POST BURN HYPERTROPHIC SCAR PLIABILITY, ITS ASSESSMENT AND TREATMENT

ZHANG WALEI

PhD

The Hong Kong Polytechnic University

2019

The Hong Kong Polytechnic University

Department of Rehabilitation Sciences

Post Burn Hypertrophic Scar Pliability, its Assessment and Treatment

ZHANG Walei

A thesis submitted in partial fulfillment of the requirements for

the Degree of Doctor of Philosophy

May 2019

CERTIFICATE OF ORIGINALITY

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it reproduces no material previously published or written, nor material that has been accepted for the award of any other degree or diploma, except where due acknowledgement has been made in the text.

ZHANG Walei

ABSTRACT

Background

Hypertrophic scar (HS) resulting from burn injuries can cause deformities that severely affect the survivor's functioning and psychological well-being, leading to a significant reduction in quality of life. Pliability is one of the most important HS parameters because it reflects the skin's flexibility, and a reduction in pliability may hinder movement and thus mobility. Valid objective assessment of pliability is crucial to monitor patients' improvement, but the most appropriate assessment method and the most effective treatment for the improvement of HS pliability have yet to be established. A combination of pressure therapy and silicone-based therapy has been recommended as the first-line noninvasive treatment, but its ability to improve HS pliability remains unclear.

Aims and Objectives

The aim of this study was to determine the proper assessment of HS pliability and to investigate the effects of a combination of pressure and silicone therapy on improving the pliability of HS. The objectives of the study were as follows.

1) to investigate the most appropriate method to assess the pliability of HS via critical appraisal of the current evidence;

2) to establish the validity of the elasticity measurement of the DermaLab Combo in the measurement of HS pliability;

3) to investigate the properties of a newly invented Smart Scar-Care pad (SSCP) as a suitable insert material for combined pressure and silicone therapy; and

4) to investigate the clinical efficacy of the SSCP in improving HS pliability with the use of objective HS assessment tools.

Methods

A systematic review was conducted to evaluate the current evidence regarding the assessment of HS pliability from a biomechanical perspective. A validation study was then performed to establish the concurrent validity and clinical relevance of the upgraded elasticity measurement of the DermaLab Combo in measuring HS pliability with a modified tissue tonometer (MTT) and the modified Vancouver Scar Scale (mVSS). As for treatment, the properties of the newly invented SSCP were investigated and compared with commercially available products in tests of biological safety, physical properties, and the ability to increase the interface pressure between the HS tissue and the pressure garment. Finally, a comprehensive treatment strategy to improve HS pliability via enhanced compression and occlusion was implemented with the SSCP. The clinical efficacy was investigated via a self-controlled clinical trial, the clinical outcomes were measured with a series of objective scar assessment tools, and patient feedback was collected.

Results

The systematic review showed that the suction method with greater suction power administered by an adhering probe on the assessment area was most appropriate for the assessment of HS pliability. Of all the equipment using the suction method, the upgraded version of the DermaLab Combo elasticity measurement used the highest pressure, which made it possible to assess the pliability of thick and stiff HS. A significant correlation was identified between HS pliability as measured by the DermaLab elasticity measurement and the hardness score as measured with the MTT. A significant correlation was also established between the DermaLab elasticity measurement and the pliability score of the mVSS.

The SSCP demonstrated superior performance over commercially available products in tests of biological safety and physical properties, and it significantly increased the interface pressure between the scar tissue and the pressure garment. In the self-controlled clinical trial, 32 subjects were recruited and 25 completed the treatment. Significant time effects were found for the Vancouver Scar Scale total score, the melanin score, pliability, and the hydration score. A significant intervention and time interaction effect was found for pliability ($p=.048$). No significant time or interaction effect was found for thickness. On the feedback questionnaire, the patients reported that the SSCP was significantly more conformable ($p=.02$) and displayed less displacement during movement than the conventional pressure insert ($p=.040$).

Conclusions

The measurement principles and administration procedures of the methods have a great effect on the clinimetrics of HS pliability measurement. The upgraded elasticity measurement of the DermaLab Combo is the most appropriate HS pliability assessment tool commercially available. The SSCP can serve as a safe and effective insert material for enhancement of the pressure interface and occlusion. Comprehensive treatment strategies implemented with the SSCP have demonstrated greater effectiveness in improving the pliability of HS and possibly in preventing its thickening; it was found to be more comfortable and less likely to become displaced during movement than the conventional pressure insert.

PUBLICATIONS ARISING FROM THE THESIS

Oral Presentation

Zhang, E. W. L., Li, T. M. H., & Li-Tsang, C. W. P. (2019 August) Objective Assessment of the Pliability of Hypertrophic Scar, a Systematic Review. Oral presentation at The 12th Asia-Pacific Burn Conference, Singapore.

Zhang, W. L., &Li-Tsang, C. W.P. (2018, November) The Development of a Comprehensive Objective Assessment Strategy for Hypertrophic Scar. Oral presentation at The 11th Pan-Pacific Conference on Rehabilitation, Hong Kong.

Zhang, W. L., &Li-Tsang, C. W.P. (2018, October) The Pattern of Hypertrophic Scar Progression Based on Comprehensive Objective Assessment Strategy. Oral presentation at The 1st Global Scar Conference, Shanghai, China.

Zhang, W. L., &Li-Tsang, C. W.P. (2018, October) Differentiating Elasticity from Pliability, and its Importance in Hypertrophic Scar Assessment. Oral presentation at 2018 Annual Meeting of Australian and New Zealand Burn Association, Brisbane, Australia.

Li-Tsang, C. W. P., &Zhang, W. L.(2018, October) The Effect of Smart Scar Care Pad (SSCP) on the Elasticity of Post Burn Hypertrophic Scar. Oral presentation at 2018 Annual Meeting of Australian and New Zealand Burn Association, Brisbane, Australia.

Zhang, W. L., &Li-Tsang, C. W.P. (2017, October) A Report on the Clinical Effectiveness of the Smart Scar Care Pad on Hypertrophic Scar Management. Oral presentation at 2017 Annual Meeting of Chinese Burn Association, Wuxi, China.

Poster Presentation

Zhang, W. L., &Li-Tsang, C. W.P. (2016, September) Validation of the DermaLab Combo Pliability Measurement on Post-burn Hypertrophic Scar. Poster presentation at the 18th Congress of International Society for Burns Injuries, Miami, U.S.A.

Zhang, W. L., &Li-Tsang, C. W.P. (2017, May) Investigation of the Clinical Effectiveness of Scar-care on Hypertrophic Scar: A pilot study. Poster presentation at the British Burn Association Annual Meeting, London, U.K.

Invited Presentation

Zhang, W. L., &Li-Tsang, C. W.P. (2017, September) Development of Smart Scar Care Pad for Optimal Treatment of Hypertrophic Scar. Invited presentation at the Centre for Children's Burns and Trauma Research, Brisbane, Australia.

Journals

Zhang, E. W., Li-Tsang, C. W. P., Li., T. M. H., Huang, L. & Cheung, K. K. *Smart Scar Care Pad (SSCP) – an innovated silicone-based insert that improved severe hypertrophic scar by integrating optimal pressure and occlusion effects.*(Accepted by Advances in Wound Care).

Zhang, E. W. L., Li, T. M. H., &Li-Tsang, C. W.P. *Objective Assessment of the Pliability of Hypertrophic Scar, a Systematic Review.* (Submitted).

Zhang, W. L., &Li-Tsang, C. W.P. *Validation of the Elasticity Measurement of DermaLab Combo in Assessing Post-burn Hypertrophic Scar Pliability.* (In preparation).

ACKNOWLEDGEMENTS

I would first like to thank my supervisor Prof. Cecilia Li of the Department of Rehabilitation Sciences at the Hong Kong Polytechnic University. The door to Prof. Li's office was always open whenever I ran into a trouble spot or had a question about my research or my career. She consistently encouraged me to pursue an academic career and to explore my own research interests, and she was always an empathetic listener when I needed one.

I would also like to thank the experts who selflessly offered their professional expertise and guidance: Dr. Alex Cheung, particularly on the part of biological safety; Dr. Ricky Au; Dr. Tim Li, and Dr. Caroline Yu. I am grateful to them for their very valuable comments on my study and on this thesis.

I would also like to thank Mr. Li Kuicheng from Guangdong Work Injury Rehabilitation Hospital and Prof. Wu Jun from China Southwest Hospital and their rehabilitation teams for their great support in recruiting patients for the study. Without their passionate participation and input, my Ph.D. research project would not have been successful.

I would also like to thank my counselor, Ms. Cynthia Cheng, for her continuous support during my Ph.D. study. She is insightful and empathetic to my situation, and I would never have completed my work without her encouragement and support.

Finally, I must express my very profound gratitude to my parents and to my friends for providing me with unconditional love and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. This accomplishment would not have been possible without them. Thank you.

Eve Zhang

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

α-SMA: a smooth muscle actin

DAI: days after injury

HS: Hypertrophic Scar

MTT: modified tissue tonometer

mVSS: modified Vancouver Scar Scale

PG: Pressure Garment

POSAS: Patient and Observer Scar Assessment Scale

PT: Pressure Therapy

SGS: Silicone Gel Sheeting

SPMS: Smart Pressure Monitored Suit

SSCP: Smart Scar Care Pad

TBSA: total burn surface area

TEWL: Transepidermal water loss

VSS: Vancouver Scar Scale

WVTR: water vapor transmission rate

Chapter One

Introduction

Chapter Summary

Hypertrophic scar (HS) is a fibroproliferative disease that has a significant effect on the overall well-being of burn survivors.

This chapter summarizes the characteristics, epidemiological data, and pathogenesis of HS. Methods of systematic assessment of various characteristics of HS are discussed from both subjective and objective perspectives. The standard noninvasive treatments for HS—pressure therapy and silicone therapy—are introduced regarding their clinical evidence, theoretical mechanisms, and implementation method.

This thesis addresses the particular challenges of the assessment and treatment of the pliability of HS. Pliability, defined as the elastic and contractile features of HS, plays a crucial role in patient functioning. Factors that contribute to abnormal stiffness of HS are explored. Various challenges regarding accurate assessment and effective treatment for HS pliability are described in this chapter.

1.1 Hypertrophic Scar

1.1.1 Definition and Characteristics of Hypertrophic Scar

HS is a fibroproliferative disorder of the skin that commonly occurs after dermal injuries such as burns. It is characterized as elevated, rigid, hypervascular scar tissue with abnormal pigmentation disposition (Gabriel, 2011; Shah, DeVore, & Silver, 2018; Zhu, Ding, Shankowsky, & Tredget, 2013). Moreover, it is associated with uncomfortable sensations like contraction, intermittent pain, and persistent itchiness (Ogawa, Akaishi, Kuribayashi, & Miyashita, 2016). HS is progressive in nature. Its abnormal development is confined within the original lesion and may persist for months before regression (Ahuja, et al., 2016; Mowbrey, Ferland-Caron, & Tredget, 2016; Ogawa et al., 2016). The maturation of HS tissue may reach or exceed 2 years, and the magnitude of natural degradation is limited and varied among individuals (Ahuja et al., 2016). HS may result in severe dysfunction, disfigurement, psychological distress, and decreased quality of life (Bock, Schmid-Ott, Malewski, & Mrowietz, 2006; Engrav, Garner, & Tredget, 2007; Mowbrey et al., 2016). Its impact on society is also enormous. In the United States, more than $20 billion is spent each year on scar intervention (Block, Gosain, & King, 2015).

1.1.2 Epidemiology of Hypertrophic Scar

Nonfatal burn injuries are the leading cause of morbidity worldwide and a key contributor to disability-adjusted life-years lost in low- and middle-income countries (WHO, 2018). Worldwide, 11 million burn injuries per year warrant medical attention (Peck, 2011). In China, burn injuries accounted for 2% of all

hospital admissions in 2016 (Chinese Burn Association & China Standard Medical Information Research Center, 2017). Reviews of the epidemiology of HS revealed an astonishing range of incidence from 30% to 91% (Bloemen et al., 2009). Moreover, a systematic review suggested that its prevalence after burn injuries could range from 32% to 72% (Lawrence, Mason, Schomer, & Klein, 2012), and Asian and African populations are especially susceptible to HS (Lawrence et al., 2012; Li-Tsang, Lau, & Chan, 2005).

1.1.3 Pathogenesis of Hypertrophic Scar

The pathogenesis of HS has yet to be fully understood, but several key factors behind the abnormal growth of HS have been identified. HS is considered the result of an aberrant wound healing process with prolonged inflammation, excessive proliferation, and ultimately unbalanced remodeling (Gauglitz, Korting, Pavicic, Ruzicka, & Jeschke, 2011; Mowbrey et al., 2016; Ogawa et al., 2016). Injury to the reticular dermis serves as a prerequisite for scar development (Dunkin et al., 2007; Ogawa, 2017), and prolonged wound healing induces chronic local inflammation, followed by excessive fibroblast recruitment and angiogenesis in the proliferation phase (Goei et al., 2016; Ogawa, 2017). During this process, genetic, systemic, and local factors could aggravate the condition (Ogawa et al., 2016). The influence of genetic factors is supported by the greater incidence in subjects of certain ethnicities or family descent (Mowbrey et al., 2016). Systemic factors that intensify inflammation and increase the risk of pathological scar formation include sex hormones and hypertension (Ogawa et al., 2011). Local factors such as delayed wound healing also induce HS via prolonged inflammation (Goei et al., 2016).

Histological studies and clinical observations in the literature have shown that local mechanical tension plays a role in inducing abnormal scar development (Duscher et al., 2014; Marshall et al., 2016; Mowbrey et al., 2016; Ogawa et al., 2016). A hypothetical schematic diagram for the pathogenesis of HS is shown based on the previous discussions in **Figure 1-1**.

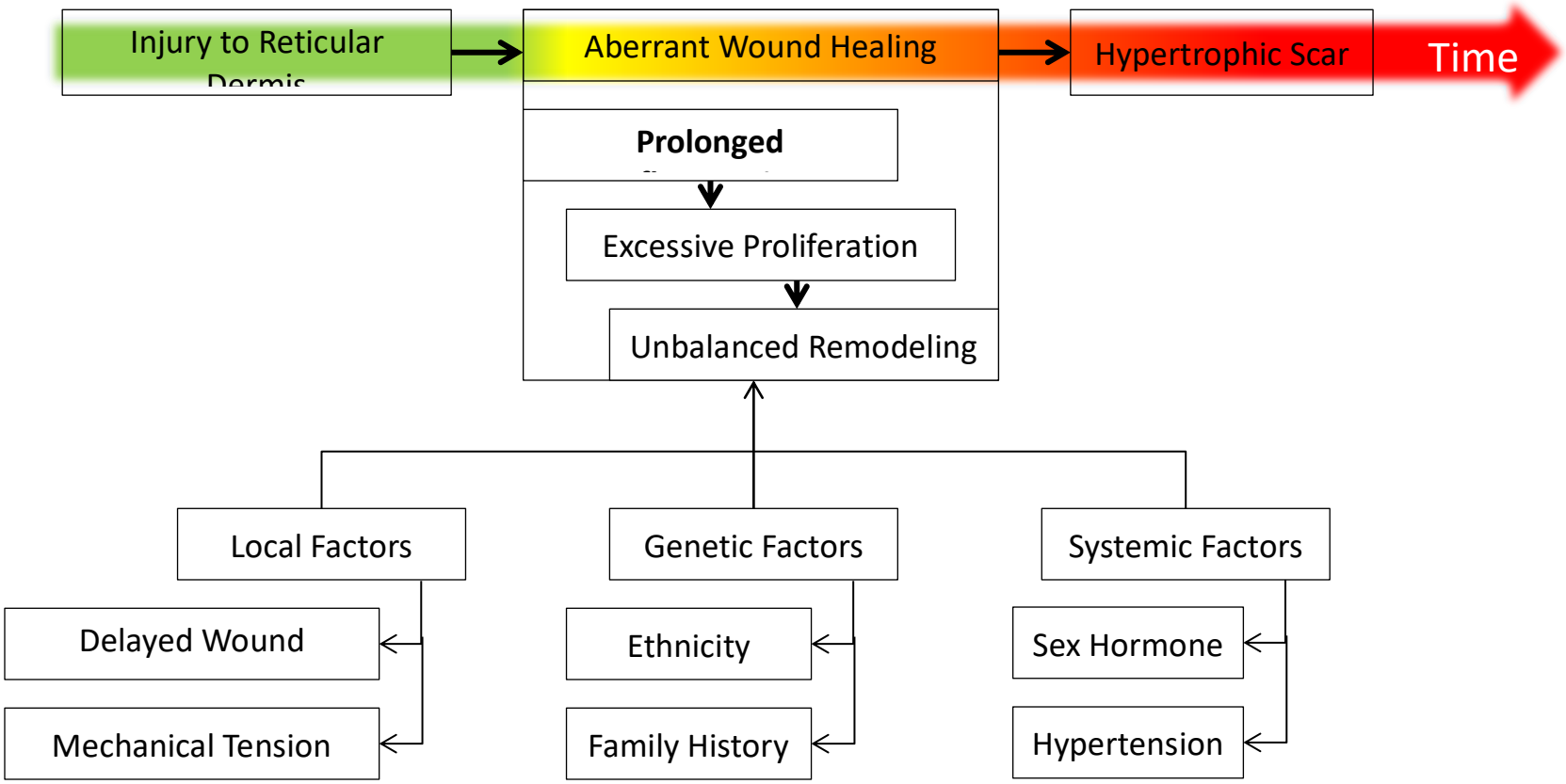


Figure 1-1 Hypothetical schematic diagram of the pathogenesis of HS

1.2 Assessment of Hypertrophic Scar

1.2.1 Parameters of Hypertrophic Scar

From a clinical perspective, proper assessment of HS is a challenge for health care professionals. A national survey of burn therapists found that only 38.1% of therapists use burn scar outcome measures, even though 95% of the therapists believe that their use is important. These survey results may reflect the limited knowledge of occupational therapists regarding burn scar outcome measures, but they also suggest the inadequacy of available knowledge and evidence regarding these measures (Forbes-Duchart, Cooper, Nedelec, Ross, & Quanbury, 2009).

In vivo noninvasive outcome measures are essential for therapists to monitor the progression and maturation of HS for both clinical and research purposes. These parameters are generally divided into three categories: physical, physiological, and sensory (Falder et al., 2009; Lee, Dretzke, Grover, Logan, & Moiemen, 2016; Ud-Din & Bayat, 2016). **Table 1-1** lists the common clinical terms used under each category and their indications. Physical parameters can be measured either subjectively or objectively (Brusselaers et al., 2010a, 2010b; Junker et al., 2014; Tyack, Simons, Spinks, & Wasiak, 2012); however, physiological parameters can only be assessed with special devices, and subjective scales are used for sensory parameters.

Table 1-1 Hypertrophic parameters: categories, terms, and indications

Category	Terms	Indications
Physical		
Color	Erythema/ vascularity	Color contributes greatly to the appearance of HS; Vascularity also reflects angiogenesis to some extent.
	Pigmentation	
Dimension	Surface area	Change in dimensions reflects proliferation and remodeling of HS; These parameters also affect its appearance, particularly the surface roughness.
	Thickness/height	
	Volume	
Texture	Surface roughness/relief	
Biomechanics	Pliability	Scar pliability can have a significant effect on the patient's function and performance.
Physiology		
	Transepidermal water loss (TEWL)	Indicates the barrier functions of the stratum corneum and reflects the maturation of HS.
	Hydration	
	Transcutaneous oxygen tension	
Sensory		
	Pain	Abnormal sensation clearly affects patient's psychological well-being and quality of life.
	Itchiness	

1.2.2 Subjective Measures

Scar assessment scales provide an overall impression of HS by incorporating several core physical parameters of HS in a quick and economical manner (Falder et al., 2009). Recent systematic reviews of subjective burn scar measures addressed all scar scales available for HS assessment and gave comprehensive information regarding those scales (Brusselaers et al., 2010a; Idriss & Maibach, 2009; Tyack et al., 2012). Despite the wide selection, there is no consensus in which scale is the most appropriate; however, it is agreed that the Vancouver Scar Scale (VSS), including its modified versions, and the Patient and Observer Scar Assessment Scale (POSAS) remain the most popular for assessment of HS (Brusselaers et al., 2010a; Falder et al., 2009; Lisa Forbes-Duchart et al., 2009; Idriss & Maibach, 2009; Tyack et al., 2012). Both scales address the core physical parameters of HS, including pigmentation, vascularity, pliability, and height, but the POSAS also includes relief as a parameter (Baryza & Baryza, 1995; Draaijers et al., 2004; Sullivan, Smith, Kermode, McIver, & Courtemanche, 1990).

As for sensory parameters, pain and itchiness can be assessed separately with a visual analogue scale, a numerical rating scale, or a verbal rating scale (Hjermstad et al., 2011). The POSAS and one modified version of the VSS also incorporate sensory parameters including pain and itchiness. The POSAS measures pain and itchiness with a numerical rating scale, and the modified version of the VSS described by Nedelec et al. measures pain and itchiness with a visual analogue scale (Draaijers et al., 2004; Nedelec, Shankowsky, & Tredget, 2000).

1.2.3 Objective Measures

Objective devices could quantify physiological and physical parameters to significantly minimize the assessor bias that commonly occurs in studies of scar management (Anthonissen, Daly, Janssens, & Van den Kerckhove, 2016; O'Brien & Jones, 2013; Sharp, Pan, Yakuboff, & Rothchild, 2015) and enable researchers to establish the clinical effectiveness of HS interventions in a more convincing and scientific manner. Several reviews have thus been conducted to explore and critically appraise objective scar assessment tools (Brusselaers et al., 2010b; Lee et al., 2016). These reviews shared similar conclusions that multiple options exist for assessment of one parameter. However, most reviews failed to give recommendations but rather listed the available options (Lee et al., 2016; van Zuijlen, Angeles, Kreis, Bos, & Middelkoop, 2002; Verhaegen, van der Wal, Middelkoop, & van Zuijlen, 2011), possibly due to the lack of evidence regarding the validity and reliability of the objective devices and the lack of a gold standard for objective assessment (Lee et al., 2016).

Only Lee's review recommended a panel of devices based on predefined criteria, including a 3D camera for dimension, a DSM II colorimeter for color, a DermaScan high-frequency ultrasound scanner for thickness, and a Cutometer for pliability. However, these recommendations may not be suitable for assessment of HS because these reviews targeted the wound healing process, or burn scar or scar in general, but not HS specifically; thus, the device selected and recommended may not be able to address the special characteristics of HS. For example, some thick

HS may exceed the capacity of both the DermaScan and the Cutometer (Lee et al., 2016).

Other than stressing the importance of objective assessment of scar, these reviews focused more on physical parameters and less on physiological parameters. Several practical issues also arose from the review, including the portability, commercial availability, and cost of the device. Some reviews also suggested the use of a multiprobe assessment device to simplify the assessment process (Lee et al., 2016; Ud-Din & Bayat, 2016).

1.3 Treatment of Hypertrophic Scar

1.3.1 Existing Treatment Modalities

Treatment of HS can be classified as invasive or noninvasive. Invasive treatment generally includes reconstructive surgery, laser therapy, microneedling, and intralesional steroid injection. Noninvasive treatment commonly refers to pressure therapy, silicone-based therapy, and massage therapy. Experts in the field have gradually reached a consensus regarding the management of HS based on the emerging evidence, even though systematic reviews and meta-analyses have shown inconsistent and inconclusive results (Ahuja et al., 2016; Al-Shaqsi & Al-Bulushi, 2016; Anthonissen et al., 2013; Gold, Berman, et al., 2014; Gold, McGuire, et al., 2014; Monstrey et al., 2014; Simons & Tyack, 2015), primarily because the studies have questionable quality and are highly susceptible to bias because they lacked a stringent research design and objective tools for the outcome measures (Ahuja et al., 2016; Anthonissen et al., 2016; O'Brien & Jones, 2013). In 2016, the

International Society of Burn Injuries (ISBI) published their most up-to-date clinical guidelines, which recommend the combination of pressure therapy and silicone therapy as “the first line of treatment” for HS prevention and treatment after burns (Ahuja et al., 2016).

Although the combination of pressure therapy and silicone is recognized as the standard of care, few studies have investigated the efficacy of this combination in HS treatment, and the results reported were elusive (Harte, Gordon, Shaw, Stinson, & Porter-Armstrong, 2009; Li-Tsang, Zheng, & Lau, 2010). Harte et al. failed to find a significant difference in the VSS total score and the individual item score between the pressure treatment group and combined treatment group (Harte et al., 2009). However, other researchers have challenged their randomized controlled trial because it did not include any objective scar measurement (Nedelec et al., 2015). In contrast, Li-Tsang et al. found that the combination of pressure and silicone therapy was more effective in reducing HS thickness (Li-Tsang, Zheng, et al., 2010).

1.3.2 Pressure Therapy

Pressure therapy refers to the application of mechanical pressure over HS tissue to minimize its effect (Pratt & West, 2014). Recent systematic reviews and meta-analyses have suggested that solid evidence supports the effectiveness of pressure therapy in reducing scar height and erythema (Anthonissen et al., 2016; Anzarut, Olson, Singh, Rowe, & Tredget, 2009; Sharp et al., 2015). Classical theory proposes that local mechanical pressure mitigates abnormal wound healing by

reducing edema, suppressing local blood flow, and facilitating collagen remodeling (Costa et al., 1999; Staley & Richard, 1997). Recent studies also suggested that deformation and elongation of local HS tissue under pressure could reduce the tension between HS and the surrounding tissues, thus promoting the wound healing process via mechano-modulation (Duscher et al., 2014; Yagmur, Akaishi, Ogawa, & Guneren, 2010).

The use of an adequate pressure dosage is essential for effective pressure therapy (Ai et al., 2017; Lai, Li-Tsang, & Zheng, 2010; Sharp et al., 2015). Systematic reviews with various inclusion criteria suggest slightly different pressure dosages. A recent meta-analysis revealed that 15 to 25 mm Hg is an effective pressure dosage (Ai et al., 2017), but another systematic review of pressure therapy recommended a pressure dosage of 20 to 30 mm Hg (Sharp et al., 2015). It is agreed that a higher pressure dosage is more effective than a lower pressure dosage, particularly for severe HS that is thick and stiff (Lai et al., 2010). However, one should also be aware that an excessive pressure (over 40 mm Hg) may be associated with an increased risk of maceration or paresthesia (Macintyre & Baird, 2006; Van den Kerckhove et al., 2005).

Various methods are used to apply mechanical pressure over HS tissue, including elastic bandages, elastic tape, pressure garments, and even splints (Chan & Association, 1998; Pratt & West, 2014; Radomski & Latham, 2014). The most common method is the compression garment made of elastic fabric because it is easy to apply and less disruptive to daily activities (Naismith, 1980). Patients are usually advised to wear the pressure garment continuously for at least 23 hours per

day, removing it only for hygiene purposes and laundering until the scar matures (Simons & Tyack, 2015). Reported complications include wound breakdown, skeletal deformation, growth retardation, and obstructive sleep apnea (Simons & Tyack, 2015).

Interfacial pressure is generated by the tension of the elastic material and is influenced by various factors, including the fabric's elasticity, the design of the garment, and most importantly, the radius of curvature of the scar sites (Chan & Association, 1998; Pratt & West, 2014; Staley & Richard, 1997). Therefore, it is agreed that regular monitoring of the garment's tension is important because the garments lose their tension over time, particularly for those used with a high pressure (Lai et al., 2010). Unfortunately, maintaining an adequate pressure dosage with a pressure garment alone is usually uncomfortable because the garment may feel too tight. Moreover, for flat body surfaces and concavities, it is nearly impossible to maintain adequate pressure with a pressure garment alone. Additional inserts under the pressure garment are required to increase the radius of curvature of the scar sites, thus increasing the pressure dosage to ensure the treatment effect (Lai & Li-Tsang, 2009; Staley & Richard, 1997; Yu, Yick, Ng, & Yip, 2016). Various types of inserts are available, and details are described in Chapter Four.

1.3.3 Silicone-based Therapy

Many silicone-based products are available, including silicone oil, silicone gel, and silicone gel sheeting (Bleasdale, Finnegan, Murray, Kelly, & Percival, 2015; Mustoe, 2008; Nedelec et al., 2015; Stavrou et al., 2010). The current evidence

suggests no difference in clinical efficacy between gel and gel sheeting (Nedelec et al., 2015). The prevailing theory holds that the silicone-based products reduce HS via occlusion (Berman et al., 2007; Bleasdale et al., 2015; Mustoe, 2008; O'Brien & Jones, 2013; Stavrou et al., 2010). In HS, the barrier function of the stratum corneum is markedly altered by excessive transepidermal water loss (TEWL), which induces a cascade of epidermal and dermal signaling that results in HS (Suetake, Sasai, Zhen, Ohi, & Tagami, 1996). In that case, it is speculated that occlusion restores homeostasis within the stratum corneum by controlling excessive TEWL and recreating the normal water-holding capacity (O'Shaughnessy, De La Garza, Roy, & Mustoe, 2009; Suetake, Sasai, Zhen, & Tagami, 2000).

Nonetheless, silicone gel sheeting remains the most popular type used in combination with pressure therapy (Harte et al., 2009; Li-Tsang, Zheng, et al., 2010; Li-Tsang, Zheng, & Lau, 2010). A Cochrane review on silicone gel sheeting found a statistically significant reduction in scar thickness and improvement in scar color (O'Brien & Jones, 2013), and it is more practical to use silicone gel sheeting with a pressure garment because the gel or oil form of silicone may damage the pressure garment fabric. Moreover, the use of gel is preferred over small areas of burn scar due to its high cost, and silicone gel sheeting is more economical because it is reusable and because its occlusive effect lasts longer. Finally, it has been shown that silicone gel sheeting can reduce the tension between scar tissue and adjacent normal tissues (Akaishi, Akimoto, Hyakusoku, & Ogawa, 2010).

The application of silicone gel sheeting for 12 to 24 hours per day has been recommended in most reviewed studies (Nedelec et al., 2015; O'Brien & Jones, 2013). With the gradual increase in contact time, strict protocols should be followed for cleaning the product and the scar. Complications from silicone gel sheeting (rash, ulcer, erythema, and pruritus) may occur due to poor execution of the application guidelines, but they are easily resolved by temporarily discontinuing therapy and resuming it with more stringent hygiene measures (Nedelec et al., 2015; Simons & Tyack, 2015).

1.4 Pliability of Hypertrophic Scar

Normal skin deforms under stress and retracts to its original state after the stress is removed. The flexibility and elasticity of normal skin is an evolutionary advancement to allow free movement of joints and is directly reflected by the Langer lines (Elsner, 2002). The distinct parameter that describes the biomechanical property of HS is pliability, as introduced by Sullivan et al., which refers to the scar's contractile and elastic texture; it is assessed by palpating the scar surface (Baryza & Baryza, 1995; Sullivan et al., 1990). Pliability is considered to be one of the most important scar parameters because it is directly related to the patient's functional performance (Forbes-Duchart et al., 2009; Harte et al., 2009; Li-Tsang et al., 2010; Steinstraesser et al., 2011).

Four structural abnormalities generally contribute to the decreased pliability in HS. First, myofibroblasts continuously present after epithelialization, causing persistent contraction via α-smooth muscle actin (α-SMA). In the normal wound healing

process, myofibroblasts usually differentiate from fibroblasts around 1-2 weeks after injury and contribute to wound contraction and closure by expressing α-SMA. The myofibroblasts will automatically undergo apoptosis after wound closure (Marshall et al., 2016). Second, excess collagen—particularly type III collagen—also influences the biomechanics of HS by increasing its resistance to deformation. In normal skin, type I and type III collagen, presented at a ratio of around 5:1, are the chief contributors to tensile strength and structural integrity (Elsner, 2002). However, in HS, the ratio of type I and type III collagen is 1:15, which means that HS is predominately composed of type III collagen and that it is the excess type III collagen that contributes to the increase in tensile strength (Ghazawi, Zargham, Gilardino, Sasseville, & Jafarian, 2018). Moreover, the increase in collagen can be observed with abundant nodules containing myofibroblasts, which serve as evidence that collagen synthesis occurs much more quickly than its degradation(Armour, Scott, & Tredget, 2007; Ghazawi et al., 2018). Moreover, it has also been observed that elastin, another key player in maintaining skin elasticity and resilience, is reduced in the deep dermis of HS (Ghazawi et al., 2018; Niessen, Spauwen, Schalkwijk, & Kon, 1999). Finally, it has also been noted that the water content of HS differs from that of normal skin and adds to the increased firmness of HS (Niessen et al., 1999).

As discussed in the previous section, the mechanism by which pressure therapy and silicone therapy improve HS can be summarized into two pathways, as shown in **Figure 1-2**; one pathway directly alleviates the abnormal wound healing process, and the other exerts an indirect effect on the wound healing process by reducing

tension. The effects of pressure and silicone therapy on HS pliability can be elucidated from the manner in which they modify the structural abnormalities or the factors to which the structural abnormalities are attributed. It has been reported that pressure therapy inhibits α-SMA and induces apoptosis of myofibroblasts (Li-Tsang et al., 2014). The collagen metabolism is regulated by increased MMP-9 activity, and ischemic cell damage is induced. Silicone therapy decreases the TGF-β level, reduces fibroblast-mediated collagen contraction, and enhances hydration of the stratum corneum. In addition, both therapies can modify the tissue water content and reduce tissue turgor (Armour et al., 2007; Mowbrey et al., 2016; Niessen et al., 1999).

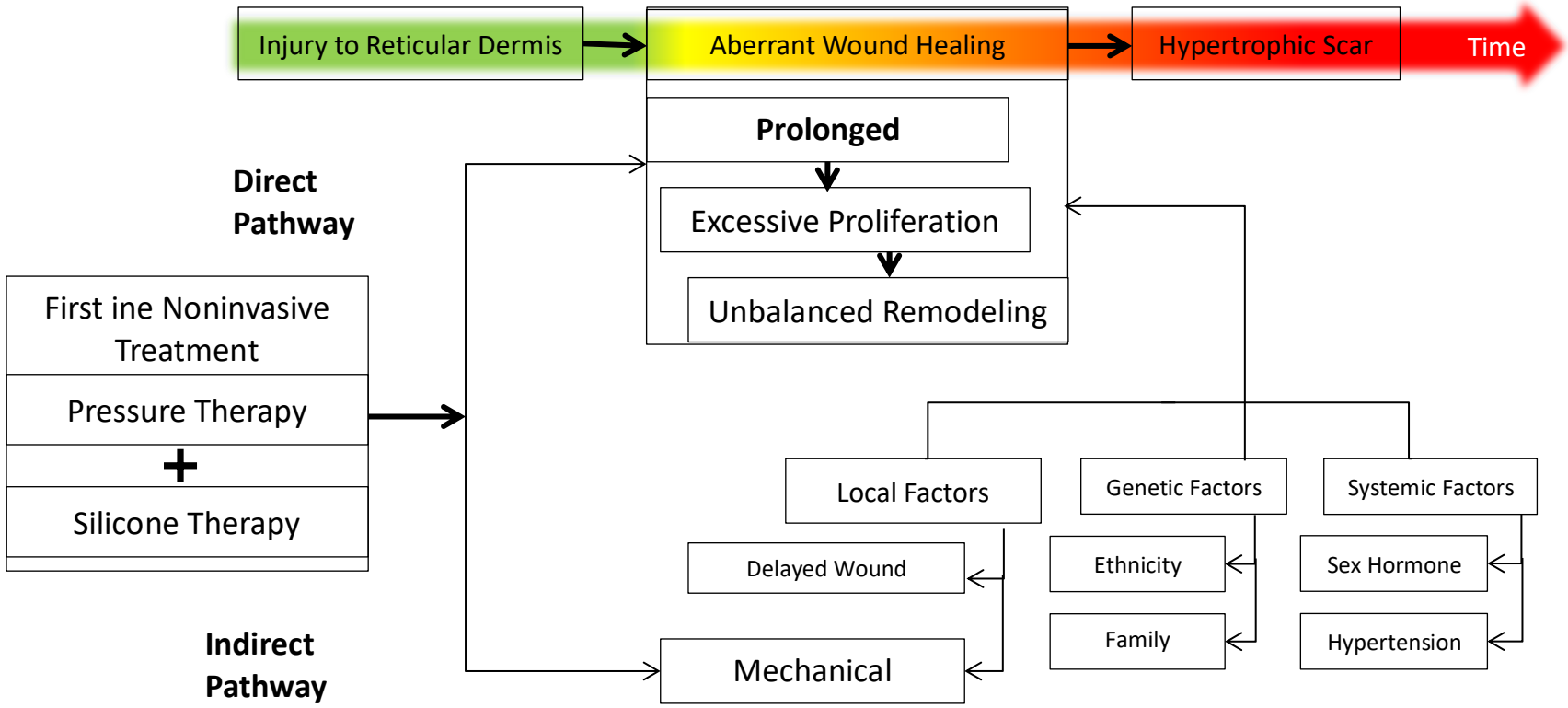


Figure 1-2 Mechanism of pressure therapy and silicone therapy on HS treatment: direct and indirect pathways

Unfortunately, even with close functional indications, there is a lack of agreement as to the proper means by which to assess HS pliability. The core concept of pliability assessment is to examine the relationship between deformation and the force that induces deformation (Elsner, 2002). In vivo measurement of pliability is a great challenge because of the particular biomechanical features of HS. HS possesses nonlinear elasticity and viscoelasticity; it is thicker than normal scar, anisotropic, and subject to pretension (Chu & Brody, 1975; Elsner, 2002). The manner in which the measurement principle and administration procedure address those biomechanical features is crucial for the validity and reliability of the approach; however, they have seldom been assessed from this perspective (Lee et al., 2016; Ud-Din & Bayat, 2016).

Therefore, a systematic review is needed to critically appraise possible methods of objective assessment of in vivo evaluation of HS pliability based on the measurement principle and administration procedure and explore their effect on the clinimetrics. The aims of this systematic review are to identify the key features of an appropriate assessment tool and identify theoretically sound devices. This part of the study is covered in the next chapter. Based on the findings of Chapter Two, a relatively new device—an upgraded version of the DermaLab Combo's elasticity measurement—was selected as an appropriate assessment tool for HS pliability, and its ability to assess HS pliability is validated in Chapter Three.

Resolving the issue of HS pliability assessment could yield the proper equipment for investigation of the clinical efficacy of combined pressure and silicone therapy on HS, particularly regarding pliability. The primary issue that must be solved is

how to implement pressure and silicone together with optimal effect. No existing insert material can enhance pressure and provide the effects of silicone at the same time. This concept of an ideal insert that combines pressure and the effects of silicone is described in Chapter Four. Chapter Four also examines the properties of a newly invented insert material based on our ideal insert concept. Finally, with proper assessment and intervention strategies, the clinical efficacy of combined pressure and silicone therapy is examined in Chapter Five.

Each of the clinical trials that examined combined pressure and silicone therapy demonstrated an improvement in pliability in the combined therapy group over that seen in the pressure therapy group, but not all showed statistical significance (Harte et al., 2009; Li-Tsang et al., 2010; Steinstraesser et al., 2011). However, because none of those studies involved an objective tool to assess scar pliability, this uncertainty also means that "a great deal of possibilities prevails" (O'Brien & Jones, 2013). Therefore, it is hypothesized that the innovated insert that combines pressure and silicone therapy will outperform traditional inserts in at least one area in a series of objective HS assessments.

This thesis addresses several issues related to the assessment and treatment of HS after burn injury. However, there is no doubt that our understanding of HS remains elusive. The assessment of HS pliability has also been restrained by the lack of a commercially available device, which would require closer collaboration among clinicians, engineers and industry. The adoption of an innovative insert material for the treatment of HS is more effective and convenient than the conventional method, but it still requires great cooperation from both patient and caregiver. The

limitations and perspectives for future development are elaborated in the final chapter.

Chapter Two

Objective Assessment of the Pliability of Hypertrophic Scar, a Systematic Review

Chapter Summary

Context: The pliability of hypertrophic scar (HS) is one of the most important factors in scar assessment because it is closely related to the patient's physical comfort and mobility. However, methods for objective assessment of HS pliability vary, so it is difficult to ascertain which method is the most appropriate.

Objective: To appraise the available methods of objective in vivo assessment of the pliability of human HS to guide clinical practice and research.

Data Sources: A systematic review of the English-language literature was performed using PubMed, MEDLINE CINAHL, MEDLINE, EMBASE, and Web of Science.

Study Selection: Research articles that addressed the noninvasive in vivo objective assessment of the pliability of human HS due to dermal injury were included.

Data Synthesis: After duplicates were removed, 699 records were obtained. After further screening and a hand search, 48 articles fulfilled the inclusion and exclusion criteria. The 25 methods of objective assessment identified can be categorized into four groups—extension, indentation, suction, and acoustic—based on the biomechanical approaches adopted. The measurement principle, the administration method, the available clinimetric data, and practicality were evaluated and summarized.

Conclusions: Of the devices identified in this review, the Cutometer was the most extensively examined from a clinimetric perspective. From a biomechanical

perspective, the suction method was more appropriate for assessment of HS pliability; however, to examine HS pliability more accurately with the suction method, a suction device with pressure of larger magnitude and an aperture of a larger diameter should be applied.

2.1 Introduction

The characteristics of HS caused by dermal injury differ significantly from those of normal skin. Among the most disturbing characteristics of HS are its abnormal stiffness and reduced elasticity, which lead to functional limitations such as a restricted range of motion and an unpleasant feeling of tightness (Busche, Thraen, Gohritz, Rennekampff, & Vogt, 2018; Tyack et al., 2012). Assessment of this abnormality was first addressed in 1975, when researchers measured the mechanical properties of HS (Chu & Brody, 1975). These mechanical propertieswere normally addressed in clinical situations via an item on an assessment scale (Garcia-Velasco, Ley, Mutch, Surkes, & Williams, 1978). The various clinical assessment scales developed, such as the VSS and the POSAS, all include scar pliability. Various terms have been used to describe the mechanical properties of scar, including consistency, pliability, and distortion (Brusselaers et al., 2010a), but the most common term is pliability.

Pliability describes the contractile and elastic texture of the scar (Baryza & Baryza, 1995; Sullivan, Smith, Kermode, Mclver, & Courtemanche, 1990). In a clinical setting, evaluation of scar pliability could facilitate prediction of the prognosis and assist in clinical decision-making and monitoring of scar progression, maturation, and treatment outcomes. In a research setting, accurately plotting the pliability of scar can help to establish treatment effectiveness in a more convincing manner (Forbes-Duchart, Cooper, Nedelec, Ross, & Quanbury, 2009; Lee et al., 2016; Ud-Din & Bayat, 2016). However, pliability is assessed by touching the scar's surface in a clinical setting, and the result is highly subject to individual differences. Thus,

demand is increasing for a method to assess pliability in an objective and noninvasive manner.

Interdisciplinary collaborations and rapid technological development have allowed the development of instruments for noninvasive assessment of pliability via various biomechanical approaches (Brusselaers et al., 2010b; Hendriks, 2001; Perry, McGrouther, & Bayat, 2010; Powers, Sarkar, Goldgof, Cruse, & Tsap, 1999; Verhaegen, van der Wal, Middelkoop, & van Zuijlen, 2011). However, with this diversity of methods, it is difficult to draw a conclusion on which is the most clinically appropriate tool, and the search continues for a reliable, valid, quick, easy, and noninvasive measurement tool for pliability (Verhaegen, van der Wal, Middelkoop, & van Zuijlen, 2012).

Unfortunately, no review of the assessment of pliability alone has been published (Brusselaers et al., 2010b; Oliveira et al., 2005; Perry et al., 2010; Verhaegen et al., 2011; Verhaegen et al., 2012); therefore, the aim of this review was to critically appraise the objective assessment of in vivo evaluation of the pliability of human HS due to dermal injury. The measurement's reliability and validity in clinical application will be examined, and their measurement principle and administration procedure will be examined from a biomechanical perspective.

2.2 Methods

2.2.1 Inclusion Criteria

Published articles that describe noninvasive objective scar assessment to measure the mechanical properties of scars were included in this systematic review. The

language was restricted to English. The study population was limited to human subjects with cutaneous scar resulting from dermal injury (i.e. thermal, surgical, or traumatic). Studies that targeted only normal skin, scar from other causes (i.e., acne), or scar of subcutaneous tissues (i.e., tendons or internal organs) were excluded, as were studies that only involved animals. Although we intend to determine an objective assessment method for HS, scars with different morphologies were also included in the analysis so that 1) we would not omit potentially appropriate equipment, and 2) additional information could be used to examine the validity of the assessment tool.

This systematic review included in vivo studies that examined the reliability and validity of these assessment tools. Because no consensus has been reached regarding a gold standard for pliability assessment in this area, studies that described the biomechanical rationale of the assessment tool, studies that compared the mechanical properties of various types of scar or with skin, and longitudinal studies that described changes in the mechanical properties of scar were also included to examine validity. Studies that were solely conducted ex vivo or that only compared the outcomes of wound or scar treatments were excluded.

2.2.2 Search methods

Searches were conducted on PubMed, CINAHL, MEDLINE, EMBASE, and Web of Science up to September 10, 2018, whereas RSS alerts were created to receive the most updated information. The search strategies for PubMed (including MEDLINE) are shown in **Table 2-1**.

2.2.3 Study Selection

The search retrieved 1,314 records, and 699 records remained after removal of duplicates. After further screening by title and abstract, 71 articles remained, of which 43 met all inclusion and exclusion criteria. The reference lists of the selected articles were also hand-searched for suitable studies, and an additional five articles were included. The total number of articles selected for review was thus 48, including 13 review articles. The selection process for the eligible articles is outlined in **Figure 2-1**.

Table 2-1 Search strategies for PubMed (including MEDLINE)

Step	Procedure
1#	scar OR scars OR scarring OR cicatrix OR keloid OR “cicatrix”[MeSH Terms] OR “keloid”[MeSH Terms]
2#	skin OR dermis OR epidermis OR dermal OR epidermal OR cutaneous OR “skin” [MeSH Terms]
3#	instrument OR scale OR questionnaire OR device OR tool OR evaluation OR assessment OR equipment
4#	instrument OR scale OR questionnaire OR device OR tool OR evaluation OR assessment OR equipment [MeSH Terms]
5#	pliability OR elasticity OR adherence OR firmness OR stiffness OR hardness OR “mechanical propert*” OR “biomechanical propert*” OR “elastic propert*”
6#	pliability OR elasticity OR adherence OR firmness OR stiffness OR hardness OR “mechanical propert*” OR “biomechanical propert*” OR “elastic propert*”[MeSH Terms]
7#	3# OR 4#
8#	5# OR 6#
9#	1# AND 2# AND 7# AND 8#

Filters for subjects were limited to humans, and the language was limited to English.

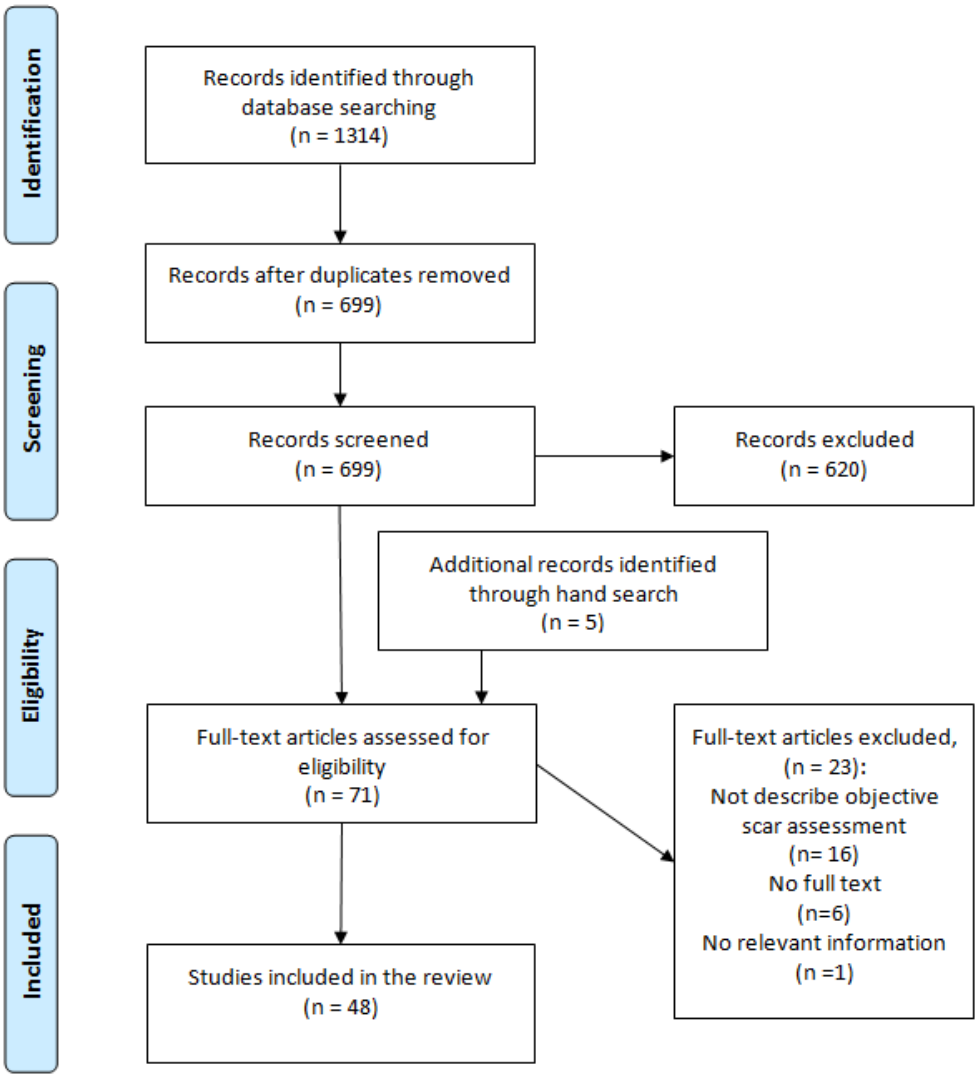


Figure 2-1 Selection process for the systematic review

2.2.4 Data Extraction

Standardized electronic data extraction forms were prepared to retrieve subject information, the mechanical principle used, the method of administration, and various clinimetric findings. The review articles were used to provide extra information.

2.2.5 Quality Assessment

The primary outcomes reported in this review included the underlying biomechanical models and outcomes of the device or method and its merits and demerits. Reliability and validity were also examined. Reliability was assessed from the perspectives of inter-rater and intra-rater reliability, which are reported as the range of the intraclass correlation coefficient (ICC), and its interpretation was elucidated as shown in Table 2-2 (Tyack et al., 2012).

Unfortunately, due to the lack of a gold standard in this area, the validity was evaluated and reported based on the following criteria: correlation with the clinical score, the ability to distinguish known differences between different skin groups (i.e., skin, scar, and HS), and the ability to depict the scar's temporal progression (Tyack et al., 2012). In addition, practicality issues such as commercial availability and portability were also reported.

Table 2-2 Interpretation of intraclass correlation coefficient (ICC)

Range	Explanation
ICC > 0.75	Excellent agreement
0.74 > ICC > 0.6	Good agreement
0.59 > ICC > 0.4	Fair to moderate agreement
ICC < 0.4	Poor agreement

2.3 Results

2.3.1 Study Characteristics

Table 2-1 summarizes the study characteristics of the 35 original research articles reviewed, including the device or method used, the population studied and cause of their scarring, the biomechanical model adopted, and the availability of clinimetric data. Fewer than half of the articles specifically targeted HS. In the 48 articles reviewed, 25 different devices or methods to assess scar pliability were identified. Despite this variety, the device or method involved can be divided into several categories according to the basic biomechanical approaches upon which the deformations were induced, including in-plane deformation methods, indentation methods, suction methods, and acoustic methods. The next part of this section will be presented according to these categories.

Table 2-3 Summary of articles reviewed

Articles reviewed (acoustic method)									
Basic Information				Outcomes Availability					
Author Year	Device or Method Described (Company)	Population Studied (N)	Cause of Scar	Mechanism	Intrarater Reliability	Interrater Reliability	Correlation with Clinical Score	Measuring Change Cross -Sectional	Measuring Change Longitudinal
Shah et al., 2018	Spectral domain optical coherence tomography + vibration analysis	NS(1) US(1)	Burn	√				√ *	
Verhaegen et al., 2010	Reviscometer (C+K Electronic, Germany)	NS(50) US(50)	Surgery	√	√	√		√	
Quatresooz et al., 2006	Reviscometer (C+K Electronic, Germany)	NS(35) AS(35) HS(35)	Surgery	√				√	
McHugh et al., 1997	Shear velocity device	NS (34) SHS (34) HS (34)	Burn	√				√	√ *

N= sample size

NS: Normal skin; HS: hypertrophic scar; KS: keloid scar; AS: atrophic scar; DS: donor site scar; UN: unspecific scar; GS: grafted scar; SHS: spontaneously healed scar

*: indicates no statistical method was adopted

Articles reviewed (continued; suction method)

Basic Information				Outcomes Availability					
Author Year	Device or Method Described (Company)	Population Studied (N)	Cause of Scar	Mechanism	Intrarater Reliability	Interrater Reliability	Correlation with Clinical Score	Measuring Change Cross -Sectional	Measuring Change Longitudinal
Busche et al., 2018	Cutometer (Courage & Khazaka, Germany)	NS(45) US(45) GS(45)	Burn	√				√	
Gabriel & Kowalske, 2015	BTC-2000 (SRLI Technologies Ltd, U.S.A.)	US(28)	Burn	√					√
Nedelec et al., 2014	Cutometer (Courage & Khazaka, Germany)	NS(46) DS(46) HS(46)	Burn	√				√	√
Gankande et al., 2014	DermaLab elasticity measurement (Cortex)	NS(30) US(30)	Burn	√	√	√			
Anthonissen et al., 2013	DermaLab elasticity measurement (Cortex)	NS(24) SHS (24) GS(24)	Burn	√	√	√		√	√
Nedelec et al., 2008	Cutometer (Courage & Khazaka, Germany)	NS(32) DS(32) HS(32)	Burn	√		√	√		
Nedelec et al., 2008	Cutometer (Courage & Khazaka, Germany)	NS (30) DS (30) HS (30)	Burn	√	√			√	
Rennekampff et al., 2006	Cutometer SEM 575 (Courage and Khazaka, Germany)	NS (33) DS (33)	Mixed	√			√	√	√
Oliveira et al., 2005	Pneumatonometer	NS (38) HS (58)	Burn	√			√ *		

	(Medtronic Solan Model 30 Classic, Jacksonville, FL, USA)							
Draaijers et al., 2004	Cutometer Skin Elasticity Meter 575 (Courage & Khazaka, Germany)	NS(20) US(20)	Burn	√	√	√		
Ho et al., 2000	DermaLab elasticity measurement (Cortex)	NS (8) US (8)	Trauma	√			√ *	
Fong et al., 1997	Cutometer (Courage & Khazaka, Germany)	HS (16) NS (29)	Burn	√	√	√ *	√ *	√ *
Spann et al., 1996	Pneumatonometer (Mentor, Inc.)	NS (17) US (17)	Burn	√		√	√	

N= sample size

NS: normal skin; HS: hypertrophic scar; KS: keloid scar; AS: atrophic scar; DS: donor site scar; UN: unspecific scar; GS: grafted scar; SHS: spontaneously healed scar

*: indicates no statistical method was adopted

Articles reviewed (continued; indentation method)

Basic Information				Data Availability					
Author Year	Device or Method Described (Company)	Population Studied (N)	Cause of Scar	Measuring Mechanism	Intrarater Reliability	Interrater Reliability	Correlation with Clinical Score	Measuring Change Cross-Sectional	Measuring Change Longitudinal
Seo et al., 2017	SkinFibroMeter (Delfin Technologies Ltd.)	NS (25) KS+HS (25)	Mixed	√			√	√	
Es'haghian et al., 2015	Optical palpation: swept-source optical coherence tomography system (OCS1300SS, Thorlabs, USA) + stress sensor	US(2) HS(1)	Burn Surgery	√				√ *	
Niyaz et al., 2012	Vesmeter (Wave Cyber Co. Ltd., Japan)	KS (6) HS (5)	Not Given	√					√ *
Vránová et al., 2009	Local dynamic deformation response	NS (2) US (2)	Surgical	√				√	√
Cleary et al., 2007	Skin compliance device (Sensory Management Services, LLC, Baltimore, MD)	NS (23) US (23)	Surgical Trauma	√	√	√		√	
Lye et al., 2006	Modified tissue tonometer (Flinders University Biomedical Engineering Department, Australia)	NS (10) HS (10)	Burn	√	√		√	√	
Corica et al., 2006	Modified tissue tonometer (Flinders University Biomedical Engineering Department, Australia)	NS (24) US (24)	Burn	√	√	√		√	
Oliveira et al., 2005	Durometer (Rex Model H 1000, Rex Gauge Company, IL, U.S.A.)	US (69)	Burn	√			√ *	√	

Magliaro & Romanelli, 2003	Durometer (Rex Model H 1000, Rex Gauge Company, IL, U.S.A.)	NS (38) HS (58)	Burn	√			√		√
Ho et al. 2000	Ballistometer (Dia-Stron Ltd, U.K.)	NS (8) US (8)	Trauma	√				√ *	
Esposito et al., 1990	Modified Schiøtz tonometer	US(10)	Burn	√			√ *		√ *
Katz et al., 1985	Cicatrometer	US(4)	Burn	√	√		√ *		√ *

N= sample size

NS: normal skin; HS: hypertrophic scar; KS: keloid scar; AS: atrophic scar; DS: donor site scar; US: unspecific scar; GS: grafted scar

*: indicates no statistical method was adopted

Articles reviewed (continued; in-plane deformation method)

Basic Information				Data Availability					
Author Year	Device or Method Described (Company)	Population Studied (N)	Cause of Scar	Measuring Mechanism	Intrarater Reliability	Interrater Reliability	Correlation with Clinical Score	Measuring Change Cross -Sectional	Measuring Change Longitudinal
Ferriero et al., 2010	Adheremeter	US (25)	Surgical	√	√	√	√		
Vránová et al., 2009	Matrix identification of static deformation	US (1)	Surgical	√					√
Zhang et al., 2004	Finite-element modeling	US (4)	Burn	√			√ *		
Boyce et al., 2000	Dermal Torque Meter (DTM 310 Dia Stron Ltd, U.K.)	NS (13) GS (10)	Burn	√				√	√
Tsap et al., 1998	Finite-element modeling	US (3)	Burn	√			√ *		
Clark et al., 1996	Quasi-static extensometer	NS (15) HS (15)	Burn	√			√ *		√ *
Bartell et al., 1988	Handheld extensometer	HS (16) NS (9)	Burn	√				√	√
Clark et al., 1987	Quasi-static extensometer	NS (15) HS (15)	Burn	√			√ *		√ *
Chu & Brody, 1975	Extensometer	NS (1) HS (1)	Burn	√				√ *	

N= sample size

NS: normal skin; HS: hypertrophic scar; KS: keloid scar; AS: atrophic scar; DS: donor site scar; UN: unspecific scar; GS: grafted scar

*: indicates no statistical method was adopted

Table 2-4 Summary of in-plane deformation method

Basic Information		Clinimetrics					Feasibility	
Equipment/Method	Outcome Measured (Unit)	Intrarater Reliability	Interrater Reliability	Correlation with Clinical Score	Measuring Change Cross-Sectional	Measuring Change Longitudinal	Portability	Commercial Availability
Extensometer[1] (Chu & Brody, 1975)	Force-displacement diagram				Observed difference in diagram NS vs. HS		N	N
Quasi-static extensometer (Clark, Cheng, Leung, & Leung, 1987; Clark, Cheng, & Leung, 1996)	Force-displacement diagram: Stiffness (Modulus/Nmm^{-1}) Extensibility (strain/%)			Observed correlation with customized rating	Observed difference in Stiffness & Extensibility NS vs. HS	Observed improvement in some cases	N	N
Handheld extensometer (Bartell, Monafo, & Mustoe, 1988)	Excursion distance (mm) Elasticity (stretch/%)				Statistical difference in Elasticity NS vs. HS**	HS Correlation of Elasticity with Burn time: r = 0.63	Y	N
Finite-element modeling (Tsap, Goldgof, Sarkar, & Powers, 1998; Zhang, Goldgof, Sarkar, & Tsap, 2004)	Relative elasticity (kPa) Relative elasticity index (unit)			Observed correlation with customized rating			N	N/A

Matrix identification of static deformation (Vránová, Zeman, Čech, & Otáhal, 2009)	Graphical analysis Average vector length (pix)					Observed improvement in one case	N	N/A
Dermal Torque Meter (Boyce, Supp, Wickett, Hoath, & Warden, 2000)	Time-deformation diagram: 1. Elastic stretch (Ue/) 2. Viscous stretch (Uv/) 3. Total extensibility (Uf/) 4.Elastic recovery (Ur/) 5.Total recovery (Ua/) 6.Residual plasticity (R/) 7.Ur/Ue (unit) 8.Uv/Ue (unit) 9.Ua/Uf (unit) 10.Ur/Uf (unit)				Statistical difference in Ue Uv Ur Ua Ur/Ue Uv/Ue Ur/Uf NS vs. HS**	GS All parameters correlate with time $r < 0.35$	Y	Y
Adheremeter (Ferriero, Vercelli, Salgovic, Stissi, & Sartorio, 2010)	Surface mobility index (SM) Adherence severity index (AS)	NS SM:0.96	NS SM: 0.98 US: SM:0.97-0.99 AS: 0.87	SM vs. VSS: r = 0.50**-0.58** SM vs. PL-VSS r = 0.39-0.58** AS vs. VSS: r = 0.41*-0.59** AS vs. PL-VSS r = 0.32-0.66**			Y	N^2

VSS: Vancouver Scar Scale, PL-VSS: pliability item of Vancouver Scar Scale
NS: normal skin; HS: hypertrophic scar; KS: keloid scar; AS: atrophic scar; DS: donor site scar; UN: unspecific scar; GS: grafted scar
Note 1: The author of the article did not give the name of the device, but based on its configuration, we can confirm that the device was a form of extensometer.
Note 2: Although it is not commercially available, the author of the article described the material and design so that it could be reproduced.
*: $p<0.05$; **: $p<0.01$

Table 2-5 Summary of indentation method

Basic Information		Clinimetrics					Feasibility	
Equipment/Method	Outcome Measured (Unit)	Intrarater Reliability	Interrater Reliability	Correlation with Clinical Score	Measuring Change Cross-Sectional	Measuring Change Longitudinal	Portability	Commercial Availability
Cicatrometer (Katz, Frank, Leopold, & Wachtel, 1985)	Dial reading (Unit)			Observed correlation with customized rating		Observed improvement in some cases	Y	N
Modified Schiøtz tonometer (Esposito, Ziccardi, Scioli, Pappone, & Scuderi, 1990)	Dial reading (Unit) Pressure (mm Hg) Firmness index (unit)			Observed correlation with customized rating		No pattern could be identified	Y	N
Modified tissue tonometer (Corica, Wigger, Edgar, Wood, Carroll, 2006; Lye, Edgar, Wood, & Carroll, 2006)	Dial reading (mm)	NS 0.892-0.915 US 0.904-0.948 Overall 0.922-0.951	NS: 0.942 US: 0.948 Overall:0.959	Reading vs. PL-VSS r = -0.442 – -0.457	Statistical difference in reading NS vs. US**		Y	N
Ballistometer (Ho et al., 2000)	First indentation depth (B/mm) Exponential decay constant for rebound peak (a/unit) Coefficient of restitution (CoR/unit)				Observable differences in B and a		Y	Y

					NS vs. US			
Durometer (Magliaro & Romanelli, 2003; Oliveira et al., 2005)	Dial reading (Unit)			Reading vs. Customized skin hardness score r = -0.769** Reported good correlation between Reading vs. VSS, yet data not shown	Statistical difference in reading VSS 1-6 vs. VSS 7-14*	Statistical difference in reading before and after treatment ($p < 0.05$)	Y	Y
Skin compliance device (Cleary, Kathryn, & Nick, 2007)	Pliability (gm/mm^2) Percentage of known pliability of a rubber(unit)	NS: 0.93-0.97 US 0.88-0.98	NS: 0.39-0.59 US 0.29-0.79		Statistical difference in pliability NS vs. US**		Y	Y
Local dynamic deformation response (Vránová et al., 2009)	Fast component Steady deformation value (L) Damping time constant (k) Frequency of damped oscillations(f) Slow component: Steady deformation value (P) Damping time constant (q) Total deformation(L+P) Ration (P/L)				Statistical difference in P NS vs. US Statistical difference in k NS vs. US (treated)	Statistical difference in L, P, L+P, P/L before and after treatment	N	N/A
Vesmeter (Niyaz, Matsumura,	Skin elasticity Viscosity					Observed marked changes	Y	Y

Watanabe, Hamamoto, & Matsusawa, 2012)	Viscoelastic ratio, Penetration depth Relaxation time Hardness					after treatment in hardness, elasticity, penetration depth, viscosity and relaxation time Observed slight changes after treatment in the viscoelastic ratio		
Optical palpation (Es'haghian et al., 2015)	Stress distribution in an elastography image				Observable differences in image NS vs. US NS vs. HS		N	N/A
SkinFibroMeter (Seo, Kang, Yoon, Lee, & Kim, 2017)	Induration value (N)			Induration value vs. PL-VSS r = 0.628**	Statistical difference in Induration Value NS vs. KS+HS**		Y	Y

VSS: Vancouver Scar Scale, PL-VSS: pliability item of Vancouver Scar Scale
NS: normal skin; HS: hypertrophic scar; KS: keloid scar; AS: atrophic scar; DS: donor site scar; UN: unspecific scar; GS: grafted scar
*: $p<0.05$; **: $p<0.01$

Table 2-6 Summary of suction method

Basic Information		Clinimetrics					Feasibility	
Equipment/Method	Outcome Measured (Unit)	Intrarater Reliability	Interrater Reliability	Correlation with Clinical Score	Measuring Change Cross-Sectional	Measuring Change Longitudinal	Portability	Commercial Availability
Pneumatonometer (Oliveira et al., 2005; Spann, Mileski, Atiles, Purdue, & Hunt, 1996)	Pressure (mm Hg)			Reading vs. PL-VSS r = 0.57 Reported good correlation between Reading vs. clinical pliability scores, yet data not shown	Statistical difference in reading NS vs. US*		Y	Y[2]
Cutometer (Busche et al., 2018; Draaijers et al., 2004; Fong, Hung, & Cheng, 1997; Nedelec, Correa, de Oliveira, LaSalle, & Perrault, 2014; Nedelec, Correa, Rachelska, Armour, & LaSalle, 2008a;	6 direct parameters[1] Immediate deformation (Ue/mm) Delayed deformation (Uv/mm) Maximal deformation (Uf/mm) Elastic retraction (Ur/mm) Maximum retraction (Ua/mm) Residue deformation (R/mm) Derived parameters[1]	NS: Uf(R0):0.81 Ua/Uf(R2): 0.43 Ur/Ue (R5):0.69 Uv/Ue (R6):0.81 Ur/Uf (R7):0.78 DS: Uf(R0):0.92 Ua/Uf(R2): 0.33 Ur/Ue (R5): -0.03 - 0.42	NS: Ue:0.83-0.95 Ur:0.85-0.96 Uv:0.75-0.93 1. Uf(R0) :0.83-0.95 Ua/Uf(R2): 0.55 Ur/Ue (R5):0.68 Uv/Ue (R6):0.86 Ur/Uf (R7):0.84	US Reading vs. Customized score Ue: r = -0.532** Ur: r = -0.455* Uv: r = -0.293** Uf(R0): r = -0.524** Ua(R8): r = -0.510** DS:	Statistical difference in Uf(R0) NS vs. DS** NS vs. GS** NS vs. HS** NS vs. US** DS vs. HS**	DS: No significant correlation between healing time and Uf(R0), Ua(R8), Ur, Ue, Uv, R,Ua/Uf(R2), Ur/Ue(R5), Ur/Uf(R7), Uv/Ue(R6)	Y	Y

Nedelec, Correa, Rachelska, Armour, & LaSalle, 2008b; Rennekampff, Rabbels, Reinhard, Becker, & Schaller, 2006)	R0 = Uf R1 = Uf - Ua R2 = Ua/Uf R3 = last max. amplitude R4 = last min. amplitude R5 = Ur/Ue R6 = Uv/Ue R7 = Ur/Uf R8 = Ua R9 = R3-R0	Uv/Ue (R6):0.11-0.48 Ur/Uf (R7):0.45 HS: Uf(R0):0.12-0.62 Ua/Uf(R2): 0.17-0.42 Ur/Ue (R5):0.16-0.37 Uv/Ue (R6):0.02-0.45 Ur/Uf (R7):0.35-0.38	Ua(R8):0.85-0.96 US: Ue:0.76-0.93 Ur:0.66-0.89 Uv:0.35-0.68 Uf(R0):0.74-0.92 Ua(R8):0.69-0.90 DS: Uf(R0):0.94 Ua/Uf(R2): 0.61 Ur/Ue (R5):0.02 Uv/Ue (R6):0.06 Ur/Uf (R7):0.66 HS: Uf(R0):0.56-0.776 Ua/Uf(R2): 0.71	Readings vs. PL-VSS Uf(R0), Ua(R8), Ur, Ue, Uv, R,Ua/Uf(R2), Ur/Ue(R5), Ur/Uf(R7), Uv/Ue(R6) No significant correlation Uf(R0) vs. PL-mVSS r = -0.47** HS Uf(R0) vs. PL-mVSS r = -0.57** HS(severe): Uf(R0) vs. PL-mVSS r = -0.23 No significant correlation	Statistical difference in Ua/Uf(R2) NS vs. GS** Statistical difference in R3 NS vs. GS* NS vs. US** Statistical difference in (Ur/Uf)R7 NS vs. GS** Statistical difference in (Ra)R8 NS vs. GS** NS vs. US**	DS & HS: Increase in Uf(R0) between 3 and 12 months ($p < 0.05$)		

			Ur/Ue (R5):0.44 Uv/Ue (R6):0.45 Ur/Uf (R7):0.55		Significant difference in Uf(R0), Ua(R8),Ur, Ue, Uv, Ur/Ue(R5), Ur/Uf(R7) NS vs. DS			
DermaLab elasticity measurement (Anthonissen et al., 2013; Gankande et al., 2014; Ho et al., 2000)	DermaLab elasticity modulus/Young's modulus (E/MPa)	NS: 0.45-0.90 SHS: 0.93 GS: 0.93 US: 0.76-0.91	NS: 0.86-0.95 SHS: 0.93 GS: 0.93 US: 0.86-0.96		Observable differences in E NS vs. US Statistical difference in E NS vs. SHS** NS vs. GS** No statistical difference in E SHS vs. GS	No significant correlation between E and time after burn	Y	Y
BTC-2000 (Gabriel & Kowalske, 2015)	Modulus (MPa) Elasticity (mm) Laxity (%)				Statistical difference in modulus	No significant difference in modulus	Y	Y

					and elasticity change between sheet and meshed split thickness autografts*	before and after treatment session		

VSS: Vancouver Scar Scale, PL-VSS: pliability item of Vancouver Scar Scale, mVSS: modified Vancouver Scar Scale

NS: normal skin; HS: hypertrophic scar; KS: keloid scar; AS: atrophic scar; DS: donor site scar; UN: unspecific scar; GS: grafted scar; SHS: spontaneously healed scar

NOTE1: The parameters of the Cutometer evolved over time; not all parameters were used in every study, but all parameters are listed here.

NOTE2: The original equipment from the company may not be available, but similar equipment is still commercially available from other companies.

*: $p<0.05$; **: $p<0.01$

Table 2-7 Summary of acoustic method

Basic Information		Clinimetrics					Feasibility	
Equipment/Method	Outcome Measured (Unit)	Intrarater Reliability	Interrater Reliability	Correlation with Clinical Score	Measuring Change Cross-Sectional	Measuring Change Longitudinal	Portability	Commercial Availability
Spectral domain optical coherence tomography + vibration analysis (Shah et al., 2018)	Tensile modulus (MPa)				Different value obtained from NS and US		N	N/A
Reviscometer (Quatresooz, Hermanns, Paquet, & Pierard, 2006; Verhaegen, Res, van Engelen, Middelkoop, & van Zuijlen, 2010)	Resonance running time measurement (RRTM/unit) Amplitude Ratio	>0.83 No data showed	NS RRTM: 0.74-0.85 Amplitude: 0.66-0.84 Ratio: 0.67-0.86 US RRTM: 0.94 Amplitude: 0.90 Ratio: 0.74		Statistical difference in mean RRTM NS vs. AS** NS vs. HS** NS vs. US** Statistical difference in mean amplitude NS vs. US**		Y	Y
Shear velocity device (McHugh et al., 1997)	Shear wave propagation velocity (m/s)				Statistical difference in velocity NS vs. HS** HS vs. SHS** NS vs. SHS*	Descriptive data were provided on one patient	Y	N

VSS: Vancouver Scar Scale, PL-VSS: pliability item of Vancouver Scar Scale, mVSS: modified Vancouver Scar Scale
NS: normal skin; HS: hypertrophic scar; KS: keloid scar; AS: atrophic scar; DS: donor site scar; UN: unspecific scar; GS: grafted scar; SHS: spontaneously healed scar
*: $p<0.05$; **: $p<0.01$

2.3.2 In-Plane Deformation Method

Under the in-plane deformation category, deformation occurred in-plane with the scar surface whether induced by stretching or torsion. This category included various forms of extensometers (Bartell et al., 1988; Chu & Brody, 1975; Clark et al., 1987; Clark et al., 1996), the Dermal Torque Meter(Boyce et al., 2000), the Adheremeter (Ferriero et al., 2010), and computational methods such as finite-element modeling (Tsap et al., 1998; Zhang et al., 2004) and matrix identification of static deformation (Vránová et al., 2009).**Table 2-4** lists the details of their clinimetric data. Little information was available regarding the reliability of this group of tools except for the Adheremeter. The only commercially available tool is the Dermal Torque Meter, although the Adheremeter can be reproduced easily with simple materials.

The earliest in vivo investigations of burn scarring adopted various forms of extensometers to investigate the tensile properties of HS (Bartell et al., 1988; Chu & Brody, 1975; Clark et al., 1987; Clark et al., 1996). The configuration of the extensometer generally involved two tabs adhered to the assessment area, which was stretched at a constant rate, and the force and displacement would be documented to derive stress and strain curves (Chu & Brody, 1975; Clark et al., 1987; Clark et al., 1996; Hendriks, 2001). For a quasi-extensometer, the modulus for stiffness and strain reflects the extensibility and was calculated based on diagram. These early extensometers were neither portable nor handy, which limited their use in the clinical setting (Chu & Brody, 1975; Clark et al., 1987; Clark et al., 1996). A handheld extensometer was later developed to assess normal skin and HS

after burn injury. Instead of stretching at a constant speed, the configuration adopted constant tension in stretching the skin, and the excursion distance was documented. The final outcome was expressed as the percentage of stretch, and a statistically significant difference ($P<0.001$) was identified between skin and HS tissue (Bartell et al., 1988). This handheld extensometer was much more straightforward, but it was unable to control the loading perpendicular to the scar surface.

Computational methods were also adopted to estimate the mechanical properties of scar. One group of researchers used finite-element modeling, a computational approach, to analyze the elasticity of scar relative to that of skin (Tsap et al., 1998; Zhang et al., 2004). In this method, images of the scar and the adjacent skin were captured before and after deformation. This could be done with or without the use of an artificial marker. The displacement of the scar and the adjacent skin were analyzed on the basis of these images to quantify the scar's elasticity in relation to that of normal skin. This method calculated the relative elasticity of the scar assessed, so the tension imposed upon the scar was considered irrelevant (Tsap et al., 1998; Zhang et al., 2004). Matrix identification of static deformation is another interesting method of analyzing the mechanical properties of scar in which both symmetrical (uniaxial) and asymmetrical loading are imposed. To implement this assessment method, a test matrix of 144 markers is drawn on the assessment area, and the displacements of the markers under loading are captured on video and calculated for analysis (Vránová et al., 2009). These methods could serve to analyze scarring over an area rather than at a point, but they require a specific setup to

capture the images and professional programming and computational methods to analyze them, so their implementation in clinical research is scarcely feasible.

With the Dermal Torque Meter, an intermediary disk applies a constant rotation or torque (10 mNm) to the skin for a fixed interval (10 seconds). Ten outcome parameters (six direct measures and four ratios)are automatically derived from a time-deformation diagram (Boyce et al., 2000), and the torsion test is considered to be advantageous because the anisotropic characteristics of scar are minimized(Hendriks, 2001). The Dermal Torque Meter was used to measure the mechanical properties of scar and successfully identified the differences between normal skin and grafted scar groups in multiple parameters (Table 2-4) (Boyce et al., 2000). An assessment of normal skin pliability was established using the Dermal Torque Meter, but no correlation was found with Cutometer data (Murray & Wickett, 1997).

Another form of uniaxial testing is performed with the Adheremeter, which measures the restriction of scar mobility when the scar was manually stretched. During measurement, the worst adherent point of the scar will be selected and stretched in four orthogonal directions. Two outcome measures are derived, the adherence's surface mobility index (SM) and the adherence severity index (AS) (i.e., the ratio of the scar's SM to the SM of its contralateral normal skin). Reports in which the Adheremeter was used to measure a surgical scar and the contralateral normal skin suggested excellent intrarater reliability in measurement of normal skin and excellent interrater reliability in measurement of normal skin and scar (Table 2-4). Both outcome parameters showed strong correlations with the VSS total score

and the VSS pliability score at moderate levels at the initial examination, but neither outcome parameter displayed any correlation with the VSS pliability score after treatment (Ferriero et al., 2010).

2.3.3 Indentometry

Indentation is performed when a rigid indenter (such as a plane-ended cylinder, a cone-shaped tip, or a sphere) applies a known force or deformation to the skin (Hendriks, 2001). This category includes various forms of tonometers (Corica et al., 2006; Esposito et al., 1990; Katz et al., 1985; Lye et al., 2006), and durometers (Magliaro & Romanelli, 2003; Seyger, van den Hoogen, de Boo, & de Jong, 1997) and variants such as the skin compliance device (Cleary et al., 2007), the Vesmeter (Niyaz et al., 2012), and the SkinFibroMeter (Seo et al., 2017). In addition to handheld devices, two types of computational method have been proposed using the indentation method, including local dynamic deformation response (Vránová et al., 2009) and optical palpation (Es'haghian et al., 2015). Another device, the ballistometer, was also included in this section even though its measuring principle is not typical indentometry (Ho et al., 2000). The basic information and clinimetric data of these devices and methods are summarized in **Table 2-5**. Of these devices and methods, the modified tissue tonometer and the skin compliance device have been evaluated with a relatively thorough method with relevant clinimetric data, but unfortunately, only the skin compliance device is commercially available.

Tonometry was initially used to measure surface tension or surface pressure. The first reported use of a tonometer in scar assessment was a cicatrometer, which

measured surface tension or stiffness as the resistance to deformation, and only arbitrary readings were obtained (Katz et al., 1985). A modified Schiøtz tonometer later advanced this method by measuring the power required to produce a given deformation (Esposito et al., 1990). Another modified tissue tonometer measured the depression or deformation of scar tissue under a given loading and was examined extensively in clinimetrics. When implemented with the existing protocol, high intra-rater reliability and inter-rater reliability could be attained in assessment of both normal skin and HS (Corica, Wigger, Edgar, Wood, & Carroll, 2006; Lye, Edgar, Wood, & Carroll, 2006), and tissue deformation of scar showed a statistically significant difference from that of normal skin. A strong negative correlation was also found with the VSS pliability score (r range,-0.442 to -0.457) (Corica et al., 2006; Lye et al., 2006). However, its implementation was reported to be difficult because the tissue tonometer had to be placed exactly vertical over the testing area despite the standardized assessment protocol. Discomfort was also experienced by some patients because the tonometer applied a constant force with a 200g weight, exerting a pressure of 29.6 kg/cm^2 at the end of the 1mmdiameter plunger, although the authors claimed that no damage would be caused to the scar tissue (Lye et al., 2006).

The ballistometer is a unique scar assessment tool that uses the indentation principle but has more features. The ballistometer has a rigid low-mass arm that can be elevated and released to the assessment site with a preset impact energy. The arm bounces repeatedly on the test surface, and the number and amplitude of bounces are recorded to reflect the mechanical properties of the tissue. Various parameters

could be retrieved, including the depth of the first indentation, which reflects the softness of the testing sample, and the exponential decay constant for rebound peaks (a) and coefficient of restitution (CoR), which reflects the elasticity of the testing samples. Differences were observed between skin and scar under different conditions; however, no statistical testing was performed (Ho et al., 2000).

The durometer, an engineering device used to test material hardness, has also been explored in scar pliability testing (Magliaro & Romanelli, 2003). It consists of a spring-loaded probe connected to a dial gauge. A direct linear relationship ($r = 0.769$) was observed between the durometer and the skin severity score ($p < 0.01$), and a statistical difference was also found in the readings before and after treatment. The durometer was also able to differentiate less severe scars (VSS score, 1 to 6) from more severe ones (VSS score, 7 to 14). The authors categorized the device as easy to use. Another report claimed that it showed good correlation with the VSS total score, but no data were given (Oliveira et al., 2005).

The skin compliance device, previously known as the Derma Durameter, measures the skin's resistance by deflection of the probe. The pliability score is then reported in grams per millimeter squared. The use of this device to measure scar was evaluated in one study, and high intra-rater reliability was reported. However, the inter-rater reliability was only reported as poor to fair for skin and poor to excellent for scar. The inconsistency of the inter-rater reliability renders this device unsatisfactory for clinical use, even though it can differentiate normal skin and scar (Cleary et al., 2007).

The SkinFibroMeter also measures skin resistance. The device comprises a 1.25mm long indenter, a reference plate, and build-in force sensors. When the reference plate contacts the skin, the skin's resistance to the indenter is recorded as the induration value in newtons. The induration value has demonstrated a strong correlation with the VSS pliability score (r=0.628), and a statistically significant difference was found between normal skin and scars (Seo et al., 2017).

The vesmeter is another form of durometer developed to assess the mechanical properties of plastics. Its two components include a personal digital assistant and a noninvasive portable sensing probe. This device can measure six physical parameters of skin: elasticity, viscosity, viscoelastic ratio, penetration depth, relaxation time, and hardness. The changes of overall hardness, viscosity, penetration depth, relaxation time and the elasticity were observed in several patients. No statistical method was applied (Niyaz et al., 2012).

The local dynamic deformation response incorporates the dynamic process of indentation into the model and calculation. The response of the tissue to indentation is divided into a fast component, which predominantly reflects the tissue's elasticity and inertia, and a slow component, which reflects the tissue's viscosity. Various parameters are measured and calculated on the basis of the two-phase model. The steady deformation value (L), the damping time constant (k) of a dynamic response, and the frequency (f) of damped oscillations are obtained for the fast component, and the steady deformation value (P) and the damping time constant (q) are obtained for the slow component. The derivative parameters total deformation response P+L and the P/L ratio can be calculated. However, when comparing scar

to skin or comparing scar before and after treatment, only the deformation-related parameters showed statistically different readings (Vránová et al., 2009).

Optical palpation, as a variant of optical coherence elastography, involves the use of optical cohesion tomography (OCT) and a translucent, compliant stress sensor and an adapted probe that serves as a compressive loading element. After loading, the strain of the compliant stress sensor is estimated via OCT. With the stress-strain behavior of the sensor material that is previously obtained, the surface stress at each lateral surface is plotted to represent the stress on the sample surface. An en face map of the stress measured at the sample surface and the spatial variation of a sample's mechanical properties is thus achieved. This method could be used to generate distinctive images between mature scars of various causes and the adjacent normal skin (Es'haghian et al., 2015).

2.3.4 Suction Method

Suction extends scars by using a vacuum to exert negative pressure upon the scar through a circular aperture (Hendriks, 2001; Lee, Dretzke, Grover, Logan, & Moiemen, 2016). Four devices were available under this category for measurement of burn scar: the Cutometer (Busche et al., 2018; Draaijers et al., 2004; Fong et al., 1997; Nedelec et al., 2014; Nedelec et al., 2008a; Nedelec et al., 2008b; Rennekampff et al., 2006), the BTC-2000 (Gabriel & Kowalske, 2015), the DermaLab elasticity measurement (Anthonissen et al., 2013; Gankande et al., 2014; Ho et al., 2000), and the pneumatonometer (Oliveira et al., 2005; Spann et al., 1996); their clinimetric data are summarized in **Table 2-6**. All devices in this group are

portable and commercially available. With the exception of the pneumatonometer, which measures the pressure required to elevate the cutaneous tissue for a certain distance, these devices measure the displacement of the cutaneous tissue under a certain pressure. The Cutometer has been extensively studied from a clinimetric perspective.

The pneumatonometer, which was initially used to test intraocular pressure, is a member of the tonometer family. It comprises a sensor, a membrane, and an air-flow system. Specifically, it measures the pressure (mmHg) required to displace a $7mm^2$ area and depth of 76 μm (Spann et al., 1996). The application of a pneumatonometer to measure cutaneous compliance in terms of surface pressure has yielded statistically significant differences in burn scars relative to normal control skin, but no reliability data are available (Oliveira et al., 2005; Spann et al., 1996).

The Cutometer has a rather long history in scar measurement (Fong et al., 1997) and is one of the most well-researched pieces of equipment evaluated herein. The Cutometer was first used in 1997 for documentation of HS pliability testing. With the Cutometer, a measuring tube with a circular aperture is gently applied to the cutaneous tissue and creates a partial vacuum for a certain time, causing elevation of cutaneous tissue, and the deformation of the cutaneous tissue is usually measured by an optical or ultrasound system (Fong et al., 1997; Hendriks, 2001). The setting configuration could be varied, but the most popular is a 6mmdiameter aperture and 500mbar suction pressure (450 mbar in more recent papers) for 2 seconds and a 2 second normal pressure release phase (Busche et al., 2018; Nedelec et al., 2014;

Nedelec et al., 2008a; Nedelec et al., 2008b). A wide selection of outcomes is generated by the device, which is summarized in **Table 2-6,**and their evolution was discussed in detail previously (Lee et al., 2016).

Of the parameters given, it is widely agreed that R0 or Uf, which refers to the maximum deformation, is sufficient for use (Draaijers et al., 2004; Lee et al., 2016). The reported intra-rater reliability is excellent for normal skin and donor site scar, and the intra-rater reliability for HS ranges from poor to good but does not reach excellent (Nedelec et al., 2008b). Excellent inter-rater reliability was reported for assessment of normal skin and donor site scar (Nedelec et al., 2008a). Another study on scar with unspecific morphology reported good to excellent inter-rater reliability (Draaijers et al., 2004);however, the inter-rater reliability for HS was only fair to excellent (Fong et al., 1997; Nedelec et al., 2008a). R0 was able to differentiate skin from scar and to differentiate among various scar subgroups (Busche et al., 2018; Nedelec et al., 2008b; Rennekampff et al., 2006). For assessment of scar with unspecific morphology, R0 has shown a strong correlation with the customized pliability score (Draaijers et al., 2004). However, for assessment of donor site scar, the correlation with the VSS pliability score was insignificant, but the correlation with the mVSS pliability score remained strong (Nedelec et al., 2008a; Rennekampff et al., 2006). For the assessment of HS, only less-severe scars demonstrated correlation with the mVSS pliability score (Nedelec et al., 2008a). From a longitudinal perspective, no correlation was found between the R0 of donor site scar and the healing time, but another study recently showed that the Cutometer could identify changes among HS after burn injury, donor site

scarring, and normal skin over 12 months when performed on a trimonthly basis (Nedelec et al., 2014; Rennekampff et al., 2006). In addition, it was also reported that caution was needed to explain the Cutometer data because its measurement of HS is subject to a ceiling effect (Nedelec et al., 2008b).

The measurement principle of the DermaLab elasticity measurement is quite similar to that of the Cutometer: a vacuum pump delivers vertical suction force through a 10mm aperture to the enclosed area. Unlike the Cutometer, the suction chamber is not handheld but is attached to the cutaneous tissue with adhesive tape. Two sensors are located inside the device, 1 and 2.5 mm above the skin, to detect the elevation of the skin/scar, and the pressure difference between the lower sensor and the upper sensor is used to calculate Young's modulus (Anthonissen et al., 2013). Previous studies indicated excellent intra-rater and inter-rater reliability in measuring scars with various morphologies; however, technical difficulties were reported with thick scars (Anthonissen et al., 2013; Gankande et al., 2014). The Young's modulus measured could reveal a significant difference between normal skin and spontaneously healed scar and between normal skin and grafted scar. However, no difference could be detected between spontaneously healed scar and grafted scar (Anthonissen et al., 2013). In addition, no significant correlation was found between Young's modulus of the scar and the time after healing (Anthonissen et al., 2013).

The BTC-2000 (SRLI Technologies Ltd.) was recently used to measure changes in the elastic properties of burn scar after various methods of grafting and therapists' treatment. It was reported that negative pressure was applied to the selected area

through a 10mmdiameter aperture at 10 mm Hg/s. The maximum pressure applied was 150 mm Hg (200mbar), and the pressure was released over three seconds once the negative pressure reached its peak, so one whole measurement took 18 seconds in total. A single-use, double-sided adherent ring was used to attach the probe to the skin or scar. Three parameters are available: modulus, laxity, and elasticity. Modulus refers to the slope of the linear stress-strain curve; laxity refers to the percentage of the change in deformation at low pressure; and elasticity refers to the amount of elastic deformation upon the release of the negative pressure. A statistically significant difference was found in the change of modulus and elasticity between two different autografts ($p = 0.0233$). Unfortunately, no relevant data on reliability or other forms of validity are available (Gabriel & Kowalske, 2015).

2.3.5 Acoustic Method

The equipment and method categorized here all involve the use of sound waves. The propagation velocity of the sound wave varies according to the resistance of the propagation medium, thus the shear velocity device (McHugh et al., 1997) and the Reviscometer (Quatresooz et al., 2006; Verhaegen et al., 2010) were developed on the basis of this principle to reflect the internal mechanical tension of the tissue assessed. Sound waves are also considered a form of energy, thus another group of researchers used sound waves to induce deformation and used OCT with vibration analysis to calculate the elasticity modulus (Shah et al., 2018). **Table 2-7**summarizestheir basic information, clinimetric data, and feasibility. All equipment and methods were able to differentiate skin and scar, but no correlation

with a clinical score has been reported. The Reviscometer is the most intensively studied and the only one commercially available.

The shear velocity device measures the velocity of an acoustic shear wave passing through soft tissue; the harder the material, the faster the transmission. When the probe of the shear velocity device is pressed against the skin, a shear wave of 5 to 8 kHz is emitted through the transmitter, propagates through the skin/scar for 1.5mm, and is received by the receiver. The authors of the study mentioned unpublished data regarding a high correlation of the shear wave propagation velocity with the Shore A durometer (r^2=0.83). Unfortunately, the clinimetric data were limited, and the equipment is not commercially available (McHugh et al., 1997).

The Reviscometer adopts the same mechanical principle as the shear velocity device but uses resonance running time measurement (RRTM) as the outcome. The probe contains a sensor to emit a 1.77 μJ acoustic shock wave and another recipient sensor 2 mm away. One of this probe's special features is its ability to perform multidirectional measurements with an interval of at least 10 degrees; thus, the assessment was made in multiple directions (from four directions to a maximum of 36) of the selected scar area, and the average RRTM was recorded. Later, the mean amplitude and the mean ratio were also used as outcomes. Excellent intra-rater reliability was reported, but no data were shown. Good to excellent reliability was found for inter-rater reliability for the mean RRTM, mean amplitude, and mean ratio for normal skin measurements; excellent reliability was found for the mean

RRTM and mean amplitude; and good reliability was found for the mean ratio for scar measurement (Quatresooz et al., 2006; Verhaegen et al., 2010).

OCT with vibration analysis has been used to evaluate the elastic modulus of a depigmented burn scar smaller than a dime. The authors of this study induced resonance of HS by applying vibration and estimated the vibration modulus using the resonant frequency obtained. The vibration modulus was then transformed into the tensile modulus via an experimentally obtained formula. Vibration was applied to the targeted tissue with an acoustic method (i.e., sinusoidal waveforms at varying amplitude and frequency generated by a loudspeaker). The peak displacement at which resonance occurred was detected via spectral-domain OCT. This method is theoretically sound and has great potential for use in a clinical setting (Shah et al., 2018).

2.4 Discussion

This review identified various devices and innovative methods for assessment of pliability, although some have already faded from clinical practice and research, such as various forms of extensometers and tonometers. Some are commercially available, such as the durometer, the Cutometer, and the Reviscometer. Others, such as optical palpation and OCT with vibration analysis, are not commercially available but demonstrate great potential for accurate measurement of the pliability of HS. There is no doubt that the Cutometer is the most thoroughly examined device, although certain limitations have been reported in its assessment of HS. The Adheremeter, the skin compliance device, the DermaLab elasticity measurement,

and the Reviscometer are all accessible and have clinimetric evidence for consideration. However, it is important to stress that the dearth of data also indicates great possibilities for future development.

Moreover, we must consider the measurement principle to address the intrinsic mechanical properties of HS. Numerous studies have suggested the anisotropic nature (the direction-dependent property) of scar, and significant differences have been found from various angles of measurement (McHugh et al., 1997; Quatresooz et al., 2006; Verhaegen et al., 2010). From this perspective, two methods are proposed to eliminate the anisotropic effect. We suggest that deformation should be induced vertically using an indentation method or suction method, which are minimally affected by the anisotropic nature of the scar, or the values should be obtained from various directions to calculate the mean, which is usually performed with an acoustic method. Another property of HS that must be taken into serious consideration is its viscoelasticity (Chu & Brody, 1975), which relates to the temporal aspect of deformation. Some devices and methods, such as the Dermal Torque Meter and the Vesmeter, have already taken viscoelasticity into consideration as a parameter. This is very important for some devices that use the indentation method; because of the viscoelastic behavior of HS, the time for the reading should be very specific or the results may not be comparable (Corica et al., 2006; Lye et al., 2006).

Some challenges very specific to in vivo testing of HS mechanical properties also exist. For one thing, HS is subject to certain pretension of the surrounding skin (Akaishi et al., 2010). In addition, the texture and thickness vary even within a

single scar, which clearly hinders the fulfillment of several prerequisites for mechanical testing. Compared to the extension method, indentation reduces the effects of skin prestress (Hendriks, 2001). However, the underlying assumptions require that the tested material have a consistent thickness and texture and that the test support is a solid and stable surface. Therefore, in addition to the differences within each scar, differences among scars in area, thickness, and the underlying tissue all contribute to the inaccuracy of the measurement. Difficulties were encountered when performing indentation tests to measure scars over bony prominences (Lee et al., 2016). As reported by Pailler-Mattei, Bec, and Zahouani (2008), measurements of skin elasticity properties with the indentation test were successfully extracted from global mechanical responses, and a two-layer elastic model was established to improve the measurement accuracy. However, advancements in theoretical modeling have not been fully used in clinical practice and tool validation. It is currently more practical to compensate by 1) making multiple measurements over one area and obtaining the average; and 2) matching locations for comparison with normal skin.

Compared with indentation methods, suction methods are less affected by the hardness and thickness of the tissue under the scar, but they also demonstrate limitations in terms of measuring thick scar (Anthonissen et al., 2013; Diridollou et al., 2000; Gankande et al., 2014; Lee et al., 2016; Nedelec et al., 2008b). Two important parameters of suction methods affect the device's performance. First, the dimension of the aperture plays an important role in the accuracy and the capacity of the measurement. It has been noted that scar thickness can affect the accuracy of

the measurement by its ratio with the aperture radius (Diridollou et al., 2000). The diameter of the aperture should be appropriate to elevate the epidermis and dermis while excluding the underlying tissues (Zheng & Huang, 2016). Another important parameter that also affects the capacity of the instrument is the maximum pressure exerted. The devices in this category were initially developed for normal skin assessment, and the skin thickness was considered to be constant in their settings (Anthonissen et al., 2013; Gankande et al., 2014; Hendriks, 2001). However, scar is known to be progressive in nature; its thickness changes over time, first experiencing elevation and then regression at a later stage (Nedelec et al., 2008a; Nedelec, Correa, Rachelska, Armour, & LaSalle, 2008b; Oliveira et al., 2005). Therefore, the tool's ability to take scar thickness into consideration is of methodological importance.

In addition, the administration procedure may introduce extra variability by exerting device prestress, thus compromising the accuracy and reliability of the measurement. This type of extrinsic error is not specific to a particular category; various handheld instruments are reported to be prone to this problem (Bartell et al., 1988; Hendriks, 2001). Therefore, it is preferable that the device be attached to the cutaneous tissue by adhesives during suction, such as with the DermaLab elasticity measurement, or that the force be controlled rather than manually applied with the indentation method, such as with the modified tissue tonometer. The growing trend is to measure pliability with minimal contact, such as with OCT with vibration analysis, in which the displacement is measured by an optical beam away from the cutaneous tissue.

Another issue related to the administration procedure is the representativeness of the measurement. It is important to know whether the tool measures a spot or a specific area. For most of the methods discussed in this review, the results obtained represent only the spot or specific area measured, which is covered by the probe(s) or indenter, due to the irregular thickness and varying locations of HS tissue. Because of this intrascar variability, deviations from each measurement reduce its reliability (Nedelec et al., 2008b). Some computational methods, such as finite-element modeling, matrix identification, and OCT plus vibration analysis, display great potential to measure the average elasticity of the scar tissue over a larger area. For manually implemented devices, it is suggested that scar locations be marked as a reference for repetition to help achieve consistency (Masters, McMahon & Svens, 2005). For indentation methods, several spots could be selected from each scar area to improve the representativeness of the measurement.

In addition to the potential to acquire the scar tissue's average elasticity, this review also revealed some computational methods that excel in accuracy and specificity. For example, both OCT methods visualized or identified that the mechanical properties of even mature scar, as reflected by photos more than 2 years after injury, could still differ greatly from those of normal skin. However, due to the complexity of the setup and the analysis, computational methods may not yet be ready for commercial availability and clinical use. However, it is believed that the development of biomedical technology will bring about more advanced techniques for clinical assessment of scar pliability.

Finally, computational methods also raise the issue of practicality, as most require equipment and specific setups that are far from portable. In addition, we would like to consider the some practical issues that might affect the measurement and the patients' compliance. For example, how many measurements should be taken to obtain a valid and reliable result? How long does it take to acquire the result of one measurement? How much training is required to implement the device or method? For example, assessment with the indentation or suction method could be finished within seconds, but the acoustic method requires more assessment time because multiple measurements are performed.

2.5 Conclusions

Objective tools for the assessment of scar pliability enable quantitative evaluation of scars, which is essential for scientific studies and for monitoring a patient's progress. The objective measurement of scar pliability has always been an effort of approximation using various biomechanical concepts. From a biomechanical perspective, the property evaluated by the suction method is more closely related to the concept of pliability and is more likely to fully address the intrinsic mechanical properties of the HS. The importance of the aperture diameter and the vacuum pressure of the suction device in accurate measurement are stressed. We also suggest several aspects that must be considered when choosing the appropriate device or method to assess HS pliability. Nevertheless, the review proves that more clinical studies and advances are warranted in the development of tools to assess scar pliability.

Chapter Three

Validation of the Elasticity Measurement of DermaLab Combo in Assessing Post-burn Hypertrophic Scar Pliability

Chapter Summary

Context: As discussed in the previous chapter, the newly upgraded elasticity measurement of the DermaLab Combo has great potential as a valid tool to assess the pliability of hypertrophic scar (HS); however, no validity was reported.

Objective: This study aimed to investigate the validity of the newly upgraded elasticity probe of the DermaLab Combo on burn patients with HS.

Methods: For the first part of the study, the pliability of 47 HS sites was assessed using both a modified tissue tonometer (MTT) and the elasticity measurement of the DermaLab Combo. For the second part of the study, another 75 HS sites were assessed using the modified Vancouver Scar Scale (mVSS) and the elasticity measurement of the DermaLab Combo. Correlations between these assessment results were examined to establish the concurrent validity and clinical relevancy. The scar thickness was measured objectively in both parts of the study. The relationship between the pliability and thickness of HS was explored using data collected in both parts.

Results: Significant correlations were identified between the scar pliability measured with the elasticity measurement of the DermaLab Combo and that measured with the hardness reading of the MTT (Pearson's $r=.355$, $p<.01$). Moderate agreement was also identified between scar pliability and the mVSS pliability score (Spearman's $rho=.426$, $p<.01$). A significant correlation was found between the measured HS pliability and the HS thickness (Pearson's $r=.296$, $p<.01$).

Conclusions: Its enhanced function allows the upgraded elasticity measurement of the DermaLab Combo to assess HS pliability in a valid manner, thus rendering it an appropriate tool for clinical assessment and study.

3.1 Introduction

In the systematic review in the previous chapter, we identified several objective methods to measure the pliability of HS. From a basic biomechanical approach, the suction method has great theoretical validity and practicality. It is less likely than other methods to be affected by the texture and thickness of the underlying tissue (Anthonissen et al., 2013; Diridollou et al., 2000; Gankande et al., 2014; Lee et al., 2016). By applying perpendicular force, the outcome obtained with the suction method is not affected by the anisotropic nature of scar tissue (Diridollou et al., 2000; Gankande et al., 2014). We also identified at least two key parameters—the suction pressure and the diameter of the aperture—in determining the validity and capacity of the suction device (Anthonissen et al., 2013; Diridollou et al., 2000; Zheng & Huang, 2016). However, administrative procedures can also affect the validity of a measurement device. It is preferable to use a lightweight probe secured by adhesive to avoid additional prestress incurred by the handheld probe. **Table 3-1** compares the existing suction devices on the basis of these criteria (Anthonissen et al., 2013; Busche et al., 2018; Cortex Technology, 2015; Draaijers et al., 2004; Fong et al., 1997; Gabriel & Kowalske, 2015; Gankande et al., 2014; Ho et al., 2000; Nedelec et al., 2014; Nedelec et al., 2008a; Nedelec et al., 2008b; Rennekampff et al., 2006).

Table 3-1 Comparison of suction devices based on key parameters attributed to validity and capacity

Device	Suction Pressure	Aperture Diameter	Probe Administration Method
Cutometer	500 mbar	2mm	Handheld
	450 mbar*	4mm	
		6mm***	
		8mm	
DermaLab elasticity measurement (updated version)	650 mbar **	10 mm	Adhesive tape
	300 mbar		
	150 mbar		
BTC-2000	200 mbar	10 mm	Adhesive tape

* Most recent model

** Setting used for HS measurement

*** Most common aperture diameter used for HS measurement

The elasticity measurement of the DermaLab Combo (Cortex Technology, Hadsund, Denmark) uses suction to measure the skin's elasticity. As shown in **Table 3-1**, the elasticity measurement of the current model of the DermaLab Combo has suction pressure up to 650 mbar, which makes it the most powerful suction device on the market. Its 10mm aperture is also more suitable for elevation of thick scar tissue. Unlike other suction devices, the probe of the elasticity measurement of the DermaLab Combo is lightweight and is secured to the cutaneous tissue by adhesive tape to significantly reduce its prestress. It is obvious that with the highest suction force, largest aperture diameter, and preferable probe attachment method using adhesive, the upgraded version of the DermaLab elasticity measurement demonstrates greatest potential as a valid tool for HS pliability measurement.

To establish the validity of the newly upgraded elasticity measurement of the DermaLab Combo, it is proposed that a dermatological method be adopted, in which the results with the DermaLab Combo are compared with those with a well-established device, because there is no gold standard of pliability assessment (Nedelec et al., 2008a; Woo et al., 2014). As identified in the last chapter, the MTT is a well-established device for pliability assessment. High intra-rater reliability (ICC, 0.91 to 0.94) and inter-rater reliability (ICC, 0.957) were reported in assessment of HS (Corica et al., 2006; Lye et al., 2006), and a moderate correlation with the VSS score was found (Corica et al., 2006; Lye et al., 2006). The disadvantage of MTT is its difficulty of use and the possibility of causing patient discomfort. Most importantly, it is no longer commercially available. Therefore,

the MTT is not recommended for use in a clinical setting, but it is suitable to serve as comparison equipment for concurrent validity.

Moreover, as suggested in the last chapter, another way to establish the validity of the elasticity measurement of the DermaLab Combo is to correlate its reading with a clinical score to establish clinical relevancy (Lee et al., 2016). The VSS and its modified versions are validated clinical rating scales for HS assessment that have been widely adopted to examine the clinical relevancy of the emerging objective scar assessment tools (Lee et al., 2016).

Finally, it was suggested in Chapter One that the thickness of the HS contributes to its stiffness. Therefore, it is hypothesized that a significant correlation should exist to some extent between HS pliability and HS thickness. Therefore, the primary aim of this study is to examine the concurrent validity of the elasticity measurement of the DermaLab Combo. Three approaches were adopted. First, the concurrent validity was established via correlations between the readings of the elasticity measurement of the DermaLab Combo and those of the MTT. The clinical relevancy of the readings of elasticity measurement of the DermaLab Combo was then investigated by correlating the readings with the VSS pliability score. Finally, the hypothetical correlation between the HS thickness and the HS pliability was examined.

3.2 Methods

3.2.1 Subjects

Patients with HS after burn injury were recruited using a convenience sampling method. The scar area was required to exceed 2.5*2.5 cm to allow adequate attachment area for the probe. Other inclusion criteria were age of at least 18 years, cooperation, and the ability to provide informed consent. Patients were excluded from the experiment if the HS area had an open wound or infection or if the HS had been treated with an invasive procedure such as laser therapy before assessment. Written consent was obtained from each subject before the experiment began. The study was approved by the ethics committee of the Hong Kong Polytechnic University.

3.2.2 Instruments

3.2.2.1 Elasticity measurement of DermaLab Combo

The elasticity measurement of the DermaLab Combo is based on the deformation and retraction of the assessment surface when a specific and preset vacuum is applied through the probe chamber. The elasticity measurement of the DermaLab Combo is performed by a closed suction chamber probe, a main-unit with a negative-pressure cylinder, and a touch screen panel. The administration of the assessment is the same as with previous models. Briefly, the probe is attached to the assessment surface with adhesive tape to ensure an air-tight assessment environment within the suction chamber (Cortex Technology, 2015). Young's modulus of elasticity (E) is calculated based on the distance that the skin/scar can be lifted, and the value of E is given in mega pascals. The basic formula for E calculation is illustrated as follows.

$$E = \Psi * \rho * r4/ \Delta\chi * s3 \quad (1)$$

where E = Young's modulus; S = thickness; ψ = constant; ρ = surface pressure; Γ = radius of surface; and Δ χ = elevation of skin. When the thickness is set constant,

$$E = C /\Delta\chi \quad (2)$$

where C is a constant, thus E is the direct function of the elevation of the skin/scar (DermaLab Series SkinLab Combo Instruction Manual).

One distinguishing feature of this new model is a function of selecting various settings in which various levels of negative pressure are exerted to the assessment surface. In this study, a hard mode with 650 mbar (0.65kPa) negative pressure was used for HS assessment. The cycle-mode of one cycle and a default setting of 1mm in thickness were selected for the assessment setting. A larger E indicates a smaller deformation and thus a less-pliable scar.

3.2.2.2 Modified tissue tonometer

In this study, we used an MTT (Flinders Tissue Tonometer BME 1428 Burns Model; Flinders University Biomedical Engineering Department, Adelaide, South Australia) that has well-established reliability and validity for use in scar assessment, as mentioned in the Introduction. In addition, an assessment protocol is available to ensure reliability. Briefly, the plunger of the MTT is placed perpendicular to the scar surface for 6 seconds, and the scar pliability is measured by depression of the plunger into the scar reflected on an analog dial with a

sensitivity of 0.01unit (Corica et al., 2006).In this thesis, the MTT reading is denoted as T. A larger value of T indicates a more-pliable scar.

3.2.2.3 Modified Vancouver Scar Scale

The modified VSS encompasses four important characteristics to describe HS: height, pliability, pigmentation, and vascularity (Nedelec et al., 2000). The scar pliability is assessed by palpating the scar tissue, and the scar pliability is rated from 0 to 4 on a nominal scale according to various descriptions. A higher rating indicates a less-pliable scar.

3.2.2.4 Ultrasound

A diagnostic ultrasound system (Mindray M5, Mindray, China) was used to measure HS thickness. The use of ultrasound to assess scar thickness was validated previously (Li, Li-Tsang, Huang, Chen, & Zheng, 2013).

3.2.3 Study Procedures

3.2.3.1 Development of 9-Point Marking System

The site selected for assessment was marked with a 9-point marking system as illustrated in **Figure 3-1.** All assessments performed in this study adopted this marking system to ensure that every measurement would be made in exactly the same place and that all HSs would be assessed in a systematic manner. The selected sites were marked with a paper ring (inner diameter, 1 cm; outer diameter, 2.5 cm). The paper ring displays the exact same shape and size of the elasticity probe of the

DermaLab Combo. When conducting elasticity measurement with the DermaLab Combo, the selected site was measured by placing the elasticity probe exactly according to the nine markers.

The 9-point marking system also serves as a reference point for measurements conducted with MTT or ultrasound. HS sites were assessed by MTT at three points of the 9-point marking system as illustrated in **Figure 3-1**: two points on opposite sides of the circumference of inner ring and one on the center of the inner ring. Each MTT measurement was conducted carefully without exerting additional pressure on the scar surface. The average score obtained from three MTT measurements was used to reflect the hardness of the selected site.

When the selected site was measured using the diagnostic ultrasound system, the center of the probe of the ultrasound machine was placed on the center of the 9-point marking system. The thickness of selected site was calculated on the basis of the average thickness of three points: one on the center of the screen, which reflected the center of the inner ring; and 5 mm on both sides of the center point, which reflected the points of circumference of the selected sites, as illustrated in **Figure 3-1**.

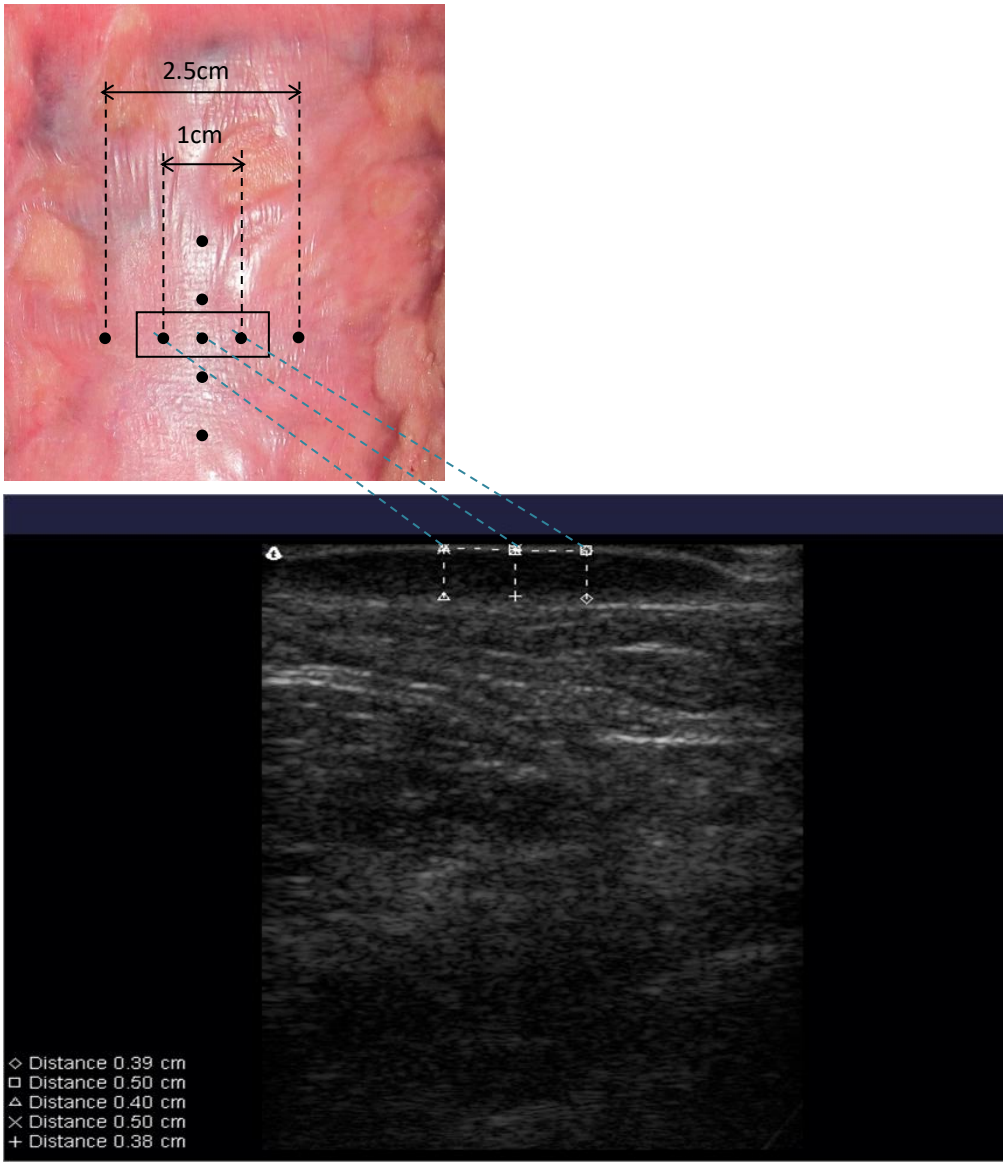


Figure 3-1 Schematic illustration of 9-point marking system

3.2.3.2 Assessment Procedure

After the subjects were recruited, basic information, including age, gender, date of injury, and total burn surface area (TBSA), was collected. The days after injury (DAI) were calculated accordingly. The validation process included three parts. In the first part, 47 HS sites were selected from 12 patients. The thickness of the marked HS sites was assessed with the elasticity measurement of the DermaLab Combo, the MTT, and ultrasound according to previously illustrated assessment protocol. In this part of the study, scar sites on bony prominences were excluded because previous studies suggested that MTT measurements were inaccurate over bony prominences (Corica et al., 2006; Lye et al., 2006).

The second part included 75 HS sites from 29 patients. In addition to the previously stated protocol, an independent assessor assessed the HS sites with the mVSS. The independent assessor was an experienced therapist specializing in burn management. For the last part of the study, the data from the first two parts were combined to explore the relationship between HS pliability and HS thickness.

3.2.4 Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics 23. The relationship between the MTT result and the E value from the elasticity measurements was analyzed using the Pearson correlation coefficient. The relationship between the total and pliability scores on the mVSS and the elasticity measurements was analyzed using Spearman's rho. Finally, the assessment results from the first two

parts of the study were combined to examine the relationships between HS pliability and HS thickness using the Pearson correlation coefficient.

3.3 Results

3.3.1 Demographic characteristics

The demographic characteristics of the subjects in this study are summarized in **Table 3-2**. For the first part, 10 of the 12 subjects were male, the mean age was 35.6 years (SD, 10.0 years), and the average TBSA was 60.6% (SD, 23.7%). The mean DAI on the date of assessment was 279.2 days (SD, 127.7 days). For the second part, 7 subjects were female and 22 were male, the mean age was 36.8 years (SD, 9.9 years), and the average TBSA was 39.8% (SD, 28.7%). The mean DAI on the date of assessment was 203.3 days (SD, 115.8 days). The 41 subjects were generally middle-aged men with a large TBSA and were assessed around 7.5 months after burn injury. The range of DAI covers very early scarring (34 days after injury) to mature scarring (499 days after injury).

3.3.2 Part I: Concurrent Validity with Modified Tissue Tonometer

The descriptive statistics and the correlation with the T score measured using the MTT are summarized in **Table 3-3**. A significant negative correlation was found between E and the MTT skin hardness score (Pearson's $r=-.361$; $p=.013$).

3.3.3 Part II: Clinical Relevance with Modified Vancouver Scar Scale

As for clinical relevance, a moderate positive correlation was shown between E and the VSS pliability score (Spearman's rho= .434; $p < .01$), as shown in **Table 3-4**.

A significant correlation was also found between E and the VSS total score (Spearman's rho = .292; p< 0.01). No correlation was found with other VSS parameters, although the correlation with the VSS height was borderline (p = .69).

3.3.4 Correlation with Hypertrophic Scar thickness

Although no statistically significant correlation was found with the VSS height score, a significant positive correlation was identified between E and the HS thickness (Pearson's r = -.296; p< .01), as shown in **Table 3-5**. The table also shows that this study encompassed a wide range of HS. The thickest scar measured in this study was 10.8mm, which served as a reference for the capacity of the elasticity measurement of the DermaLab Combo. In addition, it should also be noted that the largest E measured in this study, 34.6 MPa, did not come from the thickest scar.

Table 3-2 Demographic characteristics of subjects

	Part I (N = 12)	Part II (N = 29)	Part III (N = 41)
Age (y)	35.6 ±10.0	36.8 ±9.9	36.5±9.8
Gender (%)			
Female	16.7	24.1	23.0
Male	83.3	75.9	77.0
TBSA (%)	60. 6 ± 23.7	39.8 ± 28.7	46.4 ± 28.6
DAI (d)	279.2 ± 127.7	203.3 ± 115.8	229.4 ± 120.4

N: subject number

TBSA: total burn surface area

DAI: days after injury

Table 3-3 Concurrent validity with MTT

	Mean ± SD	Range (min, max)	Correlation	
			Pearson's r	p
E (MPa)	12.5 ± 4.1	(6.5, 26.1)	-.361	.013*
T	2.6 ± 0.6	(1.5, 4.2)		

E: Young's Modulus of elasticity

T: Hardness reading of MTT

* Correlation significant at the 0.05 level (2-tailed).

Table 3-4 Clinical relevance with VSS

	Mean ± SD	Range (min, max)	Correlation Spearman's rho	p
E (MPa)	14.4 ± 5.9	(7.1, 34.0)		
VSS -Height	3.1 ± 0.6	(1, 4)	.211	.069
VSS -Pigmentation	2.8 ± 0.6	(1, 4)	-.005	.969
VSS -Vascularity	2.3 ± 0.7	(1, 3)	.098	.402
VSS -Pliability	2.5 ± 0.7	(1, 4)	.434	.000**
VSS -Total	10.8 ± 1.7	(1, 13)	.292	.002**

E: Young's Modulus of elasticity
VSS: Vancouver Scar Scale
** Correlation significant at the 0.01 level (2-tailed).

Table 3-5 Correlation with scar thickness

	Mean ± SD	Range (min, max)	Correlation Pearson's r	p
E (MPa)	13.6 ± 5.3	(6.5, 34.6)	.296	.001**
Thickness (mm)	4.2 ± 1.9	(0.9, 10.8)		

E: Young's Modulus of elasticity

** Correlation significant at the 0.01 level (2-tailed).

3.4 Discussion

This study is the first in the field to attempt to establish the validity of the elasticity measurement of the DermaLab Combo. Based on the results described above, the elasticity measurement of the DermaLab Combo correlates well with the MTT and with the pliability and total scores of the mVSS, which makes it a valid tool for measurement of HS pliability. The elasticity measurement of the DermaLab Combo is further validated because it correlates well with the objective scar thickness measurement. Moreover the wide range of scar thicknesses and DAIs successfully measured reflects its superior capacity. Previous studies have demonstrated the excellent reliability of the elasticity measurement of the DermaLab Combo in scar measurement (Gankande et al., 2014), it has also been demonstrated that the elasticity measurement of the DermaLab Combo can differentiate normal skin and scar (Anthonissen et al., 2013). Our current data indicate that the elasticity measurement of the DermaLab Combo is a reliable and valid tool for measurement of HS pliability.

A significant change has occurred in terms of measurement principles. Previously, the elasticity measurement of the DermaLab Combo indicated the pressure difference when the skin was lifted from 1.5 mm to 2.5 mm. This is the chief factor attributed to the technical limitations in obtaining measurements of stiff scars in previous reports, because stiff scars may not be able to pass 2.5 mm or even reach 1.5 mm (Anthonissen et al., 2013; Gankande et al., 2014). The current measurement principle in which the elevation is measured by elevation of the scar alone could

improve the range of the elasticity measurements. Therefore, to reflect its advanced capacity, the largest measurements of thickness and Young's modulus were documented.

In addition, this study has demonstrated that even though thickness and pliability are related parameters, they describe different characteristics of a scar. A common misconception is that a thick scar is also stiff; however, as we proved in the previous section, the thickest scar may not be the most rigid, and vice versa. The thickness of a scar is only one factor of a scar's inability to deform. As stated in the first chapter, various factors contribute to the pliability or inelasticity of HS, including the water content, the presence of myofibroblasts, and the abnormal constitution of collagen fibers. Therefore, the complexity of the concept of pliability should be well appreciated.

The moderate correlation with mVSS is comparable to that of the Cutometer, as suggested by the systematic review. In research practice, a correlation of 0.4 or greater is considered acceptable agreement (Tyack et al., 2012).The performance is more consistent in HS measurement than previous studies, because the deformation measurement for the Cutometer failed to correlate with the mVSS pliability score in severe HS.

The systematic review of the objective pliability assessment also revealed that the Cutometer was comparable with and had greater methodological relevance than the elasticity probe of the DermaLab because both use suction extension methods. However, as described above, the Cutometer was unable to generate reliable

readings for HS, and the clinical relevance for severe HS was also poor, so the MTT was selected for comparison. The correlation with MTT is not as high as that with the mVSS pliability score, primarily due to differences in measurement principles. Both the elasticity measurement of the DermaLab Combo and the MTT measure deformation under a certain pressure; however, because the directions of deformation differ, the influences from the underlying tissue differ. The hardness of the underlying tissue contributes more to the MTT measurement than it does to the elasticity measurement of the DermLab Combo.

3.5 Conclusions

The discussion above shows that the elasticity measurement of the DermaLab Combo can generate valid readings for pliability measurement. With its solid theoretical background, improved capacity, and reliable measurement procedure, the elasticity measurement of the DermaLab Combo is suitable for use in clinical trials to provide an objective assessment of HS pliability.

3.6 Declaration

There is no conflict of interest.

Chapter Four

Development of Optimal Treatment to Improve Pliability

Chapter Summary

Context: Inserts are used in conjunction with pressure garments to improve the outcomes of hypertrophic scar (HS) treatment, either to increase the localized pressure or to provide occlusion. However, the types of insert materials currently available have many limitations that hinder their therapeutic effect. An innovative insert material, the Smart Scar Care Pad (SSCP), was invented to maximize treatment outcomes via enhanced compression and occlusion.

Aim: This study aims to investigate the properties of the SSCP and its efficacy to serve as a suitable insert material for scar management.

Methods: According to ISO10993 standards, the biological safety of the SSCP was examined in terms of its likelihood of generating any undesirable cytotoxic, irritating, or sensitizing effects. Second, we assessed its core physical properties, including its occlusive properties and conformability. Its ability to deliver pressure was also evaluated.

Results: The SSCP was equivalent or even superior to commercially available products in tests of biological safety and physical properties. Furthermore, the SSCP significantly increases the interface pressure between the scar tissue and the pressure garment.

Conclusions: The SSCP can serve as a safe and effective insert material to enhance the pressure interface and occlusion.

4.1 Introduction

Chapter One established that pressure therapy (PT) and silicone therapy have great potential in improving HS pliability. It is also believed that better clinical outcomes can be achieved with a combination of PT and silicone gel sheeting (SGS), especially in terms of scar pliability (Harte et al., 2009; Steinstraesser et al., 2011). With appropriate assessment strategies for HS pliability described in the previous chapter, we have more confidence in detecting changes in HS pliability that were only assessed subjectively in previous studies.

Inserts are used in conjunction with pressure garments to improve the outcomes of HS treatment, either to increase the localized pressure or to provide occlusion. These inserts are generally classified into two main categories. Gel-based inserts, such as SGS and non–silicone-based hydrogel sheets, are commonly used to occlude and provide hydration to scar tissues (O'Brien & Jones, 2013; Roseborough, Grevious, & Lee, 2004). Gel-based inserts are mainly used for small scars or surgical scars. They are generally costly and thin, so they cannot exert sufficient pressure. The other category is pressure inserts. In clinical practice, interface pressure is mainly delivered by a pressure garment; however, maintaining adequate pressure with a pressure garment alone is usually uncomfortable for the patient and is sometimes impossible, especially over flat or concave areas. Inserts are thus often applied in conjunction with pressure garments to increase the pressure on concave areas (Radomski & Latham, 2014).

Despite various choices of pressure inserts, the existing options are unsatisfactory from a clinical perspective. Silicone elastomers and thermoplastic polyethylene foam are widely recognized pressure insert materials (Chan & Association, 1998; Radomski & Latham, 2014; Van den Kerckhove et al., 2001). Silicone elastomers are often used to increase local pressure because their plasticity allowsthem to conform to various body contours. However, their concurrent rigidity also hinders body movement. Moreover, readjustment of the shape of the silicone elastomer is difficult because of the dynamic growth of the HS; thus, frequent replacement with new inserts to suit the purpose is necessary (Van den Kerckhove et al., 2001). In addition, like gel-based inserts, they are very expensive.

Thermoplastic polyethylene foam, or Plastazote, displays preferable properties and is thus widely used in clinical practice in some countries (Chan & Association, 1998; Lai et al., 2010). Its thermoplasticity allows it to conform to various body contours. However, its rigidity also hinders body movement. Because of its nonadhesive feature, it tends to create friction on the HS and can thus induce blisters, erosion, or even ulcers, especially during movement. Furthermore, Plastazote can shrink in thickness after long-term compression from a pressure garment, resulting in insufficient pressure and the need for frequent replacement during treatment (Van den Kerckhove et al., 2001). Some studies have documented the use of neoprene and spacer fabrics as pressure insert materials, but they have not been widely adopted in clinical practice because of limited clinical evidence (Yelvington, Brown, Castro, & Nick, 2013; Yu et al., 2016).

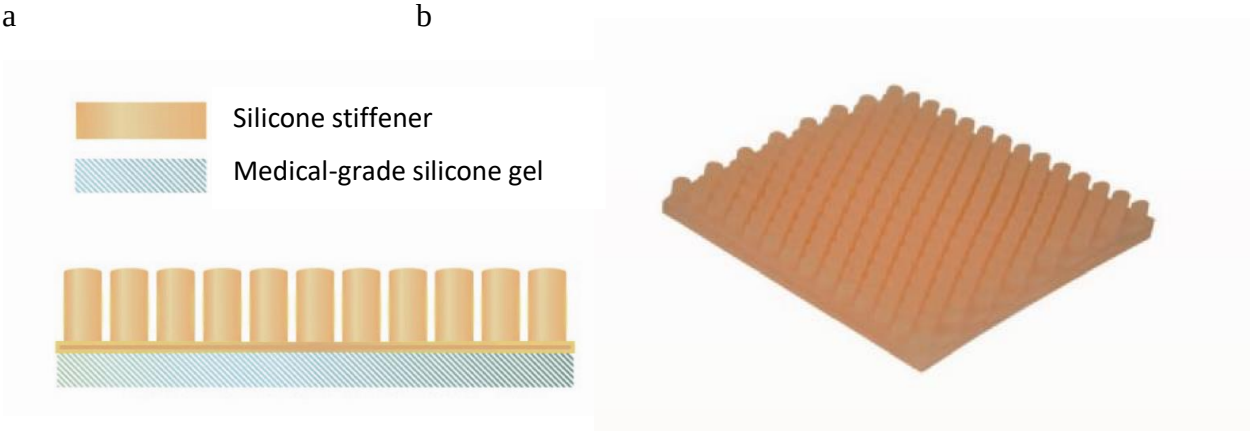
In clinical practice, therapists must make a trade-off between the pressure effect from Plastazote and the occlusive effect of SGS because patients have difficulty applying two layers of inserts under the pressure garment at the same time. In addition, when stacked together, the two separate layers of inserts become displaced from each other during movement, which can reduce the pressure effect. Thus, the limitations of the currently available inserts compromise HS treatment outcomes.

An ideal insert material should maintain sufficient rigidity and thickness to increase local pressure while retaining sufficient softness and elasticity to conform with various body contours and allow joint movement. The material should have the ability to be reshaped when the scar changes in size and contour during maturation. The material should adhere to the scar surface to provide an occlusive effect and have a certain level of extensibility to reduce friction during movement. The material should be friendly to the skin, comfortable, durable, and easy to clean, so that the patient can comply with the prolonged wearing regimen. The material should provide adequate pressure to control the growth of the HS while maintaining the occlusive property to soften the scar, thus achieving maximal clinical outcomes. Finally, the material should not impose any toxic, irritating, or sensitizing effects on the skin.

With these expectations, we recently developed a new insert material: the SSCP (China Patent No. ZL 201110327525.2, 2014).The SSCP is composed of a rubbery silicone stiffener layer and a medical-grade silicone gel layer (**Figure 4-1a**). The medical-grade silicone gel layer, which makes direct contact with the HS, serves as the occlusion layer. The rubbery silicone stiffener layer consists of a thin layer of

silicone rubber sheeting whose surface is covered with numerous studs 5 mm in diameter and with different heights (3 mm and 6 mm) aligned in a honeycomb pattern (**Figure 4-1b**). By selecting different stud heights and trimming the individual studs into gradient heights according to various body contours, one can create a tailor-made localized pressure environment and maximize conformability. Thus, the SSCP functions both to optimize local pressure and to provide occlusion to the HS tissue (**Figure 4-1c**).

a b



c

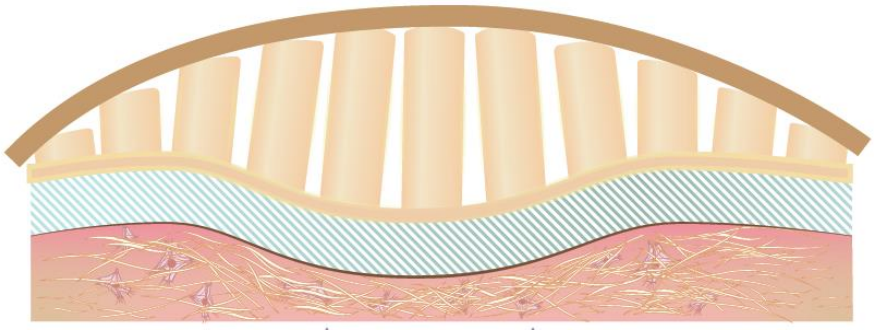


Figure 4-1Schematic illustration of SSCP

(a) SSCP is composed of a rubbery silicone stiffener layer and a medical-grade silicone gel layer. (b) The rubbery silicone stiffener layer is a thin layer of silicone rubber sheeting designed with numerous studs aligned in a honeycomb pattern. (c) In addition to occluding HS tissue, the SSCP creates a tailor-made localized pressure environment, especially over concave areas, by selection of different stud heights and by cutting the individual studs into gradient heights.

The aim of this study was to investigate the innovative SSCP as an appropriate insert material for the treatment of HS from safety and functional perspectives. First, we examined its biological safety according to ISO 10993 standards in terms of its likelihood of generating any undesirable cytotoxic, irritating, or sensitizing effects (International Organization for Standardization [ISO], 2009; ISO, 2010). Second, we assessed its core physical properties, including its occlusive properties and conformability, as well as its ability to deliver pressure.

4.2 Methods

4.2.1 Experimental Procedures Examining Biological Safety

4.2.1.1 Three-Dimensional Human Epidermis Culture Model

Human keratinocyte–derived EpiSkin (Lyon, France) was purchased. This model exhibits great resemblance to human skin, including all epidermal layers found in native human epidermis. The EpiSkin was cultured on a collagen matrix at the air-liquid interface to maintain a three-dimensional architecture. The EpiSkin was first equilibrated in maintenance medium at 37°C and 5% CO_2 24 hours before assay according to the manufacturer's instructions.

4.2.1.2 Samples

The SSCP was prepared using medical-grade silicone gel precursor purchased from Bluestar Silicones Germany (Lübeck, Germany) and silicone rubber purchased from Sharpwell Technology Ltd. (Shenzhen, China). The SSCP and a commercial SGS product (Cica Care, Smith & Nephew, U.K.) were tested for cytotoxicity,

irritability, and oxidative stress. Gel discs of uniform sizes were first made by cutting the gel sheets with an 8mm disposable biopsy punch (Kruuse, Denmark) and were autoclaved before assay.

4.2.1.3 Cytotoxicity Tests and Irritation Tests

The gel discs to be tested were applied directly onto the equilibrated EpiSkin for 15minutes. In parallel, EpiSkin treated with phosphate-buffered saline solution (PBS) only (pH 7.4; Gibco) and PBS containing 5% sodium dodecyl sulfate (SDS) were used as the negative and positive controls, respectively. The EpiSkin cultures were further incubated in fresh assay medium for 42 hours before proceeding to the tests. All experiments were performed in triplicate.

For the cytotoxicity test, the cell viability of the Episkin was determined by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. Briefly, the gel disc–treated EpiSkin was pulsed with MTT at a final concentration of 0.3 mg ml^{-1} for 3 hours at 37°C. The medium was withdrawn, and the labelled EpiSkin was incubated overnight with 500 µl of acidic isopropanol (0.04 N) at room temperature. The supernatant samples were then measured for optical density at 570 nm using a Victor3 microplate reader (Perkin Elmer, U.S.A.). The test materials were considered to be cytotoxic if the cell viability fell below 50% relative to the negative control treatment with PBS.

For the irritation test, the level of proinflammatory cytokine interleukin (IL) 1α released from the culture was evaluated using an IL-1αhuman enzyme-linked immunosorbent assay kit (Abcam, U.K.) according to the manufacturer's manual.

The testing materials were considered to be irritants if the IL-1α expression level increased by more than 50 pg ml^{-1}relative to the negative control treatment.

4.2.1.4 Sensitizing Test

The sensitizing test was based on the detection of reactive oxygen species using CellROX oxidative stress reagents (Molecular Probes, U.S.A.). First, the EpiSkin was incubated with 5μmol CellROX green dye in culture medium for 30 min to allow the dye to be taken up by the cells. The medium containing the dye was added into both the culture inserts and the culture wells to submerge the three-dimensional constructs. After incubation, the cultures were washed three times with PBS, and the sample gel discs were loaded onto the top of the cultures for 30minutes. For a positive control, the construct was treated with cigarette smoke for 30 minutes according to Rasmussen et al. (Rasmussen et al., 2010); for a negative control, the construct was immersed in PBS only. Finally, the fluorescent signals were measured at Ex/Em of 485 nm/520 nm.

4.2.2 Measurement of Physical Properties

4.2.2.1 Measurement of Water Vapor Transmission Rate

The water vapor transmission rate (WVTR) is essential to reflect the occlusive property of SGS (Gilman, 2003; Tandara & Mustoe, 2008). The WVTRs of the SSCP and Cica Care were measured and compared according to British Standard BS7209: 1990 (British Standards Institution, 1990). The aim of the WVTR test is to determine the occlusive properties of the SSCP and the currently available product for comparison.

4.2.2.2 Measurement of Tensile Properties

Tensile properties can reflect the conformability of the insert material. The tensile properties of the SSCP was tested along with those of another conventional thermoplastic insert, Plastazote (3 mm; Zotefoams, U.K.). The SSCP and the Plastazote were cut into rectangular shapes of the same size. Five specimens of each material were prepared and tested. The specimens were gripped and stretched in vertical orientation at a velocity of 600 mm min^{-1} using an Instron 5566 tensile tester (Instron, U.S.A.). The Young's modulus, yield strength, and tensile strain at yield were automatically recorded for comparison.

4.2.3 Clinical Applications

Subjects with burn injuries were recruited for the following clinical trials using a convenience sampling method, and the Vancouver Scar Scale (VSS) was used to screen candidates (Baryza & Baryza, 1995). Only scars with a total score of 4 or higher and a score for each item of 1 or greater were included. Other inclusion criteria included age between 20 and 70 years and good compliance with treatment. Patients were excluded from the experiment if (1) the HS area had an open wound or infection; (2) the HS had been treated with steroid injections or another intervention (such as traditional Chinese medicine or laser therapy) before the study; or (3) the patient had a medical condition that might affect wound healing (e.g., diabetes mellitus or another serious medical problem). Written consent was obtained from all subjects, and the pilot trials were approved by the ethics committee of the Hong Kong Polytechnic University.

Twenty scars from ten subjects with HS were studied to understand the effectiveness of the SSCP in increasing the interface pressure. A custom-made pressure garment, the Smart Pressure Monitored Suit (SPMS), was provided for each subject. The SPMS adopts a standardized measurement and a computerized pattern-drawing system to ensure a systematic means of pressure generation (Feng, Pao, Wu, Li, & Li-Tsang, 2013; Li-Tsang, Feng, & Li, 2010; U.S. Patent No. 8,386,06, 2013). Ten percent strain was provided according to local practice standards (Chan & Association, 1998). The interface pressure under the SPMS was measured by the Pliance-X system (Novel, Germany), which was validated to measure the interface pressure under the pressure garment (Lai & Li-Tsang, 2009). For scar locations that received an inadequate pressure dosage, the SSCP was inserted under the SPMS and the interface pressure measured. Because the stud height had a critical effect on the pressure dosage and the subsequent clinical effectiveness, the subjects were invited to try both the 3mm and 6mm stud height prototypes. The postinsertion pressures from both 3mm and 6mm stud heights were compared with the preinsertion pressure generated by the SPMS alone using SPSS 20 one-way repeated-measures analysis of variance with a within-subject design.

4.3 Results

4.3.1 Cytotoxicity Tests

The effects of the SSCP on the metabolic activities of EpiSkin in culture were evaluated by MTT assay and compared to the effects of Cica Care (**Figure 4-2a**). The results demonstrated that the use of 5% SDS as a positive control induced a

remarkable reduction in cell viability, whereas both SSCP and Cica Care exhibited cytotoxic effects as compared to the PBS treatment as a negative control. More than 80% viability was observed in the SSCP-treated EpiSkin samples, which is comparable to that for Cica Care.

4.3.2 Irritation Tests

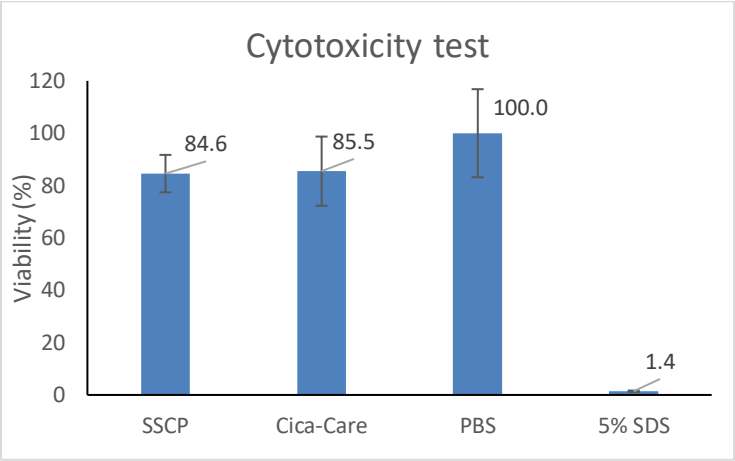
As shown in **Figure 4-2b**, the IL-1α concentration released in the negative control (PBS) was 29.94 pg ml^{-1}. For any materials to be considered irritating to skin, the IL-1α concentration should be at least 50 pg ml^{-1} more than the negative control (i.e., ≧ 79.94 pg ml^{-1}). The mean concentration of IL-1α released from the commercial gel–treated EpiSkin was slightly lower than from the negative control, whereas that released from the SSCP was even lower. The EpiSkin treated with 5% SDS produced a tremendous level of IL-1α (1883.69 pg ml^{-1}). Our results show that neither Cica Care nor the SSCP gel samples exerted any irritating effects on the EpiSkin. Importantly, SSCP produced the lowest amount of IL-1α among the samples tested.

4.3.3 Sensitizing Tests

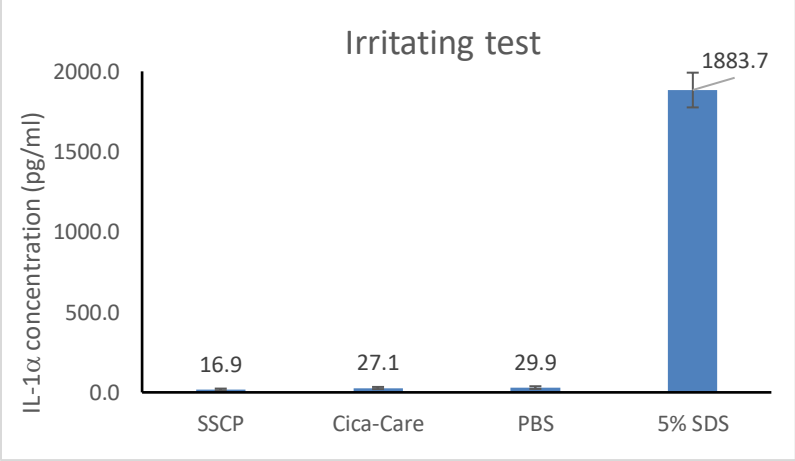
The sensitivity of EpiSkin toward ROS was assessed as a means of evaluating its response to the sensitizing agents. We used cigarette smoke as a positive control for its known effects in inducing the formation of notorious ROS that cause damage to tissue. Compared to the PBS control, cigarette smoke induced a 4-fold increase in the fluorescence signal generated by EpiSkin (**Figure 4-2c**). No difference was seen between the SSCP, Cica Care, and negative control in terms of the capacity to

induce a sensitizing response (**Figure 4-2c**). This result, together with the biological data above, shows that the SSCP was considered to be non-cytotoxic, non-irritating, and non-sensitizing.

a


Cytotoxicity test
Viability (%)
120
100
80
60
40
20
0
84.6
85.5
100.0
1.4
SSCP
Cica-Care
PBS
5% SDS

b


Irritating test
IL-1α concentration (pg/ml)
2000.0
1500.0
1000.0
500.0
0.0
16.9
27.1
29.9
1883.7
SSCP
Cica-Care
PBS
5% SDS

c

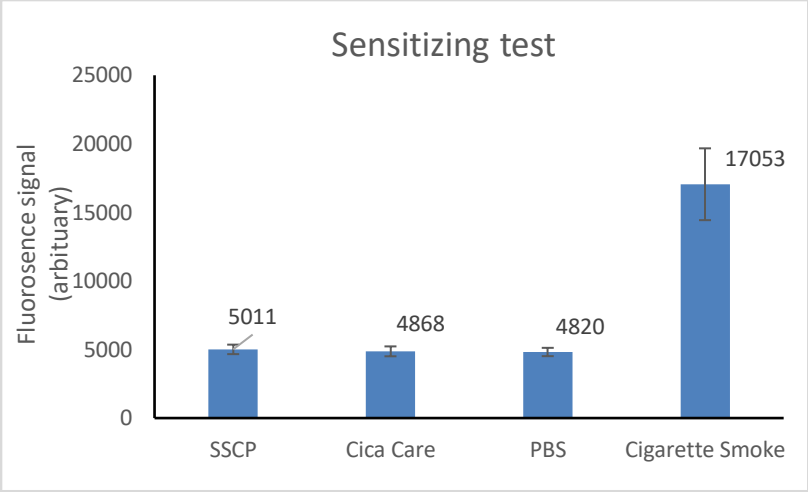


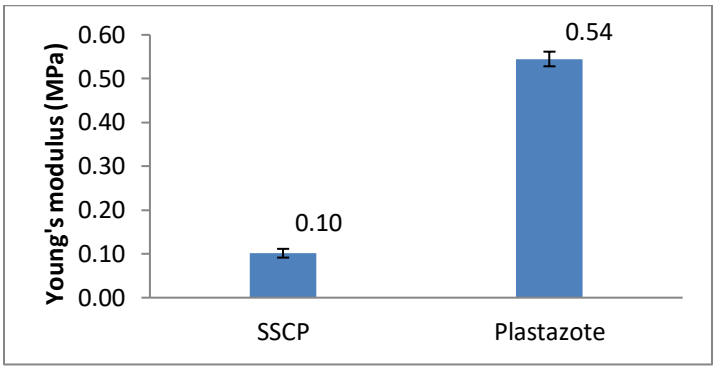
Figure 4-2Biological effects of SSCP on EpiSkin

(a) Results of MTT assay show the metabolic activity of EpiSkin as an indication of tissue viability. (b) Expression level of IL-1α (pg/ml) as an indication of irritation. (c) Fluorescence signals represent the abundance of reactive oxygen species on EpiSkin. EpiSkin was loaded separately with gel samples (SSCP and Cica Care), PBS, 5% SDS (for a and b), and cigarette smoke (for c). Percentages of viability (in a), concentration of IL-1α (in b), and fluorescence signal (in c) are expressed as mean (n = 3) ± SEM as compared to negative control (PBS).

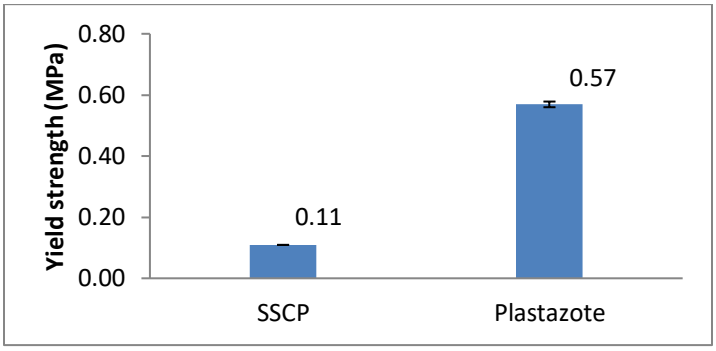
4.3.4 Physical Properties

The WVTR of the SSCP was 8.48 g day^{-1} m^2, whereas that of the Cica Care was 11.91 g day^{-1} m^2, indicating that the SSCP was more occlusive than the Cica Care. The results of the tensile properties of the SSCP and Plastazote are summarized in **Figure 4-3**. Compared to Plastazote, the SSCP had a much lower average Young's modulus (0.10 MPa) and yield strength (0.11 MPa), whereas it demonstrated greater tensile strain at yield (92.09%), suggesting that the SSCP is a softer material with a greater elasticity limit than Plastazote.

a



b



c

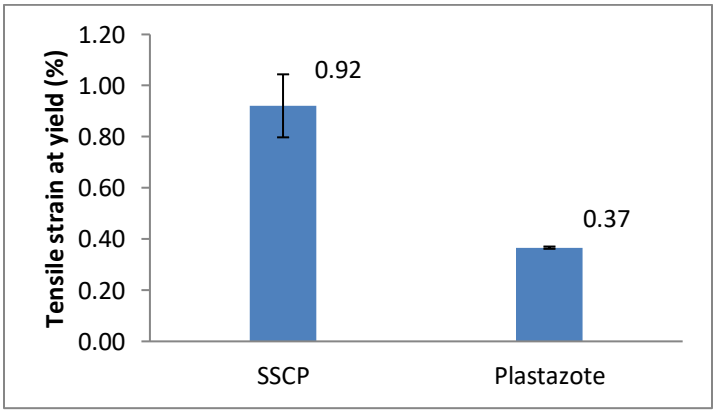


Figure 4-3 Tensile properties of SSCP and Plastazote

(a) Young's modulus; (b) yield strength; and (c) tensile strain at yield. Values are presented as mean (n = 5) ± SD.

4.3.5 Interface Pressure Measurement

Among the 20 scars measured, two scar locations were found to have pressures greater than 20 mm Hg solely with the SPMS; thus, they were excluded from the study. The results of the interface pressure measurements of the remaining 18 scar samples are summarized in **Figure 4-4**. A repeated-measures analysis of variance revealed statistically significant differences among groups ($F(2, 1467.804) = 36.756$, $p < 0.0005$). Post hoc testing using the Bonferroni correction suggested that both the 3mm SSCP prototype and the 6mm SSCP prototype were able to significantly increase the mean interface pressure from 11.8 to 22.8 and 29.7 mm Hg, respectively (PG vs. 3 mm SSCP <0.0005; PG vs. 6mm SSCP <0.0005). Moreover, the 6mm SSCP could generate greater pressure than the 3mm SSCP ($p = 0.002$). It was concluded that both prototypes of the SSCP were able to elicit significant high pressure statistically, whereas the 6mm SSCP prototype demonstrated a statistically greater pressure increase than the 3mm SSCP prototype.

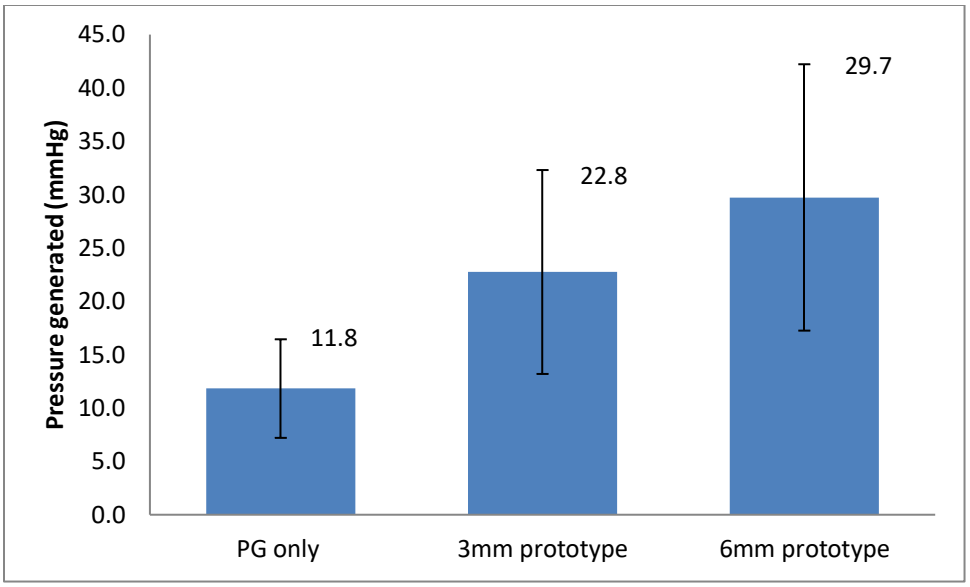


Figure 4-4 Pressure generated by pressure garment only, 3 mm SSCP prototype, and 6 mm SSCP prototype

Both SSCP prototypes were able to elicit a statistically significant pressure increase, whereas the 6mm SSCP prototype demonstrated a statistically higher pressure increase than the 3mm SSCP prototype. Values are presented as mean (n = 18) ± SD.

4.4 Discussion

To our knowledge, the SSCP is the first insert to combine the pressure-enhancing effect of a traditional pressure insert and the occlusive effect of a silicone insert. This study investigated the SSCP's ability to serve as a better alternative material for inserts for the treatment of HS. To serve as a material compatible with human skin, it is necessary for the material to be free of notorious biological effects. Our results demonstrate that the performance of SSCP in tests of cytotoxicity, irritation, and sensitization in an EpiSkin model was basically comparable to those of Cica Care and the control treatment (PBS). Our study also shows that the occlusive property of SSCP was comparable to that of commercially purchased SGS and that its texture and elasticity were better than those of a conventional thermoplastic insert. Most importantly, it was shown that the SSCP could effectively enhance the interface pressure level, which makes the SSCP an effective insert material for HS management.

The overall design of the product was guided by the concept that optimal treatment of HS could be achieved with a combination of adequate PT and SGS. Recent reviews have suggested that PT could efficiently decrease the height of HS and erythema (Anthonissen et al., 2016; Sharp et al., 2015). Our previous study also indicated that an adequate pressure dosage over the HS area was essential to achieve the optimal outcome of PT (Lai et al., 2010). It is recommended that an interface pressure of 20-30 mm Hg should be maintained throughout a 23hour wearing regime to achieve the best outcomes (Ai et al., 2017). It is necessary to apply an insert to enhance localized pressure while allowing joint movement during daily

activities. SGS was reported to be effective in reducing the thickness and improving the color (O'Brien & Jones, 2013). The underlying mechanism was believed to be occlusion (Radomski & Latham, 2014). By preventing excessive evaporation, SGS normalizes the stratum corneum functions and thus improves scar conditions (Bleasdale et al., 2015; Roseborough et al., 2004; Suetake et al., 2000; Van den Kerckhove et al., 2001). Therefore, an occlusive feature should be considered for insert design.

Silicone is potentially an ideal material for wound care management and rehabilitation because of its excellent biocompatibility, chemical stability, and nontoxic nature (McDonald & Whitesides, 2002; Van den Kerckhove et al., 2001; Xu et al., 2015). Therefore, silicone was selected as the sole composite of the SSCP. Silicone exists in a wide array of structural forms, which allows for various mechanical properties, from hard silicone rubber to soft silicone gel (LeVier, Harrison, Cook, & Lane, 1993; McDonald & Whitesides, 2002). Silicone rubber was selected for the outer layer of our insert because its stiffness can contribute to the insert's overall strength, especially under compression, whereas the limited water permeability is the main reason for the selection of SGS for the product's inner layer. In addition to functional considerations from a treatment perspective, conformability and comfort during implementation are also vital. Our study showed the combination of the two silicone forms to be elastic and compatible. Thus, the product could easily conform to various body contours and tolerate morphological changes during movement without creating discomfort or hindering movement. In

addition, the adhesive property of SGS was considered to prevent displacement with body movement.

One feature we attempted to validate in our study was the SSCP's pressure-enhancement capacity. The mechanism that governs the clinical application of pressure is the LaPlace's law, which defines local pressure as the result of tension divided by the radius of curvature (Chan & Association, 1998). The principle is manifested here in that pressure dosages vary according to the geometry of the body surface. With the same tension generated by the pressure garment, a flat surface with a large radius of curvature receives a low pressure dosage, whereas a protruding surface with a small radius of curvature receives a high pressure dosage. Under this premise, pressure inserts can increase the local pressure dosage by reducing the radius of curvature. Thicker inserts allow a greater reduction of the radius, thus intensifying the local pressure atop the scar tissue, which explains why the pressure dosage was the highest after inserting the 6mm SSCP prototype.

4.5 Conclusions

This study aimed to verify the suitability of the SSCP to serve as a new insert material for HS treatment. Our results show that the SSCP was safe to use according to ISO standards and that its physical properties were comparable to those of commercially available inserts. Its special design ensures constant adequate compression and occlusion, thus leading to better performance. At the same time, no adverse effects were reported by the patients in the preliminary trial. It is reasonable to conclude that the SSCP is a safe and effective insert material that can

potentially benefit patients with HS. Further clinical trials with an adequate sample size and stringent study design should be conducted to establish the SSCP's clinical effectiveness.

4.6 Declaration

There is no conflict of interest.

Chapter Five

Clinical Efficacy of the Combined Pressure Garment and Inserts on Management of Hypertrophic Scar

Chapter Summary

Context: A newly invented insert Smart Scar Care Pad (SSCP) was designed to treat hypertrophic scar (HS) by combining the occlusive effect of silicone gel sheeting (SGS) and the pressure-enhancing effect of conventional pressure inserts. The aim of this study was to examine the clinical efficacy of this new SSCP on HS after burn injury relative to that of a conventional thermoplastic pad.

Methods: The study adopted a self-controlled clinical study design. Consenting adults with severe HS with a Vancouver Scar Scale (VSS) total score of 8 or greater were recruited from collaborating hospitals. The subjects were treated for 45 days with SSCP at one scar site and a conventional insert at another as a control. The interfacial pressure was monitored to ensure adequate pressure. The outcome measures were obtained at baseline before intervention and after intervention. The HS parameters, including the melanin level, erythema level, pliability, thickness, hydration, and TEWL were measured objectively, and patient feedback was collected via a questionnaire.

Results: Thirty-two subjects were recruited, and 25 completed the treatment. Significant time effects were identified for the VSS total score (p=.000), the melanin score (p=.042), pliability (p =.039), and the hydration score (p=.013) using repeated-measures analysis of variance with a within-subject design. A significant intervention and time interaction effect was found for pliability (p=.048). On the feedback questionnaire, the patients reported that the SSCP was significantly more conformable (p=.02) and showed less displacement during movement (p=.040).

Conclusions: The SSCP is proved to be more effective in improving the pliability of HS, more comfortable, and less likely to become displaced during movement than a conventional pressure insert.

5.1 Introduction

HS is a common complication after dermal injuries, such as burns, surgical incisions, and trauma. It is characterized as raised, rigid, hypervascular and abnormally pigmented scar confined within the border of the initial injury. The induced aesthetic defect and impaired physical function can adversely affect quality of life (Falder et al., 2009). The incidence varies widely from 40% to 94% after surgery and from 30% to 91% after burn injury (Bloemen et al., 2009). It is reported that the Chinese population displays a higher incidence of HS than the Caucasian population (Li-Tsang et al., 2005). With the chronic and progressive nature of HS, its management continuously challenges clinicians and burdens society.

Pressure therapy (PT) and silicone therapy, such as SGS, were recommended as first-line noninvasive treatments for HS after burn injury in the ISBI guideline (Ahuja et al., 2016). Recent reviews suggested that PT can decrease scar height and erythema, but more evidence is required to support its effect on scar pliability (Anthonissen et al., 2016; Sharp et al., 2015). A Cochrane review showed SGS's ability to reduce scar thickness and improve scar color, but it did not have sufficient data to confirm its effect on scar pliability (O'Brien & Jones, 2013). Moreover, the combined effect of these two treatment techniques in scar management has long drawn interest from researchers. Studies have found that enhanced efficacy could be achieved with a combination of PT and SGS, especially in terms of scar pliability, via subjective measurements and clinical observations (Harte et al., 2009; Li-Tsang et al., 2010; Steinstraesser et al., 2011).

An adequate pressure dosage is essential for PT's treatment effect. Maintaining an adequate pressure dosage with a pressure garment alone is usually uncomfortable and sometimes impossible, especially over concave body areas. Therefore, inserts are used in conjunction with pressure garments to increase local pressure (Radomski & Latham, 2014). As a matter of fact, silicone-based products were first introduced when silicone elastomers were used as an insert for PT (Van den Kerckhove et al., 2001). However, the most widely used silicone-based product, SGS, was recognized for its occlusive effect rather than its pressure aggregation effect due to the limited thickness and rigidity of the sheeting (Bleasdale et al., 2015). In contrast, conventional thermoplastic foam inserts such as Plastazote have been commonly used because its physical properties are preferable (Candy, Cecilia, & Ping, 2010; Yu et al., 2016). Unfortunately, in clinical practice, therapists must make a trade-off between the pressure effect of the thermoplastic insert and the occlusive effect of the SGS because two layers of inserts are not only difficult for the patient to manage, but they are also inclined to become displaced from each other.

The limitations of the currently available inserts compromise HS treatment outcomes. Thus, a new pad material was invented to optimize treatment by incorporating the effects of thermoplastic inserts and SGS. The SSCP is specially designed with a rubbery silicone stiffener layer and a medical-grade silicone gel lining layer underneath. The medical-grade silicone gel lining layer serves as the occlusive layer. The rubbery silicone stiffener layer is designed with numerous studs. By cutting the individual studs into a gradient height, the SSCP can create

tailor-made localized pressure under a pressure garment. The studs are also aligned in a honeycomb style to maximize conformability over various body contours. In that case, the SSCP not only increases local pressure but also provides occlusion to the HS tissue. It is hypothesized that the SSCP will be more effective than the conventional thermoplastic foam insert, Plastazote (Lai et al., 2010). Thus, the aim of this study was to examine the clinical efficacy of the inserts, especially the new SSCP, on HS after burn injury in comparison with the conventional thermoplastic foam insert.

5.2 Material and Methods

5.2.1 Study Design

A self-controlled clinical study was conducted in several hospitals via convenience sampling method to examine the clinical efficacy of a new SSCP on HS after burn injury relative to conventional treatment with a pressure garment and thermoplastic foam insert, which is commonly used to increase local pressure. Ethical approval was obtained from The Hong Kong Polytechnic University, and written consent was obtained from each subject before their engagement in the study. The flowchart of the study is presented as **Figure 5-1**.

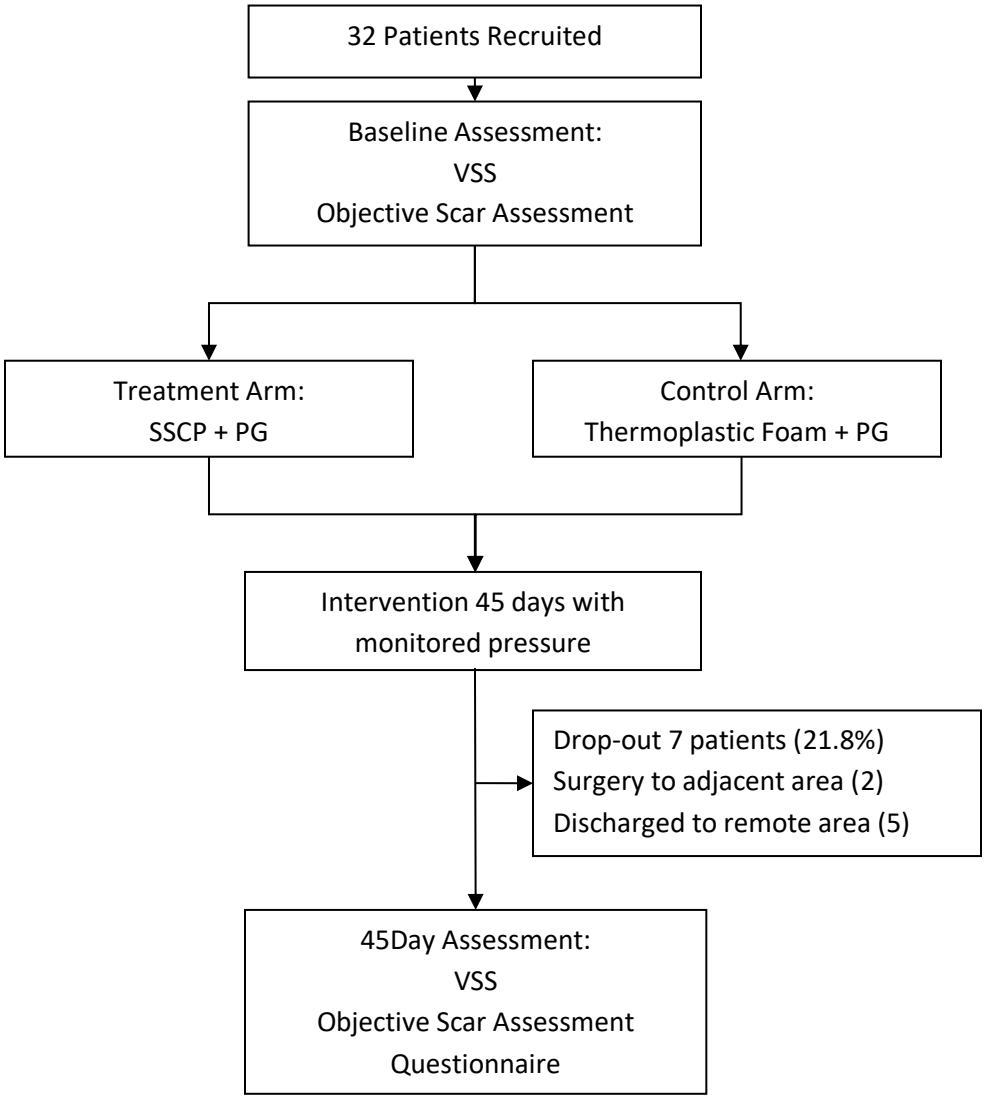


Figure 5-1 Flowchart of the clinical study

5.2.2 Population

Patients between 20 and 70 years of age with HS resulting from burn injury were screened with the VSS (Baryza & Baryza, 1995). Patients who had a total score on the VSS of 8 or higher and a score of at least 1 on each item were included (Li-Tsang et al., 2014).The other inclusion criteria were (1) existing HS on either upper or lower limbs; (2) a history of delayed wound closure (>21 days); (3) HS of 4 × 4 cm^2 or larger; and (4) cooperation and good compliance with treatment. Patients were excluded (1) if the HS had an open wound or infection; (2) if the HS had been treated with steroid injection or other intervention before the study; or (3) if the subject had a medical condition that might affect wound healing, such as diabetes mellitus, or a serious medical risk. The prospective subjects were informed of the risks and benefits, the voluntary nature of their participation, and the procedures involved in the study before they gave their consent. For each subject, at least two scars with similar burn depth, size, and healing time were selected.

5.2.3 Interventions

For each pair of scars, one scar was assigned to the treatment arm and the other to the control arm at the discretion of the assessor. Scars in the treatment arm were treated with an SSCP, and those in the control arm were treated with a thermoplastic foam insert. SSCP is a specially designed insert material with a rubbery silicone stiffener layer and medical-grade silicone gel lining layer underneath that serves the functions of both a traditional pressure insert and SGS. The selected scar sites were outlined with transparent plastic film, and the insert materials were cut

according to the scar pattern reflected on the film. The insert materials for both arms were secured by a pressure garment.

The interventions were provided by occupational therapists with qualification in the prescription of pressure garments to ensure a strict treatment and assessment protocol. The patients were instructed on the wearing regimens and care methods for their pads and pressure garments. An internationally recommended wearing regimen for SGS was introduced for SSCP (Nedelec et al., 2015). The subjects were instructed to wear it for 4 hours on the first day and to increase this time by 2 hours every other day until the total wearing time reached 23 hours. The subjects were also instructed to clean the SSCP twice a day for hygienic purposes. The subjects were instructed to wear the thermoplastic foam for 23 hours a day and only remove it to shower. Because the thermoplastic foam was wrapped with a gauge to absorb sweat, the patients were asked to replace it regularly. The maintenance for the SSCP was summarized in a pamphlet. Compliance with the wearing regimens was monitored closely by the therapists. The interface pressure between the pressure garment and the scar was monitored and regulated with the Pliance-X system, a valid system to measure the pressure applied to scar (Candy et al., 2010; Lai & Li-Tsang, 2009). The use of the Pliance-X system served to ensure that adequate pressure was given to the subjects after the treatments were prescribed.

5.2.4 Study Outcomes

Each case was assessed by a research staff on a set regimen. The demographic data collected included the total burn surface area (TBSA) and days after injury (DAI).

The VSS was used to reflect the change in the global clinical outlook of the scar conditions, including pigmentation, vascularity, pliability, and height (Baryza & Baryza, 1995). The outcome measurements also included an objective assessment of the HS parameters and an end-user feedback questionnaire. The scar thickness was measured with the M5 Diagnostic Ultrasound System (Lee et al., 2016). The DermaLab Combo was used to assess a wide array of HS characteristics, including scar color as represented by the melanin and erythema scores; pliability as represented by Young's modulus; dryness as measured by the hydration score; and stratum corneum function as represented by TEWL (Anthonissen et al., 2013; Gankande et al., 2014; Ud-Din & Bayat, 2016). An improvement in redness was reflected by a decrease in the erythema score and indicates a reduction in vascularity. The assessments of the HS parameters were conducted at baseline before intervention and 45days after the intervention. The feedback questionnaires regarding the use of the SSCP and the conventional insert were delivered via telephone interview. The questionnaire included two sections with nine 5-point Likert-type items (1 = the most unsatisfactory to 5 = the most satisfactory). The first section included three SSCP-specific items regarding the cleansing routine. This section was not applicable to the conventional insert because it cannot be washed. The section included six questions to compare the key qualities of the two inserts.

5.2.5 Statistical Analysis

The subjects' demographic characteristics were reported using frequency distributions and descriptive statistics. Chi-square and paired *t*-tests were used to

conduct between-arm comparisons.

The HS parameters were analyzed with both descriptive statistics and inferential statistics. Patients who dropped out were not included in the analyses of HS parameters. Paired *t*-tests were used to ensure that the baseline characteristics were the same between arms. Repeated-measures ANOVA was used to compare the differences between arms over time. Descriptive statistics were used for the feedback questionnaire, and paired *t*-tests were used to compare the differences between the inserts based on the second section of the questionnaire. Data analyses were performed using SPSS (V25).

5.3 Results

5.3.1 Demographic Characteristics

Thirty-two subjects were recruited, and seven had dropped out by the 45day assessment. Twenty-five subjects completed the study (dropout rate, 21.2%). Two subjects contributed more than one pair of scars, so 27 pairs of scar samples were included in the analysis. No statistically significant difference was seen between the dropout cases and the complete cases in terms of demographic characteristics (**Table 5-1**).Most subjects were middle-aged men with around 40% TBSA and were treated 8months after injury.

Table 5-1 Demographic characteristics of clinical subjects

Variables	Complete Cases (N = 25)	Dropout Cases (N = 7)
Gender (%)		
Male	80.8	71.4
Female	19.2	28.6
Age/years (Mean ± SD)	37.23 ± 8.65	41.29 ± 10.63
TBSA /% (Mean ± SD)	37.56 ± 25.14	44.36 ± 27.00
DAI/days (Mean ± SD)	232.92 ± 142.48	180.86 ± 99.91

TBSA: total burn surface area
DAI: days after injury

5.3.2 Hypertrophic Scar Parameters

Table 5-2 summarizes the descriptive statistics of the HS parameters. **Table 5-3** summarizes the results of inferential statistics. The paired *t*-tests suggest that no significant differences were identified in the HS parameters between the two arms at baseline. Significant time effects were identified for the VSS total score, the melanin score, pliability, and the hydration score. A significant intervention and time interaction effect was found for pliability.

The average VSS total scores of the two arms were the same at baseline, and both dropped more than one point by 45days after intervention (**Figure 5-2a**). It was also noted that the treatment arm showed a greater reduction in the VSS total score than the control arm. The changes in the two arms' melanin scores are illustrated in **Figure 5-2b**. Both arms demonstrated a statistically significant reduction in the melanin score and improvement in scar pigmentation. The trend of reduction was generally parallel, although greater discrepancy was observed by the 45day assessment. As shown in **Figure 5-2c**, the trend of reduction in the erythema score was also parallel in the two arms during the treatment period, but no statistically significant time effect was found. **Figure 5-2d** shows a very different trend between arms for the thickness measured by ultrasound. The thickness of the HSs in the treatment arm demonstrated a trend of reduction after 45days of treatment; however, the thickness of the HSs in the control arm demonstrated an increasing trend. **Figure 5-2e** shows that the arms had significantly different rates of improvement in pliability. An improvement of nearly 3 MPa in pliability was seen in the treatment arm, whereas the improvement in the control arm did not exceed 0.5 MPa,

and the difference in improvement was statistically significant. Figure 2f depicts the changes in the hydration levels of the two arms. The decrease in the hydration level was significant yet comparable in the two arms after intervention. However, at the 45day assessment, a smaller decrease in the hydration level was seen in the treatment arm than in the control arm. A borderline time effect was found for TEWL (**Figure 5-2g)**. Both arms showed a reduction in TEWL, but the reduction in the treatment arm was considerably greater than that in the control arm.

Table 5-2 **Descriptive statistics of treatment and control arm**

Variable	Arm	Pre (Mean ± SE)	Post (Mean ± SE)
VSS Total Score/ Unit	Treatment	11.38 ± .22	9.79 ± .43
	Control	11.38 ± .22	10.04 ± .39
Melanin/Unit	Treatment	57.10 ± 1.42	54.40 ± 1.27
	Control	56.68 ± 1.54	53.53 ± 1.21
Erythema/Unit	Treatment	17.55 ± .70	17.42 ± .63
	Control	17.27 ± .71	17.14 ± .55
Thickness /mm	Treatment	4.91 ± .34	4.78 ± .32
	Control	4.28 ± .26	4.35 ± .26
Pliability/Mpa	Treatment	14.86 ± 1.43	12.05 ± .70
	Control	12.92 ± .65	12.44 ± .87
TEWL/g/m2/day	Treatment	15.56 ± 1.57	13.55 ± 1.15
	Control	13.78 ± 1.07	13.17 ± 1.18
Hydration/uS	Treatment	190.44 ± 21.05	146.52 ± 14.37
	Control	192.44 ± 19.13	141.59 ± 15.00

Table 5-3 **Results of inferential statistics**

Variable	Paired t test	Repeated measure ANOVA with within subject design			
	p value (Baseline)	p value (T)	Observed power	p value (I*T)	Observed power
VSS Total Score/ Unit	.43	**<.001**	.99	.39	
Melanin/Unit	.99	**.04**	.54	.69	
Erythema/Unit	.61	.82		.99	
Thickness /mm	.06	.90		.36	
Pliability/Mpa	.09	**.04**	.55	**.048**	.51
TEWL/g/m2/day	.19	.08		.34	
Hydration/uS	.85	**.01**	.73	.58	

T: time

I*T: intervention*time

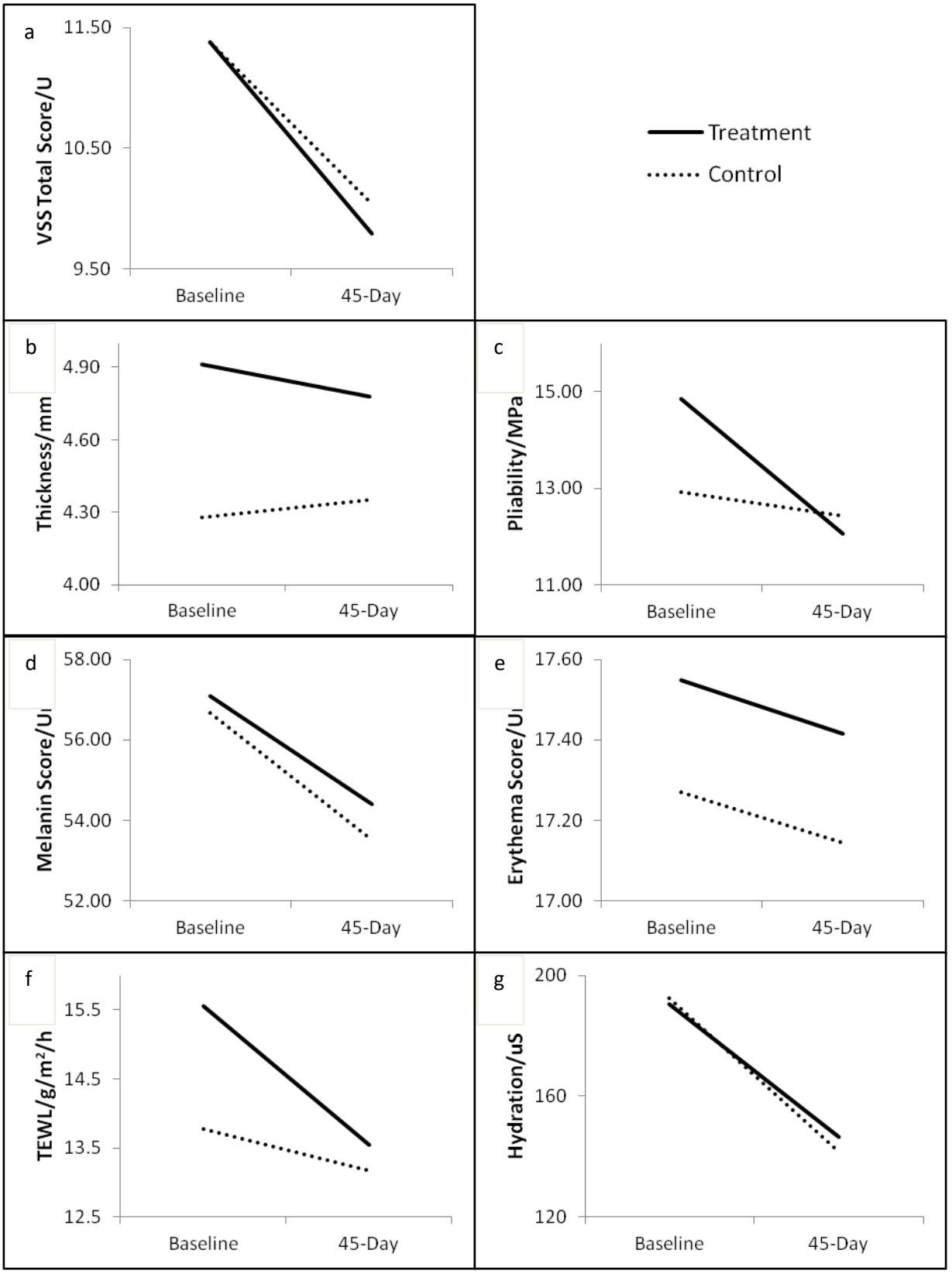

a
VSS Total Score/U
11.50
10.50
9.50
Baseline
45-Day
Treatment
Control
b
Thickness/mm
4.90
4.60
4.30
4.00
Baseline
45-Day
c
Pliability/MPa
15.00
13.00
11.00
Baseline
45-Day
d
Melanin Score/U
58.00
56.00
54.00
52.00
Baseline
45-Day
e
Erythema Score/U
17.60
17.40
17.20
17.00
Baseline
45-Day
f
TEWL/g/m²/h
15.5
14.5
13.5
12.5
Baseline
45-Day
g
Hydration/uS
200
160
120
Baseline
45-Day

Figure 5-2 Improvements in HS parameters

5.3.3 Feedback Questionnaire

Table 4 summarizes the responses of the end-user feedback questionnaire, on which the patients reported that the SSCP was significantly more comfortable to wear and showed less displacement during movement. Fourteen subjects answered the telephone interview and reported that the SSCP was very easy to clean and dry and that the pressure was considered to be well sustained after cleaning. The SSCP was reported to be easier to wear, less smelly, and less breathable than the Plastazote pad, although statistical tests show that the differences were not significant. In contrast, the SSCP was reported to have better conformability, and little or minor displacement occurred during major movements. These characteristic differences were proven to be statistically significant. In addition, both products were considered durable, but the durability of the SSCP was slightly better (i.e., a borderline p value).

Table 5-4 Feedback questionnaire

Questions	SSCP	Control	p
Question 1: Is the padding material easy to clean?	4.29		
Question 2: Is the padding material easy to dry?	4.00		
Question 3: Is the padding material able to sustain pressure after washing?	4.50		
Question 4: Compared to the other, is the padding material easy to wear?	3.71	3.20	.21
Question 5: Compared to the other, is the padding material smelly?	3.93	4.30	.26
Question 6: Compared to the other, is the padding material breathable?	2.93	3.60	.13
Question 7: Compared to the other, is the padding material conformable after use?	4.29	3.40	.02
Question 8: Compared to the other, is the padding material durable in general?	4.71	4.20	.09
Question 9: Compared to the other, was any displacement noticed during usage?	4.71	3.90	.04

SSCP : Smart Scar Care Pad

5.4 Discussion

To the best of our knowledge, this is the first clinical trial in the field to examine the clinical efficacy of pressure garment inserts on severe HS. This study compared two types of inserts: the new SSCP, which combines the functions of a pressure insert and SGS, and the conventional pressure insert. The primary working mechanism of the inserts used in this study is to increase the interfacial pressure dosage by increasing the radius of curvature of the selected HS sites, thus ensuring that adequate pressure is applied to that site without inducing much discomfort. It was shown that the inserts were able to maintain an adequate pressure dosage and improve the overall HS rating, as reflected by a decrease in the VSS score, HS pliability, and HS color, as reflected by a decrease in the melanin score.

Classical theory proposes that local mechanical pressure can mitigate abnormal wound healing by reducing edema, suppressing local blood flow, and facilitating collagen remodeling (Costa et al., 1999; Staley & Richard, 1997). The effect also concurs with the finding in our previous study of PT that adequate pressure is effective in improving the VSS score and HS color (Li et al., 2018).

The SSCP arm outperformed the control arm at the 45day assessment with a significant improvement in scar pliability and gave better patient feedback regarding conformability and tendency for displacement. It is a result of the SSCP's special design, which incorporates the function of SGS to ensure its clinical efficacy and the adhesiveness of the silicone layer in contact with the scar to ensure its conformability and stability, particularly during movement. In addition, the softer

nature of the silicone also made it more comfortable and enhanced compliance.

This is also the first clinical trial on pressure and silicone intervention to use objective assessment for comprehensive measurement of scar parameters, not only traditional scar parameters, but also parameters that indicate stratum corneum functions. Previous investigations suggested that great uncertainty lies in the effectiveness of a pressure or silicone intervention's effect on scar pliability (O'Brien & Jones, 2013; Sharp et al., 2015). Using the objective measurement of HS parameters, the effect of SSCP on HS pliability was documented and serves as solid proof of the effect of a combination of adequate PT with silicone gel therapy (Li-Tsang et al., 2010). This finding corresponds with the results of our previous study, in which HS pliability was measured subjectively. In addition, a reduction in TEWL was seen in the SSCP arm, indicating the possible effect of TEWL in normalizing the HS stratum corneum function.

The subject feedback indicates that SSCP was easy to use and more conformable and adhesive during movement than Plastazote. However, some subjects considered the SSCP to be less breathable and occasionally smelly. The decreased breathability could be regarded as a trade-off for its occlusive property. Because the mechanism of the silicone gel may be occlusion, maintaining a balance between breathability and occlusion could be a possible future direction in the development of padding materials for scar treatment. The smell of the SSCP, as reported by a few subjects, could be attributed to the subjects' failure to regularly clean the SSCP. It is suggested that subject education in terms of daily cleaning of the product should be strengthened.

HS is progressive in nature. Although no significant differences were observed in HS thickness at the 45day intervention in either the treatment or control arm, no elevation of the HS scars was observed in either arm throughout the treatment period. As a matter of fact, the HSs in the treatment arm demonstrated a trend of reduction after the 45day intervention, whereas those in the control arm demonstrated an increasing trend, but the difference was not significant. Excess collagen is the chief contributor to HS thickness (Ghazawi et al., 2018). HS is the result of a disturbance in the remodeling phase of wound healing, in which the speed of collagen synthesis is much faster than its degradation (Armour et al., 2007; Ghazawi et al., 2018). In the SSCP arm, the trend toward a reduction in thickness indicates that the speed of collagen synthesis was reduced and that the speed of collagen degradation was increased. More time is required to achieve full degradation of collagen with a more observable outcome from a macroscopic perspective.

Our study has several limitations. First, it should be recognized that this pilot study lasted only 45 days. The duration of observation was limited, and it is believed that a better effect could be achieved with a longer follow-up period. Moreover, the SSCP was implemented with extra caution and a conservative nature by gradually increasing the wearing duration. It took the subjects 2 weeks to reach the full regimen of 23 hours per day, which suggests that the whole-dose intervention for this study was only 1 month. With the implementation of objective measurements, infinitesimal changes could be identified in the HS parameters. It is suggested that, in addition to objective scar measurements, an extended follow-up period be

considered in a future study. In addition, our study was designed as a self-control study to minimize the differences between arms. However, during our clinical observation, the subjects tended to relocate the padding materials once they realized the efficacy of SSCP. Even though it was controlled by close supervision by the local staff, the subjects' noncompliance could saturate the outcomes of the treatment arm and drive the research results toward the null. In that case, a between-subjects design instead of a self-control design is recommended for a future study.

5. 5 Conclusions

In summary, inserts can maintain the interfacial pressure under a pressure garment. With adequate pressure, inserts can improve the global scar outlook, pliability, and color. As a new insert material, SSCP is particularly effective in improving HS pliability as a result of its combination of silicone and pressure. A future study is warranted that includes a stringent study design, a longer observation period, and objective scar assessment tools.

Chapter Six

Conclusions and Future Research Directions

Chapter Summary

This chapter provides a summary of the entire thesis. The key results from previous sections are summarized and conclusions presented. Although an appropriate method for assessing hypertrophic scar (HS) pliability was identified and implemented in a clinical trial, a wide range of uncertainties require future research attention. From a theoretical perspective, it is crucial to define the concept of pliability and determine an appropriate biomechanical model. Moreover, the role of thickness in the pliability measurement was not thoroughly investigated, and the temporal aspect of pliability was not addressed. These two important factors clearly warrant further investigation.

In relation to possible interventions to address pliability, further study should be conducted on the early differentiation of normal scarring, HS, and keloid scars to enhance the treatment effect and avoid excessive treatment. Moreover, further investigation should be conducted regarding the mechanism of treatment, with the goal of refining the treatment regimen. As bioengineering continues to develop, great advancements are expected in the portability, wireless connection, and virtual interface aspects of assessment devices. As new technologies are developed, more information could be gained by mapping the dynamic interfacial pressure under a pressure garment.

Health care professionals currently face great challenges in relation to patient adherence to pressure and silicone treatments. Studies of occupational performance and quality of life could lead to a better understanding of how the

experience of injury affects patients' functional capacity, and thus lead to improvements in the standard of care.

6. 1 Conclusions

The previous chapters addressed several issues related to the assessment and treatment of HS pliability after burn injury. Chapter One introduced the nature and pathogenesis of HS, which is characterized by increased volume, contractility, and erythema. It is a devastating complication after thermal or traumatic injury because it results in physical dysfunction and disfigurement, psychological distress, social isolation, and compromised quality of life (Gabriel, 2011). The general assessment and treatment strategies for HS were described on the basis of updated level-one evidence. Arising from aberrant wound healing, the reduced pliability of HS is of interest because it plays a crucial role in patients' functioning. Unfortunately, no objective assessment method has been established to assess HS pliability, nor has any treatment method been shown to improve HS pliability. These two knowledge gaps are interrelated, because without a proper objective measurement of pliability, it is difficult to ascertain a treatment effect on HS pliability.

A systematic review to identify an appropriate assessment method for HS pliability was presented in Chapter Two. Based on a critical appraisal of more than 20 objective assessment methods, devices that use suction were identified as the most appropriate among four biomechanical approaches, because of their ability to address various distinctive biomechanical features of HS. However,

there is insufficient evidence to suggest which device in this category is the most suitable. Further analysis revealed that the chief threats to the usefulness of a suction device are the suction pressure, the aperture diameter, and the method by which the probe is attached to the suction chamber.

Commercially available suction devices were compared in Chapter Three. The upgraded version of the elasticity measurement of the DermaLab Combo was found to be the most powerful, with great potential for the objective assessment of HS pliability. By comparing the elasticity measurement of the DermaLab Combo with the modified tissue tonometer (MTT) reading, the Vancouver Scar Scale (VSS) pliability score, and the objectively measured HS thickness, it was concluded that the elasticity measurement of the DermaLab Combo is a valid and clinically relevant tool for the measurement of HS pliability.

With the ultimate goal of establishing the clinical efficacy of a first-line noninvasive treatment that combines pressure and silicone therapy for HS pliability, a suitable approach to assessing HS pliability was identified. However, inadequate integration of the optimal pressure and silicone effects presented a challenge. The concept of an ideal insert was proposed in Chapter Four, and the Smart Scar-Care pad (SSCP) was selected for further investigation into its properties and suitability as insert material for scar management. Tests of biological safety and physical properties revealed that the SSCP was superior to commercially available products. Most importantly, the SSCP significantly increased the interface pressure between the scar tissues and the pressure garment

while providing an occlusive effect. Thus, the SSCP was able to achieve optimal efficacy in a combination of pressure and silicone therapy.

In Chapter Five, the SSCP's clinical efficacy for HS treatment was established via a comprehensive objective assessment protocol. The SSCP was more effective in improving HS pliability, more comfortable, and less likely to be displaced during movement than the conventional pressure insert. However, despite the determination of appropriate methods to assess and improve HS pliability, a wide range of uncertainties require future research attention, as elaborated in the following sections.

6.2 Future Research Directions for Assessment of Hypertrophic Scar Pliability

6.2.1Theoretical Construct of Pliability: Conceptual Differences among Pliability, Adhesion, and Contracture.

One issue that was not fully elucidated in the previous chapters is the theoretical construct of pliability. In Chapter One, pliability was introduced as the contractile and elastic nature of HS based on the early works of Sullivan and Barzya. In Nedelec's version of the modified Vancouver Scar Scale (mVSS), which was used in the clinical relevancy study described in Chapter Three, contracture was removed from the pliability item, leaving a 5-point Likert scale from 0 to 4points. The most severe scar, rated 4 on the mVSS, is defined as adherent, including contracture and adherence to the surrounding tissue. On the Patient and Observer Scar Assessment Scale (POSAS), pliability is defined by the 'suppleness of the scar' as tested by

‘wrinkling the scar between the thumb and index finger’ (Tyack et al., 2012). From a functional perspective (considering the real function of normal skin), the definition of pliability can be refined into two equally important components based on a biomechanical perspective: the scar tissue’s ability to deform under external force and its ability to return to normal after deformation. Based on this definition, pliability is independent of adherence in terms of a scar’s relationship with the surrounding tissue. Moreover, pliability is also independent from contracture. Scar contracture is the result of one or more of three interrelated factors: the shrinkage of HS tissue in terms of surface area, adherence to the surrounding tissue, and reduced pliability. It is important to understand the interrelationship among these three factors, making use of the objective assessment tools identified in the second chapter.

6.2.2 Theoretical Modeling of Pliability: Conceptual Differences among Hardness, Elasticity, and Pliability

As pliability is a clinical term rather than a physical measure, the objective measurement of scar pliability has always been based on an effort to approximate various physical concepts (Lee et al., 2016). Based on our review, two concepts were used to describe HS pliability. When referring to the pliability of HS, one can refer to the elasticity or the hardness of the scar. Generally, the devices and methods in the in-plane deformation group and the suction group measure the elasticity of a scar, i.e., its ability to stretch and return to its original shape. The devices and methods in the indentation group and the acoustic group normally measure the hardness of a scar. “Hardness” refers to a material’s ability to resist permanent

deformation by indentation. The devices measure deformation under a certain loading or the resistance induced by a given deformation. From a functional perspective, it is suggested that the ability to stretch and return to a normal state has greater clinical relevance. Previous studies have seldom addressed the conceptual difference between these two terms and their relevance to pliability measurement. In the previous section, the concept of pliability could easily encompass both of these concepts, so it is worthwhile to differentiate these two concepts for future studies of the effects of thickness and to understand the real biomechanical features of HS.

6.2.3 Role of Thickness in Pliability Measurement

An assumption of all previous scar assessment tools is that the scar thickness is the same for all measurements (Hendriks, 2001). In normal skin, the thickness ranges from 0.8 to 1.3 mm, which may not have a significant effect on the assessment outcomes (Marieb & Hoehn, 2014; McKinley, O'Loughlin, Pennefather-O'Brien, & Harris, 2015),or at least a lesser effect than in scar assessment because scar thickness varies from 1mm to more than 10 cm. In Chapter Three, the relationship between pliability and thickness was identified. Unfortunately, although the incorporation of scar thickness is a theoretical advancement in the understanding of the elastic feature of HS, no assessment tools are yet available to establish concurrent validity, and no test for clinical relevancy exists Moreover, scarring is known to be progressive in nature, so scar thickness changes over time, first elevating and later regressing (Nedelec et al., 2008a, 2008b; Oliveira et al., 2005).

Therefore, a tool's ability to calculate the effect of scar thickness will be of methodological importance.

6.2.4 Temporal Aspects of Pliability Measurement

Incorporating the time factor would more comprehensively represent scar pliability. The time-dependent property is not an integral part of pliability according to the definitions presented in the previous sections. However, time can have a significant effect on the pliability measurement, as mentioned in our description of the MTT and subsequent indentation measurement. Moreover, the importance of the time-dependent property has also been shown in studies of creeping behavior, which is an increase in the extensibility of human tissue over time. A dermatological study revealed the relationship between creeping behavior and an increase in the water content of tissue (Elsner, 2002).Extending our understanding of the creeping behavior of HS could benefit our clinical understanding of treatment mechanisms. The time-dependent property of HS could be measured as viscoelasticity with the multiple machines identified in Chapter Two; however, in reality, the interpretation of viscoelasticity is difficult because it cannot simply be interpreted as "the lower the better," like the elasticity modulus.

6.2.5 Portability, Wireless Connection and Virtual Interface

The use of a portable or integrated scar assessment device has been suggested in multiple reviews to reduce the burden of data collection in a clinical setting. To further simplify assessment, wireless probes should be considered, developed, and implemented. Finally, a virtual interface could allow data collection ata distance,

thus reducing the costs of the clinical trial and prolonged assessment period. For example, a finite-model analysis of scar elasticity could be achieved with a specially designed removable camera, and analysis could be performed using an app, providing instant feedback to the patient and healthcare professionals much more easily than 20 years ago when the technique was new. Each of these aspects has already been developed to a certain extent, which could lead to a paradigm shift in HS assessment.

6.3 Future Research Directions for the Treatment of Hypertrophic Scar Pliability

6.3.1 Concept of Hypertrophic Scar

In Chapter One, HS was defined as elevated, rigid, hypervascular scar tissue with abnormal pigmentation disposition confined within the original wound area. However, no quantification method has been established to differentiate HS from other types of scar, which poses a great challenge to clinical trials that target scar treatment. Previous studies tended to use injury depth, wound healing method, and wound healing time to differentiate HS from a spontaneously healed scar. For a burn of second degree or worse, healing continues for more than 21 days, and the injury site is highly likely to develop HS. Unfortunately, for large burns, it is very difficult to estimate the depth of injury and to monitor the wound closure time. In Chapter Five, HS after burn injury was selected based on VSS assessment. Patients who fulfilled the criteria of a total VSS score of 8 or higher and a score of at least 1 on each item of the VSS were included. These criteria ensured that the scar

selected for study fulfilled the characteristics of HS. However, because HS is progressive in nature, some scars that would later develop into HS were not included in the study, except for particularly severe ones. Another limitation is that the criteria cannot exclude keloid scarring, which is characterized by proliferation beyond the wound's original boundary. In fact, there is no prediction of keloid scar unless expansion of the scar area is observed. Therefore, an early, accurate method of differentiating normal scars, HS, and keloid scars would be beneficial from both clinical and research perspectives. The best treatments for normal scarring, HS, and keloids could be vastly different.

6.3.2 Mechanism of Treatment

It is crucial to expand our understanding of the mechanism of silicone-based treatment. Previous studies have stated that occlusion may be one mechanism of HS treatment (Hoeksema, De Vos, Verbelen, Pirayesh, & Monstrey, 2013; O'Shaughnessy et al., 2009).In fact, the dominating mechanism of occlusion has yet to be linked to clinical outcomes in human subjects. Information from the manufacturer suggests that different SGS products may exhibit different occlusive properties. Therefore, in addition to confirming the clinical effectiveness of SGS, it would be meaningful to correlate the clinical outcome with the occlusive properties of various SGS products manifested by the WVTR to provide greater insight into the mechanism of SGS.

This theory offers many new options and possibilities to solve some current problems. For example, if occlusion is the mechanism, then all materials with

occlusive properties could have a positive effect on scars to some degree. Occlusive treatment methods could be expanded beyond SGS (Nedelec et al., 2015). However, SGS treatments include products with various thicknesses and water vapor permeabilities (De Paepe, Sieg, Le Meur, & Rogiers, 2014; Van den Kerckhove et al., 2001). To investigate the effects of occlusion in scar treatment, a variety of insertions would require examination. Moreover, if occlusion is the primary mechanism, various occlusive properties may interact with the time of implementation and the scar characteristics to determine the best clinical outcomes.

The occlusion effect is double-edged, because adverse effects due to over-hydration have been reported (Nedelec et al., 2015; Steinstraesser et al., 2011). If the main mechanism of occlusion is maintenance of the stratum corneum homeostasis, then over-hydration will cause destruction. General guidelines for gel sheeting only became available in 2015 (Nedelec et al., 2015), and the recommended wearing regimen, as suggested in other literature reviews, is based on experience rather than on evidence (Bleasdale et al., 2015; De Paepe et al., 2014; Nedelec et al., 2015; O'Brien & Jones, 2013). The strong recommendation was in accordance with anecdote rather than an empirical account (Ahuja et al., 2016). Therefore, the best way to apply occlusive materials to maximize occlusion while avoiding negative effects is still uncertain. An improved understanding of the relationship between occlusion and the treatment regimen could help us to develop an evidence-based protocol for treatment with gel sheeting.

6.3.3 Patient Compliance

Another threat to clinical efficacy is patients' lack of compliance with treatment. It is understandable that a noninvasive first-line treatment of combined pressure and silicone therapy makes great demands of patients, particularly those with large burns. In the current treatment regime, both the pressure garment and the silicone product should be worn for 23 hours per day. The process of donning and removing the treatment material is very unpleasant and sometimes painful if the patient has open wounds. However, patients might need to tolerate this process several times per day, most commonly for various forms of physiotherapy such as exercise and massage. As the pressure garment and insert hinder movement to a certain degree (Yu, Yick, Ng, & Yip, 2015), patients are instructed to remove all treatment material during rigorous exercise, which actually reduces the intervention time. A variety of protocols exist in terms of massage therapy, and the treatment time varies on this basis. Each session generally takes 15 to 30 minutes, or longer for those with a large TBSA, which is another reason for inadequate wearing times of pressure garments (Anthonissen et al., 2016).

Another common reason for a lack of patient compliance is the recurrence of blisters that might interfere with the treatment regimen and subsequent small open wounds that require dressing changes. Without other treatment, the experience of wearing a pressure garment with inserts can still be a torment, particularly during the hot and humid weather in southern China. These external factors all affect patients' compliance with treatment.

Another limitation of the study is that we found that some patients were secretly switching the SSCP to other scar sites as they deemed necessary, especially to joint

regions before engaging in physical exercise, because they wished to benefit from its softening effect. Even though we educated the patients about the importance of adhering to the treatment regimen and persuaded them to return the SSCP to where it belonged, this disruption may have diluted the treatment effect.

6.3.4 Pressure Monitoring

Another area that requires attention is pressure monitoring. As reported in Chapters Five and Six, we were only able to measure the instant static pressure at one location. However, according to our understanding of the principle of pressure therapy and our clinical experience, a distinctive difference exists between dynamic pressure and static pressure. Patients experience greater pressure during movement with muscle contraction because it increases local stiffness and the local radius of curvature. It would be meaningful to understand how daily activities affect the pressure delivered by the pressure garment and the insert. This type of study would require multiple wearable wireless sensors with great sensitivity and an extended working time. As with the development of scar assessment devices, pressure sensors are also undergoing rapid evolution. It has been reported that various types of wearable pressure sensor have been invented that can effectively document pressure in real time (Ghassemi et al., 2015; McLaren, Helmer, Horne, & Blanchonette, 2010). Most recently, a wireless multifunction sensor was reported that can adhere to patient skin under the garment, and several sensors can work simultaneously to provide information about pressure and temperature (Han et al., 2018). However, currently only prototypes have been reported; none of these sensors are yet commercially available.

6.3.5 Effect on Functional Capacity, Occupational Performance, and Quality of Life

Another limitation of this study is its inability to account for the function, occupation, and quality of life of the patients. Burn injury is one of the leading causes of disability-adjusted life-years lost in low- and middle-income countries (WHO, 2018), and there is no doubt that the experience of a burn injury and its subsequent treatment has a significant effect on patients' functional capacity, occupational performance, and quality of life. From a client-centered perspective, whether the improvement in HS characteristics can be carried forward to improve patients' functional capacity, occupational performance, and quality of life is of great importance. In contrast, as discussed in the previous sections, intervention for severe burn HS can cause great disruption in patients' daily activities and daily routine. An understanding of the influence of treatment methods on patients' daily functioning, occupational performance, and quality of life would provide more guidance for clinical staff briefing, educating, and supporting these patients.

6.4 Prevention of Hypertrophic Scar

Although this thesis focuses on the assessment and treatment of HS after burn injury, it is very important to stress the importance of HS prevention. Preventing the occurrence of HS and its complications with the use of proper prophylactic strategies and early intervention could significantly reduce its adverse consequences, thus alleviating patient suffering and the burden to society.

HS is the result of injury to the reticular dermis after trauma, surgery, or burn injuries. Burn injuries are the most preventable of these, but the most devastating. One of the most fundamental methods for prevention of HS after burn injury is to prevent burn injury in general.

'Burns are preventable.'—WHO Burn Fact Sheet (WHO, 2018)

China has made great strides in promoting prevention strategies and improving the care of people affected by burns. However, imbalances in socioeconomic development exist among China's various regions; therefore, it is important to persist in burn prevention by specific burn hazards control, education to susceptible populations, and promoting first aid training communities (WHO, 2018).

The ISBI has provided guidelines to prevent excessive scarring after burn injury based on the severity of the burn injury. For deep dermal burns with prolonged wound healing for more than 3 weeks, aggressive and monitored scar-prevention therapies are recommended, primarily pressure and silicone therapy. Pain relief to facilitate early positioning and mobilization are also essential to prevent the complications associated with HS, such as stiffness and contracture (Ahuja et al., 2016).

On a global scale, 40% to 94% of the 250 million surgical incisions created each year will develop HS (Block et al., 2015; Bloemen et al., 2009). With the inevitability of lesions, proper strategies should be adopted to prevent the development of HS. Based on the theoretical model constructed in Chapter One, it

is important to promote speedy wound closure, suppress inflammation, and reduce local tension to prevent HS after dermal injury.

References

Ahuja, R. B., Gibran, N., Greenhalgh, D., Jeng, J., Mackie, D., Moghazy, A., ... & Watson, S. (2016). ISBI practice guidelines for burn care. *Burns*, *42*(5), 953-1021.

Ai, J. W., Liu, J. T., Pei, S. D., Liu, Y., Li, D. S., Lin, H. M., & Pei, B. (2017). The effectiveness of pressure therapy (15-25 mmHg) for hypertrophic burn scars: A systematic review and meta-analysis. *Sci Rep, 7*, 40185. doi:10.1038/srep40185

Akaishi, S., Akimoto, M., Hyakusoku, H., & Ogawa, R. (2010). The tensile reduction effects of silicone gel sheeting. *Plastic and reconstructive surgery*, *126*(2), 109e-111e.

Al-Shaqsi, S., & Al-Bulushi, T. (2016). Cutaneous Scar Prevention and Management: Overview of current therapies. *Sultan Qaboos University Medical Journal, 16*(1), e3.

Anthonissen, M., Daly, D., Fieuws, S., Massagé, P., Van Brussel, M., Vranckx, J., & Van Den Kerckhove, E. (2013). Measurement of elasticity and transepidermal water loss rate of burn scars with the Dermalab®. *Burns, 39*(3), 420-428. doi:10.1016/j.burns.2012.07.026

Anthonissen, M., Daly, D., Janssens, T., & Van den Kerckhove, E. (2016). The effects of conservative treatments on burn scars: A systematic review. *Burns, 42*(3), 508-518.

Anzarut, A., Olson, J., Singh, P., Rowe, B. H., & Tredget, E. E. (2009). The effectiveness of pressure garment therapy for the prevention of abnormal

scarring after burn injury: a meta-analysis. *Journal of Plastic, Reconstructive & Aesthetic Surgery, 62*(1), 77-84.

Armour, A., Scott, P. G., & Tredget, E. E. (2007). Cellular and molecular pathology of HTS: basis for treatment. *Wound repair and regeneration, 15*(s1), S6-S17.

Bartell, T. H., Monafo, W. W., & Mustoe, T. A. (1988). A new instrument for serial measurements of elasticity in hypertrophic scar. *The Journal of burn care & rehabilitation, 9*(6), 657-660.

Baryza, M. J., & Baryza, G. A. (1995). The Vancouver scar scale: An administration tool and its interrater reliability. *Journal of Burn Care and Rehabilitation, 16*(5), 535-538. doi:10.1097/00004630-199509000-00013

Berman, B., Perez, O. A., Konda, S., Kohut, B. E., Viera, M. H., Delgado, S., . . . Li, Q. (2007). A review of the biologic effects, clinical efficacy, and safety of silicone elastomer sheeting for hypertrophic and keloid scar treatment and management. *Dermatologic Surgery, 33*(11), 1291-1303.

Bleasdale, B., Finnegan, S., Murray, K., Kelly, S., & Percival, S. L. (2015). The Use of Silicone Adhesives for Scar Reduction. *Advances in Wound Care, 4*(7), 422-430.

Block, L., Gosain, A., & King, T. W. (2015). Emerging Therapies for Scar Prevention. *Advances in Wound Care*.

Bloemen, M. C. T., van der Veer, W. M., Ulrich, M. M. W., van Zuijlen, P. P. M., Niessen, F. B., & Middelkoop, E. (2009). Prevention and curative

management of hypertrophic scar formation. *Burns, 35*(4), 463-475. doi:http://dx.doi.org/10.1016/j.burns.2008.07.016

Bock, O., Schmid-Ott, G., Malewski, P., & Mrowietz, U. (2006). Quality of life of patients with keloid and hypertrophic scarring. *Archives of dermatological research, 297*(10), 433-438.

Boyce, S. T., Supp, A. P., Wickett, R. R., Hoath, S. B., & Warden, G. D. (2000). Assessment with the dermal torque meter of skin pliability after treatment of burns with cultured skin substitutes. *The Journal of burn care & rehabilitation, 21*(1 Pt 1), 55-63.

British Standards Institution. (1990). *Specification for Water Vapour Permeable Apparel Fabrics (BS7209:1990)*. London, UK: British Standards Institution.

Brusselaers, N., Pirayesh, A., Hoeksema, H., Verbelen, J., Blot, S., & Monstrey, S. (2010a). Burn scar assessment: a systematic review of different scar scales. *The Journal Of Surgical Research, 164*(1), e115-e123. doi:10.1016/j.jss.2010.05.056

Brusselaers, N., Pirayesh, A., Hoeksema, H., Verbelen, J., Blot, S., & Monstrey, S. (2010b). Burn scar assessment: a systematic review of objective scar assessment tools. *Burns, 36*(8), 1157-1164.

Busche, M. N., Thraen, A. C. J., Gohritz, A., Rennekampff, H. O., & Vogt, P. M. (2018). Burn Scar Evaluation Using the Cutometer ® MPA 580 in Comparison to "patient and Observer Scar Assessment Scale" and

"vancouver Scar Scale". *Journal of Burn Care and Research, 39*(4), 516-526. doi:10.1093/jbcr/irx009

Candy, L. H. Y., Cecilia, L.-T. W. P., & Ping, Z. Y. (2010). Effect of different pressure magnitudes on hypertrophic scar in a Chinese population. *burns, 36*(8), 1234-1241.

Chan, A., & Association, H. K. O. T. (1998). *Pressure Therapy Manual for Practising Occupational Therapist*: Occupational Therapist (Hong Kong).

Chinese Burn Association & China Standard Medical Information Research Center, China-WHO Biennial Collaborative Projects 2016-1017. (2017). *China Burn Annual Report 2010-2016.*

Chu, B. M., & Brody, G. (1975). Nondestructive measurements of the properties of healing burn scars. *Medical instrumentation, 9*(3), 139-142.

Clark, J. A., Cheng, J. C., Leung, K. S., & Leung, P. C. (1987). Mechanical characterisation of human postburn hypertrophic skin during pressure therapy. *Journal of biomechanics, 20*(4), 397-406.

Clark, J. A., Cheng, J. C. Y., & Leung, K. S. (1996). Mechanical properties of normal skin and hypertrophic scars. *Burns, 22*(6), 443-446. doi:10.1016/0305-4179(96)00038-1

Cleary, C., Kathryn, A., & Nick, T. G. (2007). Reliability of the skin compliance device in the assessment of scar pliability. *Journal of Hand Therapy, 20*(3), 232-237. doi:10.1197/j.jht.2007.04.016

Corica, G. F., Wigger, N. C., Edgar, D. W., Wood, F. M., & Carroll, S. (2006). Objective measurement of scarring by multiple assessors: Is the tissue

tonometer a reliable option? *Journal of Burn Care and Research, 27*(4), 520-523. doi:10.1097/01.BCR.0000225963.41796.54

Cortex Technology. (2015). *DermaLab ® Series SkinLab Combo Instruction Manual*. Hudson, Denmark: Author.

Costa, A. M. A., Peyrol, S., Pôrto, L. C., Comparin, J.-P., Foyatier, J.-L., & Desmoulière, A. (1999). Mechanical Forces Induce Scar Remodeling: Study in Non-Pressure-Treated versus Pressure-Treated Hypertrophic Scars. *The American journal of pathology, 155*(5), 1671-1679. doi:http://dx.doi.org/10.1016/S0002-9440(10)65482-X

De Paepe, K., Sieg, A., Le Meur, M., & Rogiers, V. (2014). Silicones as nonocclusive topical agents. *Skin pharmacology and physiology, 27*(3), 164-171.

Diridollou, S., Patat, F., Gens, F., Vaillant, L., Black, D., Lagarde, J., . . . Berson, M. (2000). In vivo model of the mechanical properties of the human skin under suction. *Skin Research and technology, 6*(4), 214-221.

Draaijers, L. J., Botman, Y. A., Tempelman, F. R., Kreis, R. W., Middelkoop, E., & van Zuijlen, P. P. (2004). Skin elasticity meter or subjective evaluation in scars: a reliability assessment. *Burns, 30*(2), 109-114. doi:10.1016/j.burns.2003.09.003

Draaijers, L. J., Tempelman, F. R., Botman, Y. A., Tuinebreijer, W. E., Middelkoop, E., Kreis, R. W., & van Zuijlen, P. P. (2004). The patient and observer scar assessment scale: a reliable and feasible tool for scar evaluation. *Plastic and reconstructive surgery, 113*(7), 1960-1965.

Dunkin, C. S., Pleat, J. M., Gillespie, P. H., Tyler, M. P., Roberts, A. H., & McGrouther, D. A. (2007). Scarring occurs at a critical depth of skin injury: precise measurement in a graduated dermal scratch in human volunteers. *Plastic and reconstructive surgery, 119*(6), 1722-1732.

Duscher, D., Maan, Z. N., Wong, V. W., Rennert, R. C., Januszyk, M., Rodrigues, M., . . . Gurtner, G. C. (2014). Mechanotransduction and fibrosis. *J Biomech, 47*(9), 1997-2005. doi:10.1016/j.jbiomech.2014.03.031

Elsner, P. (2002). *Bioengineering of the skin : skin biomechanics*. Boca Raton, Fla.: CRC Press.

Engrav, L. H., Garner, W. L., & Tredget, E. E. (2007). Hypertrophic scar, wound contraction and hyper-hypopigmentation. *Journal of burn care & research, 28*(4), 593-597.

Es'haghian, S., Kennedy, K. M., Gong, P., Sampson, D. D., McLaughlin, R. A., & Kennedy, B. F. (2015). Optical palpation in vivo: imaging human skin lesions using mechanical contrast. *J Biomed Opt, 20*(1), 16013. doi:10.1117/1.jbo.20.1.016013

Esposito, G., Ziccardi, P., Scioli, M., Pappone, N., & Scuderi, N. (1990). The use of a modified tonometer in burn scar therapy. *The Journal of burn care & rehabilitation, 11*(1), 86-90.

Falder, S., Browne, A., Edgar, D., Staples, E., Fong, J., Rea, S., & Wood, F. (2009). Core outcomes for adult burn survivors: a clinical overview. *Burns, 35*(5), 618-641.

Feng, B., Pao, W. Y., Wu, A., Li, H. C. K., & Li-Tsang, C. W. P. (2013). Are "Smart Pressure Monitored Suits""Smarter" than Conventional Garments in Clinical Applications? *Hong Kong journal of occupational therapy, 23*(2), 82-88.

Ferriero, G., Vercelli, S., Salgovic, L., Stissi, V., & Sartorio, F. (2010). Validation of a new device to measure postsurgical scar adherence. *Physical Therapy, 90*(5), 776-783. doi:10.2522/ptj.20090048

Fong, S. S., Hung, L. K., & Cheng, J. C. (1997). The cutometer and ultrasonography in the assessment of postburn hypertrophic scar--a preliminary study. *Burns: Journal Of The International Society For Burn Injuries, 23 Suppl 1*, S12-S18.

Forbes-Duchart, L., Cooper, J., Nedelec, B., Ross, L., & Quanbury, A. (2009). Burn therapists' opinion on the application and essential characteristics of a burn scar outcome measure. *Journal of burn care & research, 30*(5), 792-800. doi:10.1097/BCR.0b013e3181b47cc2

Gabriel, V. (2011). Hypertrophic Scar. *Physical Medicine and Rehabilitation Clinics of North America, 22*(2), 301-310. doi:http://dx.doi.org/10.1016/j.pmr.2011.02.002

Gabriel, V., & Kowalske, K. (2015). Measurement of change in the mechanical properties of burned skin to therapist intervention with a vacuum device. *Burns: Journal Of The International Society For Burn Injuries, 41*(4), 796-802. doi:10.1016/j.burns.2014.10.021

Gankande, T. U., Duke, J. M., Danielsen, P. L., DeJong, H. M., Wood, F. M., & Wallace, H. J. (2014). Reliability of scar assessments performed with an integrated skin testing device - The DermaLab Combo. *Burns, 40*(8), 1521-1529. doi:10.1016/j.burns.2014.01.025

Garcia-Velasco, M., Ley, R., Mutch, D., Surkes, N., & Williams, H. (1978). Compression treatment of hypertrophic scars in burned children. *Canadian journal of surgery. Journal canadien de chirurgie, 21*(5), 450-452.

Gauglitz, G. G., Korting, H. C., Pavicic, T., Ruzicka, T., & Jeschke, M. G. (2011). Hypertrophic scarring and keloids: pathomechanisms and current and emerging treatment strategies. *Molecular medicine, 17*(1), 113.

Ghassemi, P., Shupp, J. W., Travis, T. E., Gravunder, A. J., Moffatt, L. T., & Ramella-Roman, J. C. (2015). A portable automatic pressure delivery system for scar compression therapy in large animals. *Rev Sci Instrum, 86*(1), 015101. doi:10.1063/1.4904842

Ghazawi, F. M., Zargham, R., Gilardino, M. S., Sasseville, D., & Jafarian, F. (2018). Insights into the Pathophysiology of Hypertrophic Scars and Keloids: How Do They Differ? *Advances in Skin & Wound Care, 31*(1), 582-595.

Gilman, T. H. (2003). Silicone sheet for treatment and prevention of hypertrophic scar: a new proposal for the mechanism of efficacy. *Wound repair and regeneration, 11*(3), 235-236.

Goei, H., van der Vlies, C. H., Hop, M. J., Tuinebreijer, W. E., Nieuwenhuis, M. K., Middelkoop, E., & van Baar, M. E. (2016). Long-term scar quality in burns with three distinct healing potentials: A multicenter prospective cohort study. *Wound Repair Regen, 24*(4), 721-730. doi:10.1111/wrr.12438

Gold, M. H., Berman, B., Clementoni, M. T., Gauglitz, G. G., Nahai, F., & Murcia, C. (2014). Updated International Clinical Recommendations on Scar Management: Part 1—Evaluating the Evidence. *Dermatologic Surgery, 40*(8), 817-824.

Gold, M. H., McGuire, M., Mustoe, T. A., Pusic, A., Sachdev, M., Waibel, J., & Murcia, C. (2014). Updated international clinical recommendations on scar management: part 2—algorithms for scar prevention and treatment. *Dermatologic Surgery, 40*(8), 825-831.

Han, S., Kim, J., Won, S. M., Ma, Y., Kang, D., Xie, Z., . . . Min, S. (2018). Battery-free, wireless sensors for full-body pressure and temperature mapping. *Sci Transl Med, 10*(435), eaan4950.

Harte, D., Gordon, J., Shaw, M., Stinson, M., & Porter-Armstrong, A. (2009). The use of pressure and silicone in hypertrophic scar management in burns patients: a pilot randomized controlled trial. *Journal of burn care & research, 30*(4), 632-642.

Hendriks, F. (2001). *Mechanical behaviour of human skin in vivo-a literature review.* Paper presented at the Nat. Lab. Unclassified Report 820. Philips Research Laboratories.

Hjermstad, M. J., Fayers, P. M., Haugen, D. F., Caraceni, A., Hanks, G. W., Loge, J. H., . . . Collaborative, E. P. C. R. (2011). Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. *Journal of pain and symptom management, 41*(6), 1073-1093.

Ho, D. Q., Bello, Y. M., Grove, G. L., Manzoor, J., Lopez, A. P., Zerweck, C. R., . . . Phillips, T. J. (2000). A pilot study of noninvasive methods to assess healed acute and chronic wounds. *Dermatologic Surgery: Official Publication For American Society For Dermatologic Surgery [Et Al.], 26*(1), 42-49.

Hoeksema, H., De Vos, M., Verbelen, J., Pirayesh, A., & Monstrey, S. (2013). Scar management by means of occlusion and hydration: a comparative study of silicones versus a hydrating gel-cream. *Burns, 39*(7), 1437-1448.

Idriss, N., & Maibach, H. I. (2009). Scar assessment scales: a dermatologic overview. *Skin Research And Technology: Official Journal Of International Society For Bioengineering And The Skin (ISBS) [And] International Society For Digital Imaging Of Skin (ISDIS) [And] International Society For Skin Imaging (ISSI), 15*(1), 1-5. doi:10.1111/j.1600-0846.2008.00327.x

International Organization of Standardization. (2009). *Biological evaluation of medical devices -- Part 5: Tests for in vitro cytotoxicity* (ISO 10993-5:2009). Geneva,

Switzerland: International Organization of Standardization.

International Organization of Standardization. (2010). *Biological evaluation of medical devices -- Part 10: Tests for irritation and skin sensitization* (ISO 10993-10:2010). Geneva, Switzerland: International Organization of Standardization.

Lizeng, H. P. (2014). *China Patent No. ZL 201110327525.2*. Beijing: National Intellectual Property Administration, PRC.

Junker, J. P., Philip, J., Kiwanuka, E., Hackl, F., Caterson, E. J., & Eriksson, E. (2014). Assessing quality of healing in skin: review of available methods and devices. *Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society, 22*, 2-10. doi:10.1111/wrr.12162

Katz, S. M., Frank, D. H., Leopold, G. R., & Wachtel, T. L. (1985). Objective measurement of hypertrophic burn scar: a preliminary study of tonometry and ultrasonography. *Annals of plastic surgery, 14*(2), 121-127.

Lai, C. H. Y., & Li-Tsang, C. W. P. (2009). Validation of the Pliance X System in measuring interface pressure generated by pressure garment. *Burns, 35*(6), 845-851. doi:10.1016/j.burns.2008.09.013

Lai, C. H. Y., Li-Tsang, C. W. P., & Zheng, Y. P. (2010). Effect of different pressure magnitudes on hypertrophic scar in a Chinese population. *Burns, 36*(8), 1234-1241. doi:DOI 10.1016/j.burns.2010.05.008

Lawrence, J. W., Mason, S. T., Schomer, K., & Klein, M. B. (2012). Epidemiology and impact of scarring after burn injury: a systematic review of the literature. *Journal of burn care & research, 33*(1), 136-146.

Lee, K. C., Dretzke, J., Grover, L., Logan, A., & Moiemen, N. (2016). A systematic review of objective burn scar measurements. *Burns & Trauma, 4*(1), 14. doi:10.1186/s41038-016-0036-x

LeVier, R. R., Harrison, M. C., Cook, R. R., & Lane, T. H. (1993). What Is Silicone? *Plastic and reconstructive surgery, 92*(1), 12-167.

Li-Tsang, C. W., Feng, B. B., & Li, K. C. (2010). [Pressure therapy of hypertrophic scar after burns and related research]. *Zhonghua Shao Shang Za Zhi, 26*(6), 411-415.

Li-Tsang, C. W., Zheng, Y. P., & Lau, J. C. (2010). A randomized clinical trial to study the effect of silicone gel dressing and pressure therapy on posttraumatic hypertrophic scars. *J Burn Care Res, 31*(3), 448-457. doi:10.1097/BCR.0b013e3181db52a7

Li-Tsang, C. W. P., Feng, B., Huang, L., Liu, X., Shu, B., Chan, Y. T. Y., & Cheung, K.-K. (2014). A histological study on the effect of pressure therapy on the activities of myofibroblasts and keratinocytes in hypertrophic scar tissues after burn. *Burns*. doi:10.1016/j.burns.2014.11.017

Li-Tsang, C. W. P., Lau, J. C. M., & Chan, C. C. H. (2005). Prevalence of hypertrophic scar formation and its characteristics among the Chinese population. *Burns, 31*(5), 610-616. doi:http://dx.doi.org/10.1016/j.burns.2005.01.022

Li-Tsang, C. W. P., Zheng, Y. P., & Lau, J. C. (2010). A randomized clinical trial to study the effect of silicone gel dressing and pressure therapy on

posttraumatic hypertrophic scars. *Journal of burn care & research, 31*(3), 448-457.

Li-Tsang, W. P. C. (2013). *U.S. Patent No. 8,386,065*. Washington, DC: U.S. Patent and Trademark Office.

Li, J., Li-Tsang, C., Huang, Y., Chen, Y., & Zheng, Y. (2013). Detection of changes of scar thickness under mechanical loading using ultrasonic measurement. *Burns, 39*(1), 89-97.

Li, P., Li-Tsang, C. W. P., Deng, X., Wang, X., Wang, H., Zhang, Y., . . . He, C. (2018). The recovery of post-burn hypertrophic scar in a monitored pressure therapy intervention programme and the timing of intervention. *Burns, 44*(6), 1451-1467. doi:https://doi.org/10.1016/j.burns.2018.01.008

Lye, I., Edgar, D. W., Wood, F. M., & Carroll, S. (2006). Tissue tonometry is a simple, objective measure for pliability of burn scar: Is it reliable? *Journal of Burn Care and Research, 27*(1), 82-85. doi:10.1097/01.bcr.0000194531.93753.c5

Macintyre, L., & Baird, M. (2006). Pressure garments for use in the treatment of hypertrophic scars—a review of the problems associated with their use. *Burns, 32*(1), 10-15. doi:10.1016/j.burns.2004.06.018

Magliaro, A., & Romanelli, M. (2003). Skin hardness measurement in hypertrophic scars. *Wounds: A Compendium of Clinical Research & Practice, 15*(3), 66-70.

Marieb, E. N., & Hoehn, K. (2014). Human anatomy & physiology (Pearson new international edition, ninth edition. ed.). Harlow, Essex: Harlow, Essex : Pearson, 2014.

Marshall, C. D., Hu, M. S., Leavitt, T., Barnes, L. A., Lorenz, H. P., & Longaker, M. T. (2016). Cutaneous Scarring: Basic Science, Current Treatments, and Future Directions. *Advances in Wound Care*.

Masters, M., McMahon, M., & Svens, B. (2005). Reliability testing of a new scar assessment tool, Matching Assessment of Scars and Photographs (MAPS). *The journal of burn care & rehabilitation. 26*(3), 273-284.

McDonald, J. C., & Whitesides, G. M. (2002). Poly (dimethylsiloxane) as a material for fabricating microfluidic devices. *Accounts of chemical research, 35*(7), 491-499.

McHugh, A. A., Fowlkes, B. J., Maevsky, E. I., Smith Jr, D. J., Rodriguez, J. L., & Garner, W. L. (1997). Biomechanical alterations in normal skin and hypertrophic scar after thermal injury. *Journal of Burn Care and Rehabilitation, 18*(2), 104-108. doi:10.1097/00004630-199703000-00003

McKinley, M. P., O'Loughlin, V. D., Pennefather-O'Brien, E., & Harris, R. T. (2015). *Human anatomy* (Fourth edition. ed.). New York, NY: New York, NY : McGraw-Hill Education, 2015.

McLaren, J., Helmer, R. J. N., Horne, S. L., & Blanchonette, I. (2010). Preliminary development of a wearable device for dynamic pressure measurement in garments. *Procedia Engineering, 2*(2), 3041-3046. doi:http://dx.doi.org/10.1016/j.proeng.2010.04.108

Monstrey, S., Middelkoop, E., Vranckx, J. J., Bassetto, F., Ziegler, U. E., Meaume, S., & Téot, L. (2014). Updated scar management practical guidelines: non-invasive and invasive measures. *Journal of Plastic, Reconstructive & Aesthetic Surgery, 67*(8), 1017-1025.

Mowbrey, K., Ferland-Caron, G., & Tredget, E. E. (2016). Important Developments in the Management of Fibroproliferative Scars and Contractures After Burn Injury *Burn Care for General Surgeons and General Practitioners* (pp. 239-259): Springer.

Murray, B. C., & Wickett, R. R. (1997). Correlations between Dermal Torque Meter®, Cutometer®, and Dermal Phase Meter® measurements of human skin. *Skin Research and technology, 3*(2), 101-106. doi:10.1111/j.1600-0846.1997.tb00170.x

Mustoe, T. A. (2008). Evolution of silicone therapy and mechanism of action in scar management. *Aesthetic Plastic Surgery, 32*(1), 82-92.

Naismith, R. (1980). *Hypertrophic scar therapy: pressure-induced remodelling and its determinants.* University of Strathclyde.

Nedelec, B., Carter, A., Forbes, L., Hsu, S.-C. C., McMahon, M., Parry, I., . . . Sharp, P. A. (2015). Practice Guidelines for the Application of Nonsilicone or Silicone Gels and Gel Sheets After Burn Injury. *Journal of burn care & research, 36*(3), 345-374.

Nedelec, B., Correa, J. A., de Oliveira, A., LaSalle, L., & Perrault, I. (2014). Longitudinal burn scar quantification. *Burns, 40*(8), 1504-1512. doi:https://doi.org/10.1016/j.burns.2014.03.002

Nedelec, B., Correa, J. A., Rachelska, G., Armour, A., & LaSalle, L. (2008a). Quantitative measurement of hypertrophic scar: interrater reliability and concurrent validity. *Journal of burn care & research, 29*(3), 501-511.

Nedelec, B., Correa, J. A., Rachelska, G., Armour, A., & LaSalle, L. (2008b). Quantitative measurement of hypertrophic scar: intrarater reliability, sensitivity, and specificity. *Journal of burn care & research: official publication of the American Burn Association, 29*(3), 489-500. doi:10.1097/BCR.0b013e3181710869

Nedelec, B., Shankowsky, H., & Tredget, E. (2000). Rating the resolving hypertrophic scar: comparison of the Vancouver Scar Scale and scar volume. *The Journal of burn care & rehabilitation, 21*(3), 205-212.

Niessen, F. B., Spauwen, P. H., Schalkwijk, J., & Kon, M. (1999). On the nature of hypertrophic scars and keloids: a review. *Plastic and reconstructive surgery, 104*(5), 1435-1458.

Niyaz, A., Matsumura, H., Watanabe, K., Hamamoto, T., & Matsusawa, T. (2012). Quantification of the physical properties of keloid and hypertrophic scars using the Vesmeter novel sensing device. *International Wound Journal, 9*(6), 643-649. doi:10.1111/j.1742-481X.2011.00932.x

O'Shaughnessy, K. D., De La Garza, M., Roy, N. K., & Mustoe, T. A. (2009). Homeostasis of the epidermal barrier layer: a theory of how occlusion reduces hypertrophic scarring. *Wound repair and regeneration, 17*(5), 700-708.

O'Brien, L., & Jones, D. J. (2013). Silicone gel sheeting for preventing and treating hypertrophic and keloid scars. *Cochrane Database Syst Rev, 9*.

Ogawa, R. (2017). Keloid and hypertrophic scars are the result of chronic inflammation in the reticular dermis. *International journal of molecular sciences, 18*(3), 606.

Ogawa, R., Akaishi, S., Huang, C., Dohi, T., Aoki, M., Omori, Y., . . . Hyakusoku, H. (2011). Clinical applications of basic research that shows reducing skin tension could prevent and treat abnormal scarring: the importance of fascial/subcutaneous tensile reduction sutures and flap surgery for keloid and hypertrophic scar reconstruction. *Journal of Nippon Medical School, 78*(2), 68-76.

Ogawa, R., Akaishi, S., Kuribayashi, S., & Miyashita, T. (2016). Keloids and Hypertrophic Scars Can Now Be Cured Completely: Recent Progress in Our Understanding of the Pathogenesis of Keloids and Hypertrophic Scars and the Most Promising Current Therapeutic Strategy. *Journal of Nippon Medical School, 83*(2), 46-53.

Oliveira, G. V., Chinkes, D., Mitchell, C., Oliveras, G., Hawkins, H. K., & Herndon, D. N. (2005). Objective Assessment of Burn Scar Vascularity, Erythema, Pliability, Thickness, and Planimetry. *Dermatologic Surgery, 31*(1), 48-58. doi:10.1111/j.1524-4725.2005.31004

Pailler-Mattei, C., Bec, S., & Zahouani, H. (2008). In vivo measurements of the elastic mechanical properties of human skin by indentation tests. *Medical engineering & physics, 30*(5), 599-606.

Peck, M. D. (2011). Epidemiology of burns throughout the world. Part I: Distribution and risk factors. *Burns, 37*(7), 1087-1100.

Perry, D. M., McGrouther, D. A., & Bayat, A. (2010). Current tools for noninvasive objective assessment of skin scars. *Plastic and reconstructive surgery, 126*(3), 912-923.

Powers, P. S., Sarkar, S., Goldgof, D. B., Cruse, C. W., & Tsap, L. V. (1999). Scar assessment: Current problems and future solutions. *Journal of Burn Care & Rehabilitation, 20*(1), 54-60.

Pratt, J., & West, G. (2014). *Pressure Garments: A Manual on Their Design and Fabrication*: Elsevier Science.

Quatresooz, P., Hermanns, J. F., Paquet, P., & Pierard, G. E. (2006). Mechanobiology and force transduction in scars developed in darker skin types. *Skin Res Technol, 12*(4), 279-282. doi:10.1111/j.0909-752X.2006.00165.x

Radomski, M. V., & Latham, C. A. T. (2014). *Occupational therapy for physical dysfunction*.

Rasmussen, C., Gratz, K., Liebel, F., Southall, M., Garay, M., Bhattacharyya, S., . . . Pirnstill, J. (2010). The StrataTest® human skin model, a consistent in vitro alternative for toxicological testing. *Toxicology in vitro, 24*(7), 2021-2029.

Rennekampff, H. O., Rabbels, J., Reinhard, V., Becker, S. T., & Schaller, H. E. (2006). Comparing the Vancouver Scar Scale with the cutometer in the assessment of donor site wounds treated with various dressings in a

randomized trial. *Journal of Burn Care and Research, 27*(3), 345-351. doi:10.1097/01.BCR.0000216311.61266.00

Roseborough, I. E., Grevious, M. A., & Lee, R. C. (2004). Prevention and treatment of excessive dermal scarring. *Journal of the National Medical Association, 96*(1), 108.

Seo, S. R., Kang, N. O., Yoon, M. S., Lee, H. J., & Kim, D. H. (2017). Measurements of scar properties by SkinFibroMeter®, SkinGlossMeter®, and Mexameter® and comparison with Vancouver Scar Scale. *Skin Research and technology, 23*(3), 295-302. doi:10.1111/srt.12334

Seyger, M. M., van den Hoogen, F. H., de Boo, T., & de Jong, E. M. (1997). Reliability of two methods to assess morphea: skin scoring and the use of a durometer. *Journal of the American Academy of Dermatology, 37*(5), 793-796.

Shah, R. G., DeVore, D., & Silver, F. H. (2018). Biomechanical analysis of decellularized dermis and skin: Initial in vivo observations using optical cohesion tomography and vibrational analysis. *Journal of Biomedical Materials Research - Part A, 106*(5), 1421-1427. doi:10.1002/jbm.a.36344

Sharp, P. A., Pan, B., Yakuboff, K. P., & Rothchild, D. (2015). Development of a Best Evidence Statement for the Use of Pressure Therapy for Management of Hypertrophic Scarring. *Journal of burn care & research: official publication of the American Burn Association*.

Simons, M. A., & Tyack, Z. (2015). Splinting, Positioning, Edema, and Scar Management After Burn Injury *International Handbook of Occupational Therapy Interventions* (pp. 279-297): Springer.

Spann, K., Mileski, W., Atiles, L., Purdue, G., & Hunt, J. (1996). The 1996 Clinical Research award: Use of a pneumatonometer in burn scar assessment. *The Journal of burn care & rehabilitation, 17*(suppl_6_pt_1), 515-517.

Staley, M. J., & Richard, R. L. (1997). Use of pressure to treat hypertrophic burn scars. *Advances in wound care : the journal for prevention and healing, 10*(3), 44.

Stavrou, D., Weissman, O., Winkler, E., Yankelson, L., Millet, E., Mushin, O. P., . . . Haik, J. (2010). Silicone-based scar therapy: a review of the literature. *Aesthetic Plastic Surgery, 34*(5), 646-651.

Steinstraesser, L., Flak, E., Witte, B., Ring, A., Tilkorn, D., Hauser, J., . . . Al-Benna, S. (2011). Pressure garment therapy alone and in combination with silicone for the prevention of hypertrophic scarring: randomized controlled trial with intraindividual comparison. *Plastic and reconstructive surgery, 128*(4), 306e-313e. doi:10.1097/PRS.0b013e3182268c69

Suetake, T., Sasai, S., Zhen, Y.-X., Ohi, T., & Tagami, H. (1996). Functional analyses of the stratum corneum in scars: sequential studies after injury and comparison among keloids, hypertrophic scars, and atrophic scars. *Archives of dermatology, 132*(12), 1453-1458.

Suetake, T., Sasai, S., Zhen, Y.-X., & Tagami, H. (2000). Effects of silicone gel sheet on the stratum corneum hydration. *British journal of plastic surgery, 53*(6), 503-507.

Sullivan, T., Smith, J., Kermode, J., McIver, E., & Courtemanche, D. J. (1990). Rating the burn scar. *The Journal of burn care & rehabilitation, 11*(3), 256-260.

Tandara, A. A., & Mustoe, T. A. (2008). The role of the epidermis in the control of scarring: evidence for mechanism of action for silicone gel. *Journal of Plastic, Reconstructive & Aesthetic Surgery, 61*(10), 1219-1225.

Tsap, L. V., Goldgof, D. B., Sarkar, S., & Powers, P. S. (1998). A vision-based technique for objective assessment of burn scars. *IEEE Transactions On Medical Imaging, 17*(4), 620-633.

Tyack, Z., Simons, M., Spinks, A., & Wasiak, J. (2012). A systematic review of the quality of burn scar rating scales for clinical and research use. *Burns, 38*(1), 6-18. doi:10.1016/j.burns.2011.09.021

Ud-Din, S., & Bayat, A. (2016). Non-invasive objective devices for monitoring the inflammatory, proliferative and remodelling phases of cutaneous wound healing and skin scarring. *Experimental Dermatology, 25*(8), 579-585. doi:10.1111/exd.13027

Van den Kerckhove, E., Stappaerts, K., Boeckx, W., Van den Hof, B., Monstrey, S., Van der Kelen, A., & De Cubber, J. (2001). Silicones in the rehabilitation of burns: a review and overview. *Burns, 27*(3), 205-214.

Van den Kerckhove, E., Stappaerts, K., Fieuws, S., Laperre, J., Massage, P., Flour, M., & Boeckx, W. (2005). The assessment of erythema and thickness on burn related scars during pressure garment therapy as a preventive measure for hypertrophic scarring. *Burns, 31*(6), 696-702. doi:10.1016/j.burns.2005.04.014

van Zuijlen, P. P., Angeles, A. P., Kreis, R. W., Bos, K. E., & Middelkoop, E. (2002). Scar assessment tools: implications for current research. *Plast Reconstr Surg, 109*(3), 1108-1122.

Verhaegen, P., van der Wal, M. B. A., Middelkoop, E., & van Zuijlen, P. P. M. (2011). Objective Scar Assessment Tools: A Clinimetric Appraisal. *Plastic and reconstructive surgery, 127*(4), 1561-1570. doi:10.1097/PRS.0b013e31820a641a

Verhaegen, P. D., Res, E. M., van Engelen, A., Middelkoop, E., & van Zuijlen, P. P. (2010). A reliable, non-invasive measurement tool for anisotropy in normal skin and scar tissue. *Skin Res Technol, 16*(3), 325-331. doi:10.1111/j.1600-0846.2010.00436.x

Verhaegen, P. D., van der Wal, M. B., Middelkoop, E., & van Zuijlen, P. P. (2012). *Scar assessment*: Springer.

Vránová, H., Zeman, J., Čech, Z., & Otáhal, S. (2009). Identification of viscoelastic parameters of skin with a scar in vivo, influence of soft tissue technique on changes of skin parameters. *Journal of Bodywork and Movement Therapies, 13*(4), 344-349. doi:10.1016/j.jbmt.2008.06.004

World Health Organization. (2018). *Burn Fact Sheet*. Retrieved from https://www.who.int/news-room/fact-sheets/detail/burns.

Woo, M. S., Moon, K. J., Jung, H. Y., Park, S. R., Moon, T. K., Kim, N. S., & Lee, B. C. (2014). Comparison of skin elasticity test results from the Ballistometer((R)) and Cutometer((R)). *Skin Res Technol, 20*(4), 422-428. doi:10.1111/srt.12134

Xu, R., Luo, G., Xia, H., He, W., Zhao, J., Liu, B., . . . Wang, Y. (2015). Novel bilayer wound dressing composed of silicone rubber with particular micropores enhanced wound re-epithelialization and contraction. *Biomaterials, 40*, 1-11.

Yagmur, C., Akaishi, S., Ogawa, R., & Guneren, E. (2010). Mechanical receptor-related mechanisms in scar management: a review and hypothesis. *Plast Reconstr Surg, 126*(2), 426-434. doi:10.1097/PRS.0b013e3181df715d

Yelvington, M., Brown, S., Castro, M. M., & Nick, T. G. (2013). The use of neoprene as a scar management modality. *Burns, 39*(5), 866-875.

Yu, A., Yick, K. L., Ng, S. P., & Yip, J. (2015). The effect of pressure and fabrication of pressure therapy gloves on hand sensitivity and dexterity. *J Burn Care Res, 36*(3), e162-175. doi:10.1097/bcr.0000000000000117

Yu, A., Yick, K. L., Ng, S. P., & Yip, J. (2016). Orthopaedic textile inserts for pressure treatment of hypertrophic scars. *Textile Research Journal, 86*(14), 1549-1562.

Zhang, Y., Goldgof, D. B., Sarkar, S., & Tsap, L. V. (2004). A modeling approach for burn scar assessment using natural features and elastic property. *IEEE Transactions On Medical Imaging, 23*(10), 1325-1329.

Zheng, Y.-P., & Huang, Y.-P. (2016). Measurement of soft tissue elasticity in vivo : techniques and applications. Boca Raton, FL: CRC Press.

Zhu, Z., Ding, J., Shankowsky, H. A., & Tredget, E. E. (2013). The molecular mechanism of hypertrophic scar. *Journal of cell communication and signaling, 7*(4), 239-252.

Appendix I Ethical Approval I

THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

To	Tsang Wai Ping Cecilia (Department of Rehabilitation Sciences)		
From	TSANG Wing Hong Hector, Chair, Departmental Research Committee		
Email	rshtsang@	Date	23-May-2016

Application for Ethical Review for Teaching/Research Involving Human Subjects

I write to inform you that approval has been given to your application for human subjects ethics review of the following project for a period from 25-Apr-2016 to 30-Aug-2016:

Project Title:	Validation of DermaLab Combo on Post Burn Hypertrophic Scar
Department:	Department of Rehabilitation Sciences
Principal Investigator:	Tsang Wai Ping Cecilia
Reference Number:	HSEARS20160418006

Please note that you will be held responsible for the ethical approval granted for the project and the ethical conduct of the personnel involved in the project. In the case of the Co-PI, if any, has also obtained ethical approval for the project, the Co-PI will also assume the responsibility in respect of the ethical approval (in relation to the areas of expertise of respective Co-PI in accordance with the stipulations given by the approving authority).

You are responsible for informing the Departmental Research Committee in advance of any changes in the proposal or procedures which may affect the validity of this ethical approval.

You will receive separate email notification should you be required to obtain fresh approval.

TSANG Wing Hong Hector

Chair

Departmental Research Committee

Appendix II Ethical Approval II

THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

To	Tsang Wai Ping Cecilia (Department of Rehabilitation Sciences)
From	TSANG Wing Hong Hector, Chair, Departmental Research Committee
Email	rshtsang@ Date 05-Dec-2016

Application for Ethical Review for Teaching/Research Involving Human Subjects

I write to inform you that approval has been given to your application for human subjects ethics review of the following project for a period from 29-Jul-2014 to 30-Nov-2016:

Project Title:	The Development and Application of "Scar-care" Padding on Management of Hypertrophic Scar
Department:	Department of Rehabilitation Sciences
Principal Investigator:	Tsang Wai Ping Cecilia
Project Start Date:	29-Jul-2014
Reference Number:	HSEARS20140618002-01

Please note that it is the University's policy that all new research/teaching projects involving tests/trials on human subjects are required to take out appropriate insurance if deemed necessary by the Human Subjects Ethics Sub-committee. For such cases, investigators are not allowed to start any research/teaching projects involving tests/trials on human subjects if no appropriate insurance is or can be arranged.

You will be held responsible for the ethical approval granted for the project and the ethical conduct of the personnel involved in the project. In the case of the Co-PI, if any, has also obtained ethical approval for the project, the Co-PI will also assume the responsibility in respect of the ethical approval (in relation to the areas of expertise of respective Co-PI in accordance with the stipulations given by the approving authority).

You are responsible for informing the Human Subjects Ethics Sub-committee in advance of any changes in the proposal or procedures which may affect the validity of this ethical approval.

TSANG Wing Hong Hector

Chair

Departmental Research Committee