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Theme: Lymphoedema - alternative pathways.

Lymphatic scarring and secondary lymphoedema post breast cancer treatment.

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Introduction.

Breast cancer treatment is often followed by a decline in upper body function, even at some time distant from the therapy. Upper body dysfunction may arise shortly after therapy and resolve, arise, and persist for at least 21 months, or arise at some time distant from the therapy (Lash and Silliman, 2008).

Impairment may be due to

- Soft tissue fibrosis (scarring).
- Deficits in muscle strength and flexibility.
- Lymphatic insufficiency.
- Neural hypersensitivity.

All of which form the basis for the pathophysiological targets of rehabilitative interventions.

Transient lymphostasis is common immediately following surgery and during radiation.

Although in general, normal lymphatic homeostasis is restored uneventfully by the development of collateral lymph drainage pathways, post-operative lymphostasis may become chronic and progress to lymphoedema involving the trunk, axilla, breast and arm (Cheville & Tchou, 2007). Between 2.4% and 56% of breast cancer patients will develop lymphoedema and once established, lymphoedema cannot be cured. It is therefore essential to prevent or minimise this condition.

It is not known why only some women develop lymphoedema after breast cancer treatment, though variations in the anatomy, surgical procedure and radiotherapy may contribute to differences in outcomes (Davis, 2001). Risk factors and treatment approaches have been extensively covered in the literature, and are beyond the scope of this presentation.

Lymphoedema is the result of the functional overload of the lymphatic system in which lymph volume exceeds transport capabilities (Cheville & Tchou, 2007). It seldom exist in isolation. Soft tissue fibrosis (scarring), deficits in muscle strength and flexibility and neural hypersensitivity often co-exist in patients presenting with secondary lymphoedema. All of the above may be traced back to varying degrees of damage inflicted on the continuity of supporting and coordinating fascial and connective tissue structures and its subsequent response to the tissue healing process.

Aim

The aim of this presentation is to improve clinical reasoning and treatment planning by a better understanding of anatomy, damage and possible pathophysiology of supporting structures after the treatment for primary breast cancer.

Rationale

Secondary lymphoedema is a condition that largely develops as a secondary problem to the primary procedure – the surgical clearance of the axilla in order to evaluate distal metastatic spread and to assess prognosis of the disease, as well as the use of radiotherapy to control the disease. It is however not the focus of this presentation. An overview of the primary problem area, the axilla, will be presented. This will be done under the following headings: 1) axillary anatomy, 2) surgical procedures involving axillary clearance, 3) tissue healing and repair after primary treatment, and 4) treatment approaches aimed at the primary problem to augment our conference theme of looking at alternative pathways in lymphoedema management.

1. Axillary anatomy. Central to understanding most of the functional musculoskeletal sequelae of the treatment of primary breast cancer is the axilla.

The axilla is a pyramidal, fat-filled fascial compartment giving passage to, or housing the major “utilities” serving the upper limb. The structures passing through, or housed within the axilla are either ensheathed in a protective wrapping (neurovascular bundles within its fascial sheath), or embedded in a cushioning matrix of axillary fat (e.g. lymph nodes) that allows abundant movement freedom between the occupying structures. Well-defined muscle walls surround the pyramid-shaped space (Moore & Dalley, 2006). It should further be noted that the fasciae associated with the muscle walls forms a continuity with the brachial fascia which is of considerable functional importance (Stecco et al., 2007). Anteriorly for example, the pectoralis

major fascia is continuous with the brachial fascia in two distinct ways. Firstly, the fascia from the clavicular head of pectoralis major has a thickening of collagen fibres extending into the anterior brachial fascia over biceps and secondly, the fascia from the sterna and costal heads are continuous with the axillary fascia and then with the medial brachial fascia.

Embedded within the fibrofatty connective tissue of the axilla are all the major lymph nodes into which all the lymphatic vessels of the upper limb and most of the lymph from the breast drain. They are arranged in five identifiable groups. Medial and anterior superficial lymph vessels accompanying the basilic vein and deep vessels from the upper limb drain into the lateral (humeral) group of lymph nodes, while the lateral vessels accompanying the cephalic vein drain into the apical nodes. Seventy five percent of the lymph from the breast and areolar plexus drains into the anterior (pectoral) group of nodes before they continue to the central nodes joined by the efferents from the lateral nodes.

2. Surgery. Surgery is performed to ensure the removal of local malignant disease from the breast. As an extension of the breast procedure, various degrees of axillary clearance are also performed. This is done to control and assess routes of spread of the disease and for staging in order to plan further treatment.

The standard for comparison of results in treatment of patients with breast cancer continues to be mastectomy. This remains the most widely used procedure to ensure removal of local malignant disease in the breast. Mastectomy involves removal of the entire breast and some or all of the axillary lymph nodes. During surgery, all or some of the above anatomical structures may be compromised (pectoralis major and axillary fascia, axillary lymph nodes and its supporting fibrofatty connective tissue).

In breast conserving procedures, only the lump is removed from the breast. The axillary nodes are usually also sampled or cleared to evaluate and control distant metastatic spread. This is done through a separate incision either longitudinal along the posterolateral border of the pectoralis major muscle, or a transverse incision below the axillary hairline.

3. Wound healing. I believe that it is during the recovery period that the stage is set for future sequelae and problems in functional outcomes after the primary treatments.

Scar formation (adhesions, fibrosis) is our primary method for restoring tissue integrity. All wounds pass through the same sequence and mechanism of repair – haemostasis, inflammation, fibroplasia/proliferation and remodelling phases – towards full recovery. For open wounds (including surgical incisions) and severe internal tears (ruptured ligament or tendon) wound closure and strength are critical and thus a certain amount of scarring is necessary and inevitable. For internal tissue injuries and inflammation involving fascia and organs however, scarring and adhesions are mostly detrimental since it can contribute to maintaining the chronicity of tissue stiffness, abnormal movement patterns and pain (Bouffard et.al., 2007).

Inflammation is crucial to the highly orchestrated response to tissue injury. It persists throughout all wound healing phases, stimulating and coordinating the essential functions of wound repair. Inflammation is initiated by mediators released by resident cells of the wound bed and platelets and leukocytes delivered by the circulation starting a series of events that attempt to stabilise the wound, remove invading organisms, and return the wound to preinjury architecture.

Repair is controlled by the release of cytokines and growth factors (inflammatory mediators) in response to injury and damage. They regulate all aspects of tissue remodelling, whether planned (as in development) or unplanned (as in tissue repair after injury). Essential mediators involved in tissue remodelling after injury are transforming growth factor beta (TGF- β), platelet-derived growth factor (PDGF), basic fibroblast growth factor (FGF), tumour necrosis factor (TNF), vascular endothelial growth factor (VEGF) and interleukin-1 (IL-1). They can also be referred to as connective tissue growth factors given their strong local functions and rare systemic effects (Henry & Garner, 2003)

TGF- β 1 is unique in its widespread actions that enhance the deposition of extracellular matrix. It also acts as a potent regulator of repair, coordinating or suppressing the actions of other cytokines and mediators (Border & Noble, 1994).

After surgery, the scar initially surrounds and invades all structures, binding them together in a single unit or one large wound. As wound healing progresses, the scar “differentiates” into various tissues by means of its response to the internal (inflammatory mediators and growth

factors) and external (motion and directional stress) stresses applied (Hardy, 1986). The way in which the connective tissue matures will produce either a dense, unyielding scar, or a pliable mobile scar. A problem that may arise after surgery and even radiotherapy for breast cancer is the prolonging of the inflammatory phase of wound healing resulting in proliferative scarring and increased fibrosis within the damaged area (i.e. axilla, chest wall). Fibrosis represents a pathologic excess of the normal process of tissue repair. Excessive or sustained production of TGF β -1 is a key molecular mediator of tissue fibrosis. Whereas it can function either as an agonist or antagonist of cell proliferation and inflammation, it consistently and potently acts on cells to induce the deposition of extracellular matrix – even excessively should the inflammatory process be prolonged. The accumulation of matrix in tissues is the chief pathologic feature of fibrotic disease (Border & Noble, 1994).

Discussion

Treatment. Rehabilitation concerns the continuum of primary breast cancer sequelae. One of the primary challenges is guiding the wound to return as close to pre-surgery architecture as possible. This can only be done if we can control the inflammatory responses during the various healing stages. Bouffard et al. (2007) studied the effect of brief tissue stretching on the TGF- β and the secretion of tropocollagen during wound healing. They hypothesised that brief stretching of tissue following injury in vivo would decrease soluble TGF- β 1 levels, ease TGF- β 1 auto-induction and decrease new collagen deposition. They showed that elongation of subcutaneous tissue of the trunk by 20 – 30% for 10 minutes twice a day significantly reduces the amount of subcutaneous new collagen 7 days following subcutaneous tissue injury.

These results suggest that stretch-induced decrease in TGF- β -mediated new collagen formation may be an important natural mechanism limiting excessive scarring and fibrosis following injury supporting the long-standing, but poorly understood physiotherapy practice of using brief, judiciously applies stretching of tissue to treat excessive scarring, connective tissue adhesions, and contractures. This effect on decreasing TGF- β and collagen synthesis highlights the critical importance of “dose” (i.e. duration, amplitude, frequency) in mechanically induced connective tissue remodelling. Fully understanding the dose-related effects of mechanical stretch on TGF- β and collagen would encourage the development of therapies based on measured amounts of stretch that may decrease fibrosis at low cost.

This is exactly the realm within which the gentle techniques used in MLD and other post breast

cancer manual therapies fall. I am of the opinion that the application of these gentle graded manual tissue techniques should be extended to the earliest possible opportunity after surgery and radiotherapy. In this way one may facilitate dynamic cytoskeleton reorganisation within the damaged axillary and chest wall area, decreasing collagen laydown and fibrosis, and thereby aiding in the regeneration of a viable collateral venous and lymphatic circulation through the axilla.

Conclusion

The alternative pathway I therefore propose is seated in early graded intervention on a graded tissue stretch and mobilisation model in order to aid return of the axillary wound to pre-surgery architecture. Minimising tissue fibrosis and scarring, aiding the mediators of the healing process by mechanical induced connective tissue remodelling.

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