Thermal Variations in Osteoporosis After Aclasta® Administration: Case Study

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Abstract—Osteoporosis is a metabolic disease characterized by an imbalance between bone formation and resorption, that results in an increasing risk of fracture. The aim of the present study was to investigate changes in the thermal pattern of a 50-year-old female patient after intravenous infusion of zaledronic acid Aclasta® in the treatment of osteoporosis. Thermal images were acquired in orthostatic position of the dorsal region between the lumbar and sacral portions using a FLIR® T530 camera with a thermal sensitivity (NETD) < 30 mK and the sensor array size of 320 x 240 pixels, with an accuracy of ±2% of the reading. The image analysis was performed using the Flir Tools® 6.4 software in order to identify the minimum, average and maximum temperature values in the region of interest; and MATLAB® 2017a software to extract histograms from images. The results present a good agreement between the temperature measurements and the painful symptomatology of the sacroiliac region of the vertebral column affected by the disease. Thermography might be a promising method for monitoring bone healing process.

Keywords—Bone mineral density, diagnosis, osteoporosis, thermography, zaledronic acid.

1 Introduction

Osteoporosis is a silent metabolic disease characterized by reduced bone mineral density and the consequent increased risk of fractures caused by fragile skeletal architecture [1].

In Brazil, the annual cost of treating this metabolic bone disease reaches US$ 310 million, which is considered a serious public health problem [2].

It is also estimated that 10.2 million Americans have osteoporosis disease and 43.4 million in habitants have low bone mineral density, which represents 54% of the population over 50 years of age [3]. North American prevalence of osteoporosis and combined osteopenia diagnosis is 35.5 million in women and 18.2 million in men [4]. The incidence is especially higher among women who are on post-menopausal period, due to the decrease in sex hormones, especially estrogen [5]. Women who have had five or more pregnancies, with low weight, are pointed as in risk for the development of osteoporosis disease [6].

Bone fractures caused by osteoporosis disease and osteoporotic fragility become a growing concern. The incidence of this disease is estimated to increase by 10.4 million (19%) in 2020 and 17.2 million (32%) by 2030 [4].

According to the International Osteoporosis Foundation (IOF), approximately 200 million people worldwide live with the disease, 10 million in Brazil alone. According to IBGE (Brazilian Institute of Geography and Statistics) this figure is estimate to be at least 18 million by 2020 [7].

In the post-menopausal period, the remodeling process undergoes changes; bone resorption is intensified with a significant increase in osteoclast action and decreased of osteoblastic activity, thus exceeding the ability of the skeleton to form new bone [8, 9]. Changes in osteometabolism decrease bone strength and predispose the patient to an increased risk of fractures [10]. Therefore, anti-resorptive therapy using bisphosphonate-derived Aclasta (zoledronic acid) is a standard protocol for the treatment of osteoporosis in postmenopausal women and men after fractures. The protocol includes the prescription of zoledronic acid intravenous infusion, Aclasta®, used for the prevention and treatment of metabolic disease of osteoporosis, promoting increased bone mineral density [11]. Drug therapy stimulates increased bone mineral density and reduced incidence of spinal, hip and femur fractures [12].

The chemotherapy treatment by Aclasta drug is performed during an annual outpatient clinical procedure by intravenous drip infusion with zoledronic acid. It is an inhibitor of osteoclast-mediated bone resorption [11,12]. Intravenously administered zoledronic acid is rapidly distributed in bone and such as other bisphosphonates, accumulates preferentially at sites of higher bone turnover activity [12].

In the first applications, the most common acute side effects presented by patients are severe bone pain, mainly in the spinal regions between L1 to L5 lumbar vertebrae and S1 to S5 sacral vertebrae, and the occurrence of fever [13], chills and muscle pain in the dorsal region. Symptoms may last for 7 to 10 days after treatment [14-16].

Diagnostic assistive technologies, such as Infrared Medical Thermology (IRT), have been employed to monitor pain based on the identification of changes in skin temperature [17,18]. The IRT technique has several advantages resulting from its noninvasive approach and non-contact with the body [19], providing two-dimensional images in real-time without harmful ionized radiation effects.

The follow-up of the painful inflammatory phase, corresponding to fever (temperature corporal higher than 37.5ºC, flu symptoms such as tiredness, chills, muscle and

bone joint pain, include back pain [20], after the intravenous chemotherapy administration of the drug Aclasta®, is one of the main requirements to observe the intensity of metabolic response to the side effects of bisphosphonate usage.

Infrared thermography appears as a potential alternative for following-up physiological changes, contributing to the diagnosis and monitoring of bone lesions in the medical field [21].

Given the described scenario, the present study aimed to evaluate the thermal profile of a patient diagnosed with osteoporosis after seven days of intravenous application of Aclasta® with painful symptomatology on the lumbar and sacroiliac region.

2 Methodology

This research complies with the ethical recommendations of the Brazilian Resolution number 466/12 and was approved by the Research Ethics Committee of the Federal Technological University of Parana - UTFPR, CAEE: 36614014.0.0000.5547, under Approval letter number 3,014,748, November 20th, 2018. The sample consisted of two female: one volunteer with 53 years old woman, 1.69 m height and 54 kg body mass and one patient with 50 years old, 1.68 m height and 58 kg body mass, diagnosed with osteoporosis on May of 2019, with impairment of bone resorption in the L3 and L4 regions of the lumbar spine, according to values expressed in the bone densitometry report shown in table 1.

Table 1. Bone Densitometry, DXA results, summary Scan Lumbar Spine

Region	Area (cm2)	BMC (g)	BMD (g/cm2)	T score	Z score
L1	12.77	9.71	0.760	-2.1	-1.4
L2	12.03	9.36	0.778	-2.3	-1.5
L3	13.37	10.11	0.756	-3.0	-2.2
L4	16.35	12.00	0.734	-3.0	-2.2
L5	16.37	12.11	0.744	-3.1	-2.3
Total	54.52	41.18	0.755	-2.7	-1.9

Total BMD CV 1.0%, ACF=1.032, BCF=1.010, TH=6.730. WHO Classification: Osteoporosis Diagnostic of the Fracture - High Risk.

Bone densitometry results are presented in terms of T-score and Z-score. T-score corresponds to the number of standard deviations by which the assessed patient's bone density differs from a bone mass peak compared to a healthy young person, of the same sex and ethnicity. World Health Organization (WHO), sets up cutoff values for the T-score that define osteopenia and osteoporosis disease. A T-score in the interval $-2.5 <$ T-score < -1.0 defines osteopenia; a T score ≤ -2.5 defines osteoporosis disease.

Regarding the Z classification, it corresponds to the number of standard deviations by which bone density differs from a person of the same sex and age. This classification should be used for children, premenopausal women or men under 50 years. If the Z score is ≤ -2.0, bone density is low for the patient's age and the secondary causes of bone loss should be considered [22,23].

A FLIR® Professional Model T-530 infrared camera rated for medical diagnostics (from FLIR Systems, Inc., Wilsonville, Oregon, USA) was used to analyze the regions of interest (ROIs) of the body. The camera is equipped with a 42º lens and presents a thermal sensitivity (NETD) < 30 mK@30ºC and a sensor array size of 320x240 pixels, with an accuracy of ± 2% of the reading.

Thermal changes were analyzed in regions with painful symptoms to better understand the action of bisphosphonates.

Image acquisition of the neurovascular domains was also performed in the volunteer, not submitted to the action of Aclasta drug, to assess bone metabolic changes.

The image collection took place on June 2019, at the Laboratory of Medical Thermography at, Universidade Tecnológica Federal. The volunteers were standing still in orthostatic position during 15 min for thermal body-environment equilibrium. The laboratory temperature was maintained at 21 ºC, with less than 0.2 m/s air speed and relative humidity kept below 60 %, in accordance with the recommendations of the Ring et al., [24].

Thermal images were acquired on the anteroposterior view of the dorsal region between the lumbar portions, delimiting the region of interest (ROIs 1 and 2), covering the vertebrae of the lumbar region L1 to L5, according to Figure 1.

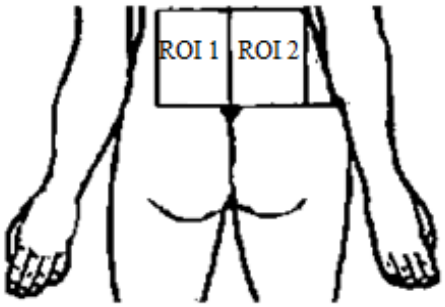

Fig. 1. Diagram of lumbosacral body segments assessed by thermography, ROIs 1 and 2.

The portions L1-L5 of each ROI have a size of 11x43 pixels and was analyzed independently, as shown in Figure 2.

The thermal images were acquired in orthostatic position, feet 0.25 m apart, without underwear, so as not to generate differential data in the interpretation of the images, arms relaxed along the body.

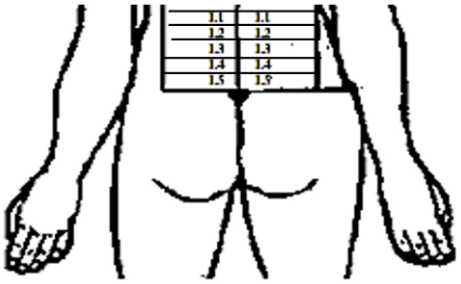

Fig. 2. Lumbar dermatomes of Lumbar segments analyzed through thermography: L1 – Thigh's upper front part; L2–Medial thigh; L3–Medial Knee; L4 and L5–Medial Ankle.

Thermal analysis was performed using Flir Tools® v6.4 software (from FLIR Systems, Inc., Wilsonville, Oregon, USA), extracting the minimum, average and maximum temperatures of the above referred ROIs.

3 Results

The average temperature of the lumbar spine of the volunteer was 32.6 ºC, on the left side (ROI1), and 33.0ºC on the right side (ROI2). On the other hand, the patient receiving Aclasta® showed an average temperature of 30.1ºC on the left side (ROI1), and 30.6ºC on the right side (ROI2), table 2. These results show a significant decrease of the average temperature of about 2.5 ºC from the volunteer to the patient, both on the left and right regions.

Table 2. Temperature of the lumbar region, ROIs 1 and 2 corresponding to the left and right sides of a volunteer and patient

	Volunteer		**Patient**	
Temperature	***Left side ROI 1 (ºC)***	***Right side ROI 2 (ºC)***	***Left side ROI 1 (ºC)***	***Right side ROI 2 (ºC)***
Maximum	35.0	35.0	34.9	34.3
Minimum	29.4	30.0	32.3	32.2
Average	32.6	33.0	30.1	30.6

The mean temperatures of the volunteer and patient, obtained in the portions of the lumbar region delimited between the vertebrae L1 to L5 were analyzed, according to the Figures 3 and 4.

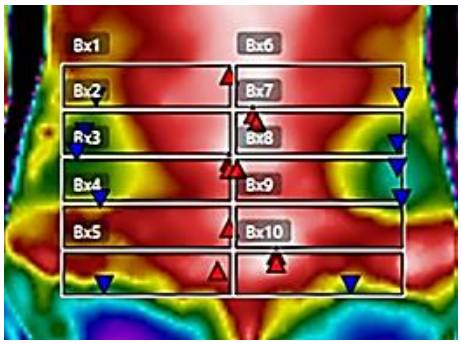

Fig. 3. Selection of the portions of analysis of the lumbar region delimited between vertebrae L1 to L5, with 11x43 pixels, on the left and right sides of the volunteer.

Each of these ROIs was break into 5 portions corresponding to L1-L5 vertebras. The volunteer showed normally higher temperatures, being these differences more significant in the lower vertebras L4 (1.8 ºC) and L5 (3 ºC). Left and right sides present similar temperatures, both in the volunteer and patient, being the left side slightly warmer, Tables 3, and 4.

Table 3. Analyzed portions of the lumbar region delimited between vertebrae L1 to L5, with the size of 11x43 pixels, on the left and right sides of the volunteer

Lumbar Region	Temperature	Left side (ºC)	Right side (ºC)
L1	Maximum	34.5	35.1
	Minimum	31.7	32.1
	Average	33.4	33.7
L2	Maximum	35.0	35.1
	Minimum	30.8	30.3
	Average	32.7	33.2
L3	Maximum	34.9	34.9
	Minimum	30.9	30.0
	Average	32.5	32.7
L4	Maximum	34.5	35.0
	Minimum	32.3	31.1
	Average	33.3	33.8
L5	Maximum	34.3	35.0
	Minimum	29.9	31.0
	Average	32.7	33.3

Table 4. Analyzed portions of the lumbar region delimited between vertebrae L1 to L5, with the size of 11x43 pixels, on the left and right sides of the patient

Lumbar Region	Temperature	Left side (ºC)	Right side (ºC)
L1	Maximum	35.1	34.6
	Minimum	31.1	31.2
	Average	33.5	33.1
L2	Maximum	34.3	33.9
	Minimum	30.3	30.6
	Average	32.7	32.4
L3	Maximum	33.6	33.4
	Minimum	30.2	30.7
	Average	32.2	32.2
L4	Maximum	33.2	32.8
	Minimum	31.7	31.0
	Average	32.4	32.0
L5	Maximum	32.7	32.0
	Minimum	29.1	28.5
	Average	31.0	30.3

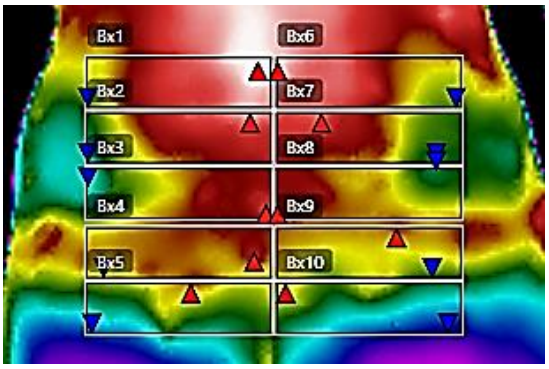

Fig. 4. Selection of the portions of analysis of the lumbar region delimited between vertebrae L1 to L5, with 11x43 pixels, on the left and right sides of the patient.

The thermographic exam showed a decrease of the temperature as result of the osteometabolic alterations in in particular in the region L5, compatible to the painful symptomatology, presented by the patient, Figure 5.

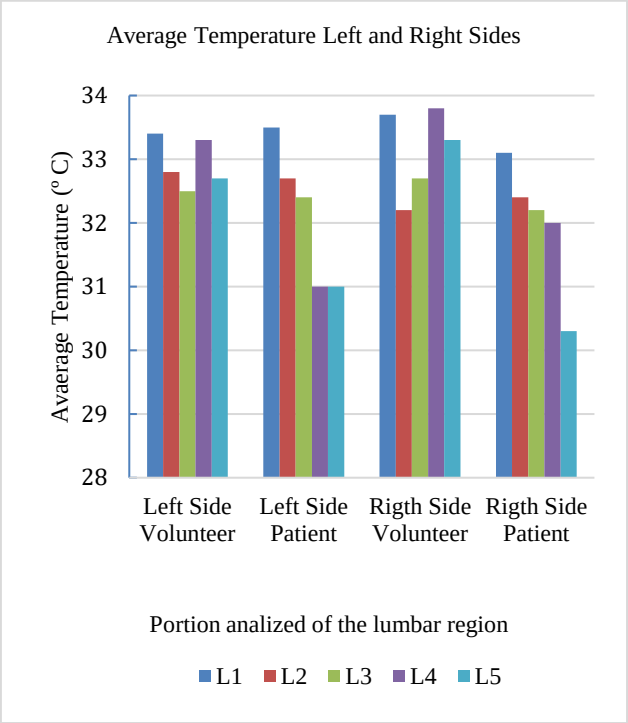

Fig. 5. Temperature analyzed in the lumbar region of the left and right sides of the volunteer and patient.

4 Discussion

The acquired thermograms showed a significate decrease in the average temperature specially in the regions L4 and L5, in the patient, while comparing to the healthy volunteer, which is according with the pain area reported by the patient during the clinical follow-up. According to [25], this significant temperature differences strongly suggest an abnormal situation.

Thus, regarding the complain of pain along the lumbar spine, the examination performed by medical thermography showed irregular thermal distribution. It suggests a decrease in bone metabolism in the regions affected by the diagnosis of osteoporosis shown in the examination of spinal bone densitometry in the incidence anteroposterior view, T-score - 2.7. The reference value recommended by the Brazilian Guideline for diagnosis and treatment of osteoporosis in postmenopausal women and men over 50 years old is T-score less than or equal to -2.5 [26,27].

Irregular thermal distribution may be suggestive of Aclasta drug action in regions with greater bone resorption. This factor could explain the patient's complaints of severe pain. Pain assessment is considered a subjective diagnosis and still a challenge in

the medical field, because the pain threshold is very specific to each patient, being some individuals more sensitive than others [26].

Medical thermography has been highlighted as an important diagnostic method during the follow-up of several pathologies [28]. This technology is being increasingly used in orthopedics and traumatology in the therapeutic decision-making process, [21]. Dua et al. suggests to be a promising method in osteoporosis bone pathology, gathering additional data of the healing process of the bone [29].

In lumbar spine osteoporosis (with losses higher of 30 %), infrared imaging may reveal thermal changes in the lumbar spine regions of interest corresponding to the pain site [30]. The evaluated regions of interest may present temperature changes related to the response to bisphosphonastine drug treatment.

With the reduction of pain symptoms, the evaluated regions of interest may completely disappear regarding the alteration of the presented thermographic pattern, denoting the importance of the evaluation through medical thermography in the monitoring of osteoporotic patients in drug treatment [31]. Several studies have been performed on bone investigations with proven results, including comparing them with other types of assessment already consolidated in the medical literature [32,33]. Among those studies, Varju et al. [32] evaluated the temperature of 91 patients regarding thermal changes on the early and late stages of osteoarthritis in the proximal and hands' distal phalanges. In the early stages of the disease, the temperature was higher; with the disease worsening, temperatures were lower than those presented by the control group when compared to the radiographic examinations. The authors point out the value of IRT for monitoring the disease evolution and nodal severity affected by the phalanges, mainly because of the non-ionized radiation and non-invasive characteristics. The findings of Varju and colleagues corroborate the results now presented for the analyses performed on osteoporosis disease in postmenopausal women due to the lower estrogen hormone action. Lower temperatures were identified in the investigation of the volunteer's case study at the regions of diagnosis of spinal osteoporosis.

The patient shows a severe bone state, presenting greater susceptibility to fractures in the lower back. It is investigated the hypothesis that this decrease in temperature may also be related to the action of the medicine Aclasta® [34] that promotes a decrease of bone resorption metabolic activity. In comparison with the healthy volunteer, the thermal amplitude at the same regions did not show significant amplitude variations regarding body thermal asymmetries.

Another study considering bone injuries was led by Selvarassu et al., [35], who suggested the use of IRT to monitor the progression of the osteoarthritis process, stress fractures, ankle injuries, and complete bone fractures.

According to Haluzan et al. [21], in an investigation conducted on thermal changes during bone healing with 25 patients, aged 50 to 80 years old, who had distal radial bone fractures it was performed IRT on the day of fracture, after three days, after five days, after 11 days and after 23 weeks for clinical follow-up. The thermal differences were statistically significant during the different phases of bone healing, presenting 1.3 ºC temperature difference between fractured and healthy bones. Haluzam and colleagues point out the medical infrared thermography as a good follow-up method in the area of traumatology.

Recently, Dua et al. [29] have tested dynamic thermography to characterize the severity of osteoporosis in human bone model. 3D finite element analyses were performed to model a bone together with skin and muscle, referring to the bone layers that present different density variations. Thermal data were analyzed in the frequency domain and showed an adequate sensitivity for diagnostics.

For lumbar spine osteoporosis disease (losses up to 30%), thermographic images may present a lumbar decrease in temperature corresponding to the pain site compared to X-ray examinations [36]. In response to treatment with calcium supplementation and intravenous bisphosphonate infusion, there may be reversal changes of the temperature. Clinical follow-up by means of thermography allows to observe the reduction of the abnormal thermal image pattern on the affected areas together with the reduction of the painful symptomatology.

In the therapeutic decision process, the thermographic images should be analyzed in conjunction with other diagnostic imaging techniques and clinical findings, as thermographic examination does not assess directly pain but thermal changes in the regions of interest.

Osteoporosis disease and its mechanisms of osteoblastic cells action by hormonal decrease continues to be investigated by medicine and has vast symptoms that directly affect the quality of life. For a proper treatment of the disease, a clinical follow-up of the correlation between the symptoms and the results of the bone densitometry imaging exams should be performed [37]. In view of this, thermography stands out as a complementary diagnostic method, since in the late stage of osteoporosis disease, patients' manifest symptoms of severe painful that may present local thermal changes due to the decreased bone mineral density.

5 Conclusion

Although this work includes just a single case, the results corroborate the applicability of thermography in the clinical practice to monitoring of the effects of Aclasta medication on the osteometabolic response in patients undergoing osteoporosis disease. Thus, further studies with a larger sample of postmenopausal patients diagnosed with osteoporosis should be analyzed to confirm the present results

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All authors declare that there is no conflict of interest.

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