BIOCYBERNETICS AND BIOMEDICAL ENGINEERING 40 (2020) 1525–1534

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/bbe

Original Research Article

Bone fracture healing under external fixator: Investigating impacts of several design parameters using Taguchi and ANOVA

Reza Kolasangiani, Yousof Mohandes, Masoud Tahani *

Department of Mechanical Engineering, Ferdowsi University of Mashhad, Mashhad, Iran

ARTICLE INFO

Article history:
Received 2 July 2020
Received in revised form
19 August 2020
Accepted 14 September 2020
Available online 07 October 2020

Keywords:
Long bone fracture
Unilateral-uniplanar external fixator
Taguchi method
ANOVA
Mechanobiology of bone healing
Finite element analysis.

ABSTRACT

In this paper we aim to improve the understanding of the relationship between unilateral-uniplanar external fixator design parameters and their influences on fixator performance. Stability and strength of bone-fixator construct as well as the quality of healing were defined as our major concerns in order to evaluate the performance of fixator. The roles of six key design parameters were assessed during the early stage of healing by using finite element models. Tissue differentiation within the callus was predicted through the implementation of a mechanoregulation theory of bone healing. Taguchi and ANOVA methods were used to achieve optimal design sets for outputs and to determine contribution percentage of each design parameter on outputs. For improving overall fixator performance, optimal set of design parameters consisting of 2 mm, 8 mm, 120 mm, 20 GPa, 50 mm and 20 mm were determined by Taguchi for pin diameter, rod diameter, rod elevation, fixator Young's modulus, distance of the nearest pin to fracture site and distance between adjacent pins, respectively. Also, results of ANOVA revealed that rod elevation is the most important design parameter, with 43 % effectiveness on overall fixator performance, which was followed by fixator material and pin diameter with 28 % and 19 %, respectively. Results of this study can assist orthopedic surgeons to achieve an optimal fixator device with respect to the patient's condition and give insight into the importance of different design parameters.

1. Introduction

The use of external fixation devices in the tibia diaphyseal fracture treatment has always been a favorable option for surgeons. Adjustability of external fixator configuration according to how healing process progresses and consequently achieving desirable micro-movement at the fracture site is the main advantage of external fixators over alternative ways of fixation [1]. Nowadays, several external fixator systems are used in clinics which can be categorized into different groups; uniplanar–unilateral, uniplanar–bilateral, bi-planar and multi-planar [2]. However, there has always been a substantial number of debates over the optimal design and various

* Corresponding author.
E-mail address: mtahani@um.ac.ir (M. Tahani).

https://doi.org/10.1016/j.bbe.2020.09.007
0208-5216/

mechanical characteristics of external fixators [3]. A properly applied external fixator can accommodate a stable condition to host the biological process of bone regeneration and also provide a required amount of flexibility at the fracture site to improve the quality of healing, while an improperly applied one may cause adverse effects on the healing process of bone fracture [2].

The healing process can be classified into two different pathways: primary healing intramembranous ossification) and secondary healing (endochondral ossification). Primary bone healing happens when absolute mechanical stabilization is associated with anatomical reduction. In this type of healing, the healing process takes place by direct bone formation in the fracture gap [4] and depending on various species can take from a few months to a few years for bone to rehabilitate its strength. Secondary healing, on the other hand, takes place in less rigid fixation conditions [5] and does not require any anatomical reductions. Goodship and Kenwright [6] showed that relative instability which can cause axial micro-movement improves the healing process considerably as compared to rigid fixation of the osteotomy site. However, too much movement and/or load will result in prolonged healing process or even non-union at the fracture site [7].

To evaluate fractured bone healing process, many mechanoregulation theories have been proposed [8–10]. Roux [11] was the first one who explained tissue differentiation process based on mechanoregulation theory. Later on, tissue differentiation based on hydrostatic compression and shear deformation [12], interfragmentary strain (*IFS*) [13], deviatoric strain [10] and so on have been investigated. Mechanoregulation theories (deviatoric strain, fluid flow, pore pressure, etc.) were analyzed and compared by Isaksson et al. [10], who concluded that simulation as a function of only deviatoric strain provides an accurate prediction of normal fracture healing. This means, the deviatoric strain is the most significant mechanical parameter that guides tissue differentiation during the secondary healing process. Based on the deviatoric strain theory, the cells are made of granulation tissues immediately after surgery, and then they turn into different tissue phenotypes (i.e. fibrous tissue, cartilage, immature, intermediate and mature bones) according to the level of deviatoric strain each experiences during the healing process.

Nowadays computational methods have become an indispensable part of orthopedic researches. It is a highly effective approach in orthopedic researches due to its ability to reduce the amount of time and cost of researches compared to experimental tests on animals. By implementing computational methods, the effects of various fixators and their variables on mechanical behaviors have been comprehensively studied [14–19]. However, most studies have never provided any insights into the secondary healing process of a fractured bone under different combinations of decisive design variables of a unilateral-uniplanar external fixator. Furthermore, to the best of our knowledge, neither the optimization of several design parameters nor their impacts on strength, stability and healing quality have yet been studied.

Additionally, the significances and weights of design variables have never been evaluated as compared to each other. For instance, in order to increase stability, orthopedics might hesitate between several ways such as adding an extra pin or bringing rod closer to the bone, due to the lack of a methodology to analyze the importance of decisive factors [20,21]. This study highlights the difference between the significance of the most important variables of a unilateral-uniplanar external fixator, which was not tackled by other researchers to date, to the best of our knowledge.

Taguchi as a design of experiment (DOE) method was applied in this study. In the field of orthopedic biomechanics, Kim et al. [22] and Sheng et al. [23] also employed the Taguchi method and FEM to conduct optimization for internal fixation system with the plate.

We simulated the mechanical behavior of the whole bone-fixator construct and studied the mechanobiological microenvironment at the fracture site in response to a partial body weight load for various combinations of design parameters using finite element models. The first goal of this study was to develop optimum values through the use of Taguchi method. For the second aim, analysis of variance (ANOVA) was used to estimate the contribution percentage of each design parameter on the output. It is essential to note that our study is an exhaustive study in terms of evaluating several design variables of unilateral-uniplanar external fixator and selected outputs as compared to other studies in the literature. A mechanoregulation theory based on deviatoric strain was employed to predict the healing process of the fractured tibia. It must be remarked that the early stage of bone fracture healing is vital in the whole process [24,25], so we focused on the post inflammatory phase, in which callus is mainly composed of granulation tissue.

2. Materials and methods

2.1. Design inputs and outputs

This numerical study focuses on the impacts of several design parameters of a unilateral-uniplanar external fixator (see Fig. 1 (a)). The fixator consists of a connecting rod on the one side of the bone and four pins which are placed into the bone, above and below the fracture site. Geometry, material properties, and components relative arrangements are general design inputs. In detail, the distance of the nearest pin to the fracture site (A), the distance between adjacent pins (B), rod elevation (C), pin diameter (D), rod diameter (E) and fixator material (pins and rod Young's modulus) (Y) were selected as design parameters in this study. All of these selected design parameters are considered as the most important inputs in designing and constructing a unilateral–uniplanar external fixator [2,26–28]. In addition, design parameters which are related to geometric features of a unilateral-uniplanar external fixator are illustrated in Fig. 1. Regarding the exact distances between components, it is necessary to note that the distances between pins were considered between centers while the distance between rod and bone was considered between outside diameters, like what surgeons consider in operating rooms.

For design parameters, a wide range of discrete values have been implemented in this study. In external fixators, pin and rod diameter range from 2–6 mm and 8–12 mm, respectively [29,30]. In constructing a unilateral-uniplanar external fixator,

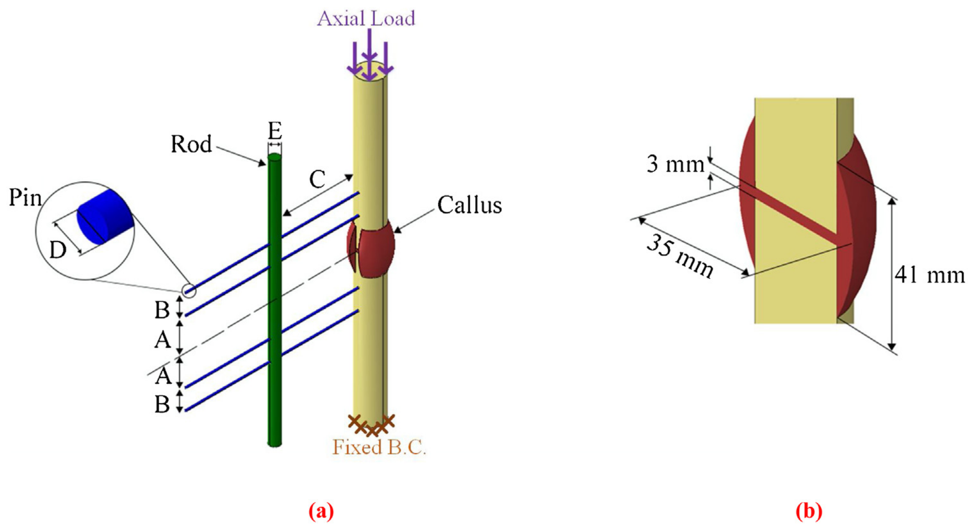

Fig. 1 – Geometric features, loading and boundary conditions applied in all design cases: (a) distance of the nearest pin to fracture site (A), distance between adjacent pins (B), rod elevation (C), pin diameter (D), rod diameter (E); and (b) cross sectional view of callus with a 3-mm transverse osteotomy.

rod elevation can differ from 40–120 mm [31]. For fixator material (Young's modulus), a wide range from 20–200 GPa was considered [32,33]. The distance of the nearest pin to fracture site and the distance between adjacent pins include all possible values, based on previous findings in the literature [31]. Discrete values of each design parameter were selected in 5 levels. Design parameters and their levels are shown in Table 1.

Von Mises stress is of significant importance in constructing and designing a fixation device. Due to possibility of failure, all von Mises stresses of pins, rod and bone should be fully analyzed [34,35]. Interfragmentary strain (*IFS*) is a simple and critical mechanical factor that could describe and evaluate the stability of various fixation devices. The *IFS* is calculated by dividing the interfragmentary movement (IFM) by the initial fracture gap size [36]. For normal healing, the *IFS* should not be more than 33% [6,37]. This is rooted in the fact that a flexible fixator which provides an *IFS* more than allowed threshold is not appropriate for treatment since the primary aim of a fixation device is to provide a stable construct for fracture.

Table 1 – Design parameters with their five levels for Taguchi design of simulations; distance of the nearest pin to fracture site (A), distance between adjacent pins (B), rod elevation (C), pin diameter (D), rod diameter (E), pins and rod Young's modulus (Y).

	Design parameter					
Level	A (mm)	B (mm)	C (mm)	D (mm)	E (mm)	Y (GPa)
Level 1	10	10	40	2	8	20
Level 2	20	15	60	3	9	50
Level 3	30	20	80	4	10	100
Level 4	50	30	100	5	11	150
Level 5	70	40	120	6	12	200

In order to evaluate the efficiency of bone-fixator construct from the biological point of view, the mechanobiological criteria were considered. Secondary healing index (*SHI*) is defined to show how much the fracture is inclined to heal through secondary pathway of healing. To predict whether a certain fractured bone is likely to heal through secondary healing or not, the amount of fibrous and cartilage tissues at early stage of healing should be analyzed. The more cartilage and fibrous tissue created in callus, the more fracture is expected to heal through secondary pathway of healing [9].

In order to reach an optimized design, a multi-objective function (*MOF*) based on normalized values was defined. Normalization used in this study was based on adjusting values measured on different scales to a common scale and to make the optimization process more efficient. All normalized values were achieved by dividing original values by the maximum value of each output. First, the *MOF* was defined as a function to achieve minimum value of stress and the maximum healing quality. To do so, a ratio of the normalized von Mises stress (NS) to the normalized secondary healing index (*NSHI*) is defined. Then, the square of the differences between normalized value of von Mises stresses of pins (*NSP*), bone (*NSB*), rod (*NSR*) and interfragmentary strain (*NIFS*) and their allowed ranges were added to the first fraction as penalty functions. With regard to allowed ranges, the *IFS* should be between 7-33% for a normal bone healing process. Yield stress of bone is considered to be 111 MPa [38] and this figure for pin and rod is about 690 MPa [39]. The *MOF* is defined by the following equation:

$$\mathrm{MOF} = \frac{\mathrm{NS}}{\mathrm{NSHI}} + \alpha(\mathrm{NSP}-\mathrm{ANSP})^2 + \alpha(\mathrm{NSB}-\mathrm{ANSB})^2 + \alpha(\mathrm{NSR}-\mathrm{ANSR})^2 + \alpha(\mathrm{NIFS}-\mathrm{ANIFS})^2 \tag{1}$$

where *ANSP* is normalized allowed stresses of pins, *ANSB* is normalized allowed stress of bone, *ANSR* is normalized allowed stress of rod, *ANIFS* is normalized allowed *IFS* and α is an empirical factor which was found to be 1 in an iterative manner until the bone-fixator construct made of optimal set of control parameters determined by Taguchi, does not violate the constraints used in this study (i.e. allowed stresses of pins, allowed stress of bone and rod). The constraints were included in the *MOF* using the same penalty coefficient since same importance was given to them.

By applying Taguchi method and ANOVA, we investigated the design parameters influencing on six specific outputs (i.e. the maximum von Mises stresses of pins, the maximum von Mises stress of bone, the maximum von Mises stress of rod, *IFS*, *SHI* and multi-objective function) which are subdivisions of our three major outputs (i.e. strength and stability of bone-fixator construct as well as the healing performance).

2.2. Taguchi and ANOVA

Taguchi technique as a DOE approach is popular among engineers and scientists because it can be adopted and applied with a basic knowledge of statistics to minimize the required number of experiments or simulations [40]. By increasing the number of design parameters, a larger number of simulations needed to be done. Taguchi method minimizes the number of simulations by using a special set of arrays called orthogonal. According to full factorial approach, required number of simulations could be calculated by powering the number of levels to the number of factors [41], which in this work is 5^6 (15625). Thanks to fractional factorial approach, Taguchi method reduces this number to only 25 simulations. The software used in this study for employing Taguchi method was Minitab 18.

In current study, 4 primary steps were carried out for Taguchi method: first, an orthogonal array (L_{25}) was selected. Second, outputs were analyzed based on the signal to noise (S/N) ratio. Third, optimum sets of design parameters for each individual output were obtained, and finally six simulations (for six above-mentioned outputs) were run to achieve optimum values.

For representing a response or quality characteristic of a system, S/N ratio is used in Taguchi approach [42]. S/N ratios can be classified into three categories: smaller-the-better (used for all outputs except *SHI*), target-the-best (which is not used in this study) and larger-the-better (used for *SHI*). In this study, mean values of S/N ratios for all levels of design parameters were calculated, then the level which had the highest S/N ratio was selected as the optimum level for each output.

Furthermore, ANOVA was utilized to estimate the contribution percentage of each design parameter on outputs. Although ANOVA is normally employed for evaluating data obtained from an experiment, in this study, like similar studies (e.g. see [41,43]), it was used as an approach to analyze results from simulations.

2.3. Finite element model

To generate the long bone geometry, the dimensions and shape of a tibia were simplified as a smooth circular shaft in ABAQUS 2017 [44,45], which was modelled as a cylinder (with a length of 300 mm) composed of cortical bone with an outer and inner diameter of 25 and 15 mm as well as bone marrow at the intramedullary canal. Then, a 3-mm transverse osteotomy (medium gap size) was mimicked on the basis of Lacroix's researches [14,36,46]. The internal callus was modelled at endosteal and intracortical locations in order to fill up the space between two bone segments. For bridging the fractured tibia segments, external callus is also modelled along periosteal. The geometry and dimensions of internal and external callus were taken from previous studies (see Fig. 1 (b)) [14,47]. Furthermore, the external fixator with single rod and two pins for each bone segment was inserted in the anterior-medial side of the tibia. Design cases were modelled based on Taguchi suggestion for analyzing different design parameters. For the sake of simplicity, clamps were not modelled [48,49], but to consider the impact of clamps on the assembled construct, tie constraints were applied between rod and pins. Likewise, tie constraints were applied between bone and pins in all 25 design cases.

Table 2 – Material properties of bone.

Material	Young's Modulus (GPa)	Poisson's ratio
Cortical bone [64]	20	0.3
Marrow [36]	0.002	0.167
Granulation tissue [53]	0.001	0.167

The material properties of the cortical bone, bone marrow and callus (made of granulation tissue) applied in this study are represented in Table 2.

All parts of bone-fixator construct were modelled using 8-node linear hexahedral solid elements with reduced integration. The most appropriate mesh size was determined by convergence study. To do so, by increasing the mesh density, the difference between axial stiffness was compared between two mesh sizes. Once this difference was less than 2%, and the results converge satisfactorily, the favorable mesh size was obtained, which was 1 mm for callus, pin and rod and a larger mesh size of 2 mm for the bone. The fracture callus, bone, pin and rod were meshed with 16112, 15600, 4000 and 24448 elements, respectively.

The bone healing process is sensitively influenced by loading conditions [50]. In this paper, AO instructions were applied for loading conditions at the fracture site. Accordingly, it is suggested that 25% of the body weight (B.W.) should be applied on the fracture site for the first six weeks after surgery [51]. We assumed a body weight of 75 kg in this study. This compressive pressure was applied at one end of the tibia bone, and a fully constraint boundary condition was set to the other end of the bone (see Fig. 1 (a)).

To validate the finite element models from a biomechanical point of view, a new case, apart from 25 design cases, was constructed so as to compare the axial stiffness of the bone-fixator construct with the results of an experimental study in the literature [52].

2.4. Mechanoregulation algorithm of bone healing

Different types of mechanoregulation algorithms have been introduced to estimate temporal and spatial tissue

Table 3 – Material properties for different tissue phenotypes [10].

Tissue type	Poisson's ratio	Young's modulus (MPa)	Deviatoric Strain
Granulation tissue	0.167	1	$\epsilon_d = 1$
Fibrous	0.167	1–5	$1 > \epsilon_d \geq 0.05$
Cartilage	0.167	5–500	$0.05 > \epsilon_d \geq 0.025$
Immature bone	0.325	500–1000	$0.025 > \epsilon_d \geq 0.0005$
Intermediate bone	0.325	1000–2000	$0.0005 > \epsilon_d \geq 0.00041$
Mature bone	0.325	2000–6000	$0.00041 > \epsilon_d \geq 0.00005$
Resorption	———	———	$0.00005 > \epsilon_d$

development during secondary healing process of a fractured bone. Among all algorithms, it has been proven that mechanoregulation algorithm based on deviatoric strain is accurate enough to predict a normal healing process [10,53]. The deviatoric strain is calculated by the following equation:

$$\epsilon_{ds} = \frac{2}{3}\sqrt{(\epsilon_1 - \epsilon_2)^2 + (\epsilon_2 - \epsilon_3)^2 + (\epsilon_3 - \epsilon_1)^2} \quad (2)$$

where ϵ_1, ϵ_2 and ϵ_3 are principal strains of each callus element.

In this paper, bone healing process (at early stage of healing) was simulated through the use of user's subroutine programmed by Python 3.1 and ABAQUS 2017. The initial callus was assumed to consist of soft tissue (granulation tissue). Based on the above-mentioned theory, new Young's modulus in all callus elements and tissue phenotypes were determined by deviatoric strain. By increasing the magnitude of Young's modulus, tissue phenotypes could differ from granulation tissue to mature bone (see Table 3). Also, Fig. 2 briefly shows all steps from creating the FE model of fractured tibia and external fixator to applying the Taguchi and ANOVA.

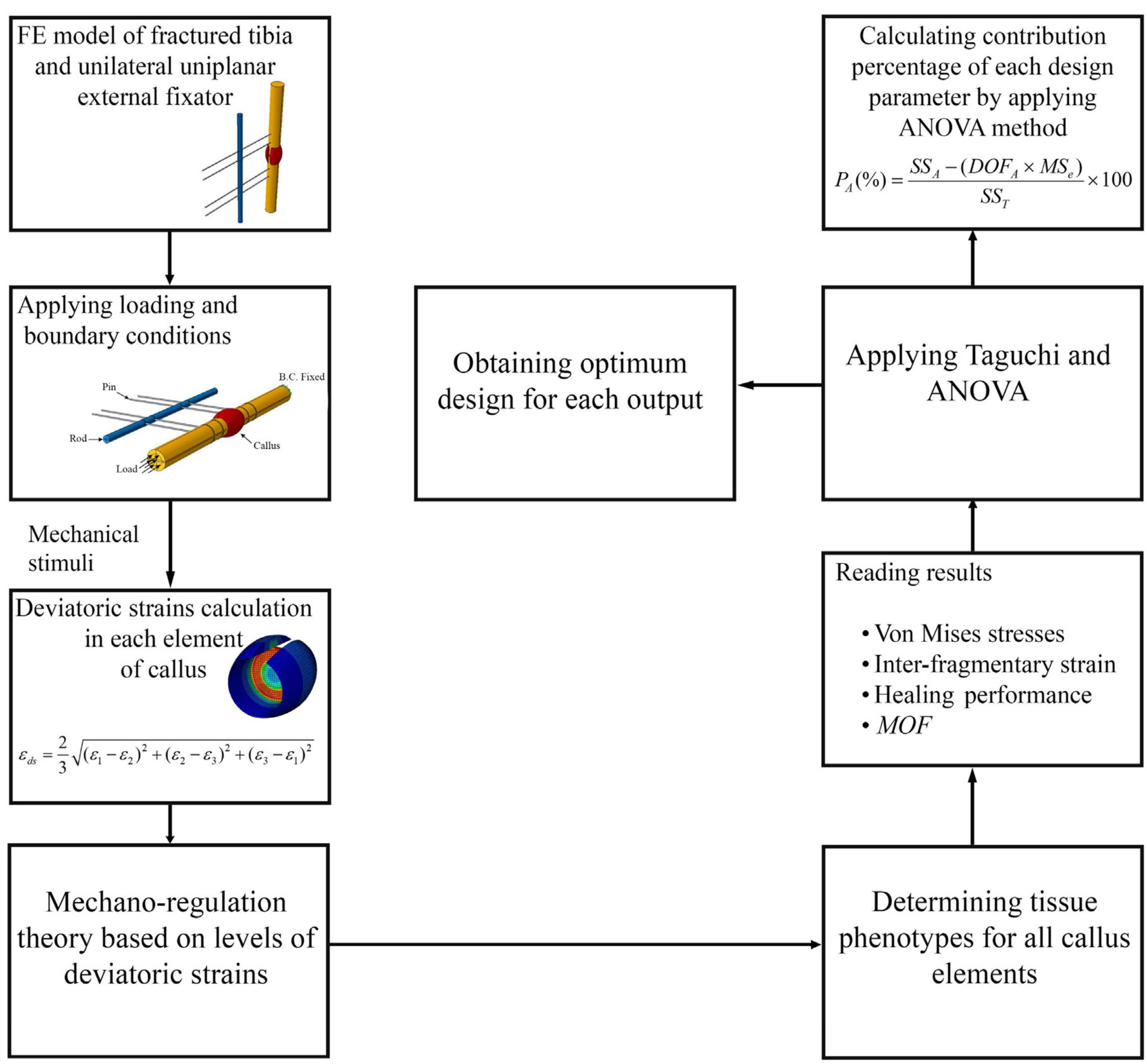

Fig. 2 – The workflow of this study to achieve two major goals.

3. Results

This section encompasses the results of finite element model validation, von Mises stresses and the *IFS* immediately after surgery as well as the patterns of tissue differentiation and *MOF* during the early stage of healing. Also, the Taguchi and ANOVA results are presented in this section.

3.1. Validation of finite element models

Validation of finite element models was conducted through comparing the values of axial stiffness of a bone-fixator construct (519 N/mm), created in this study, with a similar construct used in an in-vitro experiment (528 N/mm) [52].

3.2. Von Mises stress

Maximum von Mises stresses of all parts are represented in Fig. 3. The highest von Mises stress value of rod was 162 MPa, observed in case 15, while the lowest value was 1.98 MPa, observed in design case 9. The highest von Mises stress of pins was 105 MPa, observed in case 15, whereas case 9 with 4.39 MPa had the lowest stress as shown in Fig. 3. Likewise, the maximum and the minimum stress values of bone were 38.8 MPa and 2.37 MPa, observed in case 15 and 9, respectively. Overall, all the minimum and the maximum stresses of bone-fixator construct were observed in case 9 and 15.

3.3. The interfragmentary strain

The *IFS* was calculated by dividing interfragmentary movement by the gap size (3 mm) at four points of internal callus (medial, lateral, anterior and posterior) given that tibia experienced bending in the mid-diaphysis. The greatest of these values are presented in Fig. 4. Design case 23 with 35.9% had the highest *IFS* and case 18 with 17.1 % the lowest.

3.4. Healing pathway

As it was mentioned before, the amount of fibrous and cartilage tissues are crucial at the early stage of healing process; accordingly, secondary healing index (*SHI*) is introduced and calculated as follows:

$$\mathrm{SHI}\,(\%) = \frac{\text{The number of fibrous and cartilage tissue elements in callus}}{\text{The total number of callus elements}} \times 100 \tag{3}$$

Fig. 4 shows *SHI* of 25 cases through the use of L_{25} orthogonal array. Among all simulations, conditions 3 and 4 had the richest fibrocartilage tissues and conditions 18 and 22 had the lowest fibrocartilage tissues as presented in Fig. 4.

3.5. Multi-objective function

The *MOF* was defined in order to investigate an optimum design case that follows more than just one criterion. Fig. 5 shows *MOF* for all cases. Case 18 had the maximum value of *MOF*. This means with regard to *SHI*, von Mises stresses and the *IFS*, it is the least favorable case, while case 9 is the most favorable.

3.6. Taguchi suggestions for optimum designs

For achieving an optimum design case of each output, levels which had the highest mean values of S/N ratios were selected

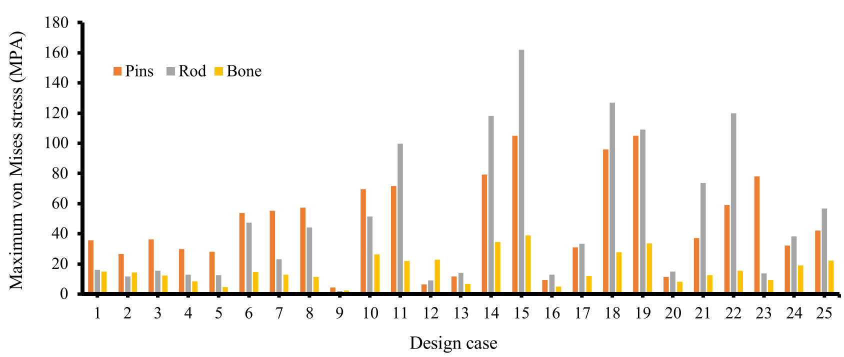

Fig. 3 – Maximum von Mises stress of pins, rod and bone in 25 design cases.

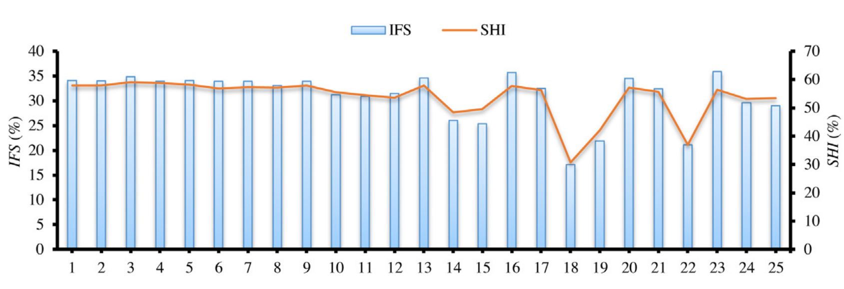

Fig. 4 – The *IFS and SHI* for 25 design cases.

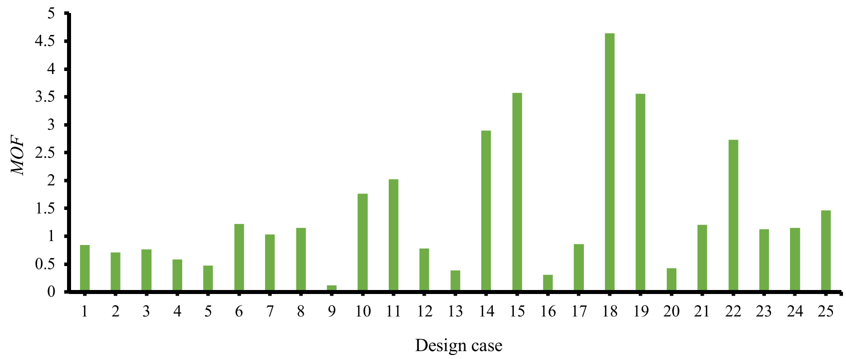

Fig. 5 – *MOF* for 25 design cases at early stage of healing.

Table 4 – Optimum level of each design parameter for outputs and results of optimized simulations.

Design parameter	Stresses of pins	Stress of rod	Stress of bone	*IFS*	*SHI*	*MOF*
A (mm)	50	70	70	20	70	**50**
B (mm)	20	20	20	40	30	**20**
C (mm)	120	120	120	40	120	**120**
D (mm)	2	2	2	5	2	**2**
E (mm)	9	9	10	11	8	**8**
Y (GPa)	20	20	20	200	20	**20**
Results	3.697	1.661	2.299	0.150	59.21	**0.108**

as the optimal levels and are shown in Table 4. Then six simulations with optimum levels of each design parameter were carried out. Table 4 also demonstrates the results. Compared to 25 design cases, the von Mises stresses of pins, rod and bone observed in optimal constructs reduced by 16 %, 17 % and 3 %, respectively. In addition, the stability increased by 11 % after optimization (by reducing *IFS*). Also, the optimized value of *SHI* was 59.21 % (higher than the maximum *SHI* in design cases by a margin of 1 %) and this figure for *MOF* was 0.108, a little less than the best case observed in 25 design cases. To conclude, by applying all suggested design sets, strength and stability of bone-fixator construct and healing quality were improved.

3.7. *Analysis of variance*

Table 5 shows contribution percentage of each design parameters on outputs. Rod elevation had the most contribution percentage on all outputs with 48% for the maximum von Mises stresses of pins, 27% for the maximum von Mises stress of rod, 37% for the maximum von Mises stress of bone, 32% for *IFS*, 35% for *SHI* and 42% for multi-objective function. Pin diameter and fixator material were also two important design parameters which had higher contribution percentage among other design parameters. On the other hand, apart from *SHI* in which the distance of the nearest pin to the fracture site had the smallest effectiveness (5.21%), the lowest impact on other outputs is related to the distance between adjacent pins, followed by rod diameter.

4. Discussion

This paper presents a combined methodology to help in the design of external fixators used to achieve proper bone fracture stabilization and healing. Six design parameters were identified initially as the most important in the problem: pin diameter, rod diameter, rod elevation, fixator material, distance of the first pin to fracture site and distance between adjacent pins. This study follows two major goals. First, Taguchi method was used to enhance the strength and the stability of bone-fixator construct and to improve the healing

Table 5 – The contribution percentage of design parameters on outputs.

Design parameter	Stresses of pins	Stress of rod	Stress of bone	*IFS*	*SHI*	*MOF*
A	5.59	4.16	17.01	7.80	5.21	**5.60**
B	3.28	2.60	1.67	7.10	8.82	**1.58**
C	48.07	27.87	37.16	32.51	35.60	**42.53**
D	7.48	26.34	27.73	21.80	26.13	**18.95**
E	6.01	2.79	8.47	8.21	6.43	**3.61**
Y	29.54	26.20	10.93	22.55	17.78	**27.70**

quality. Second, ANOVA was applied to detect the relative influence of each parameter on each output or the overall performance of fixator.

It is worth highlighting that although this study primarily concentrate on the early stage of healing, this period is influential during the entire healing process due to the fact that the early microenvironment plays a key role in cell fate which can influence the healing pathway of the progenitor cells and consequently the bone healing during all stages [24,25,54].

In our study by employing von Mises stress as a criterion for predicting the failure of ductile materials, the possibility of bone-fixator construct failure was investigated. Overall, the maximum von Mises stresses of bone in 25 design cases, on average, were lower than that of rod and pins. With regard to the aforementioned threshold (690 MPa for rod and 111 MPa for bone), no case experienced failure after applying the load during the initial stage of healing. Additionally, it is also noteworthy that ANOVA results demonstrate rod elevation is the most critical parameter affecting von Mises stresses of all parts of bone-fixator construct. Previous studies [2,32] have also declared that rod elevation plays an important role in stresses in bone and fixation device.

In terms of stability, the principal goal of the clinical treatment of bone fractures is to immobilize the fracture site. To do so, the *IFS* is a reliable indicator of bone-fixator construct rigidity. In general, for the best healing outcomes, it is expected that *IFS* to be around 7–33 %. Too rigid fixator (*IFS* $<$ 7%) will hinder any micro-movements and consequently cause primary healing. On the other hand, too much movement in the fracture site means the fixator is not rigid enough to stabilize fracture and this can bring about nonunion. So surgeons try to limit interfragmentary movement to achieve a moderate *IFS* (around mean of 7 % and 33 %) [54]. In case 18, rod elevation was 40 mm and *IFS* was 17 %, which is consistent with previous findings in terms of the favorable distance of rod to bone and a moderate *IFS* [2,54]. The ANOVA results of *IFS* indicate that rod elevation had the most contribution percentage (32.51%), meaning that changing the distance of rod to the bone can highly affect the *IFS*, more than any other design parameter. Other studies also have focused on the importance of rod elevation for increasing stability [20,55].In other words, by bringing the rod closer to the bone, it is expected that the stability improves which leads to a lower *IFS*. The *IFS* values observed in Case 14, 19 and 22, where rods are nearer to bones in comparison with other cases, clearly represent the effect rod elevation on stability.

In terms of healing, it is worth mentioning that fixator stiffness highly influences the fracture healing process. By investigating and changing design parameters throughout 25 design cases, stiffness is the most conspicuous mechanical parameter which is changing. Those cases which were more flexible experienced higher value of *SHI* compared to more rigid cases. Also, given the *IFS*, less rigid cases (lower *IFS*) generally had higher values of *SHI*, so it can be concluded that there is a positive correlation between more flexibility and higher value of *SHI*, which supports previous findings [14,15,56,57]. It is crucial to note that orthopedics should not merely focus on high value of *SHI* at early stage of healing since it is achieved by fixator destabilization which can cause failure or mal union until the end of healing process. The ANOVA results reveal that among the six parameters studied in this paper, rod elevation is the most important parameter influencing the tissue differentiation in the callus during healing process. Although the importance of rod elevation have been discussed before [20,32,55], none of previous studies provide a mechanoregulatory insight into the influence of rod elevation.

Furthermore, the relationship between the *IFS* and *SHI* is plainly visible in Fig. 4. This correlation has been studied by many researchers and it was concluded that there should be a positive correlation between interfragmentary movement (or *IFS*) and secondary healing quality, which is consistent with results of 25 design cases [58–60]

MOF is an optimized design in which all the above-mentioned outputs are considered in a single multi-objective function. All von Mises stresses, *IFS* and *SHI* are taken together in one equation in order to achieve the best design. Among all 25 design cases which were assembled based on Taguchi suggestion, case 9 showed a lower value of multi-objective function. Like other outputs, for selecting the optimum level of each design parameter, S/N ratio was employed. Then an extra simulation was run for the optimum design and the value for *MOF* was lower than case 9, which had the best *MOF* among 25 design cases. The ANOVA results show that rod elevation had the highest influence on *MOF*, which was followed by fixator material.

Overall, Taguchi optimal cases demonstrate that in most suggested design sets, less rigid fixator is recommended to achieve optimized design sets. To elaborate, suggested rod diameter, pin diameter and the distances of pins are mainly on the levels that make a bone-fixator construct less rigid. Also, suggested Young's modulus for 5 out of 6 outputs is 20 GPa. This is consistent with previous findings as biomedical materials with lower Young's modulus would be preferable for bone healing process [47,61,62]. Taguchi suggested design sets can provide surgeons with an insight to deal with various situations. To clarify, in some conditions, achieving maximum healing quality might be of little concern (in case of an old patient), while, here, maximum stability is needed. The approach used in this study can assist surgeons to deal with different conditions.

This work also includes some limitations. First, the whole study was investigated during the early stage of healing process. It is clear that the whole process is a cascade of events, which an interruption at any stages might be able to effect the healing process. Second, simplifications in finite element models, such as simplified material and structural properties (e.g. homogenous material properties, simplified bone and callus) can lead to some errors in analyzing outputs. Third, loosening of Schanz screws in external fixators, as a decisive factor in determining the failure or success of an implant was not investigated [63].

5. Conclusion

From a mechanobiological perspective, this paper provided valuable insights into the designing and applying unilateral external fixator. The finite element models developed in this study alongside the Taguchi method enabled the selection of optimum sets of design parameters (i.e. the distance of the nearest pin to the fracture site, the distance between adjacent pins, rod elevation, pin diameter, rod diameter and fixator material (pins and rod Young's modulus). A summary of findings regarding two major goals of this study are as follows:

- Given the ANOVA results of all outputs (i.e. the maximum von Mises stresses of pins, bone and rod, *IFS*, *SHI* and *MOF*), it can be concluded that rod elevation was the most important design parameter, thus it is suggested that orthopedic surgeons consider it superior to other factors in applying a fixator.
- The Taguchi optimal design cases can be used for various goals. With regard to the condition of patient and fracture type, different design sets for different aims, like increasing stability or improving healing quality, can be assembled.

Conflicts of interest

The authors declare that they have no conflict of interest.

CRediT authorship contribution statement

Reza Kolasangiani: Software, Visualization, Writing - review & editing, Validation. **Yousof Mohandes:** Conceptualization, Methodology, Project administration. **Masoud Tahani:** Supervision.

REFERENCES

[1] Fragomen AT, Rozbruch SR. The mechanics of external fixation. Hss J 2007;3(1):13–29.
[2] Roseiro LM, Neto MA, Amaro A, Leal RP, Samarra MC. External fixator configurations in tibia fractures: 1D optimization and 3D analysis comparison. Comput Methods Programs Biomed 2014;113(1):360–70.
[3] Beltsios M, Savvidou O, Kovanis J, Alexandropoulos P, Papagelopoulos P. External fixation as a primary and definitive treatment for tibial diaphyseal fractures. Strateg Trauma Limb Reconstr 2009;4(2):81–7.
[4] Andreykiv A, Van Keulen F, Prendergast P. Simulation of fracture healing incorporating mechanoregulation of tissue differentiation and dispersal/proliferation of cells. Biomech Model Mechanobiol 2008;7(6):443–61.
[5] McKibbin B. The biology of fracture healing in long bones, the Journal of Bone and Joint Surgery. British volume 1978;60(2):150–62.
[6] Goodship A, Kenwright J. The influence of induced micromovement upon the healing of experimental tibial fractures. J Bone Joint Surg Br 1985;67(4):650–5.
[7] Green E, Lubahn J, Evans J. Risk factors, treatment, and outcomes associated with nonunion of the midshaft humerus fracture. J Surg Orthop Adv 2005;14(2):64–72.
[8] Prendergast P, Huiskes R, Søballe K. Biophysical stimuli on cells during tissue differentiation at implant interfaces. J Biomech 1997;30(6):539–48.
[9] Carter DR, Beaupré GS, Giori NJ, Helms JA. Mechanobiology of skeletal regeneration. Clin Orthop Relat Res 1998;355: S41–55.
[10] Isaksson H, Wilson W, van Donkelaar CC, Huiskes R, Ito K. Comparison of biophysical stimuli for mechano-regulation of tissue differentiation during fracture healing. J Biomech 2006;39(8):1507–16.
[11] Roux W. Gesammelte abhandlungen über entwickelungsmechanik der organismen: bd. Entwicklungsmechanik des embryo. Wilhelm Engelmann; 1895.
[12] Pauwels F. Biomechanics of the locomotor apparatus. (Translated from german by P. Maquet and R. furlong). Berlin, Heidleberg: Springer-Verlag; 1980.
[13] Perren S. Physical and biological aspects of fracture healing with special reference to internal fixation. Clin Orthop Relat Res 1979;138:175–96.
[14] Byrne DP, Lacroix D, Prendergast PJ. Simulation of fracture healing in the tibia: mechanoregulation of cell activity using a lattice modeling approach. J Orthop Res 2011;29 (10):1496–503.
[15] Miramini S, et al. Computational simulation of the early stage of bone healing under different configurations of locking compression plates. Comput Methods Biomech Biomed Engin 2015;18(8):900–13.
[16] Zhang[1] L, Miramini S, Mendis P, Richardson M, Pirpiris M, Oloyede A. The effects of flexible fixation on early stage bone fracture healing; 2013.
[17] Gasser B, Boman B, Wyder D, Schneider E. Stiffness characteristics of the circular Ilizarov device as opposed to conventional external fixators; 1990.
[18] Willie B, Adkins K, Zheng X, Simon U, Claes L. Mechanical characterization of external fixator stiffness for a rat femoral fracture model. J Orthop Res 2009;27(5):687–93.
[19] Chao EY, Hein TJ. Mechanical performance of the standard Orthofix external fixator. Orthopedics 1988;11(7):1057–69.
[20] Giotakis N, Narayan B. Stability with unilateral external fixation in the tibia. Strateg Trauma Limb Reconstr 2007;2 (1):13.
[21] Roberts CS, Dodds JC, Perry K, Beck D, Seligson D, Voor MJ. Hybrid external fixation of the proximal tibia: strategies to improve frame stability. J Orthop Trauma 2003;17(6): 415–20.
[22] Kim J-D, Kim N-S, Hong C-S, Oh C-Y. Design optimization of a xenogeneic bone plate and screws using the Taguchi and finite element methods. Int J Precis Eng Manuf 2011;12 (6):1119–24.
[23] Sheng W, Ji A, Fang R, He G, Chen C. Finite element-and design of experiment-derived optimization of screw configurations and a locking plate for internal fixation system. Comput Math Methods Med 2019;2019.
[24] Epari DR, Taylor WR, Heller MO, Duda GN. Mechanical conditions in the initial phase of bone healing. Clin Biomech 2006;21(6):646–55.
[25] Klein P, et al. The initial phase of fracture healing is specifically sensitive to mechanical conditions. J Orthop Res 2003;21(4):662–9.
[26] Pettine KA, Chao E, Kelly PJ. Analysis of the external fixator pin-bone interface. Clin Orthop Relat Res 1993;293:18–27.
[27] Kim W-Y, Hearn TC, Seleem O, Mahalingam E, Stephen D, Tile M. Effect of pin location on stability of pelvic external fixation. Clin Orthop Relat Res 1999;361:237–44.
[28] Ramlee MH, Wahab AHA, Wahab AA, Latip HFM, Daud SA, Kadir MRA. The effect of stress distribution and displacement of open subtalar dislocation in using titanium alloy and stainless steel mitkovic external fixator-a finite element analysis. Malay J Fundam Appl Sci 2017;15:477–82.
[29] Sellei R, et al. Biomechanical properties of different external fixator frame configurations. Eur J Trauma Emerg Surg 2015;41(3):313–8.
[30] Sellei RM, et al. External fixation design evolution enhances biomechanical frame performance. Injury 2015;46:S23–6.

[31] Huiskes R, Chao E. Guidelines for external fixation frame rigidity and stresses. J Orthop Res 1986;4(1):68–75.
[32] Bronson DG, Ross J, Toombs J, Welch R. Influence of the connecting rod on the biomechanical properties of five external skeletal fixation configurations. Vet Comp Orthop Traumatol 2003;16(02):82–7.
[33] Sternick MB, Dallacosta D, Bento DÁ, do Reis ML. Relationship between rigidity of external fixator and number of pins: computer analysis using finite elements. Revista Brasileira de Ortopedia (English Edition) 2012;47 (5):646–50.
[34] Kaman M, Celik N, Karakuzu S. Numerical stress analysis of the plates used to treat the tibia bone fracture. J Appl Math Phys 2014;2(06):304.
[35] Saidpour SH. Assessment of carbon fibre composite fracture fixation plate using finite element analysis. Ann Biomed Eng 2006;34(7):1157–63.
[36] Lacroix D, Prendergast P. A mechano-regulation model for tissue differentiation during fracture healing: analysis of gap size and loading. J Biomech 2002;35(9):1163–71.
[37] Claes L, Augat P, Suger G, Wilke HJ. Influence of size and stability of the osteotomy gap on the success of fracture healing. J Orthop Res 1997;15(4):577–84.
[38] Wolfram U, Schwiedrzik J. Post-yield and failure properties of cortical bone. Bonekey Rep 2016;5.
[39] Allen R. Standard specification for wrought 18 chromium-14 nickle-2.5 molybdenum stainless steel bar and wire for surgical implants (F138), Annual Book of ASTM Standards. Medical Devices and Services 1998.
[40] Thamizhmanii S, Saparudin S, Hasan S. Analyses of surface roughness by turning process using Taguchi method. J Achiev Mater Manuf Eng 2007;20(1-2):503–6.
[41] Hatam A, Khalkhali A. Simulation and sensitivity analysis of wear on the automotive brake pad. Simul Model Pract Theory 2018;84:106–23.
[42] Fung C-P, Kang P-C. Multi-response optimization in friction properties of PBT composites using Taguchi method and principle component analysis. J Mater Process Technol 2005;170(3):602–10.
[43] Al-Momani E, Rawabdeh I. An application of finite element method and design of experiments in the optimization of sheet metal blanking process. JJMIE 2008;2(1):53–63.
[44] Benli S, Aksoy S, Havitcioglu H, Kucuk M. Evaluation of bone plate with low-stiffness material in terms of stress distribution. J Biomech 2008;41(15):3229–35.
[45] Ganesh V, Ramakrishna K, Ghista DN. Biomechanics of bone-fracture fixation by stiffness-graded plates in comparison with stainless-steel plates. Biomed Eng Online 2005;4(1):46.
[46] Lacroix D, Prendergast P. Three-dimensional simulation of fracture repair in the human tibia. Comput Methods Biomech Biomed Engin 2002;5(5):369–76.
[47] Son D-S, Mehboob H, Jung H-J, Chang S-H. The finite element analysis for endochondral ossification process of a fractured tibia applied with a composite IM-rod based on a mechano-regulation theory using a deviatoric strain. Compos Part B Eng 2014;56:189–96.
[48] Chen H, Zhang Y, Xia H, Wang F, Li Z, Chen X. Stability of tibial defect reconstruction with fibular graft and unilateral external fixation: a finite element study. Int J Clin Exp Med 2014;7(1):76.
[49] Radke H, Aron DN, Applewhite A, Zhang G. Biomechanical analysis of unilateral external skeletal fixators combined with IM-pin and without IM-pin using finite-element method. Vet Surg 2006;35(1):15–23.
[50] O'Sullivan ME, Bronk JT, Chao E, Kelly PJ. Experimental study of the effect of weight bearing on fracture healing in the canine tibia. Clin Orthop Relat Res 1994;302:273–83.
[51] Ruedi TP. AO principles of fracture management. Thieme; 2000.
[52] Ang B, et al. Externalised locking compression plate as an alternative to the unilateral external fixator: a biomechanical comparative study of axial and torsional stiffness. Bone Joint Res 2017;6(4):216–23.
[53] Isaksson H, Van Donkelaar CC, Huiskes R, Ito K. Corroboration of mechanoregulatory algorithms for tissue differentiation during fracture healing: comparison with in vivo results. J Orthop Res 2006;24(5):898–907.
[54] Ganadhiepan G, Miramini S, Patel M, Mendis P, Zhang L. Bone fracture healing under Ilizarov fixator: influence of fixator configuration, fracture geometry, and loading. Int J Numer Method Biomed Eng 2019;35(6):e3199.
[55] Finlay JB, Moroz T, Rorabeck C, Davey J, Bourne R. Stability of ten configurations of the Hoffmann external-fixation frame, the Journal of Bone and Joint Surgery. American volume 1987;69(5):734–44.
[56] Claes L, et al. Metaphyseal fracture healing follows similar biomechanical rules as diaphyseal healing. J Orthop Res 2011;29(3):425–32.
[57] Claes L. Biomechanical principles and mechanobiologic aspects of flexible and locked plating. J Orthop Trauma 2011;25:S4–7.
[58] Cheal E, Mansmann K, Digioia IIIA, Hayes W, Perren S. Role of interfragmentary strain in fracture healing: ovine model of a healing osteotomy. J Orthop Res 1991;9(1):131–42.
[59] Claes L, Wilke H-J, Kemper F. Interfragmentary strain and bone healing–an experimental study. J Orthop Trauma 1988;2(1):67.
[60] Meyer U, et al. The effect of magnitude and frequency of interfragmentary strain on the tissue response to distraction osteogenesis. J Oral Maxillofac Surg 1999;57 (11):1331–9.
[61] Son D-S, Chang S-H. The simulation of bone healing process of fractured tibia applied with composite bone plates according to the diaphyseal oblique angle and plate modulus. Compos Part B Eng 2013;45(1):1325–35.
[62] Mehboob H, Chang S-H. Evaluation of healing performance of biodegradable composite bone plates for a simulated fractured tibia model by finite element analysis. Compos Struct 2014;111:193–204.
[63] Pommer A, David A, Barczik P, Muhr G. Loosening of Schanz screws in external fixator montage of the lower extremity. Unfallchirurg 1998;101(9):708–12.
[64] Claes L, Heigele C. Magnitudes of local stress and strain along bony surfaces predict the course and type of fracture healing. J Biomech 1999;32(3):255–66.