

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



# Self-Regenerative Ability of Bone and Micro Processing of Bone-Component Material in Orthopedic Surgery Healing

T. Ohtani<sup>1</sup>, T. Nakai<sup>2</sup>, R. Mori<sup>2</sup> and Y. Uchio<sup>2</sup>

<sup>1</sup>*Tokyo Gakugei University*

<sup>2</sup>*Shimane University*

<sup>1,2</sup>*Japan*

## 1. Introduction

To aid healing after orthopedic surgery, bone components, such as pins or screws, are used to immobilize broken or skinned bone after a bone or joint in the human body is broken (Lima et al., 2004). Metal and plastic materials are generally used to immobilize the injured bone after surgery; however, these artificial biomaterials may have residual adverse side effects.

The use of natural rather than artificial materials seems likely to lessen adverse side effects. Natural bone material is characterized by its remodeling action and self-regenerative ability (Curry, 2002).

In this study, the development of bone components was advanced through the use of self-regenerative functions. This research was promoted by the author's collaborative group in both the surgical and the engineering fields at Shimane University (Organization for the Promotion of Project Research, Shimane University, 2008).

The project developed components for orthopedic surgery healing and created a new system to precisely manufacture bone components in surgical operating rooms. The new system is described in the following section. Fusion control during contact with bone components is important for recovery of the affected area. Furthermore, controlling the conditions that promote and delay the fusion of bone components will lead to nonconventional and more effective surgical healing techniques.

Previous research focused on titanium as a biomaterial for internal bone, and initial osteoblast adhesion and cell migration profiles on a titanium surface have been reported (Zinger et al., 2004; Itahashi et al., 1995). In particular, one study reported that self-regenerative osteoblasts could detect nanoscale holes on a titanium surface (Zinger et al., 2004). However, controlled cell migration on a natural bone surface in contact with bone material has not been investigated.

This chapter presents research (Ohtani et al., 2009) on the self-regenerative ability of bone as a result of controlled surgical healing. The next section discusses details of a new machining system for manufacturing bone components. In addition, the engineered properties of bone-

component material (Ohtani et al., 2005) and the effects of anisotropic tissue on the machining of bone material (Ohtani et al., 2009) are introduced briefly in Sections 3.1–3.3.

The properties of a processed bone model surface are described based on the engineering technology used in actual surgeries. Furthermore, fundamental research on the self-regenerative ability with respect to cell migration on a processed bone model surface is investigated by focusing on random migration which allows osteoblasts to grow via regenerative action.

## 2. Micro processing of bone components in precision machining

The first research trial in this project (Organization for the Promotion of Project Research, Shimane University, 2008) focused on the screw-shaped bone components used for orthopedic surgery. As shown in Fig. 1, the manufacturing system for bone screws used in this trial is an improved high-precision machine (MTS4) developed jointly with Nano Corporation in Japan.

The manufacturing system includes a micro processing machine, which can be brought into the surgery room and easily operated. The machine is constructed of lightweight B4-sized materials weighing 30 kg. Doctors and nurses in the surgery room can operate the system using computer-aided drawing software that executes programs quickly. The machines can be safely operated during cutting under clean conditions, which means without using cutting fluid and coolant. The system can be placed anywhere that has a 100-VAC household power supply and can be controlled by a personal computer.

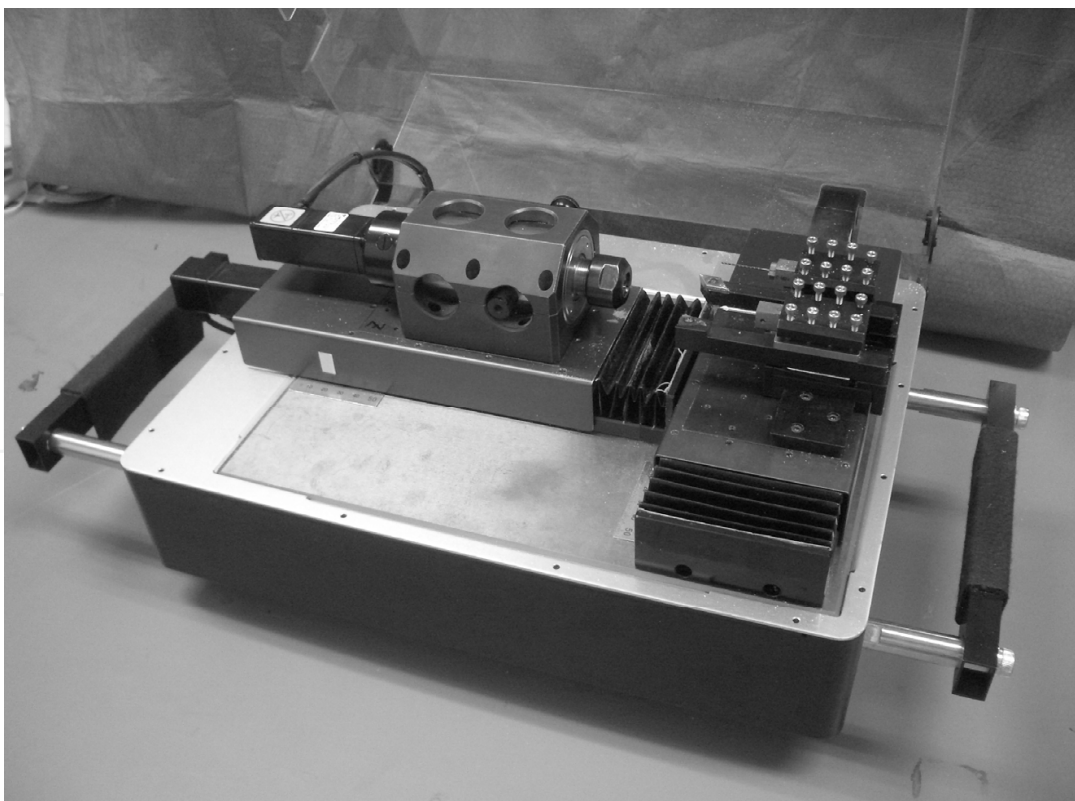


Fig. 1. The precision turning machine developed in this research project.

Fig. 2 shows examples of manufactured bone screws. The bone screws can be machined into a precise shape with a dimension of approximately 5 mm and fastened to the healing area by using a customized tool. After immobilization of the bone with the bone screw, the self-regenerative ability of the bone assimilates the bone screw with the internal bone.

In this study, it was important to clarify the effect of anisotropic bone tissue on the precise machining of the screw thread. In addition, it was important to see the effect of the formation of micro asperities in the finished surface of the machined bone screw on the assimilation period. If the assimilation period is shortened after immobilization with the bone screw, the psychological burden on the patient could be reduced.

In the following section, we introduce the material properties and effects of anisotropic bone tissue that were investigated to determine the optimum procedure to precisely machine the bone.

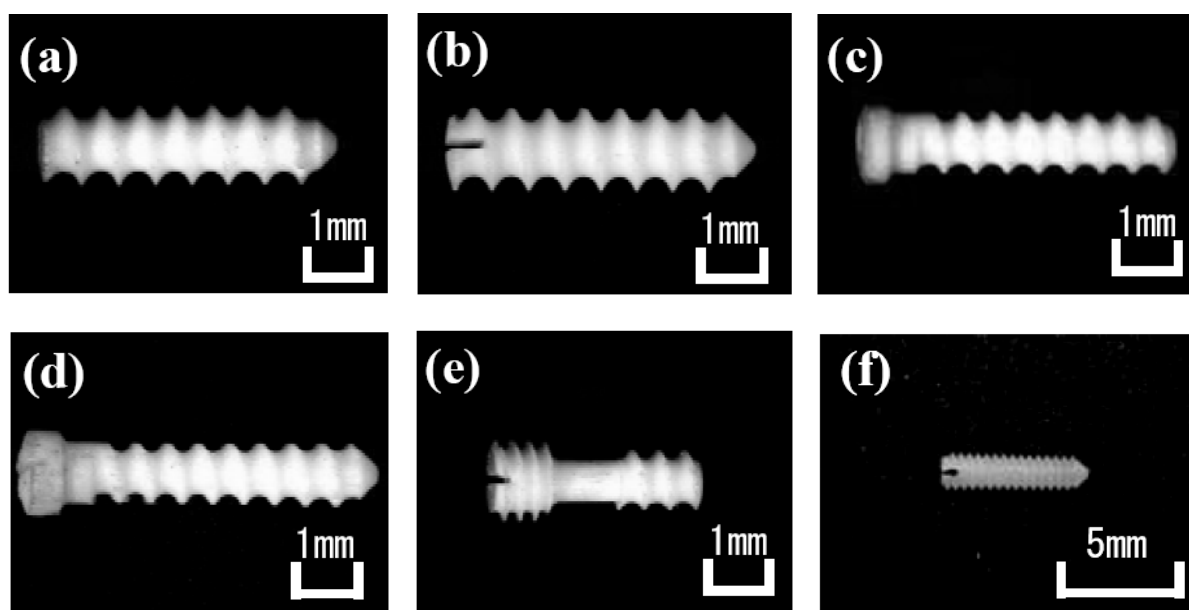


Fig. 2. Examples of manufactured bone screws.

### 3. Effects of anisotropic tissue on micro processing of bone components

#### 3.1 Inhomogeneous nature of bone tissue

Biological bone has a sandwich-like structure, with clearance space on the inside and calcified compact tissue surrounding it (Gibson, 1997). Compact bone consists of an osteon lamellar layer surrounding haversian canals, through which capillaries run. Fig. 3 (a)–(c) shows optical micrographs of the outer layer of compact bovine bone, which has the characteristic microstructure of bone tissue.

The cross-sections in this figure are in the axial [Fig. 3 (a)], radial [Fig. 3 (b)], and circumferential [Fig. 3 (c)] directions, respectively. It can be seen that the inhomogeneous property of the micro tissue might affect the minute fraction of the tool tip that is in contact with the bone for precisely machined bone components.

### 3.2 Effect of inhomogeneous microscopic tissue on bone surface hardness

The compact bone used for the component material has an inhomogeneous structure (Fig. 3). Therefore, the effect of a small amount of this tissue on the bone surface hardness was investigated. Fig. 4 shows the results of a micro-Vickers hardness test that was conducted on the bovine bone test specimen.

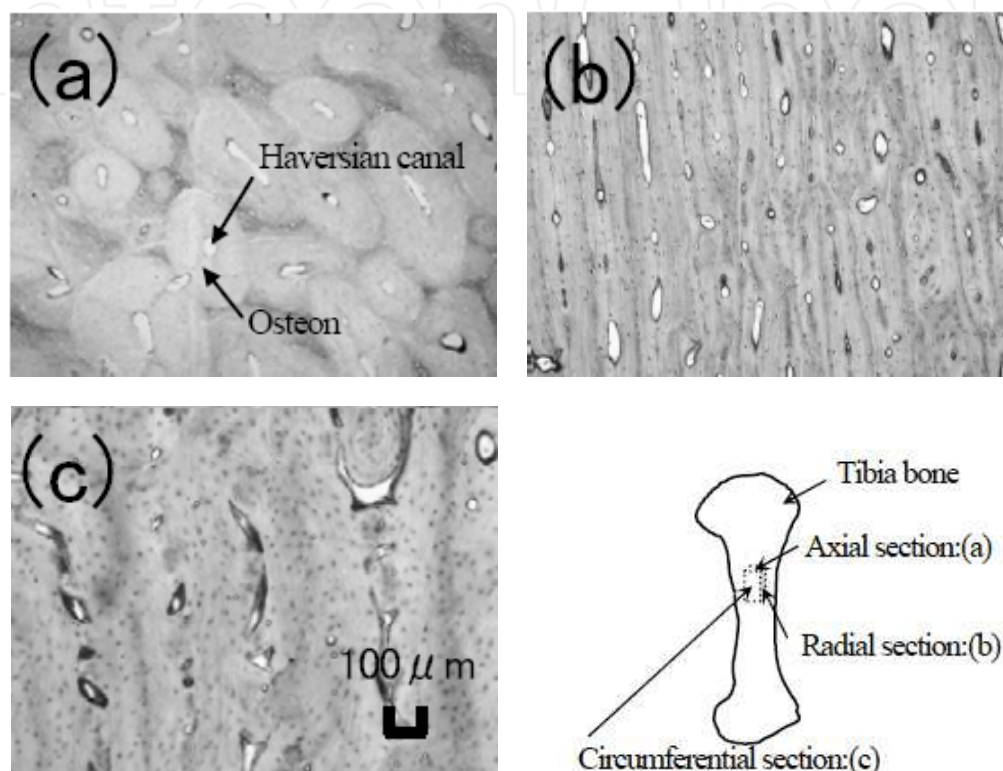


Fig. 3. Optical micrographs of the cross sections in compact bovine bone.

Vickers hardness (HV) was measured at different pressures applied via an indenter perpendicular to the axial, A (a), tangential, T (b), and radial, R (c) directions. The black circles in Fig. 4 shows the results for 30 runs. The scattered points were measured at each applied force. The white circles and error bars are the average values and standard deviations at the 95% confidence interval, respectively.

The range of HV values [Fig. 4 (a)–(c)] differed according to the applied force (F). The values were significantly lower for  $F = 1\text{ N}$  to  $2\text{ N}$ . This result indicates that the hardness values were more heterogeneous for the applied forces between  $F = 1\text{ N}$  to  $2\text{ N}$ , but were more homogeneous for the higher applied forces. In addition, the HV range differed for cross sections perpendicular to the A [Fig. 4 (a)], T [Fig. 4 (b)], and R [Fig. 4 (c)] directions ( $T > A > R$  for a smaller F). The average HV value for the cross sections perpendicular to the A and T directions was larger than that for the R direction. This result suggests that the anisotropic tissue differed for cross sections perpendicular to the A, R, and T directions [Fig. 3 (a)–(c)]. Thus, anisotropic tissue affects the bone surface hardness.

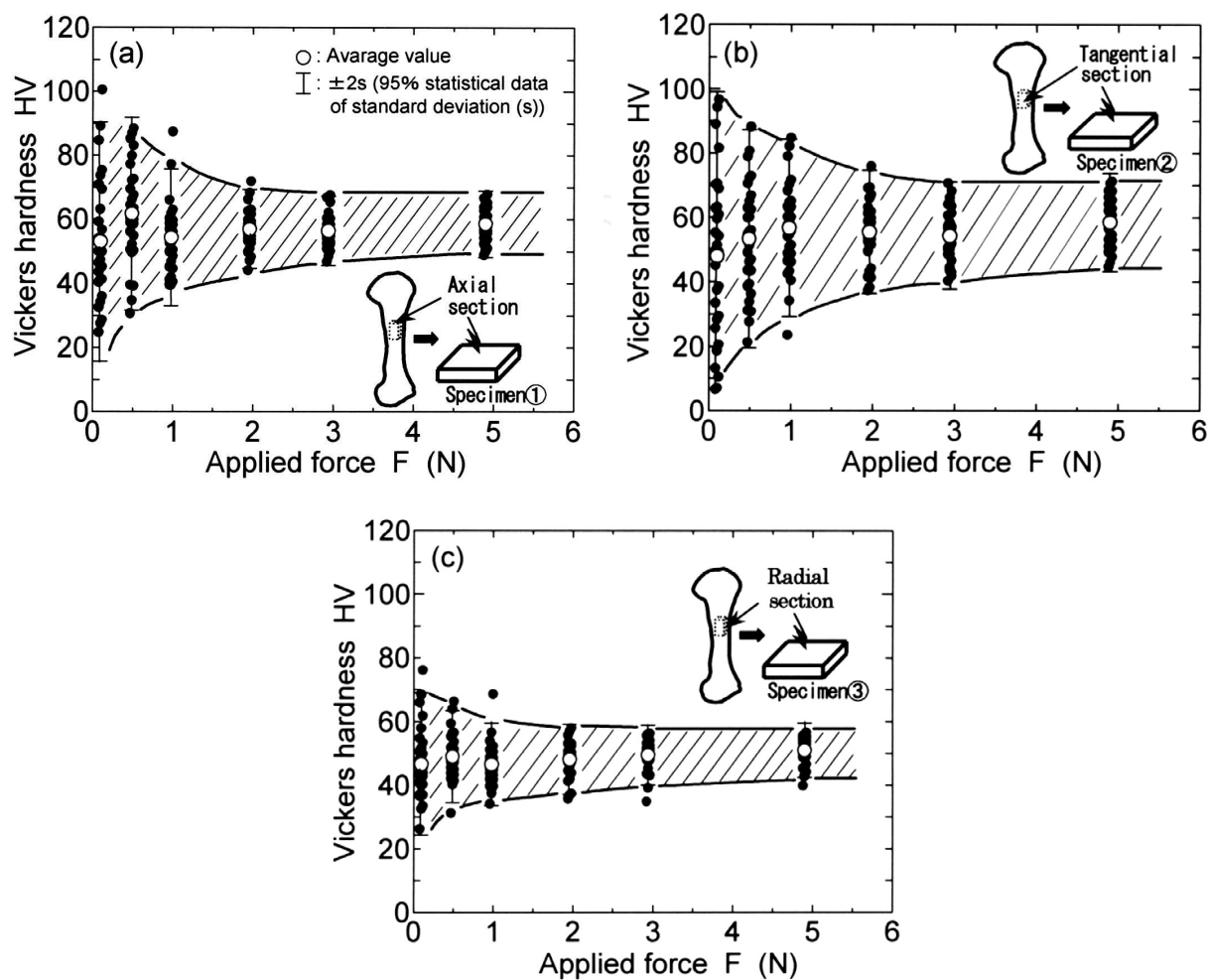


Fig. 4. Relationship between Vickers hardness (HV) and the applied force (F) in the axial (a), tangential (b) and radial (c) sections.

Fig. 5 shows the relationship between the indented depth (D) and the applied force (F) when the above data were used to investigate the heterogeneity of the hardness values displayed in Fig. 4. For this experiment, the indented depth (D) was based on the length of straight of the diagonal line indented on the bone surface, and the indentation depth of the 136° tip radius was calculated.

The indentation (D) in the cross sections perpendicular to the A, R, and T directions increased significantly with increasing F. The rate of the increase tended to decrease for F values greater than approximately 2 N. The result shown in Fig. 5 indicates that the applied force began to scatter significantly when the Vickers hardness corresponded to that at  $t = 10 \mu\text{m}$ .

Based on these results, it is suggested that the indentation depth affects the bone structure hardness and the heterogeneous microscopic tissue affects the hardness when its border is equal to the indentation depth.

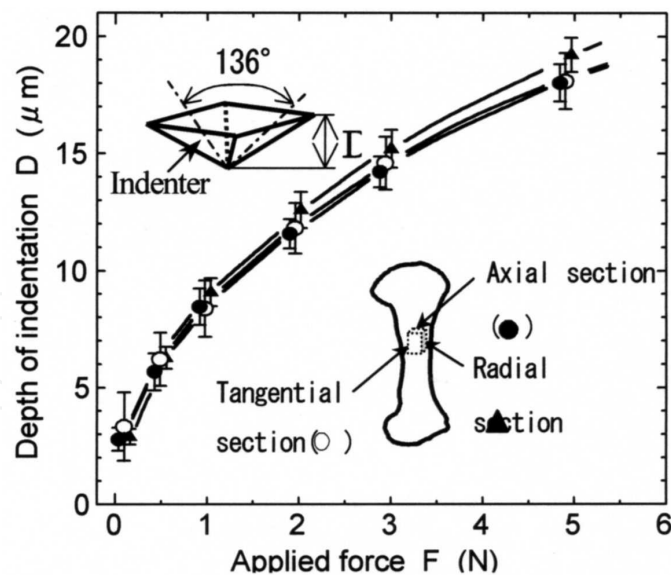


Fig. 5. Relationship between the depth of indentation ( $D$ ) and the applied force ( $F$ ) in the axial, tangential and radial sections.

### 3.3 Effect of anisotropic tissue on micro cutting

The inhomogeneity of the surface hardness was expected to affect the accuracy of the bone cutting. Fundamental bone-cutting data have been reported since the 1970s (Wiggins & Malkin, 1978). More recently, artificial joint replacement using a robotics machining system has been reported. In these more recent studies, fundamental bone-machining data were reported (Ito et al., 1983; Sugita et al., 2007); however, the effects of fractures during the cutting of calcified compact bone were not discussed in detail.

Thus, our project group has been quantitatively investigating the fracture behavior during bone cutting. With anisotropic tissue, continuous and interrupted chips are formed during the cutting process. In Fig. 6 (a)–(f), the shapes of the chips in calcified compact bone were categorized as follows: flow [Fig. 6 (a) and (b)], which generated cracks parallel to the cutting of the tool edge; shear [Fig. 6 (c) and (d)], which generated cracks along the outer edge of the osteon at the top of the tool edge; and tear [Fig. 6 (e) and (f)], which tore the osteon tissue without cutting.

The effect of the anisotropic tissue on the chip shape is observed for cutting with crack propagation. Fig. 7 shows the effects of the anisotropic tissue on bone cutting. When cutting along the osteon tissue [Fig. 7 (a)], the cut direction affected the cutting properties, and cracks propagated toward the front of the cutting tool.

It was confirmed that cracks similar to those shown in Fig. 7 (b) can occur along the outer edge of the osteon tissue, and cracks similar to those shown in Fig. 7 (c) can occur due to tearing along the osteon and not due to cutting. Thus, for precisely machined bone components, such as screws, the effect of anisotropic tissue, in particular, bone, should be considered when optimizing micro cutting conditions. In particular, the surface profiles after machining provide important information on whether the minute profile affects the self-regenerative ability of bone tissue.

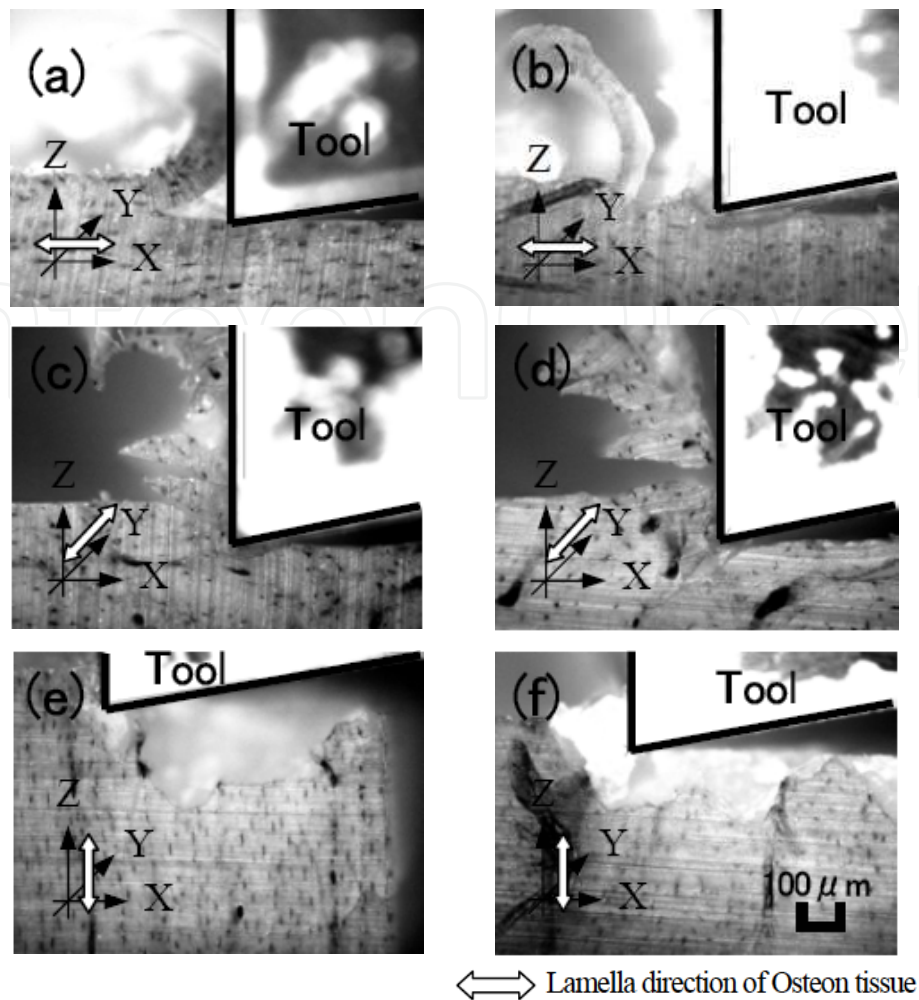


Fig. 6. Process of chip formation for the depth of cut with  $t=100 \mu\text{m}$ .

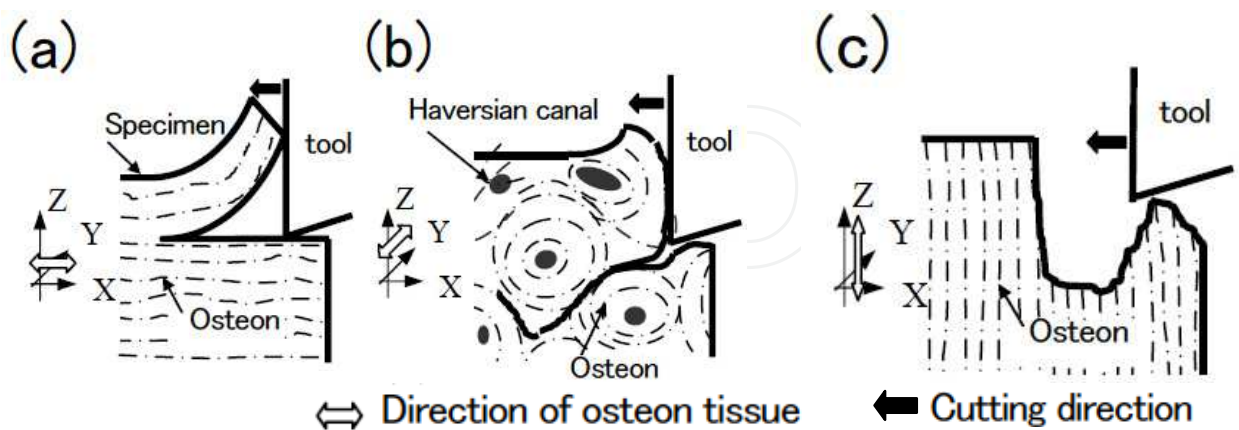


Fig. 7. Effect of anisotropic tissue in cutting of bone material with cutting.

#### 4. Properties of surgical processing mechanisms

Different instruments are used to cut and remove bone in orthopedic surgery, and the surface profiles of bone differ according to the surgical instrument used. Fig.8 (a)-(i) show



the orthopaedic surgical instruments investigated in this experiment. Destructive tools include the chisel [Fig. 8 (a)] and the clamp [Fig. 8(b)]. Saw-type tools include the manual saw [Fig. 8 (c)], the vibration saw [Fig. 8 (d)], and wire saws [Fig. 8 (e) and (f)]. Loose scratching and grinding tools include the file [Fig. 8 (g)] and revolving instruments include the steel bar and the diamond bar [Fig. 8 (h) and (i)].

Fig. 9 shows the macro-edge shape of the surgical instruments shown in Fig. 8. The chisel and clamp [Fig. 9 (a) and (b)] are used to cut and separate bone, respectively.

The tips of the saw and the wire tools [Fig. 9 (c)–(f)] can remove bone by unidirectional or reciprocating motion. The tool edges shown in Fig. 9 (g)–(i) can remove the bone surface by filing. The steel and diamond bars remove bone by mechanical revolution of the tip edge.

Fig. 10 shows scanning electron microscope (SEM) cross-sectional images of the bone surface after the tangential section was processed with the above mentioned instruments. The bone surface processed by the chisel and clamp [Fig. 10 (a) and (b)] on the lamellar layer of the osteon tissue exhibits a bumpy profile with uneven fractures. Bone tissue on the sawed surface removed by cutting shows fine debris adhered to the surface [Fig. 10 (c) and (d)]. An irregular surface was observed after wire cutting [Fig. 10 (e) and (f)] because the surface was scratched by the rugged wire edge. Fig. 10 (g)–(i) shows that the surface was gouged and scratched by the large and small edges of the tool tip.

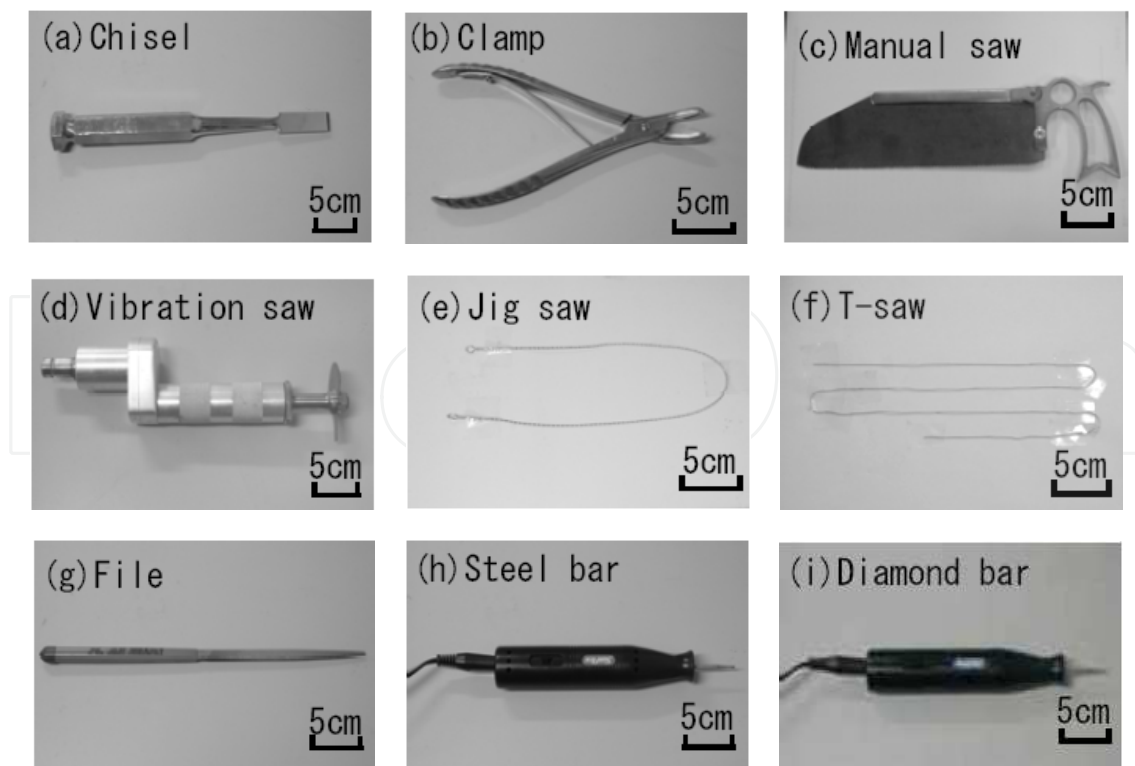


Fig. 8. Orthopaedic surgical instruments used in this experiment.

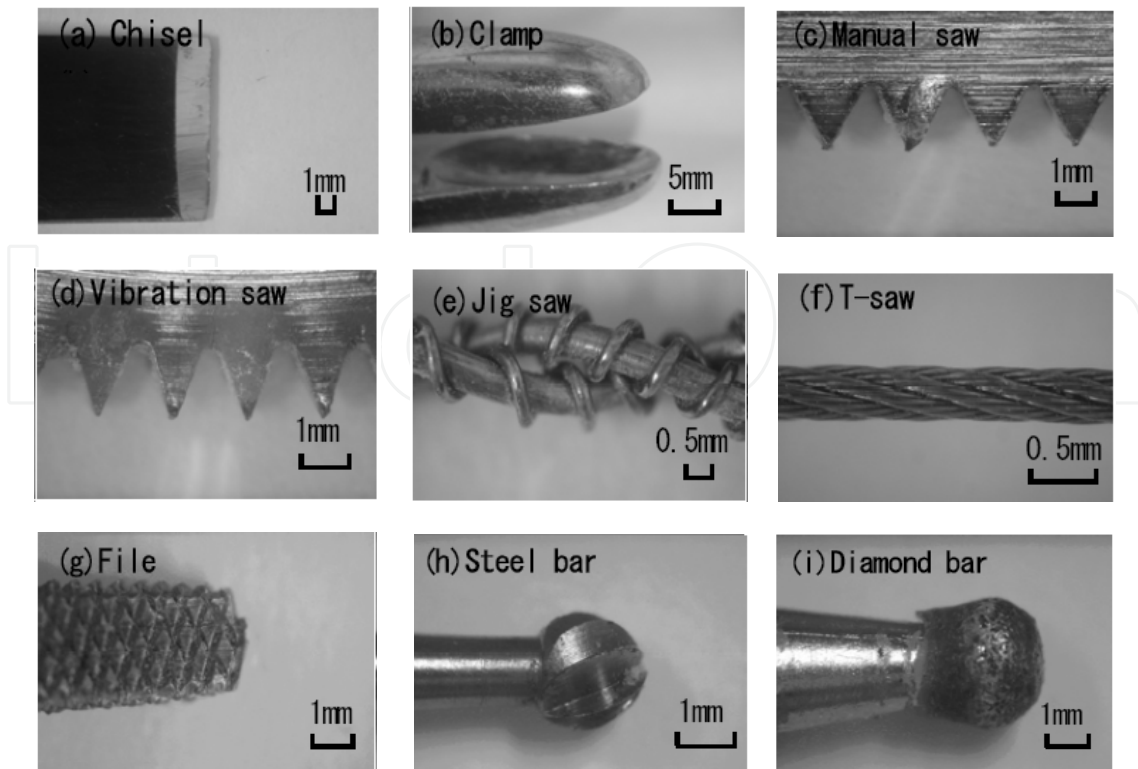


Fig. 9. Shape of edges in orthopedic surgical instruments.

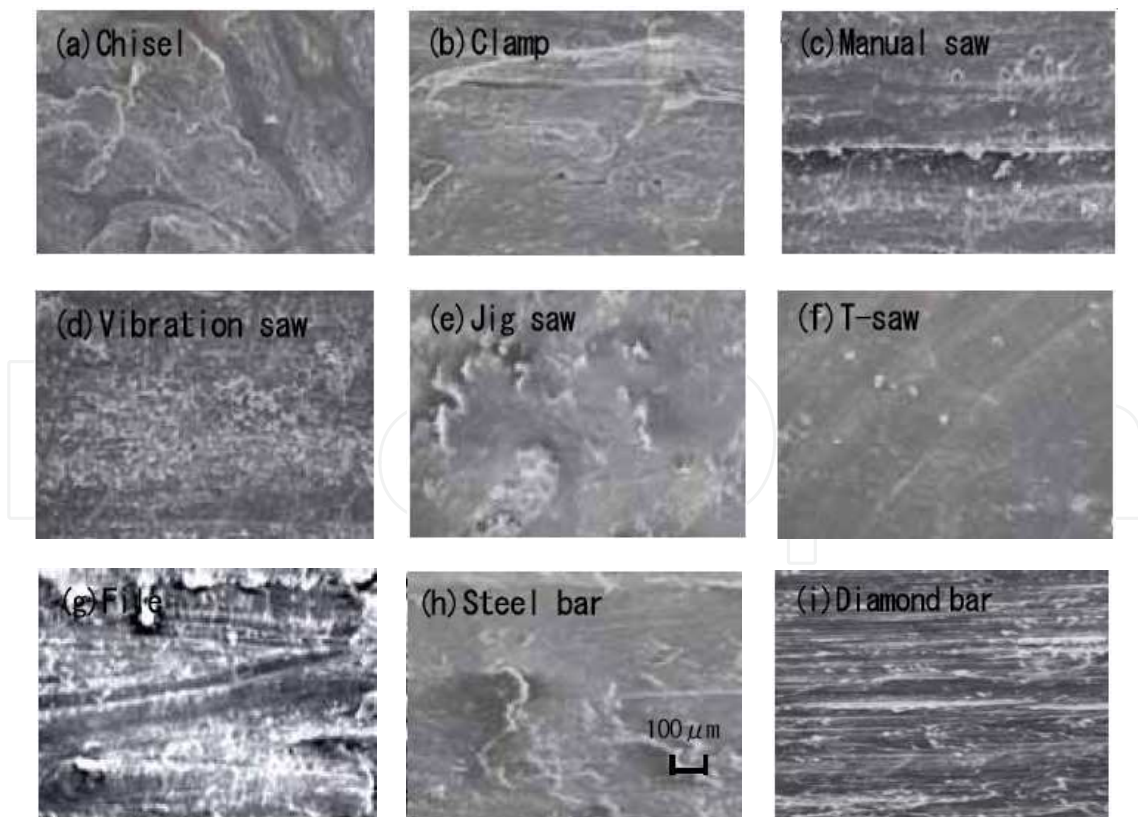


Fig. 10. Scanning electron microscope images of bone surfaces processed by orthopedic surgical instruments.

The properties of the bone surfaces processed by orthopedic surgical instruments are shown in Table 1, based on the tool tip shape. The instruments are categorized by the positive or negative rake angle of the cutting edge and the unidirectional or reciprocating motion to remove the bone material. Moreover, the table lists the properties of processed surfaces, which include directional scratches, irregular scratches, and fractures. The surface properties are related to the removal mechanism and classified as cutting, scratching due to bonded and loose abrasive grains with a negative rake angle, and cracking induced by fractures. The surgical processing mechanisms of cutting, bonded and loose abrasive grains, and cracking are related to the engineered tool tip shape.

| Surgical instruments | Rake angle | Removal direction | Property of orthopedical surgical processing | Model mechanism of engineering processing |
|----------------------|------------|-------------------|--|---|
| (c)Manual saw        | Negative   | Reciprocation     | Saw cutting                                  | Cutting                                   |
| (d)Vibration saw     | Negative   | Reciprocation     | Saw vibratory cutting                        |   |
| (g)File              | Negative   | Reciprocation     | Scratching                                   | Bonded abrasive                           |
| (h)Steel bar         | 0°         | Unidirectional    | Scratching                                   |   |
| (i)Diamond bar       | Negative   | Unidirectional    | Grinding                                     |   |
| (e)Jig saw           | Negative   | Loose direction   | Loose scratching                             | Loose abrasive                            |
| (f)T-saw             | Negative   | Loose direction   | Loose scratching                             |   |
| (a)Chisel            | Positive   | Unidirectional    | Cracking                                     | Cracking                                  |
| (b)Clamp             | 0°         | Unidirectional    | Cracking                                     |   |

Table 1. Properties of bone surfaces processed by orthopedic surgical instruments.

## 5. Cell migration on the processed bone surface

A cell culture experiment was conducted to recreate the surgical processing mechanism on the processed model surface. Fig. 11 (a)-(h) shows SEM images of the model surfaces, including cut surfaces [Fig. 11 (a) and (b)], polished surfaces with bonded and loose abrasive grains [Fig. 11 (c)-(f)], a cracked surface [Fig. 11 (g)], and a control surface which was finished lubricously by turning machine [Fig. 11 (h)].

The cell migratory distance on these model surfaces was analyzed by an X-Y coordinate diagram (Fig. 12). Based on these results, cell migration on the processed model surfaces (Table 1) was characterized.

Cells on the cut surface [Fig. 12 (a) and (b)] tended to migrate in the Y direction, and the tendency increased as the cutting depth increased [Fig. 12 (a)]. Cells on the bonded abrasive surface [Fig. 12 (c) and (d)] tended to migrate in the Y direction, and the migration was similar to that on the cut surface. Cells on the loose abrasive surface [Fig. 12 (e) and (f)] tended to spread in a concentric circle with the larger abrasive grains, but spread arbitrarily with the smaller abrasive grains. Cells on the cracked surface [Fig. 12 (g)] spread arbitrarily as compared with cells spread with the loose abrasive grains, and cells on the control surface [Fig. 12 (h)] spread significantly in all directions.

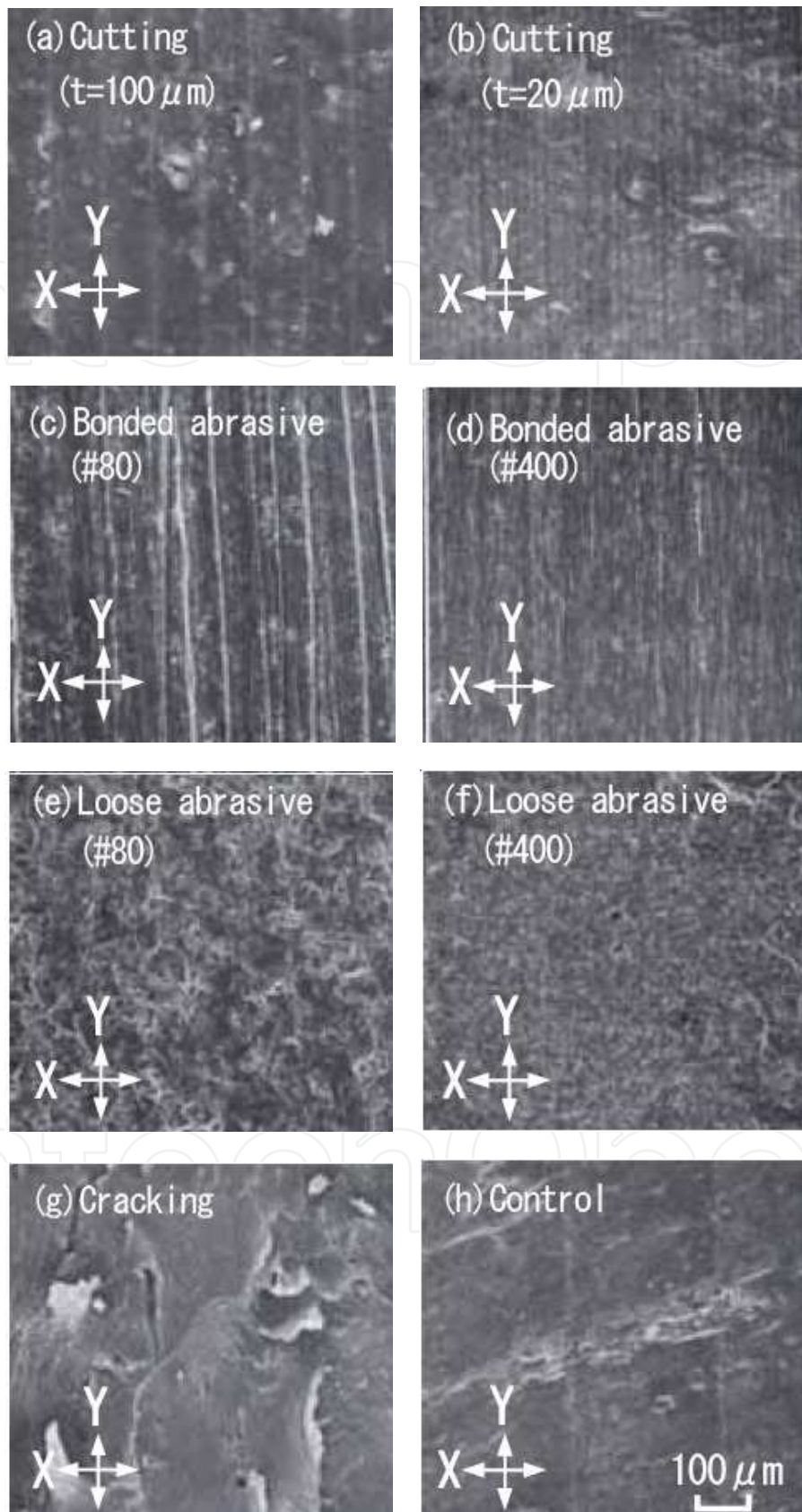


Fig. 11. Scanning electron micrographs of model bone surfaces processed by different engineering methods.

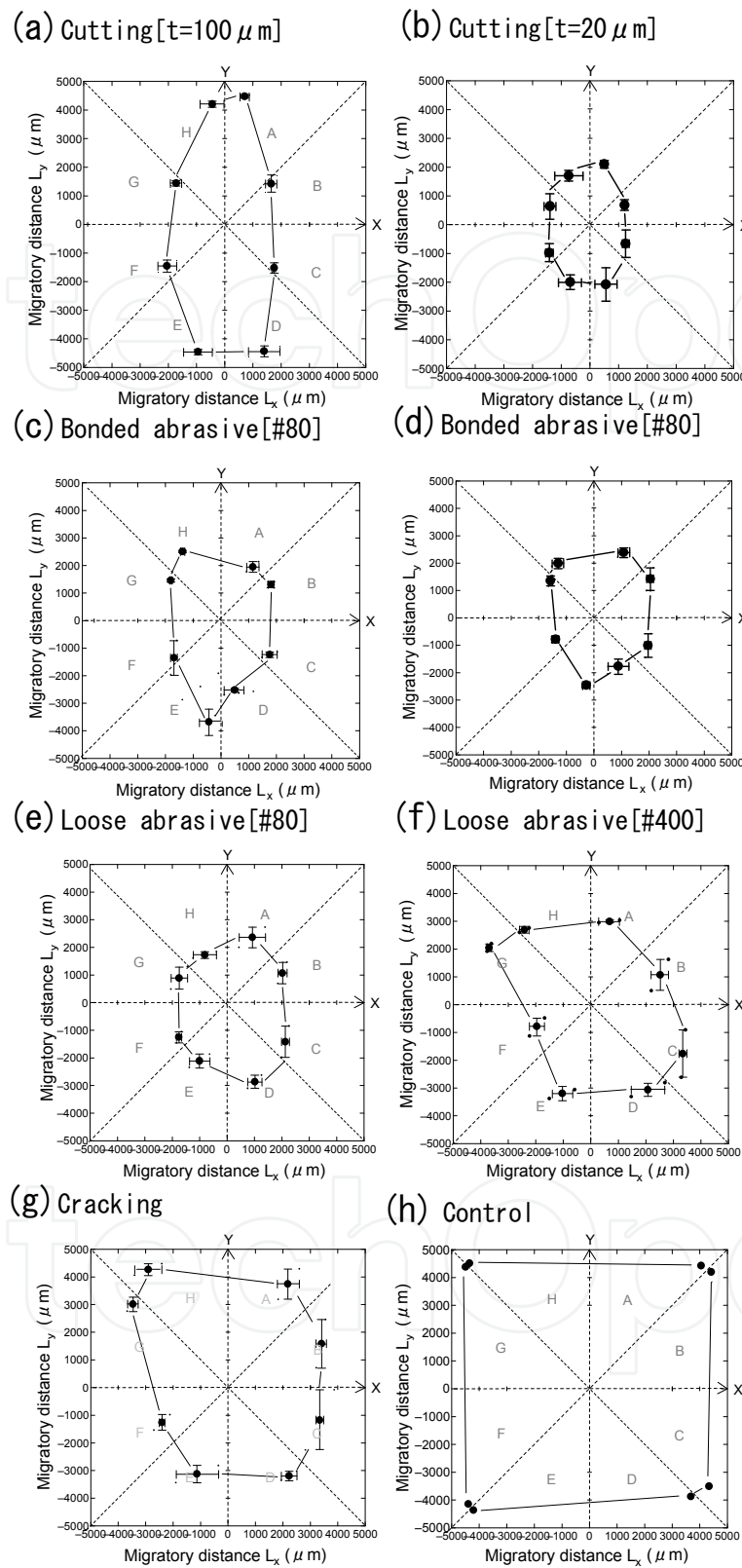


Fig. 12. X-Y diagrams of cell migratory distance on bone surfaces processed by different engineering methods: (a) and (b) by cutting [t=100 and 20  $\mu\text{m}$ ], (c) and (d) by bonded abrasives [#80 and #400], (e) and (f) by loose abrasives [#80 and #400], (g) by cracking, where (f) is the control.

Based on these results, cell migration on the processed bone model surfaces was characterized by a continuous, linear trace along the tool edges on the cut and bonded surfaces. Additionally, migration on the loose abrasive surface was random because the model surface produced random, minute asperities due to scratching of the loose abrasive edge. Because splitting at the tool edge due to irregular asperities induced the cracked model surface, cell migration tended to spread in a random direction, similarly to that of the loose abrasive surface. Cells on the flat and smooth control surfaces spread randomly.

Thus, cell migration on the processed bone surfaces can be controlled by surface asperities formed by the surface processing conditions.

## 6. Effects of surface asperities on cell migration

To investigate the effects of processed surface asperities on cell migration, the cell migratory distances  $L_X$  and  $L_Y$ , with respect to the X-Y coordinates, are shown in Fig. 13. The results show the maximum cell migratory distance on each surface for the area from A to H (shown in Fig. 12). Each cell culture experiment was conducted five times. If the plotted data lie on a diagonal dashed line, as shown in Fig. 13, the osteoblast cells migrated equally in both the X and Y directions.

In the cut model-surface data in Fig. 13 (a), cell migration in the X-Y coordinates can be classified into two primary groups. One group tended to migrate in the Y direction, and the tendency was notable when the cut depth was  $t = 100 \mu\text{m}$ . With the bonded abrasive surface [Fig. 13 (b)], one group migrated in the Y direction with a magnitude similar to that of the cut surface, and the scattered data tended to be larger than that of the cut surface. The data for the loose abrasive and cracked surfaces [Fig. 13 (c)] were randomly scattered around the diagonal line. This result indicates that cell migration was affected by surface asperities, and osteoblast cells were distributed randomly as the surface asperities changed from a regular to a mixed arrangement.

Fig. 14 shows the relationship between the average maximum height  $(R_Z)_X$  and the average cell migratory distance  $L_X$  measured with respect to the roughness profile (Fig. 13). The values of  $L_X$  for cell migration tended to decrease in the X direction for all mechanical removal actions, except for the cracked surface, as the values of  $(R_Z)_X$  increased.

Research on cell proliferation on a titanium surface shows that the amount of proliferation was remarkable on a surface with multiple holes of approximately  $30 \mu\text{m}$  (Zinger et al., 2004) and in surface asperities from  $R_Z = 20\text{--}30 \mu\text{m}$  (Itahashi et al., 1995) as compared with sub-micron holes and smooth surfaces with  $R_Z < 1 \mu\text{m}$ . Thus, these previous reports suggest that cell migration on the processed bone surface is affected by surface asperities, similarly to that on titanium, and that cell migration control is improved on mechanically removed surfaces with larger asperities.

In this project, cell migration seemed to be more affected by the surface properties of bone, such as roughness, unlike migration on titanium and cracked surfaces. This result should be studied in further detail in the future.

Thus, manipulating the processing method and surface profile can control the migration of osteoblast cells. These results provide fundamental knowledge for promoting surgical healing and controlling the local contact between bone materials.

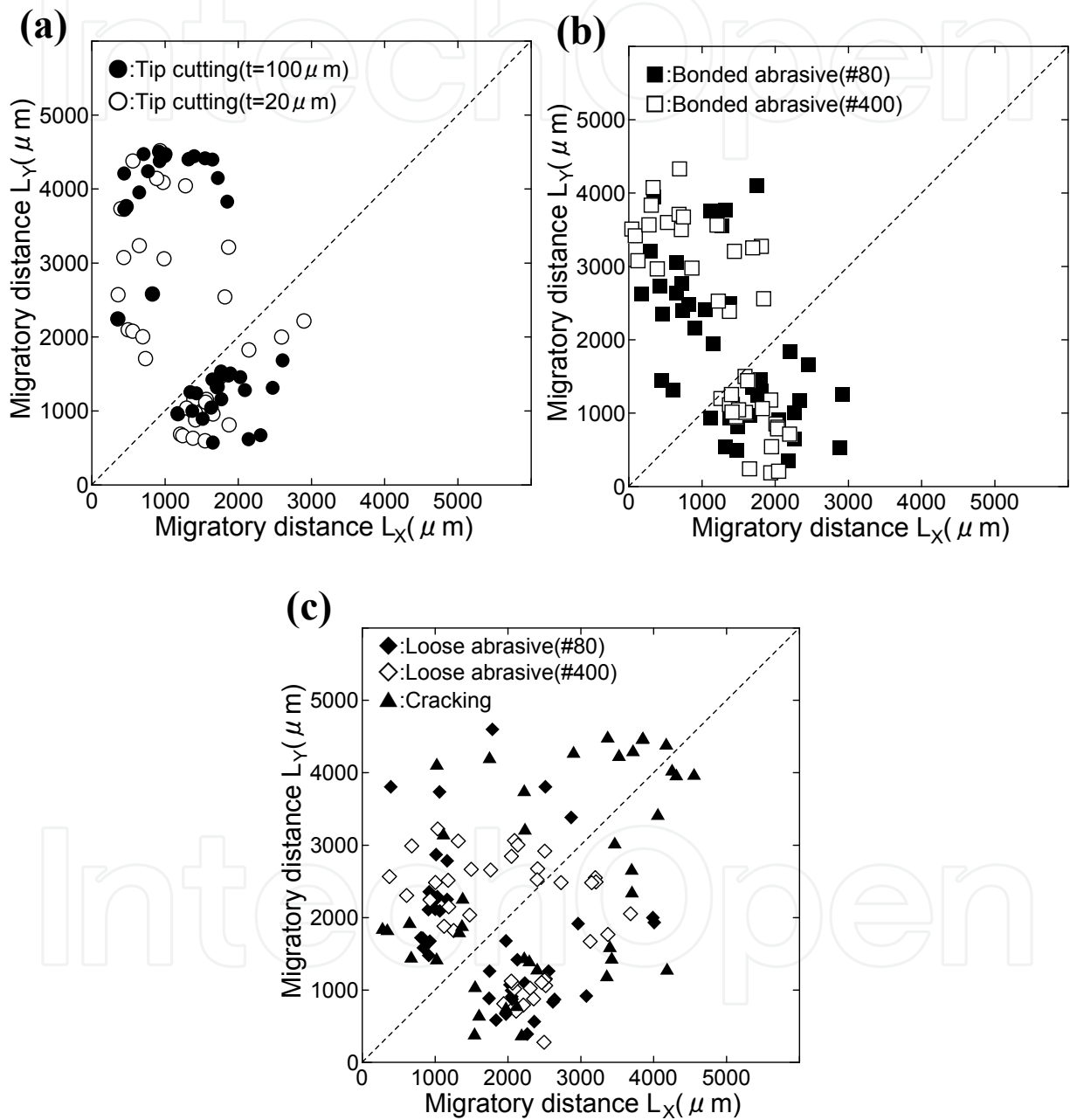


Fig. 13. Relationship between the migratory distances  $L_X$  and  $L_Y$  on the cutting surface. (a) Cutting surface, (b) bonded abrasive surface, (c) loose abrasive and cracking surfaces

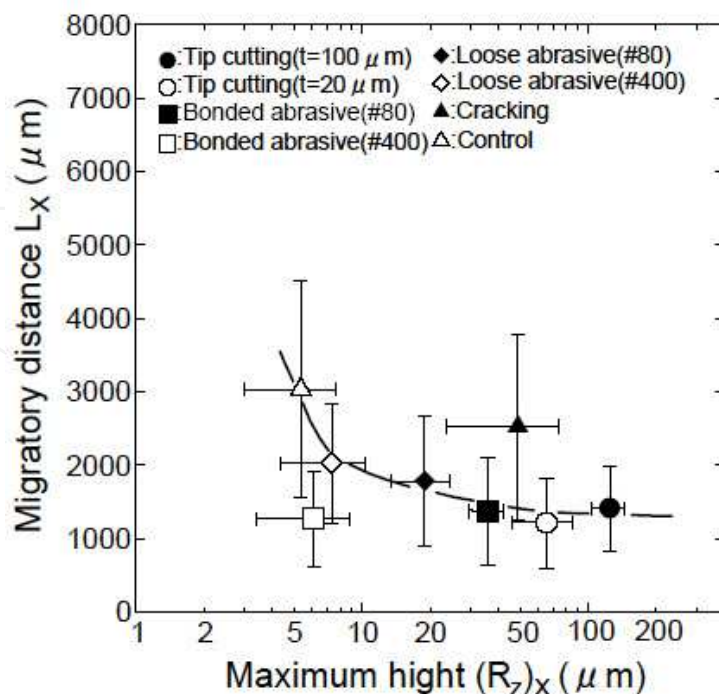


Fig. 14. Relationship between the migratory distance  $L_x$  and the maximum height  $(R_z)_x$ .

## 7. Conclusions

This research project developed bone components using the self-regenerative ability of bone and created a system to precisely manufacture bone screws in a surgical operating room. Bone material processing was investigated, including the cutting mechanism and bone properties such as hardness. The bone processing method used in the actual surgical front was also classified in terms of the engineering technology. A cell culture experiment was conducted on a model surface produced experimentally by various engineering methods. Orthopedic surgery processing was investigated and classified into four processing mechanisms: cutting, grinding, polishing, and cracking. The cell culture results showed that cell migration on the bone surface was influenced by surface asperities, which were formed by surface processing conditions. The experimental results showed that cell migration along the groove tended to spread randomly according to the changes in the groove track. Cell migration was affected by the groove track on the surface. This result was consistent with previous studies on a titanium surface. Cell migration was also controlled by the roughness of the processed surface. The results of this study can be used to promote healing and locally immobilize bone by using the appropriate bone processing method in orthopedic surgical operating rooms.

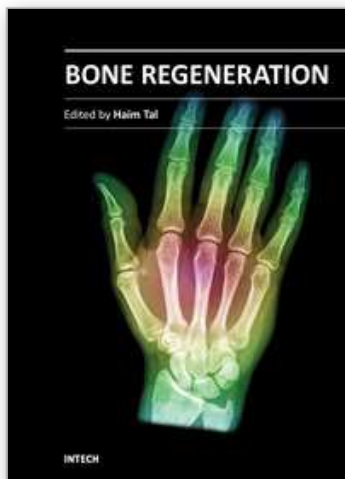
## 8. Acknowledgment

The authors thank Mr. A. Hayashi, president of Nano Corporation, for supporting part of this research and Mr. T. Hasegawa, Mr. T. Kawasaki, and Mr. S. Takai for their extensive assistance with the experimental apparatus.



## 9. References

- Curry, D.(2002), *Bones Structure and Mechanics*, p.15, Princeton University Press.
- Gibson, J, Ashby F, Cellular solids, (1997),pp.429-432, Cambridge University Press.
- Itahashi, H., Miyazaki, T., Fujimori, S, Lee, W., Early cellular responses of osteoblast-like cells in vitro on titanium surface with different micromorphologies, *Dental Materials Journal*, Vol.14, No.1, (1995), pp. 136-141.
- Itoh S., Ito Y., Shikita T., Basic study on Bone Cutting Forces for developing Surgical Instrument, *Bulletin of JSME*, Vol.26, No.222, (1983), pp.2295-2301.
- Ohtani T., Mori R., Uchio Y., Hayashi A., Effect of microscope tissue on bone machinability in cutting process, *Proceedings of the third internationa conference on leading edge manufacturing in 21<sup>st</sup> century*, Vol.2, (2005), pp.529-534.
- Ohtani T., Nakai T., Kawasaki Y., Mori R., Uchio Y., Cell Migratory Characterization in Micro-Processing Surface of Bone material for Surgery Healing Control, *Transactions of the Japan Society of Mechanical Engineers*, Vol.75 ' No.749, Series C,(2009), pp. 191-196.
- Ohtani, T., Nakai, T., Kawasaki, Y., Mori, R., Uchio, Y., Effect of anisotropic tissue on chip formation in micro cutting of bone, *Journal of the Japan Society of Mechanical Engineers*, Vol.75, No.749, Series C, (2009), pp.197-202.
- Project promote organization in Shimane University, *Annual report of 2007 year for cooperative project in field of medical, engineering and agriculture(in Japanese)*, (2008), pp.79-90, Shimane University.
- Sugita N., Mitsuichi M., Difference of Cutting Phenomena due to Material and Hydrrious Property of Bone, *Journal of the Japan Society of Precision Engineering*, Vol.73, No.3, (2007), pp.377-382.
- Wheeler, L., Mcloughlin, W., Biomechanical assessment of compression screws, *Clinical Orthopedics and Related Reserch*, No.350, (1998), pp.237-245
- Wiggins K., Malkin S., Orthogonal Marching of bone, *Transaction of the ASME*, Vol.100, (1978), pp.122-130.
- Zinger, O., Anselme, K., Denzer, A., Habersetzer, P., Wieland, M., Jeanfils, J., Hardouin, P., Landolt, D., Time-dependent morphology and adhesion osteoblastic cells on titanium model surface featuring scale-resolved topography, *Biomaterials*, Vol.25, (2004), pp.2695-2711



## **Bone Regeneration**

Edited by Prof. Haim Tal

ISBN 978-953-51-0487-2

Hard cover, 340 pages

**Publisher** InTech

**Published online** 04, April, 2012

**Published in print edition** April, 2012

Bone is a specialized connective tissue, most prominently characterized by its mineralized organic matrix that imparts the physical properties that allow bone tissue to resist load, to support functional organs, and to protect highly sensitive body parts. Bone loss and bone damage may occur as a result of genetic conditions, infectious diseases, tumours, and trauma. Bone healing and repair, involves integrative activity of native tissues and living cells, and lends itself to the incorporation of naturally derived or biocompatible synthetic scaffolds, aimed at replacing missing or damaged osseous tissues. There are several modalities of bone regeneration including tissue engineering, guided bone regeneration, distraction osteogenesis, and bone grafting. This book concentrates on such procedures that may well be counted among the recent outstanding breakthroughs in bone regenerative therapy.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

T. Ohtani, T. Nakai, R. Mori and Y. Uchio (2012). Self-Regenerative Ability of Bone and Micro Processing of Bone-Component Material in Orthopedic Surgery Healing, Bone Regeneration, Prof. Haim Tal (Ed.), ISBN: 978-953-51-0487-2, InTech, Available from: <http://www.intechopen.com/books/bone-regeneration/self-regenerative-ability-of-bone-and-micro-processing-of-bone-component-material-in-orthopedic-surg>

**INTECH**  
open science | open minds

### **InTech Europe**

University Campus STeP Ri  
Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166  
[www.intechopen.com](http://www.intechopen.com)

### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen