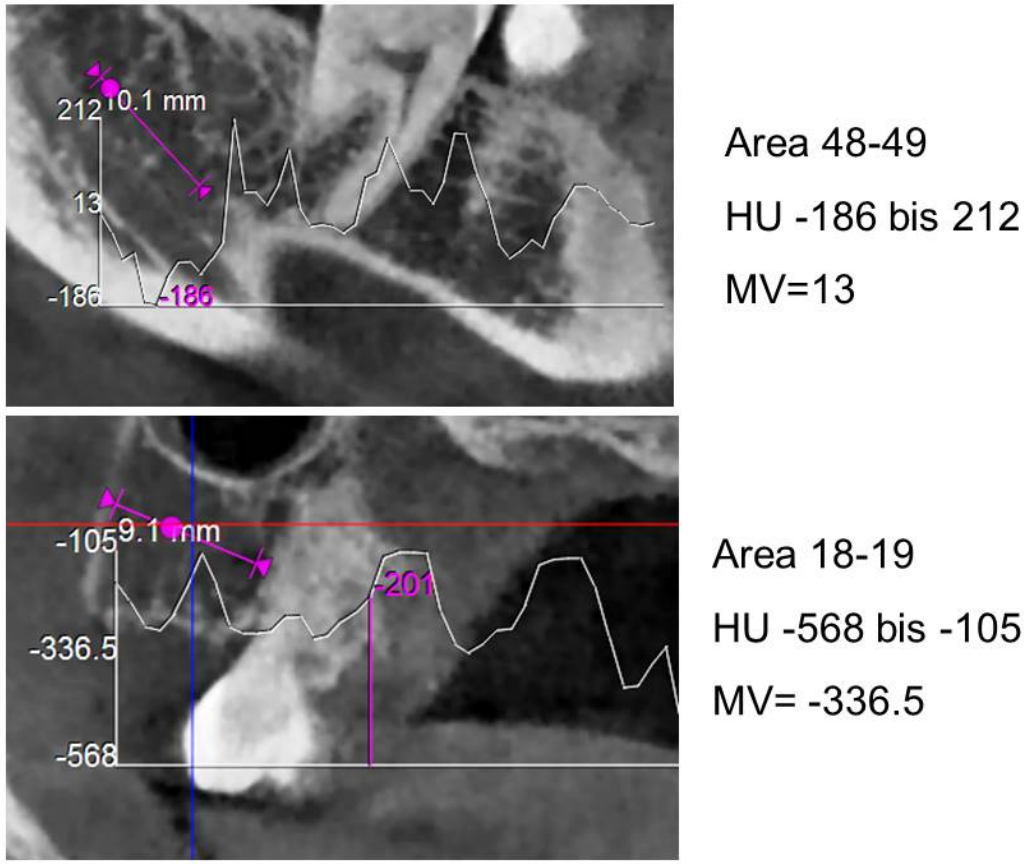

Figure 2. Example of a DVT HU measurement and evaluation of BMDJ/FDOJ: The HU attenuation coefficients are shown as a curve over the measured section. In the present validation study, only the mean values (MV) are used.

Determining BMDJ/FDOJ with TAU-n using ultrasound waves

Attenuation in the amplitude of the ultrasound wave is indicative of pathological changes in the jawbone and depends on the properties of the medium through which the wave is propagated (Mahmoud et al., 2008). Corresponding values are based on the published data from Wells (1999) and Njeh et al. (1999). TAU-n generates an ultrasound wave and passes that wave through the jawbone. This wave is produced by an extraoral transmitter and then detected and measured by a receiving unit that is positioned intraorally. Both parts (i.e., the sender and receiving unit) are fixed in a parallel position using a single handpiece. The size of the TAU-n receiving unit is configured such that it may be easily placed inside the mouth of a patient. TAU-n uses 91 piezoelectric elements that are arranged hexagonally. The jawbone must be positioned between the two parts of the measuring unit. With respect to the parts of the measuring unit to be placed inside a patient's mouth, the acoustical coupling between those parts and the alveolar ridge is performed with the aid of a semi-solid gel (QINNO GmbH Argelsrieder Feld 11, 82234 Wessling Germany). The contact between the jawbone and both the extraoral ultrasound transmitter and intraoral ultrasound receiver (Figure 3) is optimized and individualized using a special ultrasound gel cushion that was developed for this purpose. The results are shown on a color monitor that displays different colors depending on the degree of attenuation. A semi-solid, single-use gel pad is used around the receiver for hygienic reasons (Figure 4).

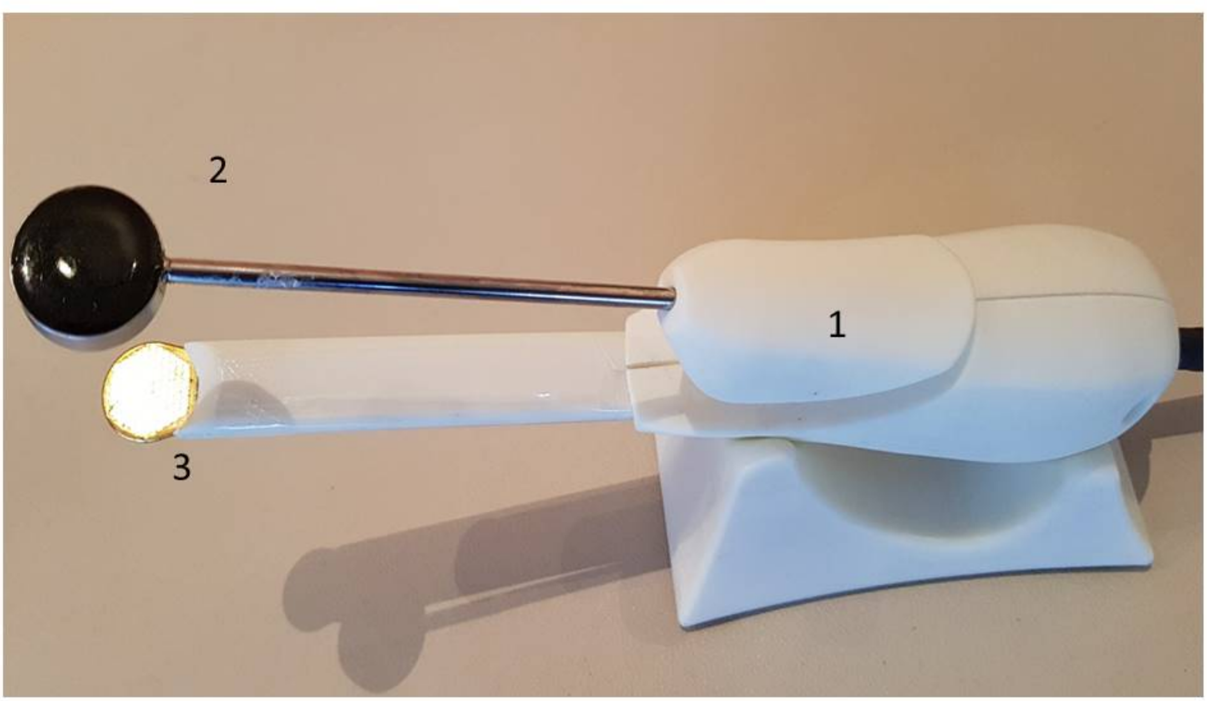

Figure 3. Legend: (1) Handpiece with an ultrasound sender and receiver unit connected to a computer and screen. (2) Ultrasound transmitter. (3) Ultrasound receiver with 91 piezoelectric elements. Coplanar and fixed arrangement of the sender and receiver.

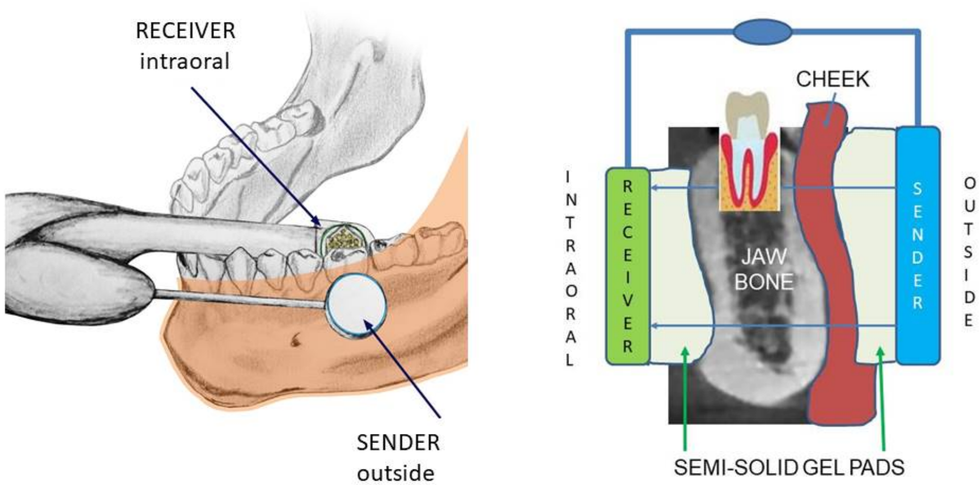

Figure 4. Legend: Left panel: Positioning of the sender (outside) and receiver (intraoral) in the lower jaw; red area marks the cheek. Right panel: The sender (in blue on the right) and receiver (in green on the left) are in a fixed coplanar position (a blue bar connects the sender and receiver); semi-solid gel pads between the sender and the cheek on the outside of the mouth and between the receiver and the alveolar ridge in the intraoral position; trans-alveolar ultrasonic impulse from the sender to receiver (blue arrows).

Color scale associated with TAU-n attenuation coefficients

Figure 5 presents the color scheme associated with the TAU-n attenuation coefficients. This scheme corresponds to an ultrasound signal strength scale (top bar) and a color scale indicating the different degrees of bone density (lower bar). This color scale shows that the colors used to indicate different densities each represent a small part of the entire signal range. Logarithmic averaging broadens the range of bone density measurements and increases the size of the area in green.

The representations of the measurements provided by the color coding scheme are concerned with two functions. With the red/green color scale, the medically relevant area of conspicuousness bone is shown. The second color coded scale shows structural differences which serves as an orientation aid for the user for the placement of the measuring receiver. In this way, the orientation and position of the receiver may be monitored (via live display) while the measurement position is slowly adjusted before the relevant area is captured and stored.

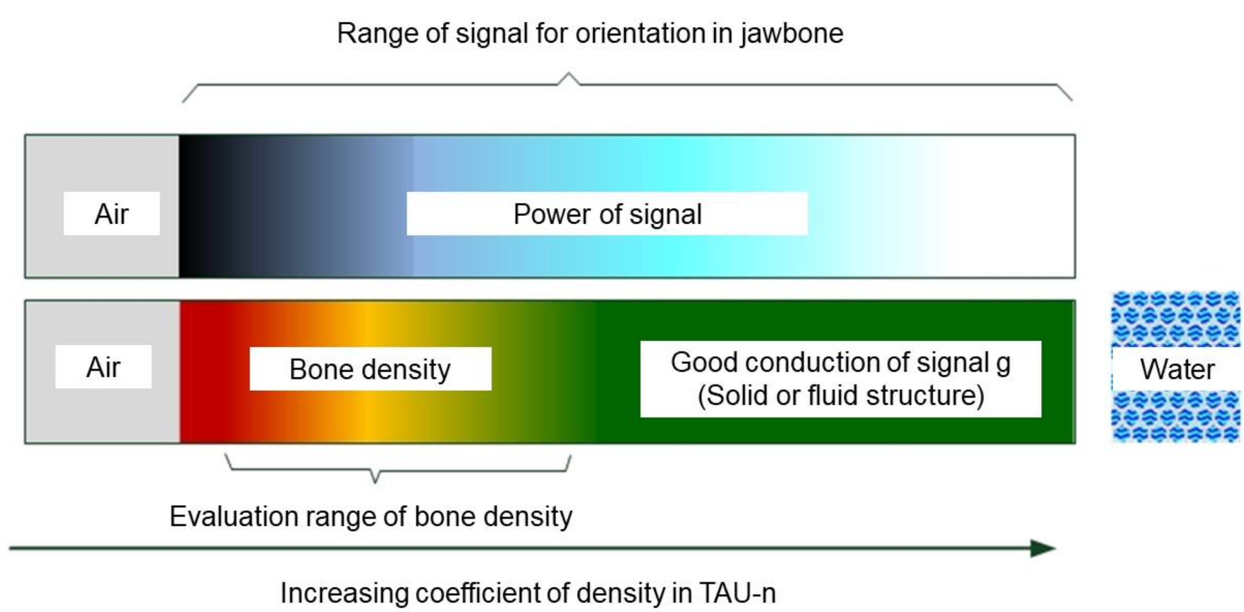

Figure 5. The color scale is used to indicate different degrees of density by TAU-n; gray corresponds to air (i.e., the far left of the scale), and the blue area corresponds to water (i.e., the far right of the scale). The signal strength received by the sensor (top bar) is displayed in blue and increases from dark to light with increasing density coefficients. Bone density (lower bar) is indicated by a colour scale ranging from red to green, representing the high attenuation of diminished bone density (red) and reduced attenuation with increasing density (green).

The TAU-n display

The TAU-n display is able to capture the following physical structures in the dentoalveolar region, with the corresponding color variations of 91 color columns per cm^2: (A) solid bone in the marginal cortical area (green or white/light blue); (B) healthy medullary cancellous bone (green or white/light blue); (C) chronic inflammatory medullary cancellous bone with fatty-degenerative components (red or black/dark blue); (D) fatty nerve structures (yellow/ light blue); and (E) extremely dense and complex structures such as teeth, implants, and crowns (green or white/light blue) (Figure 6).

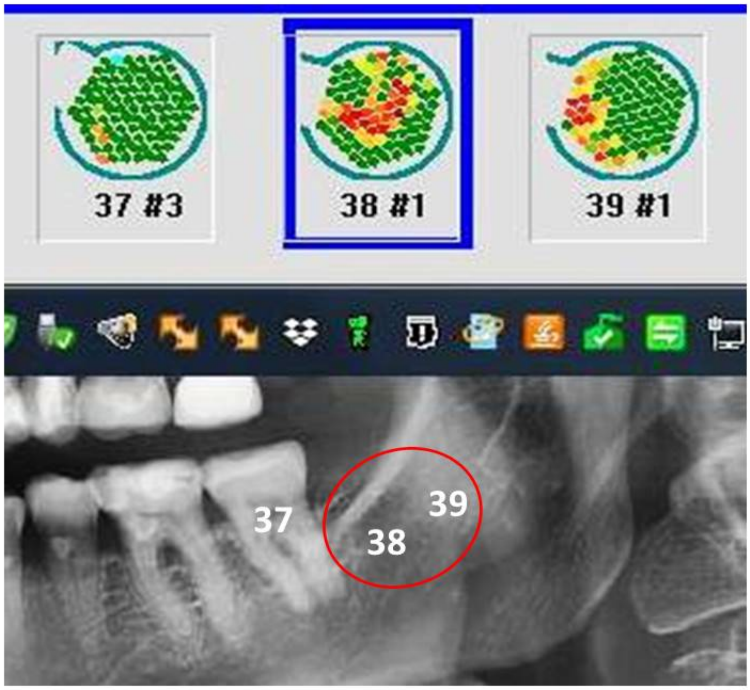

Figure 6. Example of the color coding scheme associated with attenuation used by TAU-n in area 38.

Notes: In the upper panel, the measurement of jaw areas 37 to 38/39 (i.e., the retromolar area) is presented. TAU-n displays different degrees of mineralization, as highlighted by the various color patterns of 91 individual sensor fields that correspond to each jawbone area. Green: indicates hard and dense structures that correspond to a higher degree of mineralization in spongial jawbone or cortical bone; green also denotes teeth, dental crowns, or implants. Yellow: indicates diminished bone density, and also corresponds to the nerve canal in the lower jaw. Red: indicates severely diminished bone density with a low degree of mineralization, corresponding to BMDJ/FDOJ areas.

Numerical representation of TAU-n attenuation coefficients

The TAU-n software numerically represents the attenuation coefficients of the TAU-n measurement range. By a mouse click on one of the 91 sensor fields of a given measurement, the software marks the field and displays the measured value in a logarithmic evaluation. The sensor fields that show the highest attenuation values defined by TAU-n are marked in either red or black, and this indicates the bone density of an area of BMDJ/FDOJ. TAU-n computes the logarithmic average of the sum of the sensor elements with the lowest density unit as "Average(log)", displayed in red (Figure 7, left panel). In the same way, the logarithmic average of the sensor elements with the highest density – equivalent to reduced attenuation by solid structures – is displayed in green (Figure 7, right panel). In the following sections and Table 1, the term "TAU-n log" is used to represent the numbers of “Average(log)” displayed by TAU-n.

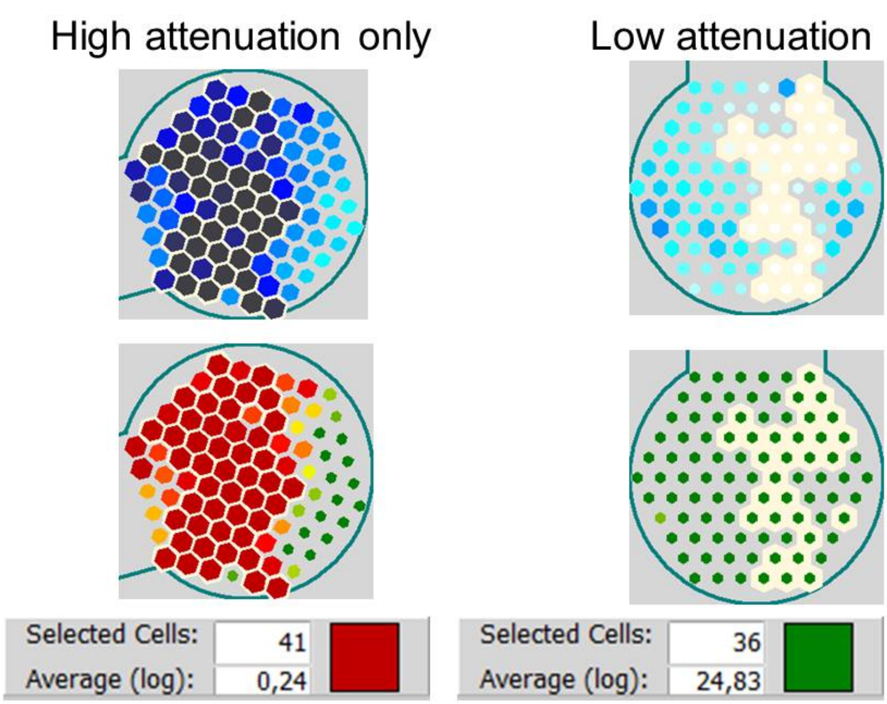

Figure 7. Sensor elements. **Notes:** Numerical representation of the TAU-n attenuation coefficients for diminished bone density (left panel) and for dense material (right

panel). Selected sensor cells (left panel: high attenuation; right panel: low attenuation) are indicated by a white border. The evaluation is presented in the window beneath for a number of selected sensor cells; the result is displayed as a logarithmic mean, which is associated with a corresponding color (i.e., left panel: red = / corresponds to high attenuation; right panel: green = / corresponds to low attenuation).

Problems of acoustic coupling in TAU-n

The practical application of the transducer and receiver with fixed geometrical positions to obtain intraoral ultrasonic measurements (i.e., within the mouth of a patient) with sufficient acoustical conductivity proved to be difficult. The ultrasonic gel, which was placed inside the patient's mouth, was shown to be the main obstacle when attempting to obtain signals from TAU-n in an easy and reproducible manner. The primary difficulty is ensuring that the ultrasonic gel is completely free from air bubbles given the high viscosity of the gel. Air bubbles interfere with obtaining reliable and repeatable measurements. In addition, the study team found that the anatomical contour of the jawbone at the site of measurement and the plane surface of the intraoral receiver did not adequately conform to one another. The distance between the surface of the receiver and that of the alveolar ridge was shown to vary widely.

As a solution, a semi-solid gel pad was placed between the receiver and the alveolar ridge of the patient. The sound velocity in the gel used should fall within the same range as that of soft tissue (i.e., 1,460–1615 m/s) and the gel should have a sound attenuation ranging from 0.3–1.5 dB/cm (1 MHz), so as not to impede the acoustical measurements in the jawbone. The haul-off speed for spontaneous resilience should not exceed 80 mm/s. The semi-solid property of the gel prevents it from evaporating/disappearing before or during the measurement. To perform the measurements, inside the gel pad is a small pocket into which the receiver can be inserted. Following the elimination of any air bubbles between the receiver and the semi-solid gel, the measuring unit is ready for use.

Calibration of TAU-n

The arrangement of the measuring unit in a defined geometry allows for the easy calibration of TAU-n. This functional test is performed with flexible gel pads covering both the transmitter and receiver. Figure 8 illustrates the procedure, i.e., the full immersion of both parts into a vessel filled with water. The complete acoustic coupling is visible when all sensor elements show the watermark in the left image of the sensor on the computer display. This calibration in a water bath at constant conditions allows for the compensation of possible deviation of the elements as a starting point for the measurement. The calibration test ensures that no air pockets interfere in the arrangement with cushions, gel, and sleeves and that no failure of elements or components leads to misinterpretation.

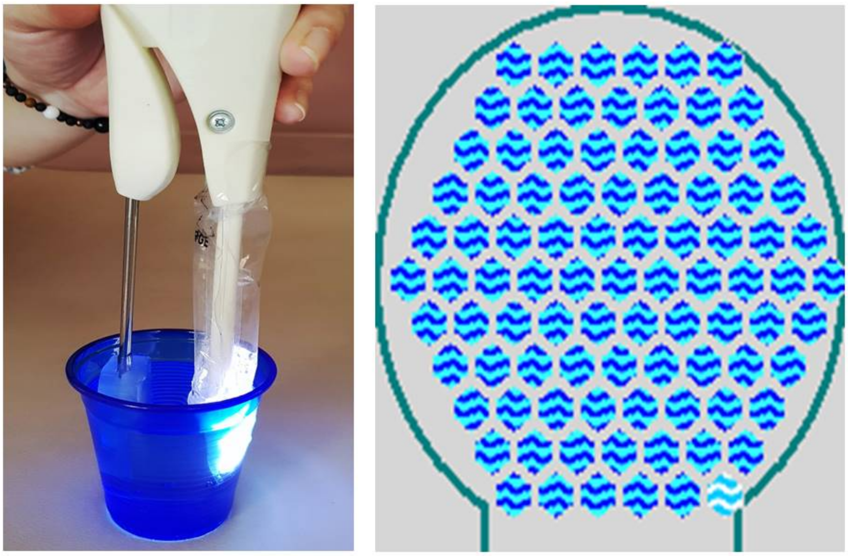

Figure 8. Water test for calibration: Left panel: Transmitter and receiver must be completely submerged in water. Right panel: All sensor elements show watermarks with the exception of the lower right sensor element.

Postoperative Method to Determine BMDJ/FDOJ

Determining BMDJ/FDOJ with RANTES/CCL5 (R/C) expression

BMDJ/FDOJ cavitations contain degenerated adipocytes that exhibit a particular expression profile of the chemokine R/C (Lechner and Mayer, 2010; Lechner and von Baehr, 2013, 2015; Lechner et al., 2017a, 2017b). Hence, BMDJ/FDOJ samples were also analyzed for the expression of the inflammatory immune mediator R/C. Laboratory procedures used to define R/C expression levels in the healthy jawbone and in BMDJ/FDOJ have been previously published; healthy jawbone showed R/C expression levels of 149 pg/mL, while a significant number of BMDJ/FDOJ samples (n=301) among patients with chronic disease (average age: 54.05 years; age range: 23–75 years; gender ratio: 89 females to 225 males) showed a 20-fold increase in R/C expression of 2,940 pg/mL (Lechner and Mayer, 2010; Lechner and von Baehr, 2013, 2015; Lechner et al., 2017a, 2017b). BMDJ/FDOJ are the only bone resorption processes that show R/C overexpression (Lechner et al., 2018). BMDJ/FDOJ also display a reduction in tumor necrosis factor (TNF)-a and interleukin (IL)-6 expression, while all other bone resorption-related diseases are characterized by TNF-a and IL-6 overexpression. In summary, the recent literature has shown that BMDJ/FDOJ are not only characterized by reduced mineralization and diminished bone density, but also play an important role in osteoimmunological processes. Thus, R/C overexpression alone is involved in the characteristic and bone-degrading aspect of BMDJ/FDOJ (Lechner et al., 2018).

Based on findings of publications and in the literature (Lechner and Mayer, 2010; Lechner and von Baehr, 2013, 2015; Lechner et al., 2017a, 2017b), it is known that an R/C expression level higher than 149 pg/mL indicates the presence of osteonecrosis or osteolysis which has resulted in diminished jawbone density. A control group of 19 patients volunteered to provide samples of healthy jawbone, which were removed using drill cores during dental implantation surgery. The inclusion criteria for this group were as follows: the absence of distinctive radiological features in 2D-OPG and 3D-DVT; inconspicuous TAU-n measurements of bone density in the implantation area. The use of bisphosphonate medication was the central exclusion criterion. The demographic data of the 19 cases in the BMDJ/FDOJ control group were: average age, 51.4 years; age range, 33–72 years; gender (female/male): 10/9.

Collection of preoperative rel-JBD, HU and TAU-n values and postoperatively measured levels of RANTES/CCL5 expression in a group of 210 patients with BMDJ/FDOJ.

In this study, a patient cohort of 210 subjects that exhibited clinical evidence of BMDJ/FDOJ (i.e., an HU value, a local R/C expression profile, and TAU-n measurements) was identified to investigate our research objective in a clinical setting. The schematic representation in Figure 9 illustrates the four validation parameters discussed and employed in this study. Each of the subjects in this group was assessed with TAU-n. To be included in this group, each patient was required to have the following with respect to the area of BMDJ/FDOJ investigated: positive preoperative TAU-n measurements, low bone density (in HU values), and a postoperative evaluation of R/C expression. We compared the preoperative TAU-n and HU values of the research group with the postoperatively obtained laboratory results of R/C expression of the corresponding jawbone areas of BMDJ/FDOJ.

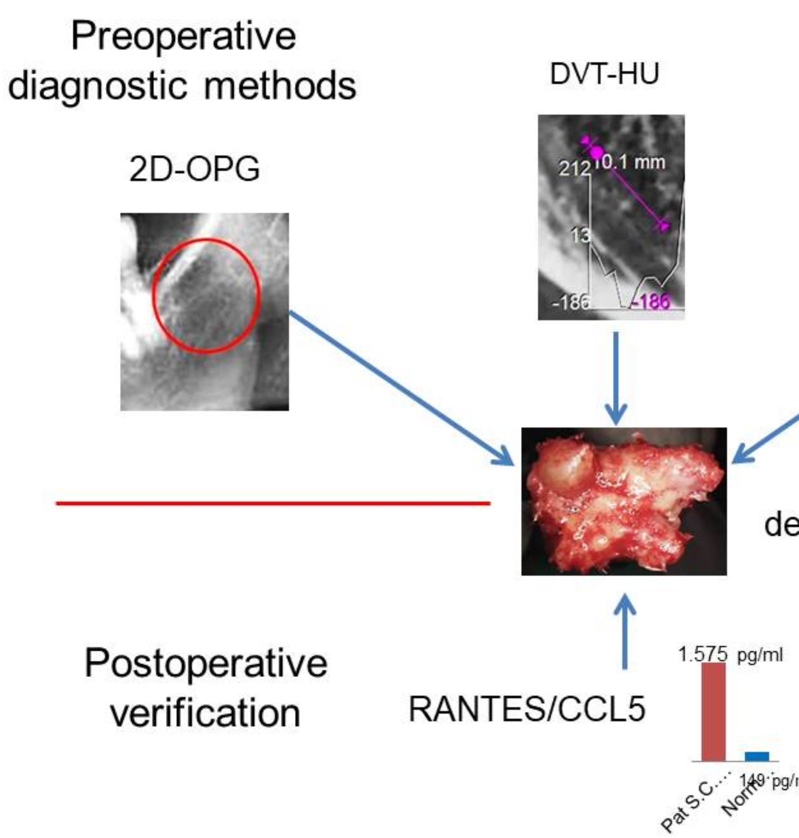

Figure 9. The possible methods used to localize BMDJ/FDOJ. **Notes:** Preoperative 2D-OPG is insufficient, while DVT with the possibility of HU measurement may provide a clear indication of BMDJ/FDOJ. The use of TAU-n as a novel, radiation-free measurement option is evaluated in this report. Postoperative multiplex analysis shows extreme R/C overexpression, providing evidence of inflammation.

Statistical analysis

The statistical analysis was conducted using the statistical software R version 3.5.1. The similarity between the HU and TAU-n methods was verified by means of Spearman's correlation coefficient.

Results

Comparison of preoperative TAU-n and HU values with postoperative evaluation of RANTES/CCL5 expression in a group of 210 patients with BMDJ/FDOJ

After evaluating the detection of BMDJ/FDOJ using TAU-n, we established clinical evidence of the TAU-n attenuation coefficients by comparing and verifying preoperative HU and TAU-n values with the postoperatively determined R/C expression levels of corresponding BMDJ/FDOJ areas. The results are shown in Table 1. In Figure 9, we present three preoperative methods and one postoperative method used to assess BMDJ/FDOJ. For this group of 210 patients, we carried out each of these four methods and compared the results, i.e., (B) the preoperative HU attenuation coefficients; (C) the corresponding TAU-n attenuation coefficients of BMDJ/FDOJ according to "Average(log)" in the TAU-n software (TAU-n Log in Table

1; see Figure 7); and (D) the R/C expression levels in the fatty degenerated samples obtained during BMDJ/FDOJ surgery (Table 1).

Patient#	OPG	HU	AvLog CaviTAU	RANTES pg/ml
1	0,6	-29,0	1,35	8.212,50
2	0,4	-96,0	1,41	2.762,50
3	0,7	-533,0	0,67	5.700,00
4	0,75	-326,0	4,49	3.250,00
5	0,3	-316,0	0,3	3.925,00
6	0,5	-591,0	0,33	3.762,50
7	0,6	-295,0	0,36	2.162,50
8	0,4	-93,0	0,44	2.187,50
9	0,4	-250,0	0,84	2.850,00
10	0,65	-745,0	1,58	722,50
11	0,55	-263,0	0,84	1.825,00
12	0,5	-311,0	0,46	1.787,50
13	0,45	89,0	0,67	1.725,00
14	0,4	-300,0	1,37	5.387,50
15	0,45	-340,0	0,87	992,50
16	0,5	-306,5	1,04	2.512,50
17	0,3	-228,5	0,82	2.362,50
18	0,65	11,5	0,9	3.862,50
19	0,6	-58,5	0,64	457,50
20	0,5	-659,0	0,85	873,75
21	0,35	-447,0	0,31	706,25
22	0,4	-431,0	0,83	2.825,00
23	0,4	-31,5	0,64	1.165,00
24	0,55	-450,0	1,12	405,00
25	0,45	-565,0	0,69	146,25
26	0,4	-68,0	0,72	766,25
27	0,55	-647,0	2,58	5.525,00
28	0,5	54,5	1,52	7.275,00
29	0,6	-549,0	0,82	2.112,50
30	0,4	-130,0	0,76	2.575,00
31	0,65	120,5	0,94	5.562,50
32	0,7	-345,0	0,95	1.612,50
33	0,6	-77,5	0,58	205,00
34	0,65	72,5	1,85	2.962,50
35	0,55	-173,0	1,07	1.875,00
36	0,5	-249,0	0,66	267,50
37	0,4	-413,0	0,38	1.750,00
38	0,7	-291,0	0,52	1.887,50
39	0,6	-238,5	1,32	2.000,00
40	0,6	-537,0	1,22	1.337,50
41	0,65	-676,0	0,79	702,50
42	0,4	-62,0	0,54	846,25
43	0,4	-179,5	2,58	408,75
44	0,6	-243,0	1,26	810,00
45	0,4	-560,0	1,5	518,75
46	0,6	-494,0	0,84	486,25
47	0,55	-387,0	0,75	2.875,00
48	0,6	-379,0	1,14	2.737,50
49	0,4	-228,0	0,32	2.425,00
50	0,5	-440,0	0,68	1.078,75
51	0,6	-308,0	0,54	1.800,00
52	0,6	-322,0	1,21	19.125,00
53	0,5	-589,0	2,29	645,00
54	0,55	-518,0	1,21	1.575,00
55	0,45	-294,0	0,51	2.187,50
56	0,55	-671,0	0,89	767,50
57	0,55	-244,0	1,89	580,00
58	0,3	-573,0	1,77	8.062,50
59	0,65	-454,0	0,93	910,00
60	0,4	99,0	1,57	5.025,00
61	0,2	-182,5	1,78	4.562,50
62	0,6	-335,0	1,03	3.725,00
63	0,4	-288,0	0,79	3.587,50
64	0,5	-132,0	1,75	840,00
65	0,6	-202,0	1,03	2.300,00
66	0,3	-418,0	0,81	5.362,50
67	0,45	-290,0	1,38	1.637,50
68	0,6	-41,0	0,96	636,25
69	0,4	-184,0	1,67	2.200,00
70	0,5	-227,0	1,11	863,75
71	0,6	-198,0	1,38	1.587,50
72	0,45	-261,0	1,65	3.987,50
73	0,55	-543,0	1,01	3.937,50
74	0,6	-363,0	1,19	1.275,00
75	0,45	-268,0	0,32	10.150,00
76	0,55	-110,0	1,69	573,75
77	0,75	-248,0	1,61	1.337,50
78	0,65	-142,0	1,28	611,25
79	0,35	-264,0	2,51	893,75
80	0,45	-301,0	0,86	2.100,00
81	0,5	-654,0	1,05	866,25
82	0,75	-168,0	1,53	1.775,00
83	0,4	146,0	0,79	1.400,00
84	0,4	123,0	1,37	1.800,00
85	0,4	-222,0	0,77	1.925,00
86	0,6	-36,0	1,23	303,75
87	0,4	-5,0	1,15	1.215,00
88	0,25	-213,0	1,52	412,50
89	0,5	88,0	1,24	495,00
90	0,25	-347,0	1,19	1.600,00
91	0,45	45,0	1	1.725,00
92	0,4	-38,0	0,47	527,50
93	0,5	160,0	1,28	3.612,50
94	0,5	-313,0	0,82	1.337,50
95	0,55	119,0	1,38	1.192,50
96	0,4	-196,0	0,8	1.246,25
97	0,55	-17,0	0,96	638,75
98	0,3	-457,0	0,47	6.512,50
99	0,3	-373,0	0,7	456,25
100	0,5	-209,0	1,25	3.275,00
101	0,4	-438,0	0,81	2.262,50
102	0,5	-38,0	0,88	447,50
103	0,45	-404,0	0,47	746,25
104	0,35	-170,0	1,64	1.400,00

105	0,4	126,0	1,07	436,25
106	0,55	103,0	1,05	588,75
107	0,4	96,0	0,84	1.312,50
108	0,7	162,0	0,97	1.500,00
109	0,6	-66,0	1,12	223,75
110	0,45	-105,0	1,21	373,75
111	0,5	-20,0	0,98	277,50
112	0,5	-208,0	1,58	705,00
113	0,6	-264,0	1,8	1.912,50
114	0,6	-83,0	0,81	3.962,50
115	0,6	-38,0	0,67	432,50
116	0,4	-348,0	1,33	1.675,00
117	0,4	150,0	1,17	311,25
118	0,4	-166,0	1,35	1.023,75
119	0,55	144,0	1,37	996,25
120	0,45	-94,0	1,71	498,75
121	0,5	41,0	2,67	3.187,50
122	0,5	-157,0	1,4	417,50
123	0,45	-291,0	0,61	1.325,00
124	0,6	77,0	1,17	917,50
125	0,35	-96,0	1,89	1.687,50
126	0,4	4,0	0,98	228,75
127	0,25	-183,0	1,58	355,00
128	0,45	-43,0	1,18	407,50
129	0,4	-147,0	0,36	541,25
130	0,4	-145,0	0,73	408,75
131	0,4	-245,0	0,73	572,50
132	0,65	150,0	1,24	1.600,00
133	0,4	-87,0	1,59	586,25
134	0,2	-138,0	1,38	1.287,50
135	0,5	-27,0	1,09	945,00
136	0,35	-257,0	1,22	647,50
137	0,35	-120,0	0,31	267,50
138	0,35	-116,0	0,95	233,75
139	0,55	-30,0	1,38	572,50
140	0,4	150,0	1,57	673,75
141	0,6	-155,0	1,12	2.862,50
142	0,55	157,0	1,11	691,25
143	0,5	-127,0	0,67	1.650,00
144	0,3	-110,0	0,93	565,00
145	0,55	84,0	0,84	1.137,50
146	0,45	-414,0	0,87	8.087,50
147	0,45	-122,0	1,53	1.217,50
148	0,4	-145,0	1,5	4.075,00
149	0,6	170,0	0,67	562,50
150	0,5	97,0	0,97	1.337,50
151	0,45	197,0	0,5	1.875,00
152	0,6	-117,0	1,6	950,00
153	0,4	-363,0	1,95	1.111,25
154	0,35	16,0	1,26	4.437,50
155	0,55	-123,0	0,76	2.750,00
156	0,4	23,0	1,58	370,00
157	0,35	52,0	1,48	370,00

158	0,35	320,0	0,58	518,75
159	0,4	-108,0	0,36	1.475,00
160	0,6	-23,0	1,04	5.175,00
161	0,4	-566,0	1,26	873,75
162	0,5	-55,0	1,28	2.637,50
163	0,45	-305,0	0,85	486,25
164	0,5	93,0	1,9	460,00
165	0,55	42,0	0,75	457,50
166	0,5	59,0	1,46	1.312,50
167	0,5	-175,0	0,96	5.462,50
168	0,4	-450,0	1,07	11.437,50
169	0,5	107,0	1,66	1.163,75
170	0,45	-8,0	1,86	650,00
171	0,6	192,0	1,56	1.300,00
172	0,35	43,0	0,62	573,75
173	0,45	-120,0	0,73	190,00
174	0,6	-96,0	1,35	966,25
175	0,55	-58,0	1,09	3.137,50
176	0,25	-69,0	0,77	3.225,00
177	0,5	-420,0	0,94	978,75
178	0,4	-225,0	0,84	2.675,00
179	0,35	123,0	0,89	2.287,50
180	0,6	-115,0	0,7	1.825,00
181	0,3	-63,0	1,31	1.250,00
182	0,4	-175,0	1,57	1.108,75
183	0,6	97,0	1,79	1.425,00
184	0,5	2,0	1,56	1.750,00
185	0,55	179,0	1,5	647,50
186	0,45	40,0	1,89	968,75
187	0,4	65,0	0,67	733,75
188	0,7	200,0	1,41	555,00
189	0,5	-44,0	1,23	1.950,00
190	0,35	-58,0	1,44	631,25
191	0,4	-116,0	1,34	2.362,50
192	0,35	-293,0	1,28	338,75
193	0,35	153,0	0,71	985,00
194	0,5	-316,0	1,32	1.600,00
195	0,2	-231,0	0,35	4.574,00
196	0,5	-162,0	1,09	3.400,00
197	0,4	-94,0	0,73	1.675,00
198	0,6	167,0	1,89	370,00
199	0,45	-62,0	1,25	324,00
200	0,55	-327,0	1,01	1.132,00
201	0,6	-210,0	1,02	863,00
202	0,35	-197,0	1,42	2.350,00
203	0,5	-550,0	1,88	1.850,00
204	0,6	-290,0	0,32	863,00
205	0,5	-68,0	1,22	2.887,00
206	0,3	-192,0	1,48	7.912,00
207	0,5	63,0	1,56	1.625,00
208	0,5	37,0	1,1	2.237,00
209	0,45	-57,0	1,28	950,00
210	0,6	-154,0	0,73	661,00
	0,48	**-165,7**	**1,2**	**1950,38**

Table 1: This table presents the four values measured to assess BMDJ/FDOJ for a group of 210 patients. The four relevant values are listed individually for each patient. The mean value obtained preoperatively for 2D-OPG was a relative bone density of 0.48; for 3D-DVT HU the value was -165.7 (norm = >300) and for CaviTAU® AverageLog the value was 1.2 (normal bone density >2.0). For R/C expression, the mean was 1,950.38 pg/ml (norm = 149.9 pg/ml). **Notes:** Comparison of preoperative HU attenuation coefficients and corresponding TAU-n attenuation coefficients (TAU-n Log; columns in grey), and postoperatively measured levels of R/C expression (RANTES pg/mL) from the samples obtained during surgical treatment for BMDJ/FDOJ (columns in blue). MV refers to the medium values obtained in the course of our research, and the final row compares the corresponding values of healthy jawbone found in the literature (HU; Guglielmi and de Terlizzi, 2009; Komar et al., 2019; Mah et al., 2010) and RANTES levels (pg/mL; Klein et al., 2008; Lechner and Mayer, 2010; Lechner and von Baehr, 2013, 2015; Lechner et al., 2017a, 2017b).

Comparison of rel-JBD, HU, and TAU-n values of healthy jawbone

To ensure that TAU-n generates significantly higher attenuation values in jawbone where BMDJ/FDOJ is not present, we measured rel-JBD, HU, and TAU-n values in healthy jawbone. To obtain valid negative results, we focused on bone marrow areas beneath healthy molar teeth. The process of determining rel-JBD and HU was shown above in Figure 1. The results obtained for healthy jawbone in 10 patients are presented in Table 2. R/C values were unable to be measured as surgical intervention in areas of healthy jawbone was not possible for ethical reasons.

Table 2

Patient	area	OPG	HU	TAU
pat#1	37	0,55	272	7,02
pat#2	37	0,5	599	8,49
pat#3	47	0,55	97	4,46
pat#4	37	0,45	193	7,14
pat#5	36	0,55	678	6,89
pat#6	37	0,45	271	11,51
pat#7	36	0,35	744	6,71
pat#8	46	0,6	306	10,51
pat#9	47	0,4	329	6,16
pat#10	37	0,4	315	9,79
MV		0,48	380,4	7,868

Table 2. Measurement of rel-JBD, HU, and TAU-n values in healthy jawbone.

Comparison of rel-JBD, HU, and TAU-n values of healthy jawbone and BMDJ/FDOJ areas

The bone density measured in healthy jawbone and BMDJ/FDOJ areas are compared as mean values. There is clear agreement in the rel-JBD values obtained with 2D-OPG, (4,8 BMDJ/FDOJ : 4,8 healthy), while the HU values (-165 BMDJ/FDOJ : 380 healthy) and particularly TAU-n values (1,2 BMDJ/FDOJ : 7,8 healthy) differ significantly (Figure 10).

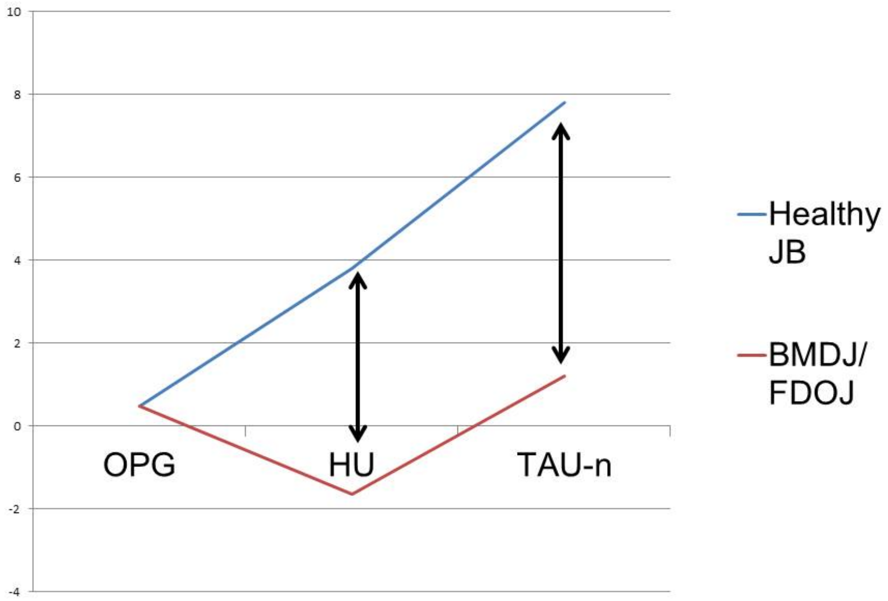

Figure 10. This graph shows the comparison of relative bone density values determined with 2D-OPG, attenuation coefficients in HU (1:100) and TAU-n values in healthy and BMDJ/FDOJ collectives.

Discussion

On "bone marrow defects" and 2D-OPG

In order to compare the results documented in Table 1 in terms of their clinical significance, we calculated 10 mean values of jawbone density measurements obtained with 2D-OPG from three different dental colleagues with available radiographs. The five control parameters comprised the following measurements: cortical bone on the mandibular branch, all-ceramic crown, the canal of infra alveolar nerve, cancellous bone normal and cyst lumen. Figure 11 shows these values in blue. Bone density values in areas of BMDJ/FDOJ collected from the cohort of 210 patients are presented in red.

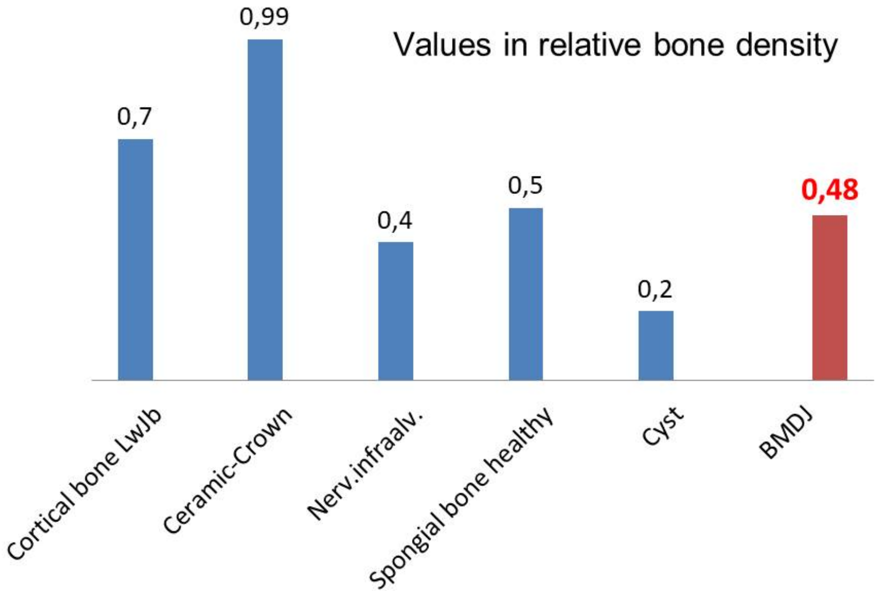

Figure 11: Comparison of various density values with BMDJ/FDOJ values obtained using 2D-OPG. This shows that normal bone density measured in healthy spongial cancellous bone structure with a value of 0.5 is only slightly "denser" than the mean value of the 210 BMDJ/FDOJ areas we examined with a medium value of 0.48. This explains, in part, the/is one reason why there is widespread doubt among dentists in the discussion about/concerning the actual existence of BMDJ/FDOJ. In summary, a critical detection of medullary bone density in BMDJ/FDOJ areas is not possible with 2D-OPG (Lechner J. 2014)

On "bone marrow defects" and 3D-DVT

As with the 2D-OPG radiographs, in order to compare the results documented in Table 1 in terms of their clinical significance, we calculated 10 mean values of 3D-DVT measurements from three different dental colleagues with existing radiographs, as above. Figure 12 shows these HU values in blue. The bone density value of -169 HU in the BMDJ/FDOJ areas collected from the cohort of 210 patients is presented in red.

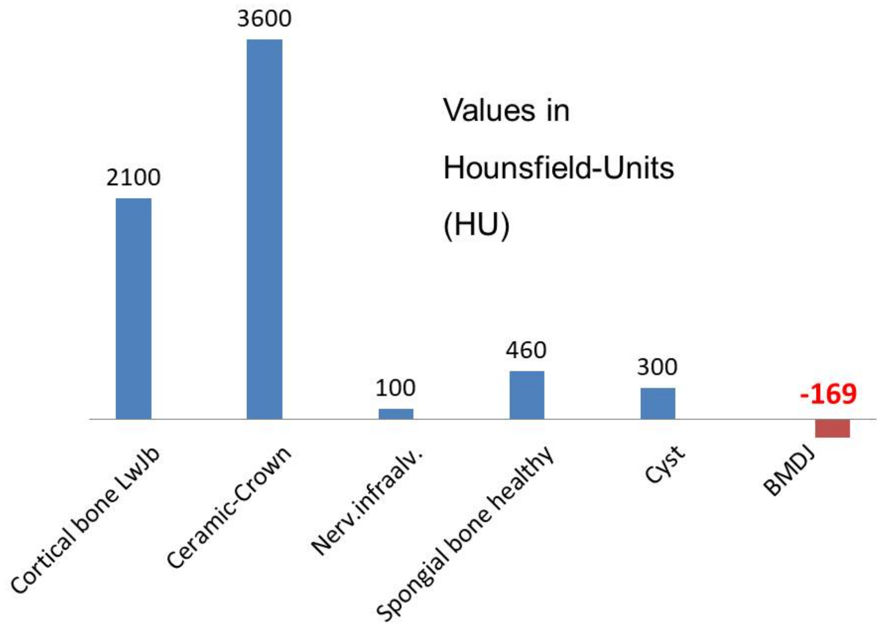

Figure 12: Comparison of a wide variety of density values with BMDJ/FDOJ values obtained with 3D-DVT. This shows that the HU value of -169 produced by the reduced X-ray attenuation in the softened BMDJ/FDOJ areas is significantly less than the minimum value of 300 reported as healthy in the literature.

A reliable assessment of the medullary bone density in areas of BMDJ/FDOJ is possible with the HU values derived using high-quality 3D-DVT (Loubele M et al. 2008. Roberts JA, Drage NA, Davies J, Thomas DW. 2009). However, this method of examination requires a relatively high radiation exposure. Furthermore, DVT devices which provide the HU measurement necessary are costly. In our experience, inexpensive DVT units fail to achieve the requisite quality and lead to incorrect assessments based on purely subjective evaluation.

On "bone marrow defects" and TAU-n

When the TAU-n AverageLog values are compared with the DVT-HU values determined in this study, both correspond to reduced bone density, which infers the presence of BMDJ/FDOJ. Further, the general correlation of HU and R/C multiplex analysis with the "AverageLog" values generated using the TAU-n software may be confirmed. In previous publications, light microscopy also confirmed the reduction of bone density determined by the CaviTAU® AverageLog values (Lechner J, Zimmermann B, Schmidt M, von Baehr V. 2020)

The threshold for which TAU-n Log indicates BMDJ/FDOJ

As shown in Table 1, the mean value of 210 TAU-n measurements in BMDJ/FDOJ areas is 1.2 with a range of 0.3 (#5) to 1.95 (#153). Accordingly, we defined the threshold for which a TAU-n Log indicates diminished bone density that corresponds to a BMDJ/FDOJ area at a TAU-n scale of 2. A TAU-n value of 2.29 with respect to patient #53 was the only measurement determined beyond the threshold of 2, however, a four-fold overexpression of R/C was also detected in this case.

RANTES/CCL5 expression in BMDJ/FDOJ

The values of R/C expression in the samples of BMDJ/FDOJ analyzed postoperatively with multiplex methods in the laboratory average at 1,950.38 pg/ml, which is 13 times the normal value of 149.9 pg/ml found in healthy jawbone previously published by the authors (Lechner J, von Baehr 2013). First and foremost, the application of TAU-n allows for the use of low radiation levels in the stress-free detection of mineralization and metabolic disorders in the medullary region of the jawbone. Medical devices that aim to measure specific phenomena must be able to consistently reproduce their results. In this respect, the measurements obtained with TAU-n are reliable and primarily free of operator errors, as the TAU-n transmitter and receiver are positioned along a coplanar axis in a fixed arrangement. This ensures the necessary independence from the operator and the reproducibility of TAU-n measurements. Errors in acoustic coupling are avoided by displaying a gray sensor field, which is not associated with ultrasound transmission during the measurement process.

Limits in the comparability of the measured HU and TAU-n values

A 1:1 correlation of the measured values obtained with DVT in HU and using TAU-n is not possible since both examination methods are physically different and thus measure different distances in the jaw. However, a general technical correlation may be made as follows: The measured HU values correspond to a selected cross-sectional slice of the jaw, while TAU-n penetrates through the entire distance from the transmitter to the sensor and thus reproduces the typical reflective and scattering properties of ultrasound. As such, TAU-n is unable to isolate particular sections within the jawbone. Furthermore, the attenuation coefficients of both methods behave in completely opposite ways. With HU, the denser the irradiated object, the greater the positive attenuation coefficients and the lower the transmission. With TAU-n, the greater the density of the object to be examined, the lower the attenuation coefficients and, thus, the greater the sound transmission. A relationship between the two methods may still be established, however, as conspicuous areas assessed using HU are also detectable with TAU-n and vice versa. To ensure that TAU-n is a reliable indicator of poor bone quality, this approach should be validated in patients without BMDJ/FDOJ. Here, we face an ethical obstacle, as patients with HU values

>300 and TAU-n Log >2 are inappropriate candidates for jawbone surgery. Thus, it is not possible to obtain R/C values in such cases. As such, the study design employed is unable to fully answer the initial question posed in this study.

Summary

The interest in the application of TAU-n lies in the decrease in bone density in BMDJ/FDOJ due to osteolysis. The upper limit of DVT HU values of interest with respect to BMDJ/FDOJ is +300, as at this point there is a transition to healthy cancellous bone. Values over +300 HU thus fall outside the necessary detection range of TAU-n. The HU values produced in this study (range: -680 to +150) indicate BMDJ/FDOJ in class 5 cases (Mah et al., 2010). The data presented here shows that HU values demonstrate osteolysis and these values also correspond to R/C overexpression in BMDJ/FDOJ areas (Lechner et al., 2018). When the data derived from both methods used to evaluate BMDJ/FDOJ (i.e., HU values and R/C expression) are compared with the TAU-n results, there is a correlation between the attenuation coefficients of HU and TAU-n. Thus, it may be assumed that TAU-n, which uses ultrasound waves, is able to provide an accurate representation of the degrees of mineralization and bone density in the jawbone area.

- Using the AverageLog values generated with TAU-n, we confirmed a general correspondence between HU values and R/C multiplex analysis in a cohort of 210 BMDJ/FDOJ patients.
- Table 1 shows two cases (#53 = 2.29 and #123 = 2.67) with an AverageLog value of >2 from the total of 210 cases.

- Here, HU values and postoperatively measured levels of cytokine expression confirm the reliability of TAU-n measurements with respect to displaying decreased bone density in cases of BMDJ/FDOJ.

Conclusion

A newly developed ultrasonography device (TAU-n) is able to detect and localize BMDJ/FDOJ caused by the fatty degenerative dissolution of medullary trabecular structures in the jawbone. As other studies have confirmed (Guglielmi and de Terlizzi, 2009; Komar et al., 2019), ultrasonography is a low cost and efficient means of assessing jawbone health, and this was replicated with the use of the new TAU device presented here. This study established a new value using TAU-n which provides a reliable indicator of poor bone quality, rendering the device a useful tool for treatment planning strategies in implantology, as well as for fostering cooperation among professionals when assessing or treating osteoimmunological diseases and linking such diseases with the immune system. TAU-n thus provides a non-harmful alternative to the use of X-ray irradiation, which is increasingly criticized (Brenner et al., 2001; Vano et al., 2017), particularly in view of more stringent radiation protection laws (Strahlenschutzgesetz, 1966). TAU-n represents a novel type of imaging acquisition process in dentistry and offers the ability to non-invasively assess hidden BMDJ/FDOJ in the human jawbone. Further extensive clinical trials and multicenter comparative measurements examining TAU-n should be carried out to establish a new classification based on ultrasound and perform a reliability assessment.

Limitations

The limitations of this study include the sample size employed. Bias may also be present due to the fact that not all parameters were validated in the healthy jawbone patient cohort. For ethical reasons, surgical intervention and the measurement of R/C expression in healthy jawbone, without any sign of BMDJ/FDOJ, was not applicable.

Conflicts of Interest

CaviTAU® (Munich, Germany), the company that designed the new TAU-n apparatus and associated software, provided these tools without charge for the purposes of this study. The ultrasonography procedure was carried out at the Clinic for Integrative Dentistry (Munich, Germany). CaviTAU® and the Clinic for Integrative Dentistry are engaged in ongoing discussions regarding numerous collaborative arrangements to further improve and verify the new TAU apparatus, CaviTAU®, as it is introduced to the market. The corresponding author is the holder of a patent used in CaviTAU®.

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