Abstract: Purpose: Very high or low temperatures will lead to bone damage. The objective of this review was to analyze threshold values for thermal bone necrosis. Methods: Histological animal studies evaluating thermal effects on bone necrosis were selected via electronic and hand searches in English and German language journals until 1 November 2019. The outcome measures were temperature-exposure intervals and laser settings affecting bone damage. Furthermore, investigated parameters were the bone-to-implant contact ratios (BIC) and infrabony pockets around dental implants after thermal treatment. For quality assessment of studies, the CAMARADES study quality checklist was applied. Results: A total of 455 animals in 25 animal studies were included for data extraction after screening of 45 titles from 957 selected titles of the MEDLINE (PubMed), The Cochrane Library, Embase and Web of Science search. The threshold values for bone necrosis ranged between 47 °C and 55 °C for 1 min. A threshold value for cryoinsult and laser treatment has not yet been defined. However, temperatures in the vicinity of 3.5 °C produce a histologically proven effect on the bone and in the surrounding tissue. At 50 °C for 1 min, BIC values significantly decreased and infrabony pockets increased. Bone quality had an influence on the outcome, as cancellous bone suffered higher bone damage from thermal treatment compared to cortical bone. Conclusion: No clear threshold value for bone necrosis is available according to the current literature for warm and cold stimuli. More in-depth and clinical studies are required to provide further insights in assessing the potential of thermal necrosis for implant removal.

Keywords: bone; necrosis; thermal; heat; cryoinsult

1. Introduction

The exposure of bone to high temperatures will lead to bone damage and necrosis [1]. Not only heat, but also targeted cooling affects the bone structure and vital cells in the surrounding tissue [2,3]. A single cold stimulus at −10 °C inevitably leads to surrounding skin and bone necrosis. [2,3]. This is also called “cryoinsult”.

Bone remodeling is a continuous process in which old bone tissue is broken down by osteoclasts and re-formed by osteoblasts at the same or a different site [4]. This physiological repair mechanism is also effective in the event of thermal damage to the bone. Surgical procedures often involve the risk of overheating [4,5]. Cutting, rotating, and vibrating instruments are used regularly in contact with the hard and soft tissue under cooling [6]. As soon as the cooling is no longer sufficient, temperatures rise rapidly [7]. When drilling into the bone in particular, overheating of the drill hole must always be avoided, as otherwise there is a risk of subsequent implant loss [8]. Moreover, there are also far-reaching consequences.

This review was also conducted in order to define a threshold bone necrosis level according to the current literature for further thermo-explantation research. If a dental implant has to be removed due to inflammation, there have been reports of the explantation being carried out with a targeted implant overheating [9,10]. In order to minimize bone damage resulting from implant explantation using drills and milling devices, there were several publications that used ultra-high frequency surgical devices for thermo-explantation [9,10]. Another study involved a CO₂ laser as a thermal device for implant removal [11]. These surgical procedures are currently neither suitable nor approved for clinical application. The risk of bone necrosis seemed high and uncontrollable as the implants were unevenly heated without considering threshold levels [12–14].

Heat may be caused by surgical procedures with insufficient cooling, such as implant drilling and bone cutting, or electrical, water, and laser devices [15,16]. Authors treated the cancellous and cortical bone with several devices, such as heated fluids, electric thermal probes, laser devices, and heated implants in order to gain knowledge of bone behavior and remodeling on thermal irritations [1,17–19]. Heat generation during bone drilling, especially in implantology, is a well-investigated field [20]. Nevertheless, published threshold levels present widely varying values. A critical reflection of cadaveric models revealed that no blood flow was present in these studies. Therefore, the definition of reliable threshold temperature values requires in vivo investigations. The blood flow in the bone can cause faster heat dissipation [21]. Poor thermal tissue conductivity results in local heat accumulation. If the heat is dissipated very slowly, an extended exposure time will produce heat damage [22]. As clinical studies do not carry out histopathological analyses for ethical reasons, conclusions were therefore drawn from animal experiments.

The scope of this study was to review the pertinent literature systematically regarding results of various in vivo animal investigations evaluating threshold values for thermal bone necrosis. Our aim is to provide insights into the temperature and exposure time that produce thermal bone damage in order to prevent the development of jaw necrosis. Furthermore, laser settings effecting bone damage were evaluated.

2. Materials and Methods

The protocol for this systematic review was registered on PROSPERO (CRD42019141867). This systematic review was reported according to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P [23]) statement, using the Population, Intervention, Comparison and Outcome (PICO) method [24].

2.1. Focused Question

The focused research question (PICO) of this review was to define the threshold values for thermal bone necrosis in animal studies.

2.2. Search Strategy

MEDLINE (PubMed), the Cochrane Library, Embase and Web of Science database searches were performed to find articles published in the English language up to and including 1 November 2019 (Figure 1). For the MEDLINE search, the following terms and combinations were applied:
(animal study) OR in vivo OR histopathology AND thermal osteonecrosis) OR thermo necrosis) OR thermal bone damage) OR heat induced osteonecrosis) OR cryoinsult induced osteonecrosis.

With regard to The Cochrane Library search, the following combinations were used: histopathology in All Text AND thermal osteonecrosis in All Text OR thermo necrosis in All Text OR thermal bone damage in All Text OR heat induced osteonecrosis in All Text OR cryoinsult induced osteonecrosis in All Text.

With regard to the Embase search, the following combinations were used: ‘(animal study’ ti,ab,kw OR ‘in vivo study’: ti,ab,kw OR histopathology:ti,ab,kw) AND ‘thermal osteonecrosis’: ti,ab,kw OR ‘thermo necrosis’: ti,ab,kw OR ‘thermal bone damage’: ti,ab,kw OR ‘heat induced osteonecrosis’: ti,ab,kw, OR ‘cryoinsult induced osteonecrosis’: ti,ab,kw.

For the Web of Science search, the following terms and combinations were applied: topic: (animal study) and topic: (in vivo) and topic: (histopathology) and topic: (thermal osteonecrosis) or topic: (thermo necrosis) or topic: (thermal bone damage) or topic: (heat induced osteonecrosis) or topic: (cryoinsult induced osteonecrosis).

In addition, the electronic search was complemented by a manual search of the reference lists of all included full texts. For the electronic MEDLINE search, a reference management software (Endnote X 8.2, Thomson Reuters) was used. The obtained publications from The Cochrane Library search were also imported into the reference management software and finally screened.

2.3. Inclusion Criteria

The inclusion criteria for the studies were as follows:

1. In vivo animal studies
2. Studies investigating thermal bone damage by histopathology
3. Studies at all levels of evidence, except case reports and expert opinion
4. Studies reporting on at least one of the outcome measures
5. Language: German or English

2.4. Exclusion Criteria

Studies from which data on selected outcome variables could not directly be retrieved or calculated were not considered. Systematic reviews, studies with missing thermal input, in vitro studies, randomized clinical trials and other clinical studies and cadaver studies were excluded.
2.5. Selection of Studies

After elimination of duplicates, 2 calibrated reviewers (KK, AM) independently reviewed titles, abstracts, and full texts in accordance with the inclusion criteria. All titles were included in the abstract screening. If the information in the abstract was not clear enough for selection purposes, the full text was reviewed.

2.6. Data Extraction

Data extraction was independently performed on all included studies using data extraction tables. If data for individual parameters of the systematic review was sufficient, a meta-analysis was performed. Any disagreement with regard to inclusion and exclusion was resolved by discussion between the reviewers. In case of missing or unclear data, or if the information was still not sufficient for evaluation, the study was excluded for the present review (Table 1).

Table 1. Studies excluded after full-text screening.

| Author (Year)            | Reasons of Exclusion                |
|-------------------------|-------------------------------------|
| Gholampour and Deh 2019 | No histological evaluation          |
| Fuchsberger 1988        | No histological evaluation          |
| Fontana et al., 2004    | No histological evaluation          |
| Connor and Hynynen 2004 | No histological evaluation          |
| Baker et al., 2011      | No histological evaluation          |
| Bonfield and Li 1968    | No histological evaluation          |
| Barnett 2001            | No requested outcome measures       |
| Myers et al., 1980      | No requested outcome measures       |
| Dolan et al., 2012      | No requested outcome measures       |
| Petersohn et al., 2008  | No requested outcome measures       |
| Posen et al., 1965      | No requested outcome measures       |
| Ivancev et al., 2002    | Only in vitro analysis              |
| Lai et al., 2011        | Only in vitro analysis              |
| Van Egmod et al., 1994  | Only in vitro analysis              |
| Ryan et al., 1991       | Only in vitro analysis              |
| Danckwardt-Lillistrom 1969 | Only in vitro analysis          |
| Matthews et al., 1984   | Only in vitro analysis              |
| Franssen et al., 2008   | No thermal values                  |
| Carvalho et al., 2011   | No thermal values                  |
| Stubinger et al., 2009  | No animal study                    |

2.7. Parameters Were Classified as Follows

1. Temperature and exposure time leading to bone damage
2. Laser settings producing bone damage
3. Bone-to-implant contact ratio (BIC) around implants after thermal treatment
4. Infrabony implant pockets after thermal treatment

2.8. Risk of Bias in Individual Studies

For quality assessment of studies, the CAMARADES study quality checklist was applied [25]. The bias evaluation included sample size calculation, animal exclusion or the blinded assessment of outcome, blinded induction of the model, statement of potential conflicts, random allocation, compliance with the animal welfare regulations, and whether the studies were published in peer-reviewed journals.

2.9. Statistical Analysis

BIC around implants after thermal treatment and infrabony implant pockets after thermal treatment were considered as outcomes to describe differences between test and control groups after thermal
treatment. Effect sizes of continuous outcomes for each study were reported as mean differences, along with 95% confidence intervals (CI). We planned to conduct a meta-analysis only if studies were comparable, i.e., if treatments, participants, and the underlying clinical question are similar enough for pooling. To evaluate the statistical heterogeneity between studies, the Q-test of homogeneity and I2 statistics as a percentage of the total variability across studies were used. The significance level of the Q-test was set to 0.10, and I2 values were categorized as 25%, 50%, and 75% for low, moderate, and high heterogeneity, respectively [26]. All analyses were performed with RevMan 5.3.5 (Cochrane C., London, UK). Given the clinical heterogeneity across trials, we have abstained from summarizing the study specific effects into one overall effect. Results were expressed by effect sizes for each study and corresponding forest plots.

3. Results

3.1. Study Characteristics

After application of the inclusion criteria, 25 animal studies were selected for review (Tables 2–4) [1,2,12,14,17,18,27–45].

A total of 455 animals were evaluated across multiple different species, including 224 rats, 117 rabbits, 70 emus, 41 sheep, and 10 dogs. 18 studies assessed temperature/time intervals and seven studies investigated the effect of laser application on bone necrosis. For temperature control, 11 studies used thermocouples and two infrared thermography. Bony regions of interest were 8 mandibles, 6 femurs, 5 tibiae, 4 calvarias, and one maxilla and iliac crest. Histopathological parameters evaluated 24 cortical and 16 cancellous sites. Due to the quality of reported data and the high clinical heterogeneity between studies, no meta-analysis was performed; nevertheless, the effect estimates of each study regarding BIC (Bone-to-Implant Contact) around implants and infrabony implant pockets after thermal treatment were presented (Figures 2 and 3).

| Study or Subgroup | test group | control group | Mean Difference IV, Fixed, 95% CI |
|-------------------|------------|---------------|---------------------------------|
|                   | Mean      | SD Total      | Mean      | SD Total      |                |
| 1.1.2 50°C        |            |               |          |               |                |
| Trisi 2014        | 39.25      | 7.85          | 31.94    | 18.1          | 7.31 [-15.02, 29.64] |
| Trisi 2015        | 25.98      | 5.42          | 38.05    | 1.38          | -12.06 [-19.81, -4.31] |
| 1.1.3 60°C        |            |               |          |               |                |
| Trisi 2014        | 27.23      | 12.44         | 31.94    | 18.1          | -4.71 [-29.56, 20.14] |
| Trisi 2015        | 25.42      | 1.49          | 38.05    | 1.38          | -12.63 [-15.44, -9.82] |

Figure 2. Forest-plots of the bone-to-implant contact ratio (%) values of the thermally treated implants (50 °C and 60 °C) compared with the control group.

| Study or Subgroup | test group | control group | Mean Difference IV, Fixed, 95% CI |
|-------------------|------------|---------------|---------------------------------|
|                   | Mean      | SD Total      | Mean      | SD Total      |                |
| 1.2.2 50°C        |            |               |          |               |                |
| Trisi 2014        | 0.01       | 0.01          | 0.56     | 0.49          | -0.55 [-1.10, 0.00] |
| Trisi 2015        | 3.01       | 0.31          | 1.21     | 0.61          | 1.80 [0.39, 3.21] |
| 1.2.3 60°C        |            |               |          |               |                |
| Trisi 2014        | 1.07       | 0.44          | 0.56     | 0.49          | 0.51 [0.24, 1.26] |
| Trisi 2015        | 3.11       | 0.33          | 1.21     | 0.61          | 1.90 [0.94, 2.88] |

Figure 3. Forest-plots of the infrabony pockets (mm) around the implants that were thermally treated (50 °C and 60 °C) compared with the control group.
Table 2. Included animal studies evaluating temperature parameters of \(-273\) °C to 50 °C on bone damage (BIC = bone-to-implant contact ratio, n.s. = not specified, s = seconds, m = minutes, h = hours, d = days, w = weeks, and mon = months).

| N | Author, Year | Species | Bone Area | N Animals | Thermal Application | Temperature Measurement System and Location | Temperature Max. in °C | Time | Effect on Bone | Follow up Time | BIC% |
|---|--------------|---------|------------|-----------|---------------------|---------------------------------------------|----------------------|------|---------------|---------------|------|
| 1 | Fan et al., 2011 | Emu | Femoral head cortical and cancellous | 20 | Liquid nitrogen and radiofrequency heating | Cryoprobe with external control system | \(-273\) | 9 m nitrogen and 5 m heat | Necrosis | 16 w | n.s. |
| 2 | Conzemius et al., 2002 | Emu | Femoral head cortical and cancellous | 22 | Pressurized liquid nitrogen | n.s. | \(-196\) | 15 s | Necrosis | 6 w | n.s. |
| 3 | Goetz et al., 2011 | Emu | Femoral head cortical and cancellous | 28 | Kirschner wire | Cryoprobe with two thermocouples at the exposed tip and one on the resistance-heated shaft | \(-50\) | 9 m | 1410 necrosis volume (mm³) | 1 w | n.s. |
|   |              |        |            |          |                     |                                             | \(-40\) | 9 m | 1190 necrosis volume (mm³) | 1 w | n.s. |
|   |              |        |            |          |                     |                                             | \(-30\) | 9 m | 1000 necrosis volume (mm³) | 1 w | n.s. |
|   |              |        |            |          |                     |                                             | \(-20\) | 9 m | 700 necrosis volume (mm³) | 1 w | n.s. |
|   |              |        |            |          |                     |                                             | \(-10\) | 9 m | 400 necrosis volume (mm³) | 1 w | n.s. |
| 4 | Lye et al., 2011 | Monkey | Mandible cortical and cancellous | 6 | Cemented endoprothesis | One external thermocouple at the test location | 33.0 | 11 m | No thermal damage | 3 m | n.s. |
| 5 | Yoshida et al., 2009 | Rat | Calvaria cortical | 120 | Thermosimulator Device with internal thermocouple | | 37 | 15 m | Control, TRAP-positive cells were reduced | 1 w, 3 w and 5 w | n.s. |
|   |              |        |            |          |                     |                                             | 43 | 15 m | TRAP-positive cells and ALP-positive cells were mostly absent on the bone surface after 1 w | 1 w, 3 w and 5 w | n.s. |
|   |              |        |            |          |                     |                                             | 45 | 15 m | Rising average of dead osteocyte layers | 1 w, 3 w and 5 w | n.s. |
|   |              |        |            |          |                     |                                             | 48 | 15 m | Apoptotic osteocytes were detected, high count dead osteocytes, no bone necrosis | 1 w, 3 w and 5 w | n.s. |
| 6 | Calvo-Guirado et al., 2015 | Dog | Mandible cortical and cancellous | 6 | Implant drill | Two external thermocouples next to the drill hole | 38.9 | up to 4 m | No thermal damage | 1 m | mean 43.1% SD 2.80 |
| 7 | Mai et al., 2007 | Sheep | Mandible cortical and cancellous | 12 | Frictional heat pins | n.s. | 40 | 4 h | No thermal bone damage | 2 w and 9 w | n.s. |
| 8 | Eriksson et al., 1984 | Rabbit | Tibia cortical and cancellous | 10 | Heated saline solution in the Thermostat | External thermocouple in the Thermostat | 50 | 1 m | No thermal bone damage | n.s. | n.s. |
| 9 | Lundskog 1972 | Rabbit | Tibia cortical and cancellous | n.s. | Electric thermal probe | Infrared thermography | 50 | 30 s | Threshold necrosis | n.s. | n.s. |
Table 3. Included animal studies evaluating temperature parameters of 47 °C to 190 °C on bone damage (BIC = bone-to-implant contact ratio, n.s. = not specified, s = seconds, m = minutes, h = hours, d = days, w = weeks, and mon = months).

| N | Author, Year | Species | Bone Area | N Animals | Thermal Application | Thermal Measurement System and Location | Temperature Max. in °C | Time | Effect on Bone | Follow up Time | BIC% | Infra-bony Pockets | Implant |
|---|--------------|---------|-----------|-----------|-------------------|----------------------------------------|-----------------------|------|---------------|---------------|------|------------------|---------|
| 10 | Eriksson and Albrektsson 1983 | Rabbit | Tibia cortical and cancellous | 15 | Heated implant chamber | Thermocouple inserted in the chamber with direct contact to the observed bone | 47 | 1 m | Hyperemia, no vessel long term effects, 2 d slower fat cell resorption, slower new fat cell formation, slower bone resorption after 30 d and remodeling | up to 4 w | n.s. | n.s. |
|  | | | | | | | 47 | 5 m | Hyperemia, 5 d vessel diameter increase, 2 d fat cell resorption, 3 w new fat cell formation and bone resorption, 30 d up to 30% bone resorption and remodeling | up to 4 w | n.s. | n.s. |
| | | | | | | | | | | | | |
| 11 | Eriksson et al., 1982 | Rabbit | Tibia cortical and cancellous | 5 | Heated implant chamber | Thermocouple inserted in the chamber with direct contact to the observed bone | 53 | 1 m | Stop of blood flow up to 3–4 w revascularization, after 2 d connective tissue injury, 6–8 w formation of new fat cells, after 5 w bone remodeling and osteogenesis | up to 10 w | n.s. | n.s. |
| 12 | Thompson 1958 | Dog | Mandible cortical and cancellous | n.s. | Frictional heat pins | Infrared thermography | 40–67 | n.s. | Osteocyte degeneration and hyperemia | n.s. | n.s. | n.s. |
| 13 | Berman et al., 1984 | Rabbit | Tibia cortical | 18 | Heated isotonic fluid | Internal thermocouple in the bath | 45–55 | 1 m | Inflammation and fibrous tissue scar | 1, 2 and 3 w | n.s. | n.s. |
| 14 | Rouiller 1953 | Rabbit | Calvaria, metatarsi and Radix cortical | 27 | Heated metal | Thermocouple at the tip of the probe | 46 | 5 m | Necrosis | 1, 2 and 3 w | n.s. | n.s. |
| 15 | Tillotson et al., 1989 | Dog | Femur cortical and cancellous | 4 | Radiofrequency electrodes | Internal thermocouple in the device | 55 | 1 m | Proliferation | 24 h | n.s. | n.s. |
| 16 | Trisi et al., 2015 | Sheep | Iliac crest cancellous | 2 | Heated electronic device | Thermocouple in the device | 50 | 1 m | Bone necrosis diameter 0.9. 1.3 cm, muscle necrosis | 6 w | n.s. | n.s. |
| 17 | Trisi et al., 2014 | Sheep | Mandible cortical | 3 | Heated electronic device | Internal thermocouple in the device | 50 | 1 m | Peri-implant bone loss, low density bone is more subject to heat-induced injury | 2 m | n.s. | n.s. |
| 18 | Arnoldi et al., 2012 | Rabbit | Femur cortical and cancellous | 10 | Ultrasonic energy pins | None | 180–190 | several seconds | —5 d cortical sites were more sensitive compared to cancellous sites, —4 w. No signs of tissue degeneration, new bone formation | 5 d and 4 w | mean 39.25% | mean 1.07 | n.s. |

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*Notes:*
- BIC%: Bone-to-implant contact ratio.
- n.s.: Not specified.
- Infrabony Pockets: Presence or absence of infrabony pockets.
- Implant: Type of implant used in the study.
Table 4. Included animal studies evaluating laser parameters on bone damage (n.s. = not specified, s = seconds, m = minutes, h = hours, d = days, w = weeks, and mon = months).

| N  | Author, Year | Species | Bone Area            | N of Animals | Thermal Application                       | Temperature Measurement System | Laser Settings | Exposure Time | Effect on Bone                                                                 | Follow up          |
|----|--------------|---------|----------------------|--------------|------------------------------------------|--------------------------------|----------------|--------------|--------------------------------------------------------------------------------|-------------------|
| 19 | Martin et al., 2011 | Rat     | Mandible cortical    | 20           | Er:YAG laser (cooled)                     | n.s.                          | 300 mJ/6 Hz, 350 mJ/6 Hz, and 400 mJ/6 Hz | 10 s          | Similar healing pattern, 7 d thermal damage with thin layer of surface carbonization, 60 d amorphous layer persisted, residual thermal damage was observed | up to 90 d         |
| 20 | Nakamura et al., 1999 | Rat     | Mandible cortical    | 30           | Excimer laser                            | n.s.                          | 1.0 J/pulse and 10 Hz, 0.12 W, wavelength 193 nm (pulse duration: 10-12 ns, energy density 270 J/cm² for 90 s with 34 °C and 360 J/cm² for 120 s with 45 °C) | 90 s and 120 s | Neither carbonization nor necrotic zone was observed at the surrounding tissue. Some vascular degeneration of osteocyte adjacent to the defect was observed. Minimal thermal damage. | directly after irrigation |
| 21 | Pourzarandian et al., 2004 | Rat     | Calvaria cortical   | 24           | Er:YAG laser (cooled)                     | n.s.                          | 100 mJ/pulse and 10 Hz, 1 W, wavelength 2.94 μm (pulse duration of 200 μs) | 1.6 mm/s       | —10 min a granular precipitate, red blood cells in aggregates of varying density predominant, thin fibrillar strands and inflammatory cells between cell aggregates. —6 h many polymorphonuclear leukocytes, —1 d decrease in the number of red blood cells. Polymorphonuclear leukocytes and macrophages. | up to 14 d         |
| 22 | Rayan et al., 1992 | Rabbit  | Femur cortical and cancellous | 20           | CO₂ laser (not cooled)                    | n.s.                          | 4 W, continuous wavelength of 10.6 μm | 2.5 mm/sec     | —3 d maturation of the fibrin clot, and a reduced red blood cell population. The polymorphonuclear leukocyte population increased and fibroblasts. Phagocytosis and angiogenesis. —7 d cell-rich granulation tissue contained fibroblasts, and clusters of osteoblasts closely adapted to the bone, spots of mineralization identified, collagen fibrils surrounding osteoblasts. —14 d new bone formation. —10 μm a carbonized layer with microcracks and porosities, a zone of thermal necrosis. —6 h many polymorphonuclear leukocytes. —1 d the population of polymorphonuclear leukocytes increased. —3 d polymorphonuclear leukocytes predominant, proceeding to clear the necrotic or carbonized material. Healing started —7 d fibrillar strands organized. —14 d carbonized tissue still covered the treated surface. spots of mineralization, percentage of the area of new bone formation of Er:YAG laser and no significant new bone formation of CO₂ laser. 4- and 6-week bony healing. Superficial zone on the inner cortex carbonization, residuals from vaporized tissues. bone resorption encapsulated by reactive cells, evidence of new bone formation, deeper region of cellular thermal damage and bone necrosis but without vaporization. Active resorption by osteoclasts, histologic changes had less than 40 pm | up to 14 d         |
| 23 | Stubinger et al., 2011 | Sheep   | Tibia cortical an cancellous Mandible and maxilla cortical | 24           | Er:YAG laser (cooled)                     | n.s.                          | 1000 mJ/pulse and 12 Hz, energy density 157 J/cm² (pulse duration of 300 μs, applied water spray level was 40–50 mL/m) | 2 mon 254.33 s | No thermal damage | 2 w and 6 w |
| 24 | Wang et al., 2005 | Rabbit  | Contact Er:YAG laser (not cooled) Non-contact Er:YAG laser (not cooled) | 12           | Er:YAG laser (cooled)                     | n.s.                          | 20 Hz, 2 W (emitting at 2.78 lm, pulsed with a duration of 140–200 ns, tip used was 400 lm in diameter and 8.0 mm in length) | 10 s          | 70–90 micron bone necrosis (mean 30) | directly after irrigation |
| 25 | Yoshida et al., 2009 | Rat     | Calvaria cortical | 30           | Contact Er:YAG laser (not cooled) Non-contact Er:YAG laser (not cooled) | n.s.                          | 115 mJ/pulse and 10 Hz. Contact focused irradiation (energy density: 40.7 J/cm²/pulse) 115 mJ/pulse and 10 Hz. Non-contact defocused irradiation (6.6 J/cm²/pulse) | 1 cm per 3 s | No major thermal changes were noted around the ablation defect | up to 6 m         |


3.2. Temperature and Exposure Time Leading to Bone Damage

Cold and warm stimuli lead to bone damage and should therefore be separated. Three studies [2,29,31] reported cryoprobes in an emu model. The aim was to induce femoral head necrosis with temperatures ranging from \(-273^\circ C\) to \(-10^\circ C\). The exposure time varied between 15 s and 9 min, producing bone necrosis in all cases. The lowest necrosis volume was reported at a temperature of \(-10^\circ C\) and an exposure time of 9 min. Goetz et al., 2008 concluded that temperatures below 3.5 \(^\circ C\) to 1 \(^\circ C\) produced histologically proven bone necrosis.

The remaining part of 15 studies analyzed the effect of heat on bone structure at temperatures ranging from 33 \(^\circ C\) to 190 \(^\circ C\). Heat stimuli of 44 \(^\circ C\) and 1 min had not caused any damages on bone [12]. First tissue reactions, such as hyperemia, started at 47 \(^\circ C\) for 1 min. Bone resorption and dead osteocytes have been reported at temperatures up to 50 \(^\circ C\) [13]; however, no long-term thermal bone damage could be evaluated due to bone remodeling [14]. Furthermore, Lundskog, 1972 declared a temperature of 50 \(^\circ C\) and an exposure time of 30 s as the threshold value of bone necrosis. Yoshida et al., 2009 had reported the results of the calvarial bone study, in which 48 \(^\circ C\) and 1 min of heat stimuli had caused apoptosis of osteocyte and it had taken 5 weeks to regain bone formation.

From those studies, the heat boundary stimuli of bone necrosis, which is no relation with species and sites, are likely to be 48 to 50 \(^\circ C\) for 1 min, and that is almost compatible with Langskog’s report. Nevertheless, one study [39] stated that the threshold value must be 55 \(^\circ C\) with an exposure time of 1 min. According to Arnoldi et al., 2012, a high temperature of 180–190 \(^\circ C\) for only a very short time of a few seconds did not lead to bone necrosis.

3.3. Laser Settings Producing Bone Damage

Stubinger et al. (2011) assessed that, with a cooled Er:YAG laser with an energy output of up to 1000 mJ/pulse and 12 Hz, no thermal damage resulted. One study assessing an Er:YAG laser (cooled) with the settings of 2 W and 20 Hz led to a small bone necrosis layer directly after irrigation [43]. On the other hand, a CO\(_2\) laser (not cooled) at 20 W and 2 kHz produced an active resorption by osteoclasts; however, the histologic changes had less than 40 pm layer thickness after 6 weeks [38]. Pourzarandian et al., 2004 compared the Er:YAG and CO\(_2\) lasers. For the Er:YAG laser, the results after 14 days were a carbonized tissue that covered the treated surface, spots of mineralization, and new bone formation in a percentage of the treated area. Compared to that, there was no significant new bone formation after application of the CO\(_2\) laser.

3.4. BIC around Implants after Thermal Treatment

A temperature elevation up to 38.9 \(^\circ C\) for 4 min and 1-month follow-up [28] showed similar BIC values around treated implants (mean 43.1% SD 2.80) and untreated implants (45% SD 1.30). Higher temperature values [17,18] of 60 \(^\circ C\) for 1 min led to reduced BIC values around heated implants (mean 25.42% SD 1.49 in cancellous bone, mean 27.23% SD 12.44 in cortical bone) versus untreated implants (mean 38.05% SD 1.38 in cancellous bone, mean 31.94% SD 18.10 in cortical bone). However, only the implants inserted in the cancellous bone [17] presented significant differences. Similarly, at a lower temperature of 50 \(^\circ C\) for 1 min, the cancellous bone led to a significantly lower BIC value, whereas around implants that were inserted in more cortical bone [18] no deviating BIC values were evaluated.

3.5. Infrabony Implant Pockets after Thermal Treatment

Higher temperature values [17,18] not only led to loss of bone contact, but also the infrabony pockets next to the treated implant increased. Pocket values ranged around heated implants (60 \(^\circ C\) for 1 min) at a mean 3.11 SD 0.33 in cancellous bone, mean 1.07 SD 0.44 in cortical bone and around untreated implants at a mean 1.21 SD 0.16 in cancellous bone, mean 0.56 SD 0.49 in cortical bone. The infrabony pockets were significantly larger compared to the control group in the cancellous area of the iliac crest of the sheep at 50 \(^\circ C\) for 1 min (Figure 3) [17]. In contrast, the cortical area of the
sheep mandible did not present any significant differences between the test and control groups for the same temperature/time interval. On the other hand, at 60 °C for 1 min, treated implants showed larger infrabony pockets for both treated groups, the cortical and cancellous groups (Figure 3). However, only the implants inserted in the cancellous bone [17] presented significant differences. The bone quality has had an influence on the outcome, as the iliac crest presented greater amount of bone pockets compared to the mandible.

3.6. Risk of Bias in Individual Studies

For quality assessment of studies, the CAMARADES study quality checklist was applied (Figure 4).

![Figure 4. Quality assessment of studies using the CAMARADES study quality checklist.](image)

4. Discussion

The purpose of this review was to define threshold values for thermal bone necrosis in order to assess the potential of thermal necrosis for implant removal. Based on our findings no clear threshold value for bone necrosis is available according to the current literature. The researchers focused on several parameters, such as temperature and exposure time leading to bone damage, laser settings producing bone damage, BIC values around implants, and infrabony implant pockets after thermal treatment.

In recent years, advanced water-cooling systems have been quite effective in reducing heat storage during implant drilling. Therefore, there is currently only a limited number of recent clinical studies on the topic of heat-induced bone necrosis and implant loss available. Several authors have investigated the temperature thresholds leading to jaw necrosis with widely varying results [12,14,30,32]. The differences in the values may be attributed in part to the diversity of the experiments and the many different influencing variables such as blood flow, bone structure, and more [27]. In 1983, Eriksson and Albrectsson stated a temperature of 47 °C with an exposure time of 1 min as the threshold value for bone damage [12]. This value reflects the lower limit of possible damage and corresponds to the threshold values published by Lundskog (50 °C with an exposure time of 30 s) [32]. Berman et al., 1984 concluded that cortical bone is more resistant to heat than cancellous bone [1]. Jacobs et al., 1972 did not explicitly aim to determine a threshold value; however, they produced osteonecrosis at lower temperatures [46]. Other studies describe damage at temperatures from 43 to 68 °C [41,47].

A similar effect to that of heating can be achieved by targeted cooling. Temperatures in the range of 1 °C to 3.5 °C produce a histologically proven effect on the bone and in the surrounding tissue (max. 0.7 mm) [2,3]. An isotherm of 3.5 °C was published by Goetz et al., 2008 which best corresponded to the boundary of the osteonecrotic lesions; however, this was a cadaver study without in vivo results [3]. This review focused only on in vivo animal studies. A single cold stimulus from –10 °C to –20 °C inevitably leads to surrounding skin and bone necrosis.

Furthermore, it is known that osteocytes can be damaged by exposure to temperatures above 45 °C for 15 s [44]. The degree of damage depends on the temperature and the exposure time.
Several threshold values for bone necrosis have been announced by multiple studies. In 1972, Lundskog claimed 50 °C for 30 s [32], and in 1953, Rouiller stated 55 °C for 1 min for the exact threshold boarder [39]. Both investigations took place in rabbits. However, Lundskog studied the cortical and cancellous tibia bone and Rouiller preferred the cortical calvaria, metatarsi, and radii. It may be hypothesized that in the same individual, different regions lead to divergent threshold values. Therefore, it remains unclear if these values are transferable to the jawbone, especially the human jawbone.

Furthermore, defined threshold values for cold stimulus and laser treatment leading to bone necrosis have not yet been published. Bone irritations of −10 °C or a laser setting of a cooled Er:YAG laser with 20 Hz and 2 W evidently led to bone necrosis. In particular, it remains difficult to compare different laser devices, as there is a variety of variable and adjustment possibilities, such as fiber thickness, device, wavelength, distance between objects, energy output, and continuous-wave or pulsating settings.

A critical reflection on this review showed that not all studies used thermocouples for exact temperature measurement. Thermocouples and thermocouples were described as temperature control systems. Especially with thermocouples their position is finally decisive. Internal systems are located directly at the point of measurement, whereas external remote systems cannot detect the individual temperature loss over the individual distance [48]. Additionally, the reduced thermal conductivity and the inhomogeneous properties of the bone must be considered. In contrast, the infrared thermographic camera only records the surface temperature, so that the temperature at the actual measuring point can only be determined to a limited extent. The different threshold values could either be explained by the different measurement techniques, or the individual bone characteristics during examination.

Furthermore, due to different methods (e.g., different thermal devices, different species and bone areas), the overall threshold values may be considered as an average value. Additionally, the statistical results of this systematic review should be interpreted considering the high degree of study heterogeneity. Due to the heterogeneity of the current literate and in order to avoid misleading results no meta-analysis was performed.

The current literature could not give a clear threshold to clinicians concerning heat generation and osteonecrosis because studies presented widely varying results. It is difficult to apply these numerical results directly to humans. Each animal species has an individual bone metabolism that can differ from humans. Up to now it is completely unclear whether an implant can be loosened in this temperature range without triggering a starving necrosis. In order to avoid thermal bone damage in humans, the limit of 47 °C for 1 min should not be exceeded. However, in order to further explore thermo-explantation, these numerical values can only be used as a guideline and before applied to humans further preclinical studies should follow. Based on these findings more preclinical studies regarding the effect of temperature and time intervals on the development of a limited bone necrosis within the range between 47 °C and 55 °C for 1 min are necessary.

5. Conclusions

It can be concluded that no clear threshold value for bone necrosis is available according to the current literature. The values ranged between 47 °C and 55 °C for 1 min. A threshold value for cryoinsult and laser treatment has not yet been defined. Bone quality had an influence on the outcome, as cancellous bone suffered higher bone damage compared to cortical bone. It is suggested that more in-depth and clinical studies are required to provide further insights in assessing the potential of thermal necrosis for implant removal.

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**References**

1. Berman, A.T.; Reid, J.S.; Yanicko, D.R.; Sih, G.C.; Zimmerman, M.R. Thermally induced bone necrosis in rabbits. Relation to implant failure in humans. *Clin. Orthop. Relat. Res.* 1984, 284–292. [CrossRef]

2. Goetz, J.E.; Robinson, D.A.; Pedersen, D.R.; Conzemius, M.G.; Brown, T.D. Cryoinsult parameter effects on the histologically apparent volume of experimentally induced osteonecrotic lesions. *J. Orthop. Res.* 2011, 29, 931–937. [CrossRef] [PubMed]

3. Goetz, J.E.; Pedersen, D.R.; Robinson, D.A.; Conzemius, M.G.; Baer, T.E.; Brown, T.D. The apparent critical isotherm for cryoinsult-induced osteonecrotic lesions in emu femoral heads. *J. Biomech.* 2008, 41, 2197–2205. [CrossRef] [PubMed]

4. Paiva, K.B.S.; Granjeiro, J.M. Matrix Metalloproteinases in Bone Resorption, Remodeling, and Repair. *Prog. Mol. Biol. Transl. Sci.* 2017, 148, 203–303. [PubMed]

5. Tawy, G.F.; Rowe, P.J.; Riches, P.E. Thermal Damage Done to Bone by Burring and Sawing With and Without Irrigation in Knee Arthroplasty. *J. Artroplasty.* 2016, 31, 1102–1108. [CrossRef] [PubMed]

6. Fugito Junior, K.; Cortes, A.R.; de Carvalho Destro, R.; Yoshimoto, M. Comparative Study on the Cutting Effectiveness and Heat Generation of Rotary Instruments Versus Piezoelectric Surgery Tips Using Scanning Electron Microscopy and Thermal Analysis. *Int. J. Oral Maxillofac. Implant.* 2018, 33, 345–350. [CrossRef] [PubMed]

7. Di Fiore, A.; Sivolella, S.; Stocco, E.; Favero, V.; Stellini, E. Experimental Analysis of Temperature Differences During Implant Site Preparation: Continuous Drilling Technique Versus Intermittent Drilling Technique. *J. Oral Implantol.* 2018, 44, 46–50. [CrossRef] [PubMed]

8. Piattelli, A.; Piattelli, M.; Mangano, C.; Scarano, A. A histologic evaluation of eight cases of failed dental implants: Is bone overheating the most probable cause? *Biomaterials* 1998, 19, 683–690. [CrossRef]

9. Massei, G.; Szmukler-Moncler, S. Thermo-explantation. a novel approach to remove osseointegrated implants. *Eur. Cells Mater.* 2004, 7 (Suppl. 2), 48.

10. Curlliffe, J.; Barclay, C. Removal of a dental implant: An unusual case report. *J. Dent. Implant.* 2011, 1, 22–25. [CrossRef]

11. Worni, A.; Marchand, L.; Sailer, I.; Cornish, D.; Hicklin, S.P. Explantation of an Osseointegrated Titanium Implant Using Laser-Induced Thermo-necrosis: A Case Report. *Int. J. Oral Maxillofac. Implant.* 2018, 33, e151–e155. [CrossRef] [PubMed]

12. Eriksson, A.R.; Albrektsson, T. Temperature threshold levels for heat-induced bone tissue injury: A vital-microscopic study in the rabbit. *J. Prosthet. Dent.* 1983, 50, 101–107. [CrossRef]

13. Eriksson, R.A.; Albrektsson, T. The effect of heat on bone regeneration: An experimental study in the rabbit using the bone growth chamber. *J. Oral Maxillofac. Surg. Off. J. Am. Assoc. Oral Maxillofac. Surg.* 1984, 42, 705–711. [CrossRef]

14. Eriksson, R.A.; Albrektsson, T.; Magnusson, B. Assessment of bone viability after heat trauma. A histological, histochemical and vital microscopic study in the rabbit. *Scand. J. Plast. Reconstr. Surg.* 1984, 18, 261–268. [CrossRef]

15. Stobinger, S.; Ghanaati, S.; Saldamli, B.; Kirkpatrick, C.J.; Sader, R. Er:YAG laser osteotomy: Preliminary clinical and histological results of a new technique for contact-free bone surgery. *Eur. Surg. Res.* 2009, 42, 150–156. [CrossRef]

16. De Cremers, K.; Braem, A.; Gerits, E.; De Brucker, K.; Vandamme, K.; Martens, J.A.; Michiels, J.; Vleugels, J.; Cammue, B.P.; Thevissen, K. Controlled release of chlorhexidine from a mesoporous silica-containing macroporous titanium dental implant prevents microbial biofilm formation. *Eur. Cell. Mater.* 2017, 33, 13–27. [CrossRef]
17. Trisi, P.; Berardini, M.; Falco, A.; Vulpiani, M.P. Effect of temperature on the dental implant osseointegration development in low-density bone: An in vivo histological evaluation. *Implant. Dent.* 2015, 24, 96–100. [CrossRef]

18. Trisi, P.; Berardini, M.; Falco, A.; Vulpiani, M.P.; Masciotra, L. Effect of 50 to 60 degrees C heating on osseointegration of dental implants in dense bone: An in vivo histological study. *Implant. Dent.* 2014, 23, 516–521. [CrossRef]

19. Rayan, G.M.; Pitha, J.V.; Edwards, J.S.; Everett, R.B. Effects of CO2 laser beam on cortical bone. *Lasers. Surg. Med.* 1991, 11, 58–61. [CrossRef]

20. Mohlhenrich, S.C.; Modabber, A.; Steiner, T.; Mitchell, D.A.; Holzle, F. Heat generation and drill wear during dental implant site preparation: Systematic review. *Br. J. Oral Maxillofac. Surg.* 2015, 53, 679–689. [CrossRef]

21. Clattenburg, R.; Cohen, J.; Conner, S.; Cook, N. Thermal properties of cancellous bone. *J. Biomed. Mater. Res.* 1975, 9, 169–182. [CrossRef] [PubMed]

22. Leunig, M.; Hertel, R. Thermal necrosis after tibial reaming for intramedullary nail fixation. A report of three cases. *J. Bone Jt. Surg. Br.* 1996, 78, 584–587. [CrossRef] [PubMed]

23. Moher, D.; Shamseer, L.; Clarke, M.; Gherzi, D.; Liberati, A.; Petticrew, M.; Shekelle, P.; Stewart, L.A. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst. Rev.* 2015, 4, 1. [CrossRef]

24. Schardt, C.; Adams, M.B.; Owens, T.; Keitz, S.; Fontelo, P. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med. Inform. Decis. Mak.* 2007, 7, 16. [CrossRef] [PubMed]

25. Sena, E.; van der Worp, H.B.; Howells, D.; Macleod, M. How can we improve the pre-clinical development of drugs for stroke? *Trends Neurosci.* 2007, 30, 433–439. [CrossRef]

26. Higgins, J.P.; Thompson, S.G.; Deeks, J.J.; Altman, D.G. Measuring inconsistency in meta-analyses. *BMJ* 2003, 327, 557–560. [CrossRef]

27. Arnoldi, J.; Henry, P.; Procter, P.; Robioneck, B.; Jonsson, A. In vivo tissue response to ultrasound assisted application of biodegradable pins into cortical and cancellous bone structures: A histological and densitometric analysis in rabbits. *J. Biomat. Sci. Polym. Ed.* 1992, 3, 3461–3471. [CrossRef] [PubMed]

28. Calvo-Guirado, J.L.; Delgado-Pena, J.; Mate-Sanchez, J.E.; Mareque Bueno, J.; Delgado-Ruiz, R.A.; Romanos, G.E. Novel hybrid drilling protocol: Evaluation for the implant healing-thermal changes, crestal bone loss, and bone-to-implant contact. *Clin. Oral Implant. Res.* 2015, 26, 753–760. [CrossRef]

29. Conzemius, M.G.; Brown, T.D.; Zhang, Y.; Robinson, R.A. A new animal model of femoral head osteonecrosis: One that progresses to human-like mechanical failure. *J. Orthop. Res.* 2002, 20, 303–309. [CrossRef]

30. Eriksson, A.; Albrektsson, T.; Grane, B.; McQueen, D. Thermal injury to bone. A vital-microscopic description of heat effects. *Int. J. Oral Surg.* 1982, 11, 115–121. [CrossRef]

31. Fan, M.; Peng, J.; Wang, A.; Zhang, L.; Liu, B.; Ren, Z.; Xu, W.; Sun, J.; Xu, L.; Xiao, D.; et al. Emu model of full-range femoral head osteonecrosis induced focally by an alternating freezing and heating insult. *J. Int. Med. Res.* 2011, 39, 187–198. [CrossRef] [PubMed]

32. Lundskog, J. Heat and bone tissue. An experimental investigation of the thermal properties of bone and threshold levels for thermal injury. *Scand. J. Plast. Reconstruct. Surg.* 1972, 9, 1–80. [PubMed]

33. Lye, K.W.; Lee, S.; Tideman, H.; Merks, M.A.; Jansen, J.A. Temperature changes in a cemented mandibular endoprosthesis: In vitro and in vivo studies. *Int. J. Oral Maxillofac. Surg.* 2011, 40, 86–93. [CrossRef]

34. Mai, R.; Lauer, G.; Pilling, E.; Jung, R.; Leonhardt, H.; Proff, P.; stadlinger, B.; Pradel, W.; Eckelt, U.; Fanghanel, J.; et al. Bone welding—A histological evaluation in the jaw. *Ann. Anat.* 2007, 189, 350–355. [CrossRef] [PubMed]

35. Martins, G.L.; Puricelli, E.; Baraldi, C.E.; Ponzoni, D. Bone healing after bur and Er:YAG laser ostectomies. *J. Oral Maxillofac. Surg. Off. J. Am. Assoc. Oral Maxillofac. Surg.* 2011, 69, 1214–1220. [CrossRef] [PubMed]

36. Nakamura, Y.; Hossain, M.; Watanabe, H.; Tokonabe, H.; Matsumoto, N.; Matsumoto, K. Morphological changes of rat mandibular bone with ArF excimer laser in vivo. *J. Clin. Laser Med. Surg.* 1999, 17, 145–149. [CrossRef]

37. Pourzarandian, A.; Watanabe, H.; Aoki, A.; Ichinose, S.; Sasaki, K.M.; Nitta, H.; Ishikawa, I. Histological and TEM examination of early stages of bone healing after Er:YAG laser irradiation. *Photomed. Laser Surg.* 2004, 22, 342–350. [CrossRef]

38. Rayan, G.M.; Stanfield, D.T.; Cahill, S.; Kosanke, S.D.; Kopta, J.A. Effects of rapid pulsed CO2 laser beam on cortical bone in vivo. *Lasers Surg. Med.* 1992, 12, 615–620. [CrossRef]
39. Rouiller, C.; Majno, G. Morphological and chemical studies of bones after the application of heat. *Beitr. Zur Pathol. Anat. Und Zur Allg. Pathol.* 1953, 113, 100–120.

40. Stubinger, S.; Nuss, K.; Pongratz, M.; Price, J.; Sader, R.; Zeilhofer, H.F.; von Rechenberg, B. Comparison of Er:YAG laser and piezoelectric osteotomy: An animal study in sheep. *Lasers Surg. Med.* 2010, 42, 743–751. [CrossRef]

41. Thompson, H.C. Effect of drilling into bone. *J. Oral Surg.* 1958, 16, 22–30. [PubMed]

42. Tillotson, C.L.; Rosenberg, A.E.; Rosenthal, D.I. Controlled thermal injury of bone. Report of a percutaneous technique using radiofrequency electrode and generator. *Invest. Radiol.* 1989, 24, 888–892. [CrossRef] [PubMed]

43. Wang, X.; Zhang, C.; Matsumoto, K. In vivo study of the healing processes that occur in the jaws of rabbits following perforation by an Er,Cr:YSGG laser. *Lasers Med. Sci.* 2005, 20, 21–27. [CrossRef] [PubMed]

44. Yoshida, K.; Uoshima, K.; Oda, K.; Maeda, T. Influence of heat stress to matrix on bone formation. *Clin. Oral Implant. Res.* 2009, 20, 782–790. [CrossRef]

45. Yoshino, T.; Aoki, A.; Oda, S.; Takasaki, A.A.; Mizutani, K.; Sasaki, K.M.; Kinoshita, A.; Watanabe, H.; Ishikawa, I.; Izumi, Y. Long-term histologic analysis of bone tissue alteration and healing following Er:YAG laser irradiation compared to electrosurgery. *J. Periodontol.* 2009, 80, 82–92. [CrossRef]

46. Jacobs, R.L.; Ray, R.D. The effect of heat on bone healing. A disadvantage in the use of power tools. *Arch. Surg.* 1972, 104, 687–691. [CrossRef] [PubMed]

47. Pallan, F.G. Histological changes in bone after insertion of skeletal fixation pins. *J. Oral Surg. Anesth. Hosp. Dent. Serv.* 1960, 18, 400–408.

48. Pandey, R.K.; Panda, S.S. Drilling of bone: A comprehensive review. *J. Clin. Orthop. Trauma* 2013, 4, 15–30. [CrossRef]