CHAPTER II
REVIEW LITERATURES

2.1 Introduction

Systemic sclerosis (SSc) is an autoimmune disease of the connective tissue. The cause of SSc is unknown (Shoenfeld et al., 2005). It is a clinically heterogenous, systemic disorder which affects the connective tissue of the skin, internal organs and the wall of blood vessels (Varga, 2008). Researchers have found some evidences that genes are important factors, but the environment also seems to play a role. Morbidity and mortality in systemic sclerosis depend on the organ or system involved. Early recognition and diagnosis are important because effective therapies for many of the systemic manifestations are available, but timely treatment is required (Eisenberg et al., 2008).

Cellular infiltrates (perivascular or diffuse) have been demonstrated in skin, lungs (alveolitis), smooth muscle cells, esophagus, ileum and jejunum, synovium, and liver. These cells consist of T lymphocytes ($CD4^+$, $CD8^+$), B lymphocytes, and other nonspecific inflammatory cells, such as macrophages, mast cells, and eosinophils. Adhesion molecules are involved in accumulation of lymphocytes and other inflammatory cells in the tissues and may play a role in the formation of cellular infiltrates in SSc. Vascular involvement in SSc affects mainly capillaries, arterioles, and small arteries. The vascular pathology consists of absence or reduction in capillaries and ectasia of capillaries (telangiectases), often accompanied by an increase in endothelial cell proliferation. Soluble mediators, adhesion molecules, and cytotoxic factors have been incriminated in the mechanism of endothelial cell damage, including plasma factor VIII (von Willebrand factor), transforming growth factor β, platelet-derived growth factor, granzyme A, vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and endothelin-1.

The mechanism of fibrosis in SSc is not fully understood, even though it is known that soluble mediators (transforming growth factor β, platelet-derived growth factor, interleukin [IL] 4, IL-6, tumor necrosis factor [TNF] α) can affect the behavior

of fibroblast growth, proliferation, collagen synthesis, and chemotaxis. The role of humoral immunity in SSc is also unknown, although about 90% of patients with SSc show circulating antinuclear antibodies.

Skin changes usually involve the hands and can extend to variable degrees proximally to involve the forearms, arms, face, trunk (Li et al., 2008). The structural damage that occurs in SSc starts with small vessel endothelial activation (Sherer, Shoenfeld, 2006). The microvasculature is primarily affected, however, large-vessel disease also occurs (Szucs et al., 2007) and subsequent platelet activation which lead to release of the vasoconstrictors platelet-derived growth factor and thromboxane A_2 (Nietert et al., 1998). At the same time that vasoconstriction is occurring, other immune cells such as lymphocytes and monocytes migrate to injured tissue and blood vessels, producing cytokines and growth factors. In the blood vessel, intimal hyperplasia occurs, leading to vasculopathy and tissue ischaemia such as gangrene of the finger. In addition, local fibroblasts increase synthesis of collagen and extracellular matrix components, producing the thickened skin and organ fibrosis that characterize SSc (Li et al., 2008).

2.2 Classification of Scleroderma

SSc is divided into diffuse and limited subtypes based mainly on the extent of skin involvement, but also on differences in organ involvement and prognosis. Patients with diffuse systemic sclerosis tend to present with rapidly progressive skin thickening, soon after the onset of Raynaud symptoms. These patients are at greater risk of developing life threatening interstitial lung disease, renal and cardiac diseases early in the course of disease. The diffuse form generally carries a worse prognosis (Altman et al., 1991).

Limited systemic sclerosis is also known as CREST syndrome, an acronym for calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangectasia. Patients with limited systemic sclerosis typically present with distal skin thickening, often many years after the onset of Raynaud symptoms. These patients rarely develop renal disease but disabling gastrointestinal disease and cardiopulmonary disease including interstitial lung disease and pulmonary arterial hypertension can occur. Patients with limited systemic sclerosis generally have a

better prognosis than those with diffuse systemic sclerosis, except in the presence of pulmonary arterial hypertension (Li et al., 2008).

Disease progression of SSc is divided into 3 phases. (1) Edematous phase, the patients with SSc show swelling of upper and lower extremity, especially in hand. Skins involvements are concluded on face neck and trunk. Manual therapy doesn't recommend in this phase as a result of muscle inflammation and pain is dominant in this phase. (2) Indurative phase, the upper and lower extremity in the patients with SSc in this phase decrease swelling, but skin becomes induration. Fingers turn into severe pale when cold exposure (2^{nd} Raynaud's phenomenon in SSc) and digitals pitting scar at finger tip. Early treatment with range of motion exercise and superficial heat for hand are suggested in this phase. (3) Atrophic phase is final stage of disease progression. The characteristics of skins in the patients with SSc become dark and atrophic with muscle and bone can not picking up. Face is skinny as a result of atrophic skin and loss of subcutaneous lipid. Skins are thin and leading wound, especially at bone prominent such as dorsum of finger joint. Rehabilitation for the patients with SSc in this phase are important for maintain or restoration in atrophic skin, especially in hand. Disease progression in patients with SSc different in an individual patients. Some case has rapidly progression, such as 1-2 month can find finger flexion contracture.

2.3 Prevalence

Compared with other connective tissue diseases SSc is relatively rare. The prevalence of SSc is reported to be between 13-105 and 13-140 per million in North America, Australia and Europe, respectively (Abraham, Varga, 2005). In Thailand, SSc affects 10 per million adults, shows a female preponderance in ratio 2:1. SSc has the highest case fatality among the connective tissue diseases, with a 10-year survival of 55% (Nilakanuwong, Prichawong, 2005).

2.4 Raynaud's phenomenon and scleroderma

According to the so-called vascular hypothesis, Raynaud's phenomenon (RP) is one initial event in the pathophysiological cascade to SSc. It is observed in 90-98 % of patients with SSc. It may precede SSc for years and its presence may have

predictive value for the subsequent development of SSc, in particular in association with abnormal nailfold capillaries and the occurrence of antinuclear antibodies (ANA). When no underlying condition is known, it is called the primary RP, whereas the secondary RP is used when there is a causal relation to an underlying disease or intake of certain drugs. Secondary RP is most frequently in SSc (Flavahan et al., 2003), and is associated with other autoimmune diseases (Sunderkotter, Riemekasten, 2006). In SSc, secondary RP is the initial symptom in over 90% of patients, and it may lead to thickening of skin (LeRoy, 1996). RP is reversible vasospasms of small arteries and arterioles, involving usually the digital arteries in fingers and toes, triggered primarily by cold, vibration or emotional stress. Classically, the digits turn white (ischaemia), then blue (deoxygenation), then red (reperfusion) (Herrick, 2005).

2.5 Hand deformity and scleroderma

Hand deformity is the major problem of SSc. In the advanced phase, the skin is tight, pale, and waxy; the patient has a progressive impairment of finger flexion, evolving into finger retraction, which gives the claw hand deformity. The long-term ability to perform activities of daily living is of interest to physical therapist that play a role in preventing deformities and maintaining hand function in patients with SSc. Previous studies observed clinically to be correlated with the potential to perform daily tasks. The presence of swelling and deformed finger correlated with the decreasing of hand ability to eat, dress, brush teeth, reach and grasp (Poole, Steen, 1991). Moreover, the ability to hold four common objects (glass, saucepan handle, key, and coin) decreased by hand deformity (Poole, 1994). Thus, the hand rehabilitation program is required for preventing of hand deformity and maintaining quality of life of patients with SSc.

2.6 Treatment of scleroderma

The treatment of systemic sclerosis is difficult and remains a great challenge to the clinician. Because the cause of disease is unknown, the therapeutic options discussed for the treatment of SSc include pharmacological and non-pharmacological treatments.

2.6.1 Pharmacological treatments

Pharmacological treatments are managed to improve peripheral blood circulation with vasodilators and antiplatelet aggregation drugs, to prevent the synthesis and release of harmful cytokines with immunosuppressant drugs, and to inhibit or reduce fibrosis with agents that reduce collagen synthesis or enhance collagenase production. The current therapeutic options discussed for the treatment of systemic sclerosis include the use of

(a) Vasodilators (calcium channel blockers [nifedipine], angiotensin-converting enzyme inhibitors [captopril, losartan potassium], and prostaglandins [iloprost, epoprostenol]),

(b) Immunosuppressant drugs (methotrexate, cyclosporine, cyclophosphamide, and extracorporeal photopheresis), and

(c) antifibrotic agents (D-penicillamine, colchicine, interferon gamma, and relaxin) (Sapadin, Fleischmajer, 2002).

However, vasodilator agents have varieties of side effects such as back pain, muscle spasm, fatigue and insomnia (Dziadziol et al., 1999). Abnormal bone marrow, kidney, gastrointestinal hypomobility which effected by antifibrotic agents (Clement, Furst, 1999, and hypertension, renal crisis, and malignant tumor, especially in lymph system is side effect of immunosuppressant drugs (Clements et al., 1993).

While lung, heart, and kidney involvement need pharmacological approach predominantly, it is accepted that the major rehabilitative problems arise from skin induration and muscle and joint involvement. Rehabilitative strategies and treatments are very important to patients with SSc. In spite of the poor prognosis, in recent years impressive improvements in diagnostic procedures have been made and an early diagnosis, as well as early aggressive treatment, is now possible (Black, Stephens, 1993). This has led to patients with SSc surviving longer, increasing the need to intervene against the development of tissue fibrosis and contractures (Casale et al., 1997).

2.6.2 Non-pharmacological treatments

In recent years non-pharmacological treatments have been great increases in the number of strategies and procedures employed in clinical-fields. Even though clinicians are interested in the importance of rehabilitative approaches

to disabilities deriving from skin and joint adjustments, only scanty specific study on this subject is available. However, few data are available in the literature to assess the efficacy of interventions (Mouthon et al., 2006).

Patients with SSc suffer from reduced quality of life and disability, caused by skin, joint, muscle, and internal organs involvement (Khanna et al., 2007). Therefore intervention against the development of fibrosis and contractures is needed, and it might include appropriate rehabilitation programs for decreasing burden of organ damage and disability (Mouthon et al., 2006).

The purpose of rehabilitative approach to skin involvement is to prevent or delay tightness of skin. There are no rehabilitative guidelines for skin problems of patients with SSc, but the experience gained in the rehabilitation of skin burns may form the principle of a rehabilitative approach. Motion exercises (Mugii et al., 2006), massage (Bongi et al., 2009), heat (Mancuso, Poole, 2008), acupuncture, and Transcutaneous Electrical Nerve Stimulation (TENS) (Jansen et al., 1989) are used to solve skin problems generally.

In the majority of patients with SSc, the articular involvement is caused by skin thickening and retraction over the joint leading to joint disease. Mild weakness and progressive muscular atrophy might be present and accompanied by the elevation of muscular enzymes. Rest (Nicholas, Ziegler, 1977), exercises (active and passive) (Black, Stephens, 1993), heat (Lehmann et al., 1970), stretching (Kottke et al., 1966), splinting, and prosthesis (Melvin, 1976) are modified to improve the functional capacity of joints, tendons, and muscles.

Although analgesic medications may be sufficient, anti-inflammatory and analgesic treatments may present additional side effects in these patients in whom esophageal reflux and gastrointestinal involvement are very frequent. Physical therapy is recommended to apply the treatments as a safe approach for pain management, such as TENs (Willer et al., 1982), Laser (Ceccherelli et al., 1989), and thermotherapy (heat and cold) (Oosterveld, Rasker, 1994).

Ninety percent of patients with SSc complain of loss of hand grasp ability because of skin traction and musculoskeletal problems (Alpiner et al., 1995). Factor such as puffy fingers, calcium deposits, and wrist extension reduction have been identified as risk factors for late development of hand disability (Poole et

al., 2004). Treatments started during the early phase of the disease may help to prevent the extreme disability seen in untreated patients. Flexion contractures of the proximal interphalangeal joints may limit tip-to-tip precisions or complete grasp and lead to weak lateral pinch, result in decrease dexterity. As a result, patients cannot perform manual activities that require grasping or pinching, and many daily living activities and work capacity are frequently impaired (Casale et al., 1997).

Rehabilitation can not stop the pathogenic progression of SSc. However, exercise perform on regular basis may against contracture. Rehabilitation programs also may reduce social handicaps in the family and the workplace, and improve general lifestyle and activities of daily living.

There are several methods of treating the indurative skin, such as motion exercise, massage, heat, and TENS. Many researchers are interested in the therapeutic effects of massage for improving the skin flexibility. Because basic characteristics of massage are gliding, stroking, kneading, and compression of soft tissue. So, massage may increase skin flexibility and temperature. Among various kinds of massage, connective tissue massage and soft tissue mobilization (STM) have been usefully employed in patients with SSc. Although no comparative data of efficacy are available, these types of massage place fascia and muscle in an elongated position and may be helpful when tissue fibrosis is not dominant (Casale et al., 1997).

The Dutch Association for Manual Therapy describes manual therapy (MT) as a specialization within physiotherapy characterized by the analysis, interpretation and treatment of complex health problems resulting from arthrogenic, muscular and neurogenic disorders of the spinal column and extremities using specific manual diagnostic and manual therapeutic techniques (Trijffel et al., 2009). Although contrary of definition to many other countries, but main idea is also beside. Manual therapy (MT) includes a variety of techniques used in clinical practice for the treatment of musculoskeletal pain which target the skeletal system, soft tissue, and nervous system (including soft tissue techniques, mobilization, exercise and manipulation), divided in to 3 categorization of MT techniques (Bialosky et al., 2008).

The first MT techniques categorize is "Joint biased" consist in Manipulation and Mobilization; refer to passive movement of a joint beyond the normal range of motion, and within its normal range of motion, respectively. These

techniques promote range of motion, decreased muscle spasm, and decreased pain (Pickar, 2002).

The second MT techniques categorize is "Soft tissue biased" for example massage, and Traditional Thai Massage etc. Improvements of blood circulation, decreased muscle spasm, relaxation, re-align soft tissue, break adhesions, and increase range of motion are desire outcomes (Buttagat et al., 2009).

The third MT techniques categorize is "Nerve biased" consist in neural dynamics. It refers to passive the specific nerve and/or combined movement of the spine and extremities within their normal range of motion. Improvements of range of motion and decreased pain are desire outcomes (Coppieters, Alshami, 2007).

Based on the pathology of SSc, It involves with the abnormality of skin, joint and muscle. Therefore, manual therapy is suggested as an alternative treatment choice for patients with SSc (Casale et al., 1997).

2.7 Massage and scleroderma

Patients with SSc have a dramatic decrease in cutaneous oxygenation due to vessel obliteration (Matucci-Cerinic et al., 1995). Massages may complement ROM in stimulating vascular function. Massage may mobilize skin fluids, reduce edema, and increase skin temperature by dilating microcirculation through a local or reflex action (Skull, 1945); it may also have a local analgesic effect by increasing the pain threshold (Haldeman, 1989). Basic maneuvers are gliding, stroking, kneading, and compression of soft tissues. Among various kinds of massage (Mennell, 1940), "Bindegewebsmassage" or connective tissue (reflexogenie) massage" (Dicke, 1956) and Soft Tissue Mobilization (STM) (Geiringer et al., 1988) have been usefully employed in our patients. Although no comparative data are available, these types of massage place fascia and muscle in an elongated position and may be helpful when tissue fibrosis is not dominant.

The use of heavy pertolatum or lanolin lubricants to protect the skin during massages has been proposed in patients with SSc (Winkelmann et al., 1971). Lubricants have also been recommended for sexual intercourse because vaginal dryness occurs in a high percentage of patients with SSc (71%) leading to ulcerations and dyspareunia (Bhadauria et al., 1995). Sexual problems may also occur in men

with SSc because of skin induration leading to a loss of penile length and erectile function (Aversa et al., 2005). Penile implantation surgery has been proposed (Nehra et al., 1995), but no extensive follow-up data are available.

Moreover, massage therapy has been effective in promoting growth (Field et al., 2004), decreasing depression (Diego et al., 2002), and enhancing attentiveness (Escalona et al., 2001), reducing pain (Field et al., 2002), and improving immune function (Field et al., 2001). Therefore, massage may useful for improvements of clinical problems in patients with SSc.

2.8 Traditional Thai Massage (TTM) and scleroderma

TTM is an integral part of the culture of Thailand and more importantly the healthcare system. The foundation of Primary Health Care System focuses on the role of an individual and responsibility for health. By utilizing TTM as a means of preventive and curative care the Thai community can inexpensively and actively take responsibility for their own health. In addition, TTM is an effective treatment for various types of clinical conditions used in conjunction with other treatments and also alone (Chatchawana et al., 2005).

The focus of TTM is completely different from a western style of massage, like the Swedish massage. It consolidates soothing massage techniques, including gentle muscular stretches of Hatha yoga, which is energizing, and thumbing techniques similar to acupressure, which is stimulating. Patterns of gentle rocking, thumbing, and rhythmic palming ease the body into a deeply relaxed meditative state (Buttagat et al., 2009).

By pressing various points along the Sen Lines, the massage activates and restores the flow of energy throughout the body. By manipulating the energy body, energy blockages are removed balancing the essence of life, earth, air, wind, and fire. As these elements of the invisible energy body become balanced, pain, discomfort, illness, and disease are reduced and eliminated (Brust, 1993).

Previous studies have been shown the therapeutic effect of TTM in various conditions such as pain relieve in Myofascial Trigger Points (MTrPs) in patients with low back pain (Chatchawana et al., 2005), reduction of sympathetic nervous system activity and increasing of parasympathetic nervous system activity (Cowen et al.,

2006), and inflammatory mediators reduction, pain threshold increasing (Mackawan et al., 2007). Moreover, parasympathetic nervous system activity such as heart rate variability (HRV) is increased by used TTM in patients with back pain associated with myofascial trigger points (Buttagat et al., 2009).

Although TTM has been used in various conditions, it is the first study of the therapeutic effect of TTM in patients with SSc. From basic maneuvers of TTM, it may promote the skin flexibility and hand temperature for improvement of hand functions in patients with SSc.

2.9 The evaluation of hand temperature

In this study, Thermography (Fluke Ti1) was used for evaluating difference of skin temperature. It is a high sensitive, reliable and non-invasive procedure to detect infrared radiation from all objects base on their temperatures. It identifies even small temperature differences that could indicate problems with excellent thermal sensitivity. The detail of this procedure shows in Appendix A. A previous study investigated the effect of massage on the skin and the intramuscular circulatory change by thermography (JTG-3300) in normal subjects (Mori et al., 2004).

2.10 The evaluation of hand mobility

Hand Mobility in Scleroderma (HAMIS) is a hand function test for persons who have systemic sclerosis (scleroderma). The purpose of HAMIS is to obtain an estimation of the hand mobility that is precise enough to detect limitation of motion at the same time as it indicates the ability to use the hand in daily occupations. Items of HAMIS were designed to measure all movements assessed in an ordinary range of motion (ROM)-measured hand test (Sandqvist, Eklund, 2000a). HAMIS consists of 9 items, which assess finger flexion and extension, abduction of the thumb, pincer grip, finger abduction/swelling, dorsal extension and volar flexion of the wrist, pronation and supination. Each item is graded on a 0–3 scale, where 0 corresponds to normal function and 3 denotes that the individual is unable to perform the item. Each hand is assessed separately. The total score of HAMIS for each hand is 27, which represents a high degree of dysfunction (Sandqvist, Eklund, 2000b).