v1: 12 November 2024

Research Article

Evaluation of the Tobacco Heating System (THS) During Closed Lower Limb Fracture Healing in Trauma Smokers' Patients

Peer-approved: 12 November 2024

Qeios, Vol. 6 (2024)
ISSN: 2632-3834

Moritz Herbst[1], Romina Aspera-Werz[1], Benedikt Braun[1], Kevin Schulz[1], Mika F. Rollmann[1], Tina Histing[1], Andreas Nussler[1]

1. Siegfried Weller Research Institute, BG Trauma Center Tübingen, Department of Trauma and Reconstructive Surgery, University of Tübingen, Tübingen, Germany

Background: Since 1976, it has been recognized that increased cigarette consumption correlates with decreased bone density, hindering fracture healing and leading to prolonged hospitalization. Although prior research has shown the relatively less harmful effects of electronic nicotine delivery systems (ENDS) on bone cells in lab settings and animal models, clinical evidence regarding their impact on fracture healing remains scarce. This study aims to investigate whether switching to a tobacco heating system (THS) post-orthopedic surgery improves outcomes for smoking patients during tibia or femur fracture healing over a 6-month period.

Methods: The study is a prospective, open-label, non-parallel, single-center trial involving 150 patients from a Level 1 Trauma center in Germany, diagnosed and treated for closed tibia, closed femur shaft, or closed distal femur fractures (according to AO/OTA: 41A2-41C3, 42A-C, 43A-C, 32A-C, 33A2-3, 33B-C). Participants will be categorized into three groups based on smoking behavior: smokers (no intervention), THS (participants switching from cigarettes to THS), and ex-smokers (participants abstaining from cigarettes or ENDS during the study). Clinical, radiological, and laboratory data will be collected during preoperative and postoperative assessments at 6, 12, 18, and 24 weeks. The primary outcome will be the serum concentration of N-terminal propeptide procollagen type 1, a bone formation marker. Secondary outcomes include bone metabolism, healing, immunological, blood count, and clinical parameters. Approval for the study protocol and consent declarations was obtained from the ethics committee of the medical faculty of Eberhard Karls University (724/2022BO1).

Discussion: The study results will provide evidence that switching to THS after previous orthopedic intervention improves clinical outcomes during closed tibia or femur fracture healing in smoking patients due to a reduced bone resorption rate consequent to the diminished activity of cigarette smoke-activated osteoclasts.

 doi.org/10.32388/DEoEAE.2

Corresponding author: Andreas Nüssler, andreas.nuessler@med.uni-tuebingen.de

1. Introduction

According to the World Health Organization, due to cigarette smoke (CS), 8 million deaths per year are expected to occur in 2030[1]. In 2015, nearly 1 billion people smoked worldwide[2]. CS represents a major health risk that affects the entire human body and is linked to several health conditions (*e.g.*, coronary heart disease, chronic obstructive pulmonary disease, cerebrovascular disease, and cancer)[3][4][5][6]. Moreover, CS is a risk factor for impaired bone homeostasis, resulting in secondary osteoporosis and associated bone fractures, osteoarthritis, and correlates with an increased risk of post-surgical complications such as delayed or impaired bone healing and infections[7][8][9][10][11][12][13][14].

Osteoblasts (bone-forming) and osteoclasts (bone-resorbing) are the central bone cells involved in maintaining the constant equilibrium of bone tissue, and these cells also play a crucial role during the reparative phase of bone fracture healing[15][16]. A fracture occurs when the continuity of the bone tissue is disrupted due to high-force impact, stress, or other medical conditions *(e.g.*, osteoporosis, cancer, or osteogenesis imperfecta). Bone fractures are the most common reason for orthopedic trauma surgery.

Since 1976, several studies have demonstrated a positive association between the number of cigarettes consumed and reduced bone tissue mass[17][18][19]. Moreover, CS not only increases the risk of delayed fracture healing[20], non-union[9], and complications[21] but also leads to longer hospital stays[8][9][22][23][24]. Based on clinical observations, the risk of non-union after ankle arthrodesis increased 3.75-fold in smokers[25]. It was shown that in the first 1-2 years after two-level laminectomy, 40% of smokers developed non-union, while only 4% of non-smokers developed non-union[26]. Additionally, smokers undergoing orthopedic surgeries experienced a higher risk of postoperative complications (*e.g.;* infections, implant revisions) than non-smokers[23][27]. Delays in fracture healing, non-union, an increased complication rate, and extended hospital stays increase health system costs. Therefore, developing alternatives for smoking orthopedic trauma patients that improve bone healing is strongly needed.

Our previous study confirmed that CS is a major risk factor for complications such as infection, delayed healing, and revision surgery in orthopedic patients from a Level 1 Trauma center[24]. Unexpectedly, our orthopedic patients who smoke were, on average, 5.4 years younger than non-smokers, demonstrating the harmful effect of smoking on bone quality, with a high risk of bone fracture at younger ages[24]. This finding supports the lower bone quality for young smokers reported by Rudang *et al.*[7]. Additionally, our study showed the immunosuppression status of smokers (reduced levels of pro-inflammatory markers [*e.g.* IL-1β, IL-6, and TNF-α])[24]. This reduction is consistent with the already reported increased risk of infection in smokers compared with non-smokers[28][29]. This is in line with other reports[9][30][31].

Cigarette smoke contains more than 6,000 different molecules, of which the toxicity has already been proven for more than 150[32][33]. Nicotine is the most pharmacologically active component of tobacco smoke. Its effect on the proliferation and differentiation of mesenchymal stem cells, which play an essential role in fracture healing through migration and osteogenesis, has long been the subject of controversy. Depending on the dose, both positive[34][35] and negative effects[36][37] have been demonstrated. In 2018, our working group showed that nicotine and its most important metabolite, cotinine, have no direct effect on the osteogenetic differentiation of mesenchymal stem cells at physiological concentrations[38]. These results are in line with clinical studies that demonstrated a reduced complication rate after orthopedic trauma surgery for patients with non-electronic nicotine replacement therapies compared to smokers[30][39]. Hence, it can be hypothesized that the harmful effects of CS are related to the molecules produced by the combustion of tobacco.

Quitting smoking is the most effective method to reduce the detrimental effects of cigarette smoke on the human body[21]. Several studies have demonstrated that cigarette smoking abstinence pre-orthopedic intervention reduces postoperative complications[40][41]. Moreover, smoking abstinence with non-electronic nicotine replacement therapies (*e.g.* nicotine patches, sprays, or chewing gums) intervention reduced the complication rates in orthopedic surgery[30][39][42]. These results also demonstrated that the impaired bone homeostasis observed in smokers is not associated with nicotine exposure. It is linked to other molecules generated from the combustion of tobacco.

Although the positive effects associated with smoking abstinence are well-proven, many smokers cannot, do not wish to, or fail to quit cigarette smoking[43]. Unfortunately, non-electronic nicotine replacement therapies fail in most smokers due to a lack of the smoking ritual. Therefore, new technologies are based on preserving the smoking ritual while providing less harmful constituents and maintaining the same nicotine levels found in conventional cigarettes. Tobacco heating systems (THS) avoid tobacco combustion at 800°C by only heating tobacco up to 350°C[44]. Interestingly, a study from our group showed that mesenchymal stem cells and human osteoblasts exposed to aqueous extract from THS for 21 days showed less impact on cell viability, function, and oxidative stress levels than CS[45]. Additionally, an osteoporotic-like environment is 'generated' in a direct co-culture system containing osteoblast/osteoclast exposure to total particulate matter extract from CS in contrast to THS[46].

Besides, we could also demonstrate that e-cigarette aerosol does not affect bone morphology, structure, and strength compared with CS in a mouse model exposed to these compounds for six months[47].

Although there is *in vitro* evidence of the less harmful effect of electronic nicotine delivery systems on bone cell function and those devices did not negatively influence bone homeostasis in an animal model, there is still no clinical evidence regarding the role of electronic nicotine delivery systems during fracture healing after orthopedic surgery.

2. Methods and Analysis (including design; selection/treatment of subjects; interventional methods; data analysis)

2.1. Aim

The study aims to investigate the role of switching from cigarette smoking to THS on the clinical outcome of closed tibia or femur fractures in patients at the Level 1 Trauma center. Validated and standardized assays and medical states will be evaluated in trauma patients who smoke conventional cigarettes or switch from CS to using THS throughout six months after surgery relative to control. We hypothesize that switching to THS perioperatively to an orthopedic surgery improves the outcomes during tibia or femur fracture healing in smoker patients due to a reduced bone resorption rate consequent to the diminished activity of CS-activated osteoclasts.

2.2. Design

The study will be an open-label, three non-parallel groups, single-center clinical study. Patients from a Level 1 Trauma center in Germany diagnosed and treated for closed tibial fracture, closed femoral shaft fracture, or closed distal femoral fracture, including non-smokers and smokers, will be screened for the study. The inclusion and exclusion criteria are summarized in Table 1.

Inclusion criteria	Exclusion criteria
• Closed tibial fracture, closed femoral shaft fracture, or closed distal femoral fracture (according to AO/OTA: 41A2-41C3, 42A-C, 43A-C, 32A-C, 33A2-3, 33B-C) which is surgically treated within 14 days after the trauma at the Level 1 Trauma center, Germany. • Patients > 18 years of age Additional inclusion criteria for the smoking and THS groups • Smokers with > 10 packyears smoking history • Smoking history > 10 years • Decision not to participate in the free smoking cessation seminars.	• Legal guardian or loss of capacity to consent. • Refusal to participate in the study. • Open fractures or concomitant injuries or complications requiring surgery existing at the time of surgical indication. • Initial surgical treatment of the fracture has occurred *ex-domo*. • No initial surgical treatment within 14 days of sustained trauma. • Using nicotine delivery electronic devices (*e.g.;* E-cigarette) during the observation process after surgery. • Pre-existing autoimmune, immunological, bone, or malignant diseases. • Pregnant, breastfeeding, and women of childbearing age with an existing desire to have children (during the next 6 months). • History of alcohol abuse or drug abuse. • Taking antioxidants approved by the German Federal Institute for Drugs and Medical Devices (BfArM). • Taking drugs with known effects on bone metabolism (according to Institute for medical and pharmaceutical examination issues (IMPP): allosteric CaSR modulators, bisphosphonates, calcium release inhibitors, alkaline earth ions, RANKL inhibitors, calcitriol, cholecalciferol).

Table 1 Inclusion and exclusion criteria

2.3. Selection/treatment of subjects

All participants recruited will be advised of the benefits of quitting smoking and the risks of the adverse outcomes of smoking cigarettes during fracture healing. If the participant does not want to quit smoking conventional cigarettes, THS will be offered (preferential study design). All smokers will be offered a certified anti-tobacco addiction training session, aimed at trying to convince participants to quit smoking. For those participants who switch to THS, the trainer will introduce them to the correct use and maintenance of the device. Additionally, for those patients who decide to quit smoking or switch to THS, smoking cessation support will be offered (online) during the entire study period by the trainer. The trainers are qualified nurses with a completed 24-hour Smoke Free Training Course certified by the Institute for Therapy Research - IFT.

2.4. Interventional Methods

The study will be composed of 3 groups, all lower limb (tibia or femur) fracture orthopedic trauma patients, who will undergo surgery (internal or external fixation, which involves using screws, plates, or nails to hold the bone fracture). The study groups will be the following: Smokers willing to switch to THS (experimental), Smokers (no intervention), and Ex-Smokers (active comparator - control) (figure 1).

After the fracture is diagnosed, the pre-operative phase is up to one to two weeks depending on surgery scheduling. During this pre-operative phase, the participant's recruitment, enrollment, smoker's decision to quit smoking or switch to THS, and switching training process will start. The post-operative phase lasts about six months as the expected healing time for tibial or femoral fractures. During this pre- and post-operative phase, five visits will take place at the Level 1 Trauma center in Germany according to the standard clinical protocol (figure 1).

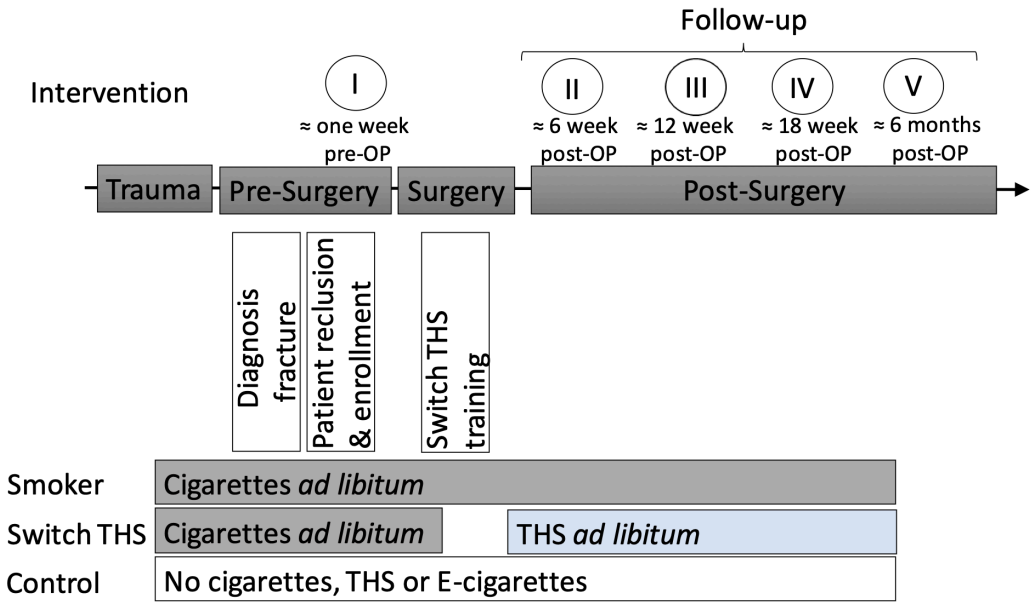

Figure 1. Experimental setup.

During the first visit (approximately between 1 and 2 weeks pre-surgery), the participants will be asked to answer the initial questionnaire. This initial questionnaire will collect general background information regarding socio-economic status, smoking habits, level of nicotine dependence, and medical history (estimated with the Fagerström Test for Nicotine Dependence (FTND) and Global Health Issues PROMIS® (Short form)). In addition, the first clinical examination will be carried out, including routine blood sampling, X-ray, computed tomography scan (CT) of the fracture, classification of the fracture, as well as planning the surgical intervention.

Following surgery, all smokers participating in this study will be offered training to quit smoking. Those who did not want to quit smoking but decide to switch to THS will further receive the assistance of an anti-smoker trainer.

The second visit will take place approximately six weeks (± 2 weeks) post-surgery, including a clinical examination with blood sampling and X-ray as defined in the routine clinical protocol. The third and fourth visits are also part of the standard clinical examinations twelve weeks and 18 weeks (± 2 weeks) after surgery, including blood sampling and X-rays. The last intervention is scheduled approximately six months (± 2 months) after the operation; the orthopedic surgeon will evaluate the participant's clinical-functional outcome, as well as the bone healing through X-ray or CT scan and blood sampling.

During the follow-up phase, participants' smoking status will be monitored during the visits at the Level 1 Trauma center as well as regularly online (twice a week for the first four weeks and then once a week for the following months) by measuring the breath carbon monoxide levels using the Smokerlyzer® piCO ™ (CE 2797, Bedfont, England). All participants will also fill out the self-report follow-up questionnaire every three weeks for the following months. The follow-up questionnaire will collect information regarding smoking history and urges, nicotine withdrawal syndrome, as well as the ability to perform everyday tasks (estimated by the Questionnaire of Smoking Urges (QSU-b), Global Health Issues PROMIS® (Short form), and Lower Extremity Functional Score (LEFS), respectively).

Additionally, when the visits to the Level 1 Trauma center (defined as I, II, III, IV, and V) take place, the determination of white blood cell total count, soluble intercellular adhesion molecule-1, and high-density lipoprotein cholesterol level from blood samples will be analyzed to ensure participants' smoking status and to monitor whether or not patients have switched to THS[48].

2.5. Data Analysis

The case report form (CRF) will be used as a data collection tool for the study. Electronic CRF data will be entered at the clinical trial site by authorized clinical staff via an access-controlled, audit-proof, ICH/GCP-compliant, and validated system. The SecuTrial clinical data management system (CDMS) will be used to collect, process, and store study data. Changes in the CDMS can be tracked via an audit trail. The correctness of the entries in the CRF will be confirmed by the dated signature of an authorized investigator. The investigator is responsible for ensuring that all sections of the CRF are completed correctly and that the entries can be verified against the source data. The investigator must verify the CRFs by dated signature/electronic signature at specific points during the study and after completion of the CRF. The entered data is subjected to a plausibility check, implemented directly in the CRF, the monitoring, and the medical review. Implausible or missing data is queried and must be explained. The database is locked after completion of data entry, data cleansing, and a final data check. Analog CRF data will be entered into a database as recorded in the paper-based CRF. Double data entry will be performed to ensure data quality.

As the study's primary outcome, serum levels of the bone formation marker, N-terminal propeptide procollagen type 1 (CICP), will be determined. As a secondary outcome, the following parameters will be measured/monitored: bone turnover and healing, immunological, clinical, complications, and smoking abstinence. An overview of the endpoints and outcomes to be determined in the study is shown in Table 2.

Outcomes		Visits				
		I	II	III	IV	V
Initial Questionnaire		X				
Classification of the injury	Injured side	X				
	AO classification	X				
	Tscherne/Oestern classification	X				
Details of surgical care and aftercare	Time between accident and first treatment of the fracture [days]	X				
	Time between accident and definitive treatment of the fracture [days]	X				
	Number of operations	X				
	Type of definitive treatment (fixator, plate osteosynthesis, nail osteosynthesis, combination, others)	X				
	Load specification (sole contact load; partial weight-bearing; full weight-bearing)	X				
Follow up Questionnaire *		X	X	X	X	X
Adverse events	a- Wound healing disorder (yes/no)	X	X	X	X	X
	b- Fracture related Infection (yes/no)	X	X	X	X	X
	c- Implant failure	X	X	X	X	X
	d- radiological relaxation signs (yes/no)	X	X	X	X	X
	e- secondary displacement of the fracture (yes/no)	X	X	X	X	X
	f- Thrombosis/embolism (yes/no)	X	X	X	X	X
	g- Pneumonia (yes/no)	X	X	X	X	X
Clinical parameters	Range of motion knee joint Neutral-0 Method: Extension/Flexion: X°/X°/X°	X	X	X	X	X
	Ankle Range of Motion Neutral-0 Method: Extension/Flexion: X°/X°/X°	X	X	X	X	X
	Achieved limb load: Absolute in N, and as % of body weight	X	X	X	X	X
	Function IndeX for Trauma Score	X	X	X	X	X
Bone turnover parameters	Tartrate-resistant Acid Phosphatase [U/I]	X	X	X	X	X
	Bone-specific Alkaline Phosphatase [µg/L]	X	X	X	X	X
	Osteoprogesterin [pg/ml]	X	X	X	X	X
	Osteopontin [ng/ml]	X	X	X	X	X
	N-terminal telopeptide [ng/ml]	X	X	X	X	X
	Procollagen Type 1 N-Terminal Propeptide [ng/ml]	X	X	X	X	X
Immunological parameters	IL-1β [ng/ml]	X	X	X	X	X
	IL-6 [ng/ml]	X	X	X	X	X
	TNF-α [ng/ml]	X	X	X	X	X

Outcomes		Visits				
		I	II	III	IV	V
	IFN-γ [ng/ml]	X	X	X	X	X
Fracture repair parameters	RX number cortices bridged	X	X	X	X	X
	CT number cortices bridged	X				X
	Bone Stiffness [kPa]	X				X
Blood analysis	leucocytes [N°/µl]	X	X	X	X	X
	erythrocytes [mio/µl]	X	X	X	X	X
	hemoglobin [g/dl]	X	X	X	X	X
	thrombocytes [N°/µl]	X	X	X	X	X
	hematocrit [%]	X	X	X	X	X
	Mean corpuscular hemoglobin [pg]	X	X	X	X	X
	Mean corpuscular volume [fl]	X	X	X	X	X
	corpuscular hemoglobin concentration [g/dl]	X	X	X	X	X
	protein c reactive	X	X	X	X	X
	white blood cell total count	X	X	X	X	X
Smoking abstinence parameters	carbon monoxide *	X	X	X	X	X
	soluble intercellular adhesion molecule-1	X	X	X	X	X
	high density lipoprotein cholesterol levels (HDL)	X	X	X	X	X
Complication parameters	Hospital stay [days]					X
	Infections incidence					X
	Wound healing disorder incidence					X
	Further operations incidence					X
	Thrombosis incidence					X
	Duration of incapacity for work [days]					X

Table 2. Summary of parameters and time points for the study

* *additional online monitoring every 3 weeks,* * * *additional online monitoring twice a week for the first 4 weeks, then once a week*

2.6. Case number

The number of cases was calculated in consultation with the Institute for Clinical Epidemiology and Applied Biometry at the Eberhard Karls University of Tübingen. If bone cells are exposed to cigarette smoke, osteoblast activity is significantly reduced, while osteoclast activity is increased, leading to osteoporotic changes in the bone[45][46][49][50]. *In vitro* results show that exposure to THS extract does not significantly affect the homeostasis of bone-forming and bone-resorbing cells compared to conventional cigarette smoke[45][46].

We hypothesize that smokers will have significantly lower serum CICP levels than patients using a THS. In contrast, we do not expect a significant difference in serum CICP levels between patients using THS and the control group.

According to our hypothesis, the groups "smokers," "controls," and "THS" will be formed. The primary

research hypothesis is that the CICP levels are higher in the THS group than in the smoker group. Furthermore, the known difference between controls and smokers should be confirmed. The comparison between the THS group and the control group is, therefore, exploratory. The empirical basis of the case number estimation is summarized in Table 3.

doi.org/10.32388/DEoEAE.2

CICP [ng/L]					
Smoker		THS		Control	
Average	Standard deviation	Average	Standard deviation	Average	Standard deviation
92.7	47.4	120	32.6	127.9	29.5

Table 3. Number of cases calculation based on[24]. Depicted are the average concentrations of CICP in ng/L and the standard deviations.

The case number estimation was carried out for a one-factorial analysis of variance with different group sizes. The standard deviation was conservatively set at the maximum value of 47.4 for all groups. To demonstrate a difference between the three groups with a significance level of 5% for the overall test in the one-factorial analysis of variance with 80% power, 40 smokers, 40 THS users, and 50 controls are sufficient. For the pairwise comparison between THS users and smokers, a power of 83% results, and for the pairwise comparison between controls and smokers, a power of 97%, both with two-sided testing at the 5% significance level. Due to the study's cross-sectional nature, a very low drop-out rate is expected; should drop-outs occur, they will be recruited. The calculations were carried out with nQuery release 4.0. The analysis will be carried out in two stages, initially as an overall test to compare all three study groups in a one-way analysis of variance. If no differences are found, the test procedure is terminated. If the overall test is significant, all three pairwise comparisons will be carried out without correction for multiple testing. The primary evaluation population is the modified intention-to-treat population, which consists of all participants with a primary endpoint of CICP (6 months follow-up). Interim and subpopulation analyses, as well as imputation of missing values, are not planned.

3. Discussion

According to the German Ministry of Food and Agriculture, CS causes 25.4 billion euros in direct costs for the social security system every year, of which 22.76 billion euros are spent on medical treatment[51]. In the United States, the National Center for Chronic Disease Prevention and Health Promotion reported that more than 240 billion dollars in costs associated with CS are spent on healthcare. In addition to the harmful health aspects, socio-economic reasons highlight the need to reduce cigarette smoking prevalence. Cigarette smoking has been shown to lead to an increased risk of bone fracture[11][14], delayed fracture healing[52], failure of healing[9], and an increased rate of postoperative complications[21], resulting in prolonged hospitalization[9][22][23][24][53]. Complications, in particular, cause especially high costs as they are often associated with intensive care stays, revision operations, or interventions of all kinds[54]. Our previous retrospective study demonstrated that current and former smokers had a significantly longer hospital stay of 18.4 days compared to non-smokers, who were discharged after 15.3 days on average[24]. The immobilization associated with the longer hospital stay increases the risk of other adverse events, such as thrombosis. This results in an additional burden for the healthcare system and society[54].

So far, cigarette smoking cessation is the only alternative proven to reduce harmful effects on the human body[21]. Several studies have shown a reduced postoperative complication rate for patients who quit smoking cigarettes preoperatively[40][41], whereby the World Health Organization suggested four weeks of smoking abstinence prior to surgical intervention[55]. Despite all the positive effects associated with smoking cessation, many smokers are unable or unwilling to quit cigarette smoking or fail in their attempts. Without additional support alternatives or therapy, an attempt to quit smoking after one year is successful on average in only 3-5% of cases[56]. For instance, the retrospective study from Hall *et al.* showed that only 23% of total joint arthroplasty patients were able to quit smoking for one year[57].

Although there are many nicotine-based replacement alternatives on the market, such as gum, patches, and

sprays, the lack of ritual provides a major disadvantage that minimizes the chances of success in quitting cigarette smoking[58]. Therefore, it is essential to explore alternatives that support patients in quitting smoking but maintain the ritual associated with CS.

THS are newly developed technologies to reduce the consumer's exposure to potentially harmful substances produced during tobacco combustion, as well as to maintain smoking rituals and provide similar nicotine levels to cigarettes[59][60]. Given this, it can be assumed that there is a high level of acceptance by smokers.

In vitro, a significantly less harmful effect of THS compared to CS on mesenchymal stem cells and human osteoblasts has been demonstrated[45]. Additionally, an osteoporotic-like environment was generated in a direct co-culture system containing osteoblast/osteoclast exposure to extract from CS in contrast with THS[46]. The described *in vitro* results suggest that THS may be a less harmful alternative for smokers' orthopedic patients concerning fracture healing. However, the effect of switching from cigarettes to THS on the fracture healing process has not been explored in humans. Therefore, this study tests the hypothesis that switching to a THS after prior orthopedic surgery improves outcomes in orthopedic smoking patients during lower limb fracture healing over six months.

The main strength of this prospective, open-label study will be evidence of an increased serum concentration of CICP (primary outcome) in THS participants compared to smokers due to a reduced bone resorption rate. The study will also examine additional secondary parameters related to bone metabolism, bone healing, immunological, blood count, and clinical and sociodemographic parameters that facilitate our understanding of the overall status of the participants.

There are potential limitations to the study that need to be acknowledged. This study explores the effect of the switch from CS to THS only on the fracture healing of lower limb "long" bones. Since maxillofacial bones are directly exposed to the particulates contained in smoke or aerosols generated by cigarettes or THS molecules, the influence on bone cell homeostasis may differ from that on long bones. Additionally, blood sampling will take place during the clinical interventions in the late morning (between 9 and 12 PM). However, serum CICP concentrations have a circadian variation, with the highest concentration detected in the early morning[61], potentially causing the differences between the groups to be less significant.

Notes

Trial registration: The study is registered on ClinicalTrials.gov (NCT05859451).

Abbreviations

- BfArM: German Federal Institute for Drugs and Medical Devices
- CDMS: Clinical data management system
- CICP: N-terminal propeptide procollagen type 1
- CRF: Case report form
- CS: Cigarette smoke
- CT: Computed tomography scan
- ENDS: Electronic nicotine delivery systems
- FTND: Fagerström Test for Nicotine Dependence
- GCP: Good clinical practice
- ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
- IFT: Institute for Therapy Research
- IMPP: Institute for medical and pharmaceutical examination issues
- LEFS: Lower Extremity Functional Score
- QSU-b: Questionnaire of smoking urges
- THS: Tobacco heating system
- ZKS: Center for Clinical Studies

Statements and Declarations

Conflicts of Interest

The study was partially funded by Philip Morris International. However, the authors declare no personal conflicts of interest related to this work.

Ethics Statement

The study protocol and the declarations of consent were approved by the ethics committee of the medical faculty of Eberhard Karls University (724/2022BO1). Written informed consent to participate in this study was obtained from participants.

Monitoring procedure

Monitoring for this study is provided by the Zentrum für Klinische Studien Tübingen (ZKS Tübingen). The monitoring was conducted according to ZKS Tübingen internal Standard Operating Procedures (SOPs) and a dedicated monitoring manual for the study. The monitoring timelines include an initiation visit, regular monitor visits during the course of the trial, as well as a close-out visit. Usually, monitoring ends with the last

visit after full documentation of the last patient enrolled (close-out visit). All investigators agree that the monitors regularly visit the trial site, assure that the monitors receive appropriate support in their activities, and have access to all trial-related documents. The aim of the monitoring is to ensure patient safety and rights, data accuracy, and that the study is conducted in accordance with the approved protocol and applicable regulations.

Data Availability

Documents required to support the study protocol can be supplied on reasonable request to the corresponding author. After study closure, anonymized data will be made available upon reasonable request to the corresponding author.

Author Contributions

The study was designed by RA, MH, BB, and AKN. RA and MH wrote the original draft of the manuscript. Additionally, AKN served as the project administrator. All authors provided critical feedback and reviewed, edited, and approved the final manuscript.

Funding

This work was partially supported by Philip Morris International.

Acknowledgments

We thank all the BG clinic medical staff who assisted in the recruitment of participants, in particular Dr. med. Leyla Tuemen and Dr. med. Tanja Maisenbacher. We acknowledge Bianca Braun for her excellent technical assistance. We acknowledge support from the BG Clinical Study Center.

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Declarations

Funding: This work was partially supported by Philip Morris International.

Potential competing interests: The study was partially funded by Philip Morris International. However, the authors declare no personal conflicts of interest related to this work.