

The Role of Wound Healing and Its Everyday Application in Plastic Surgery: A Practical Perspective and Systematic Review

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Background: After surgery it is often recommended that patients should refrain from strenuous physical activity for 4–6 weeks. This recommendation is based on the time course of wound healing. Here, we present an overview of incisional wound healing with a focus on 2 principles that guide our postoperative recommendations: the gain of tensile strength of a wound over time and the effect of mechanical stress on wound healing.

Methods: A systematic search of the English literature was conducted using OVID, Cochrane databases, and PubMed. Inclusion criteria consisted of articles discussing the dynamics of incisional wound healing, and exclusion criteria consisted of articles discussing nonincisional wounds.

Results: Experiments as early as 1929 laid the groundwork for our postoperative activity recommendations. Research using animal models has shown that the gain in tensile strength of a surgical wound is sigmoidal in trajectory, reaching maximal strength approximately 6 weeks postoperatively. Although human and clinical data are limited, the principles gained from laboratory investigation have provided important insights into the relationship among mechanical stress, collagen dynamics, and the time course of wound healing.

Conclusion: Our postoperative activity recommendations are based on a series of animal studies. Clinical research supporting these recommendations is minimal, with the most relevant clinical data stemming from early motion protocols in the orthopedic literature. We must seek to establish clinical data to support our postoperative activity recommendations so that we can maximize the physiologic relationships between wound healing and mechanical stress. (*PRS GO 2013;1:e10; doi:10.1097/GOX.0b013e31828ff9f4; Published online 25 April 2013.*)

Wound healing consists of three phases: inflammation, proliferation, and remodeling.¹ Each of these phases interacts through complex cellular and molecular processes, with the purpose of establishing and maintaining wound clo-

sure. An incisional wound is initially held together with suture material, but it must gain enough inherent strength to maintain closure.² Patients with surgical wounds are discharged home with instructions to refrain from strenuous physical activity for 4–6 weeks. This postoperative regimen is outlined in almost all textbooks of surgery.^{3–5} What is the basis on which this recommendation was developed? Are there valid scientific data to support the rationale for not resuming strenuous physical activities for at least 4 weeks postoperatively?

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Two principles of wound healing have provided the foundation for our postoperative recommendations. The first principle involves the gain of tensile strength of wounds over time. Understanding the process of strength gain is fundamental to assessing the safety of patient activity. The second principle involves the effect of mechanical stress on tensile strength gain. Here, we review the literature behind these principles so that we may use this information to inform our postoperative recommendations.

All surgical wounds are not created equal, as there are a wide range of wound types encountered depending on the surgery performed. It is important to note, therefore, that the information obtained from our literature search may not apply to all wound types and will need to be interpreted as such. Our goal is to review what literature is available on the topic of incisional wounds where data have been published. We believe that this will provide important insights into what is known and unknown to better guide us in forming evidence-based recommendations.

METHODS

A systematic search of the English literature was conducted using OVID, Cochrane databases, and PubMed. Article selection was limited to those published between January 1, 1900, and August 1, 2012. Inclusion criteria included articles discussing the dynamics of wound healing over time, factors influencing wound healing, and the molecular biology of wound healing. Our initial search resulted in a total of 14,678 articles, and filtering with inclusion criteria resulted in a total of 6708 published articles. Inclusion criteria required articles to relate to wound-healing biology, wound-healing dynamics, patient activity and wound healing, and wound healing of surgical incisions. Exclusion criteria included articles discussing nonincisional wounds. Title screen yielded a total of 255 potentially relevant articles. Abstract review resulted in a total of 120 articles, all of which were reviewed in their entirety for content and relevance to the current study. A total of 24 articles not in the original search were cited and reviewed for content. In total, 109 articles were found to meet all criteria for review and are presented here (Fig. 1).

TENSILE STRENGTH

Animal Studies

Reliable analysis of the quality of wound healing via visual inspection is inaccurate due to the inability to see beneath the epithelium. Therefore, progress must be measured using physiologic parameters. Tensile strength is defined as the breaking strength of a material divided by its cross-sectional area and is

therefore the most accurate physiologic measure for assessing a wound's ability to withstand tension.^{6,7} A series of classic articles using tensile strength as a measure of wound healing in animal models has led to the recommendation that patients should abstain from full physical activity for 4–6 weeks after surgery.^{8–12}

One of the earliest publications regarding wound tensile strength was written by Howes et al¹³ in 1929. In a rat model, it was found that tensile strength of a surgical wound was almost negligible until postoperative day 5, after which it increased to a maximum at 2 weeks. It was also concluded that over time the final strength of the wound became equal to that of intact skin based on extrapolation of their results (Fig. 2A).^{9,12}

In 1965, Levenson et al found that rather than 2 discrete phases, there was 1 prolonged phase of tensile strength gain with a sigmoidal trajectory (Fig. 2B).^{12,14} Tensile strength continued to increase rapidly until week 6, after which it slowly reached a maximum at 3 months (Fig. 2B).^{12,14} In addition, Levenson et al found that healed skin only reached 80% of the tensile strength of unwounded skin.¹²

These findings are the foundation for our modern understanding of the time course of wound healing. Since the original results of Levenson et al, numerous investigations using animal models support the conclusion that 1 week postoperatively, there is a rapid gain in tensile strength lasting approximately 6 weeks.^{15–25} To demonstrate this, we developed a curve reflecting the findings of individual studies (Fig. 3A) and one with averaged data (Fig. 3B) to explore the trend (Table 1). Studies reporting breaking strength rather than tensile strength were excluded (Table 2). These results first show that the time course of wound healing is consistent among species.¹¹ It is also evident from these graphs that the trend of tensile strength gain over time of a healing wound in animal models has remained consistent since the original studies by Howes and Levenson.

Human Studies

There are limited human data on the wound-healing trajectory. Given the obvious ethical barriers to studying tensile strength in humans, few studies have been published on the topic. Sandblom and later Lindstedt et al measured tensile strength at a single time point in human patients but did not measure strength gain over time.^{26,27} Other studies have sought to measure wound-healing progression in humans through subcutaneous polytetrafluoroethylene tubes that measure hydroxyproline content and other markers of collagen maturation.^{28–31} For example, a recent randomized trial investigated this concept by measuring hydroxyproline concentration and mRNA levels for type I and III procollagen.³²

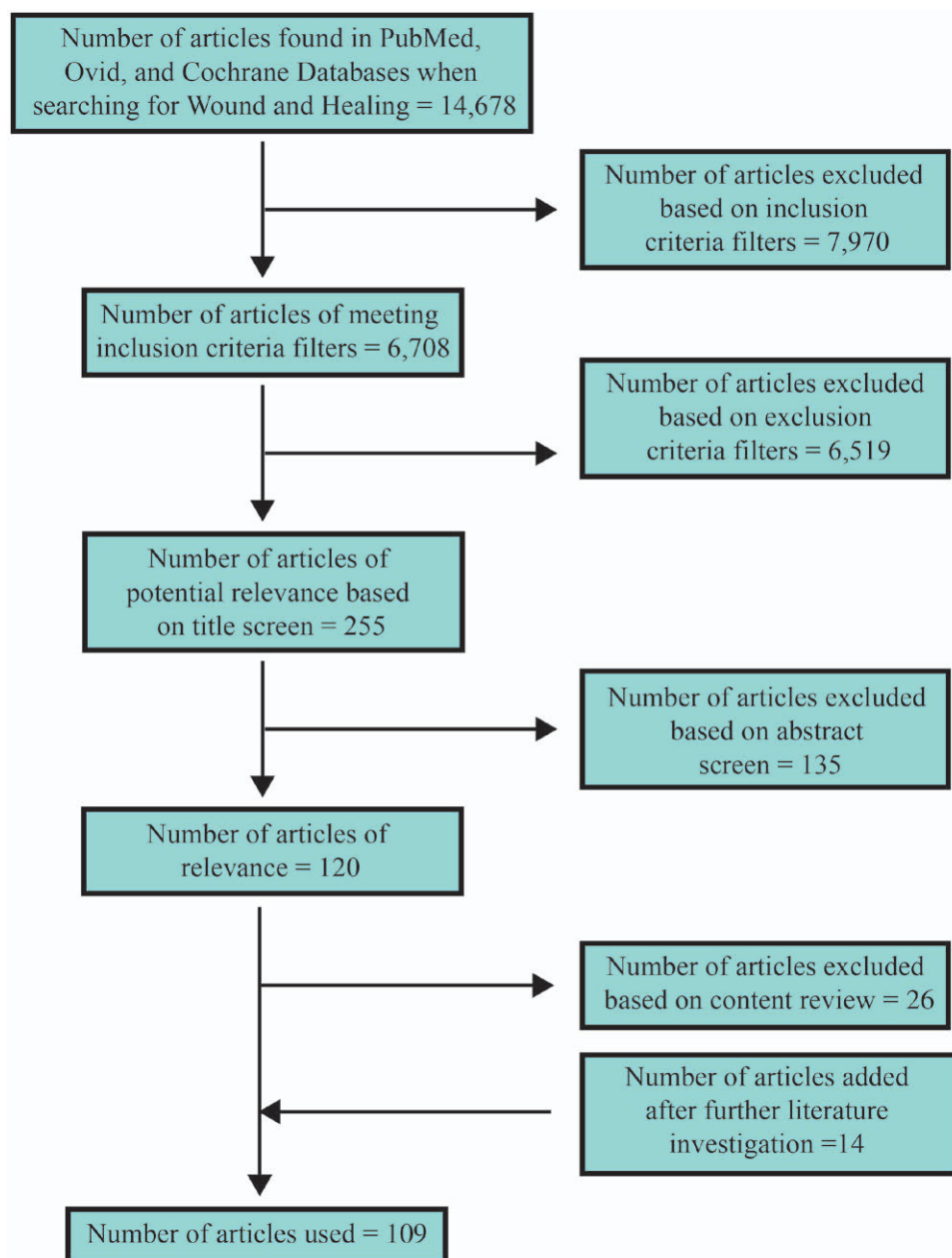


Fig. 1. Flow diagram of article selection.

This was correlated with wound strength by measuring breaking strength of biopsies taken from the same wounds. If we could reliably correlate molecular findings such as these to a tensile strength curve, we may be able to indirectly assess the effect of patient activities on tensile strength.

PHYSIOLOGY OF THE WOUND-HEALING TRAJECTORY

The laboratory data elaborating the gain of tensile strength of incisional wounds over time are supported by the physiology of wound healing during

the postoperative period. As with the biomechanical studies, much of the data regarding the physiology and histology of surgical wound healing come from animal models. The information presented below serves as a model for understanding how a simple incisional wound gains strength over time.

Week 1

Within the first 4 days after surgery, a surgical wound has minimal inherent strength because the dermal edges are held together solely by a hemostatic plug and sutures.^{12,33,34} Cytokines and growth factors released by local platelets, notably platelet-

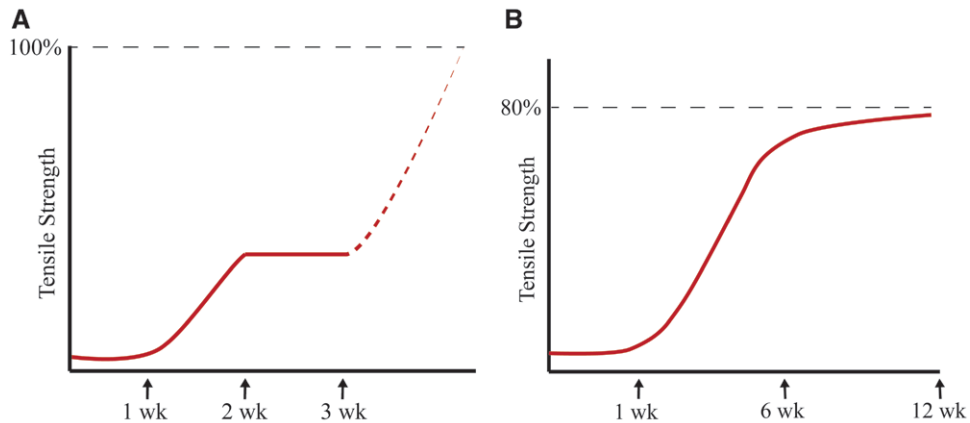


Fig. 2. A, Adaptation of Howes et al's original experiments. B, Adaptation of Levenson et al's tensile strength versus time curve.

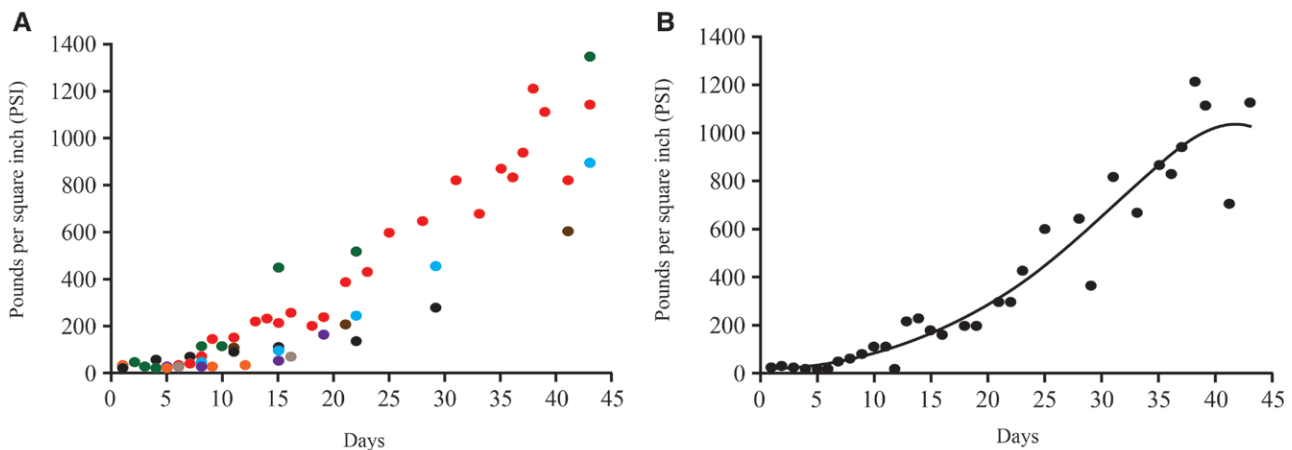


Fig. 3. Combined results of studies listed in Table 1 with units converted to PSI. A, ● Howes et al¹³; ● Levenson et al¹²; ● Forrester et al¹⁴; ● Garden et al²¹; ● Wickens et al²³; ● Fried et al, 2000³⁵; ● Kaplan et al⁴⁷; ● Cornacoff et al²⁴. B, Average PSI across all studies. PSI = pounds per square inch.

derived growth factor, stimulate the migration of the inflammatory cells to the wound site.³⁶ This phase correlates to the latency period of the wound-healing trajectory (Fig. 2B). The latency period allows for proper wound healing by giving inflammatory cells, such as neutrophils and macrophages, time to proliferate and clean the wound of necrotic debris and bacteria before complete closure.^{37,38}

In addition, throughout the latency period, inflammatory cells release transforming growth factor beta (TGF- β) and epidermal growth factor (EGF). These growth factors have been shown to stimulate immature fibroblasts to migrate into the wound and secrete type III collagen.^{35,39-42} Type III is a loose reticular form of collagen that interacts with the extracellular matrix, giving the wound its first degree of inherent strength.

Week 2

During the second postoperative week, fibroblasts proliferate rapidly and begin to produce type I col-

lagen in addition to type III.^{35,39,43-45} Connective tissue growth factor (CTGF), a downstream mediator of TGF- β 1, is believed to be the signal for increased production of type I collagen (Fig. 4).^{3,4,46,47} It is the accumulation of propeptide type I collagen in the extracellular space during this phase that leads to a significant increase in tensile strength.^{47,48} Procollagen is cleaved by peptidases to facilitate the formation of fibrils, which are strong, covalently linked collagen peptides (Fig. 5). Type III collagen does not undergo fibril formation due to its amino acid structure; therefore, type III collagen is weaker than type I.³⁵ Although the amount of type I collagen increases during the second week, type III remains the dominant form. Thus, the strength of the wound is still limited to less than 10% of its final strength. Clinically, this is supported by the highest rate of wound dehiscence occurring during the second postoperative week.^{10,12,21,23,39,49} Disruption of the wound at this time can delay and reduce the slope of tensile strength gain.¹⁸

Table 1. Summary of Studies Reporting Tensile Strength Included in Figure 3

	Model	Study Time Points	Unit of Strength Measurement	Study Purpose
Cornacoff et al ²⁶	Macaques	Days 4, 8, 11	Mm Hg	Development of a method to measure tensile strength in macaques
Kaplan et al ⁴⁹	Rabbit	Days 3, 5, 7, 15	N/mm ²	Zinc, ascorbic acid, and hydroxyproline levels in relation to tensile strength during wound healing
Fried et al. ³⁵ 2000	Guinea pigs	Days 0–28	kg/cm ²	Comparing effectiveness of laser skin welding compared with standard suture closure
Wickens et al ²⁵	Rats	Days 0, 4, 5, 14, 18	kg/cm ²	Effect of intraoperative pneumoperitoneum on wound healing
Garden et al ²³	Mini pigs	Days 1–90	mPa	Comparing tensile strength after laser versus suture versus staple wound closure
Forrester et al ¹⁶	Rats	Days 10–150	pounds per square inch	Tape versus suture closure of skin wounds
Levenson et al ¹²	Rats	Days 7–365	g/mm ²	Development of an accurate wound healing trajectory
Howes et al. ¹³ 1929	Rats	Days 3–210	g/mm ²	Wound healing trajectory in various species

Table 2. Summary of Studies Reporting Breaking Strength

	Model	Time Points	Unit of Strength Measurement	Study Purpose
Savunen et al ²⁴	Guinea Pig	Days 7, 14, 21	N	Development of a model to predict tensile strength using number of inflammatory cells present per time point
Kursh et al ²²	Rats	Days 5, 10, 15	g	Collagen formation and tensile strength in the setting of uremia
Bryant et al ²¹	Rats and Mice	Days 7–10	g	Wound healing trajectory of primary versus secondary wounds
Bains et al ²⁰	Rats	Days 1–42	g	Relationship of chronic anemia and tensile strength of healing wounds
Hickman et al ¹⁹	Dogs	Days 7, 10, 14	g	Tensile strength in setting of hypothermia
Calnan et al ¹⁸	Rats	Days 4–9	g	Influences of secondary wounds on primary wound tensile strength

Weeks 3–5

The wound's strength grows rapidly as type I fibrils cross-link and aggregate into large fibers.^{35,40,42,45,50} This step improves the tensile strength of incisional wounds because the fibers bind to cell-membrane proteins across the wound interface.^{51,52} The fibers, therefore, act as a bridge between the 2 wound edges and provide significant resistance to tensile force (Fig. 6).

As the healing process continues, the fibers further organize by forming a dense three-dimensional matrix that is stronger than the individual fibers alone.^{12,53} Matrix formation is mediated by interactions between the collagen fibers and the surrounding extracellular matrix components, including heparin sulfate and other proteoglycans.^{54,55} Growth factors released by fibroblasts and other late inflammatory mediators are also believed to play a role in matrix organization.^{40,56} This period corresponds to the continued steep slope of the wound-healing trajectory, and by 4 weeks postoperatively, the gain in tensile strength is over 50% complete.^{12,16,23}

Week 6 to 1 Year

By week 6, the concentration of strong collagen fibers begins to resemble that of intact skin. The collagen matrix matures to become denser and more uniformly aligned.^{12,35,47} Wound disruption is unlikely because the tensile strength of the wound is approaching 80% of intact skin.¹² This is why nearly all surgery textbooks recommend advising patients against resuming strenuous physical activity until 6 weeks postoperatively.^{1,4,57} Over the next 2 months, a small gain in strength will result from further aggregation of type I collagen fibrils into fibers.^{43–45,47} The alignment of those fibers into an organized scar will continue throughout 1 year.^{10,12,35} This process correlates with the plateau of the wound-healing curve.

MECHANICAL STRESS AND WOUND HEALING

We have discussed in detail the first guiding principle behind postoperative activity recommendations: the gain in tensile strength of a wound over

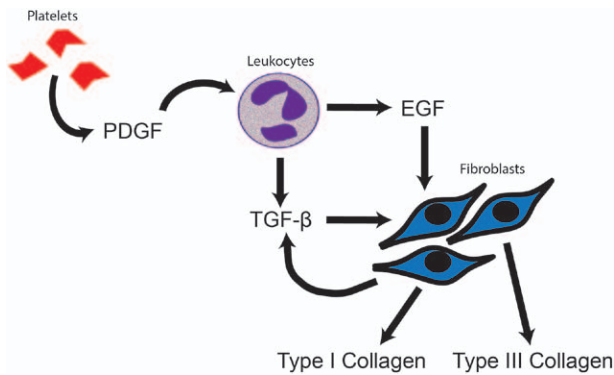


Figure 4. Platelet-derived growth factor (PDGF); epidermal growth factor (EGF); transforming growth factor beta (TGF-β). PDGF released by activated platelets stimulates leukocytes to secrete growth factors, such as EGF and TGF-β. These growth factors stimulate the migration of fibroblasts to the wound site. TGF-β is the primary signal for type I and III collagen production and is released by both leukocytes and fibroblasts.

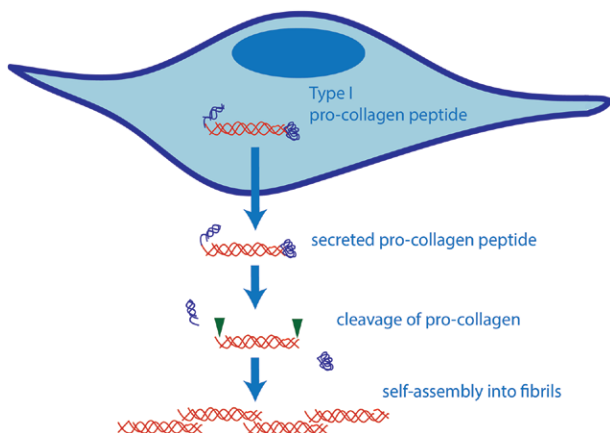


Fig. 5. Collagen synthesis pathway. Procollagen with N and C terminal cleavage domains is secreted into the extracellular space by fibroblasts. The N and C terminal chains are cleaved by peptidases, resulting in a mature collagen peptide. The peptides then self-assemble into fibrils.

time. The second key principle is the effect that mechanical stress has on the strength curve. Although excess mechanical stress through patient activity can lead to wound disruption, we do not keep our patients bedbound for 4–6 weeks postoperatively. Aside from the risks of venous thromboembolism, pneumonia, and pressure ulcers, there are reasons related to wound healing as well that encourage us to recommend limited activity. Tensile strength gain depends on collagen production and organization, which is intimately related to mechanical stress.^{12,18,58} This is a principle that has significant implications in clinical practice, as it formed the basis for Ilizarov’s bony distraction experiments.^{59–61}

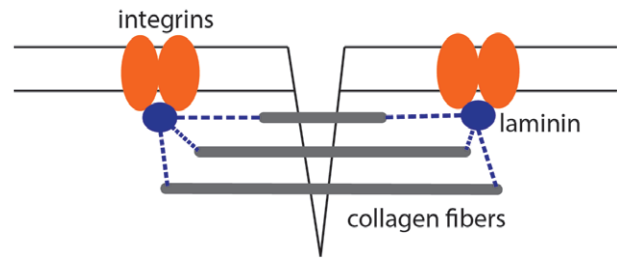


Fig. 6. Collagen fibrils aggregate into fibers, which have the ability to bind cell-membrane proteins such as integrins. The collagen, therefore, serves as a bridge among the wound edges and provides significant resistance to tensile force across the incision.

Laboratory Studies

Mechanical stress is required for the gain of tensile strength of a wound over time.⁶² This has been demonstrated in studies using space environments and limb offloading models, where the strength gain of healing wounds is significantly impaired in the absence of mechanical stimuli.^{62–66} Davidson et al found that wounds from rats in space had 62% less collagen after 10 days compared with controls in a normal gravity environment.⁶³ The mechanism by which mechanical stress stimulates wound healing is not entirely understood but is believed to be due to the stimulation of TGF-β and other growth factor signaling pathways by mechanoreceptors in the skin.^{62,67} This theory is supported by investigations showing that mechanical force on a wound is required for angiogenesis and the migration of fibroblasts, all of which have been associated with TGF-β activity.^{65,68–71}

Mechanical stress is not only required for normal wound healing, but it also accelerates the gain in tensile strength. This is likely due to the upregulation of the aforementioned growth factors, enhancing collagen production and angiogenesis.^{65,71–73} This principle was demonstrated by Langrana et al, who found that episodic and sequential tissue expansion of a surgical incision beginning 1 week after surgery was not only tolerated but resulted in significantly greater tensile strength at each time point compared with controls.⁷⁴ Similarly, van Royen et al found that joint rotation initiated 1 week after surgery in rabbits significantly increased the tensile strength of healing wounds compared with immobilized controls.⁶⁶

Clinical Studies

The clinical literature directly supporting our postoperative recommendations that patients avoid strenuous activity for 4–6 weeks postoperatively is minimal. However, the use of controlled mechanical stress is supported by the orthopedic literature, where the safety of early postoperative movement has been well documented. Joint rotation protocols beginning ear-

ly in the postoperative period after orthopedic procedures are common and do not confer additional wound-healing complications.^{75–80} A study by Wasilewski et al even showed a reduced incidence of surgical wound-healing complications in those undergoing early movement protocols.⁸¹ These studies challenge us to consider what role early controlled movement may have in surgical wound healing within the realm of plastic surgery. Incision-directed exercises, in addition to simple ambulation, may stimulate particular wound types and accelerate tensile strength gain.^{66,76–78,80,81}

MECHANICAL STRESS AND SCARRING

Because it is uncommon for elective surgical wounds to come apart in the postoperative period, the most practical concern regarding patient activity in the postoperative period is the possibility of abnormal scarring.^{71,80–84} The relationship between mechanical stress and collagen dynamics can have negative implications for scar formation.^{21,50,58,87,88} This is supported by the increased incidence of abnormal scar formation in areas subject to the most movement, such as the scapular region and chest.^{69,89,90} Minimization of movement over these areas has been shown to reduce the degree of abnormal scarring.^{73,83,91,92} A number of investigations have found that mechanical force on wounds, particularly cyclical force, stimulates the release of growth factors such as TGF- β .^{56,93–97} The upregulation of these factors and their receptors is associated with keloid and hypertrophic scar formation.^{97–100} These studies suggest that although mechanical force has the potential to accelerate tensile strength gain, the trade-off may be an increase in abnormal scarring.

Conversely, some investigations have shown reduced scar formation in the setting of controlled mechanical stress. Langrana et al found that in episodically expanded surgical incisions, scar forma-

tion was significantly reduced on both gross and microscopic levels.⁷⁴ Other histologic studies have found earlier and more uniform alignment of collagen in wounds subject to controlled mechanical stress.^{16,87,101–109} On a molecular level, a recent study found that CTGF was significantly downregulated after 24 hours of cyclically stretching fibroblasts in culture.⁸⁷ The exact mechanism by which earlier collagen organization reduces later scar formation is unknown. However, one theory is that improved tensile strength early in the wound-healing process may protect the wound from later excessive shear stress that would otherwise cause excessive scarring.⁷⁰

DISCUSSION

The work of Howes and Levenson laid the groundwork for our clinical recommendation to have patients abstain from strenuous physical activity for 4–6 weeks after surgery. From the scientific data available and our understanding of wound-healing physiology, we can indirectly make informed recommendations for patients after surgery (Table 3). It is important to note, however, that we do not yet have the scientific basis to directly apply the data to human patient activity. Further research is needed to understand how these biomechanical results can be extrapolated to human patients. We must also investigate how the time course of wound healing varies in different cutaneous regions and from different types of incisions.⁸¹ This knowledge would allow more accurate and region-specific postoperative activity planning, which would have a direct effect on patient care.

Another area of research that has shown great progress is the use of molecular markers for collagen maturation, such as hydroxyproline content and mRNA levels of collagen subtypes. This potential area of research is more feasible in humans than studying tensile strength directly as it would be much

Table 3. Summary of Physiology and Activity Recommendations

Week	Wound Physiology	Final Tensile Strength* (%)	Corresponding Activity
1	Wound edges approximated; reformation of the basement membrane; minor mechanical forces required for angiogenesis, fibroblast differentiation, and migration of keratinocytes; immature fibroblasts	3	Avoid bed-bound states/ambulate early; continuous passive motion safe
2	Abundant loose type III collagen; type I collagen production increases; new vascular channels present	7	Episodic mechanical stress to stimulate tensile strength gain; avoid constant tension on wound
3	Fibroblasts dominate cellularity; type I collagen fibrils	18	Continue increasing stress episodically to stimulate tensile strength gain
4	Fibroblast proliferation tapering; extensive interlacing of the collagen matrix	34	Gradually increase mechanical stress on wound
5	Type I fibrils form fibers; tighter interlacing matrix of collagen	50	Increase frequency and intensity of activity
6	Acellular; multiple thick fibers of collagen; compact organization of collagen matrix; vascularity restored	68	High levels of mechanical stress likely tolerated

*Percent of strength gained based on curve by Levenson et al¹².

less invasive. Further research is needed to generate a reproducible correlation between subcutaneous markers and the tensile strength curve in humans. Understanding how these molecular markers correspond with patient activities in the postoperative period would provide us with a greater scientific basis for our recommendations.

Early motion research has highlighted potential applications for controlled movement protocols beyond basic patient activities for accelerating wound healing. We need to understand how specific activities or incision-directed exercises fit into the wound-healing curve. It is especially important to understand how specific patient activities in the postoperative period affect scar formation. Although the literature favors a negative impact of mechanical stress on scarring, the available research suggests that the timing and character of mechanical stress are important factors dictating the fibrotic response. There may be a role for controlled mechanical stress early in the postoperative period for certain wound types. Further research is needed to understand how best we can take advantage of the stress-collagen relationship without increasing scar formation.

CONCLUSION

Two principles are fundamental to understanding our postoperative activity recommendations: the process by which wounds gain strength and the effect of mechanical stress on wound healing. Although many studies have explored the time course of wound healing in animal models, further research needs to be done in humans to allow for more accurate and patient-specific protocols. This information will help us translate wound-healing dynamics into clinical practice and improved patient outcomes.

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