Massage can provide several benefits to the body such as increased blood flow, reduced muscle tension and neurological excitability, and an increased sense of well-being.

The effects of massage are most likely produced by more than one mechanism (Tappan et al., 1998; Goats, 1994; Braverman et al., 1999). There are a theoretical model of how biomechanical, physiological, neurological and psychological mechanisms (Braverman et al., 1999; Bell, 1964).

Research has reported massage is beneficial on cellular (increasing the number of mitochondrias, inducing cell signaling and transduction), physiological (blood flow and blood-borne substance), neurological (investigated by H-reflex) and psychological (investigated by questionnaire and physiological parameters such as heart rate, blood pressure mechanisms). The mechanical mechanisms of pressure and motion of massage on muscle properties such as passive or active muscle stiffness need further studies to be dilucidated.

**Expected mechanism of massage**

- **Cellular effects**
  - Mechanotransduction
  - Pressure
  - Electrical
  - Neurological

  - Number of mitochondrias
  - Cellular recovery
  - Collagen and wound healing
  - Inflammation
  - Collagen fibres
  - Reorientation
  - Skeletal muscle tension or spasm
  - Neuromuscular excitability
  - Pain

- **Biomechanical effects**
  - Mechanical changes in tissues

- **Physiological effects**
  - Changes in tissue or organ
  - Muscle blood flow
  - Skin blood circulation
  - Parasympathetic activity
  - Relaxation hormones
  - Stress hormones

- **Neurological effects**
  - Reflex stimulation
  - Neuromuscular excitability
  - Pain
  - Muscle tension and spasm

- **Psychological effects**
  - Increased relationship between body and mind
  - Relaxation
  - Anxiety

- **Mechanism of action at cellular level**
**Cell signaling and massage therapy**

Inflammation and pain are a usual response to muscle damage. This is associated with immune cell activation and cytokine release from muscle and adjacent immune cells (Crane et al, 2012; Tidball, 2005). Massage therapy uses physical manipulation to exert a therapeutic effect on the damaged tissue. Mechanical stimuli are transformed into cell signaling by a process called Mechanotransduction, which has been extensively studied and reviewed by a number of authors (Geiger et al, 2009; Martin 2009; DuFort et al, 2009; Hahn and Martin, 2009; Wang, 2009).

Several components can sense mechanical force and induce changes in gene expression (see figure below).
The conversion of mechanical stimulation into cellular signaling was first studied in the context of sensory cells, for example hair cells in the inner ear. Further studies in mechanically stressed tissues, for example muscle, cartilage, or vascular system, that are targets of massage therapy, were studied in the context of disease (muscular dystrophies, cancer, arthrosclerosis, etc) and to understand the basic biology of tissue maintenance and function (for example bone, skin, etc) and have been the object of extensive reviews (Geiger et al, 2009; Martin 2009; DuFort et al, 2009; Hahn and Martin, 2009; Wang, 2009).

The ability of cells to sense and respond to changes in their physical environment is important in maintaining homeostasis but also to respond to injury. Almost all cells rely on Mechanotransduction signaling:

- Mechanotransduction, cells convert mechanical stimulus into biochemical activity by inducing synthesis of enzymes, neurotransmitters or structural proteins.
- Neural response, conversion of mechanical signals into electrical signals by physical stimulation of mechanoreceptors in neurons change in the excitability of specialized sensory cells and sensory neurons.

Massage therapy consists of the physical manipulation of muscle and lumber tissue at the site of injury, stiffness, or soreness; with the aim of reducing pain and promoting recovery (Cherkin et al, 2003; Barnes et al, 2008). The partial or complete rupture of connective tissues causes changes in their structure and physiology, and modifies the normal interaction between adjacent tissues, producing pain and reducing movement in joints.

There is an increasing interest in understanding the molecular basis of massage therapy. A recent paper by Tarnopolsky and co-workers studies the effects of massage therapy on inflammatory markers of muscle injury (Crane et al, 2012). This seminal work showed an effect on massage on regulation of NFkB, a key mediator of inflammation, and increased production of mitochondria, accelerating the healing process. The results show that massage therapy does have an effect on mediators of inflammatory response in a controlled clinical study, and are in good agreement with the biology of Mechanotransduction and cellular signaling. These studies are limited by the lack of delivering a consistent and reproducible therapy to the patients; this limitation is being addressed by MC Health Tech devices, that control the amount and strength of the therapy in a measurable way and each patient can receive a standard treatment protocol, independently of the provider or practice.
Mechanotransduction

Cells have an integrated tension system that maintains its morphology and function (Janmey et al, 2007; Ingber, 2006; Ingber, 1993; Ingber, 1997; Ingber, 2003; Ingber, 2003). The interactions between the extracellular microenvironment and cellular function are complex. Alterations of the extracellular matrix (ECM) can sustain tensional homeostatic changes in the cell, by translating mechanical forces and deformations into biochemical signals (DuFort et al, 2011; Fukada, 1982; Guzelsu, 1982; Gross and Williams, 1982). Mechanotransduction can occur simultaneously via the ECM or cell–cell junctions (Chen et al, 2004).

ECM signaling is transmitted to keratinocytes and fibroblasts linked through adhesion molecular connections. The ECM is dynamically regulated by mechanical forces that alter the folding and constraining training of matrix elements to expose binding sites. The number and clustering of binding sites is regulated by con training changes due to mechanical distortion, proteolysis, surface adsorption, and other mechanisms (Stevens et al, 2005). These changes in the con training of ECM and subsequent binding to receptors impact signal transduction (Stevens et al, 2005).
The effects of the ECM are primarily mediated by integrins, a family of cell surface receptors that attach cells to the ECM, that transmit the mechanical and chemical signals (Schwartz, 2010). Integrin receptors can activate a number of intracellular signaling pathways following ECM adhesive interactions. They have the ability to bind fibronectin, laminins, collagens, tenascin, vitronectin, or thrombospondin. When a signal transduction occurs, integrins transfer the information on chemical composition and mechanical status of the ECM into the cell (Stevens and George, 2005). These transmembrane receptors tether the cell cytoskeleton to the fibers of the ECM, forming local focal adhesions. When bound, they activate a cascade of intracellular signaling pathways like cytoplasmic kinases, growth factor receptors, and ion channels that effects the organization of the intracellular actin cytoskeleton (Pawson and Nash, 2000; Geiger et al, 2009; Wang, et al, 1993).

The cytoskeleton is a fibrillar structure in the cytoplasm, formed by microtubules of tubulin, and actin filaments, which are major elements of the contractile device of the cell. The cytoskeleton maintains cell shape in front of the mechanical stresses, with an elastic network of microfilaments (consisting of semiflexible actin monomers; microtubules, rigid polymers, and inner filaments, and highly flexible polymers) which resist detraining (Janmey et al, 2007; Ingber, 2006; Ingber, 1993; Ingber, 1997; Ingber, 2003; Ingber, 2003).

These filaments and fibrils are organized in a network that expands the cytoplasm, and links cellular organelles with the nucleus and cytoplasmic membrane. The cytoskeleton transmits the amount and intensity of impulses conducted from the ECM into the cell (Jain et al, 1990). Mechanical forces can be channelled along cytoskeleton filaments and concentrated at distant sites in the cytoplasm and nucleus (Wang et al, 2011). In the nucleus this signaling leads changes in gene expression and affect most aspects of cell behaviour, modifying differentiation and proliferation.
The cytoplasmic tail of integrin serve as a binding site for α-actinin activating the FAK (Focal Adhesion Kinase). Phosphorylation of FAK, lead to the activation of numerous kinases. These kinases are key regulators of gene expression via the phosphorylation of multiple transcription factors (Chambers et al, 2009, Chambers et al 1995; Sakamoto et al, 2003; Sasai, et al 2010).

The effects of massage on Mechanotransduction signaling were evaluated in a controlled clinical study by Crane et al (2012) in young male participants after exercise-induced muscle damage. They observed that massage activated the Mechanotransduction signaling pathways FAK and extracellular signal–regulated kinase 1/2 (ERK1/2), potentiated mitochondrial biogenesis signaling (nuclear peroxisome proliferator–activated receptor g coactivator 1a (PGC-1a)), and mitigated the rise in nuclear factor kB (NFkB) (p65) nuclear accumulation caused by exercise-induced muscle trauma. Massage also attenuated the production of the inflammatory cytokines tumor necrosis factor–a (TNF-a) and interleukin-6 (IL-6) and reduced heat
shock protein 27 (HSP27) phosphorylation, thereby mitigating cellular stress resulting from myofiber injury. The conclusion is that, when administered to skeletal muscle acutely damaged, massage therapy appears to be clinically beneficial by reducing inflammation and promoting mitochondrial biogenesis.

Others authors also observed that the stretching of skeletal muscles (Hornberger, et al, 2005; Kumar et al, 2002), activates the kinase cascades and the regulatory factors that modulate protein synthesis, glucose uptake, and immune cell recruitment (Cara et al, 2001; Chambers et al, 2009; Hornberger et al, 2006).

Fibroblasts are key modulators in the inflammatory responses in the connective tissues. They synthesize abundant IL-1 in contact with a relaxed three-dimensional collagen network, which up regulates the production of additional inflammatory mediators, for example IL-6 and COX-2. The therapeutic effect of massage is similar to NSAIDs and can provide equivalent benefits without the side effects of NSAIDs.

- Tissue injury triggers both inflammatory and repair responses that lead to fibrosis. The healing of an injured site starts by a mechanical stimuli that activate the fibroblasts. It produces the migration of fibroblasts and the increasing of the collagen and other components of extracellular matrix. The repetitive application of massage (mechanical stimuli) sessions stimulates the activity, proliferation and collagen production and form the collagen deposits at the site of injury producing a fibrosis. Fibrosis is characterized by the persistence of activated myofibroblasts, ineffective re-epithelialization, and variable degrees of inflammation within injured tissues (Selman et al., 2001; Thannickal, 2004). Transforming growth factor β1 (TGF-β1) is a multifunctional growth factor that plays a central role in tissue homeostasis, reparative responses (Blole et al, 2000; De Wever et Mareel, 2003; Leask and Abraham, 2004). TGF- m is one of the key cytokines regulating the response of fibroblasts to injury, as well as the pathological production of fibrosis (Barnard et al., 1990; Sporn and Roberts, 1990; Leask and Abraham, 2004). Elevated extracellular levels of TGF-β1 have a major impact on ECM composition by causing autocrine and paracrine activation of fibroblast cell surface receptors, leading to increased synthesis of collagens, elastin, proteoglycans, fibronectin, and tenascin (Balza et al., 1988; Bassols and Massague, 1988; Kahari et al., 1992; Cutroneo, 2003). In vivo, connective tissue remodelling also occurs in response to changing levels of externally applied mechanical forces. It reduces collagen deposition during tissue repair and scar training (Cummings and Tillman, 1992). Boufard et al (2008) observed that a tissue stretch can attenuate the increase in both soluble TGF-β1 (ex vivo) and Type-1 procollagen (in vivo) following tissue injury. This decreased fibrogenic response with brief, moderate amplitude stretch is in marked contrast to the well-established increase in TGF-β1 and collagen following prolonged low amplitude mechanical.
Fig. 6.4. Effect of tissue stretch in vivo on subcutaneous tissue Type-1 procollagen in mouse microinjury model. A: average ± SE procollagen percent staining area in non-injured versus injured sides, without stretch (N = 11) and with stretch (N = 10); B,C: Type-1 procollagen in non-stretched and stretched tissue (both injured). Scale bars, 40 μm (Bouffard et al 2008)

The mechanical stimuli acts on the endothelial cells producing new capillary network. The mechanical stimuli also produce the chain of electrophysiological events that speed up the process of collagen deposit and the correct orientation of collagen fibrils. This process restores the normal anatomical structure in place of an original injury or somatic pathology.

- **Mechanism of action at biomechanical level**

  On a clinical level, biomechanics permits understanding patterns of injury and for developing physical therapy programs which will increase strength. Massage acts on the biomechanical level in:

  - **Pumping**: The stroking movements in massage suck fluid through blood vessels and lymph vessels. By increasing the pressure in front of the stroke, a vacuum is created behind.

  - **Increasing tissue permeability**: Deep massage causes the permeability in tissue membranes, enabling fluids and nutrients to pass through. This helps remove waste products such as lactic acid and encourage the muscles to oxygen and take nutrients which help them recover quicker.

  - **Stretching**: Massage can stretch tissues that could not be stretched in the usual methods. Bundles of muscle fibers are stretched lengthwise as well as sideways and fascia that surrounds the muscle, so releasing any tension or pressure build
Massage: Mechanism of action

- **Breaking down scar tissue:** Scar tissue is the result of previous injuries or trauma and can affect muscle, tendons and ligaments. This can lead to inflexible tissues that are prone to injury and pain.

- **Improving tissue elasticity:** Static flexibility is defined as the range of motion available to a joint or series of joints, (Gleim and McHugh, 1997) and is usually measured with a goniometer (Clarkson, 2000). The majority of studies were based on range of motion measurement (Leivadi et al, 1999; Nordschow M, Bierman, 1962; Wiktorsson-Moller et al, 1983).

- **Redacting muscle spasm:** Massage may contribute to rearrange muscle fibers and increase microcirculation. The realignment of muscle fibers may help to reduce muscle spasm that stimulates pain receptors and assist in reducing the pressure on the surrounding blood vessels. The improved circulation would help to increase nutritive blood flow to the damaged area.

- **Opening microcirculation:** Massage does increase blood flow to tissues, by opening or dilating the blood vessels and by stretching them.

**Mechanism of action at physiological level**

Massage is thought to induce a variety of positive physiological effects (Wright and Sluka, 2001), that may contribute to tissue repair, pain modulation, relaxation, and improved mood and that has beneficial effects on arterial and venous blood flow and edema (Goats, 2004).

Massage at the physiological level:

- **Increasing local Temperature:** Mechanical pressure might help to increase blood flow by increasing the arteriolar pressure, as well as increasing muscle temperature from rubbing (Weerapong et al, 2005). Local heating increases local blood circulation (Black et al, 2003; Weerapong et al, 2005; Longworth, 1982). The intense massage strokes (friction, percussion) release a greater amount of vasoactive substances and triggers local and general vasodilation.

- **Increasing Blood Flow:** Massage promotes acceleration of muscle and venous blood flow, increased blood volume and reduced muscle tightness (Dubrovsky (1983, 1990), a local and general vasodilation triggered by release of vasoactive substances from the massaged tissues: histamine, bradykinin and kalidin (Kutz et al., 1978; Kuprivan, 1995, Yang et al, 2009). These substances trigger local and general vasodilation if their concentration in the blood increases.

A vigorous massage increase local blood flow and cardiac stroke volume, as well as improve lymph drainage. Massage increases in muscle blood flow, enhance muscle recovery from intense exercise and remove Lactate from the muscles. It is thought that massage also presents an anticoagulant effect.
• **Promoting parasympathetic activity:** Massage stimulates the skin receptors and subcutaneous tissues, stimulating the vagal activity (Field, 1998), which elevates parasympathetic responses (Field, 1998). The stimuli are transmitted from the afferent fibers of the PNS to the spinal cord to the central and ANS (Wall and Melzack, 1984). Some of these effects stimulate vagal activity, resulting in a feeling of sedation and a reduction of heart rate (Wall and Melzack, 1984) that may reduce anxiety, depression, and pain.

Massage can stimulate parasympathetic activity by reducing heart rate and blood pressure (Longworth, 1982; Labyak et al, 1997), increasing relaxation substances such as endorphins (Kaada B, Torstein B, 1989) and increasing cardiac parasympathetic activity and improving measures of relaxation (Delaney et al, 2002).

• **Promoting the liberation of neuroendocrine substances:** Massage decreases hormone levels (cortisol and serotonin) (Leivadi et al, 1999; Hernandez-Reif et al, 2001) (Hernandez-Reif et al, 2001). The stimulation by the massage of the parasympathetic activity reduces cortisol from the saliva.

Massage can increase levels of endorphins (Kaada and Torsteinbo, 1989), decrease arousal level (Longworth, 1982) and increase parasympathetic response endorphins (Kaada and Torsteinbo, 1989).
Massage: Mechanism of action

- **Mechanism of action at neurological level**

  Massage stimulate receptors or nerve endings to obtain a neural response. Mechanical force is necessary to initiate a chain of neurophysiologic responses which produce the outcomes associated with massage therapy. The response at neurological level are complex interactions of both the peripheral and central nervous system which comprise the pain experience.

  Nervous system is involved in the control of skeletal muscles, analgesia processes, neuromuscular excitability and the Hoffman reflex, and general well being.

**Pain**
**Mechanism of analgesia of a massage therapy:**

1. **Conduction of the nervous impulses to the CNS through nervous fibers.**

   The large, unmyelinated C fibers that conduct the nervous impulses at low speed. It produces a slow pain that is dull, aching and poorly localized. They conduct the nervous impulses generated in the peripheral receptors of the skin and connective tissue structures by massage strokes. The myelinated A fibers conduct the nervous impulses at high speed and a sharp and precisely localized pain.

   Massage might stimulate large fast nerve fibers (unmyelinated C fibers) and block the smaller, slower nerve fibers (myelinated A fibers) that detect pain. This effect presumably could produce a local lateral inhibition in the spinal cord (Guyton, 2000) and explains why touching the painful area is an effective strategy for relieving pain.

   Massage activate the 'pain gate' mechanism and so produces short-lived analgesia

2. **Inhibition of the hypothalamo-cortical activity**

   The chronic pain stimuli that reach the spinal cord can inhibit the activity of the hypothalamo-cortical and consequently inhibiting areas of cortex that previously were overstimulated by the permanent bombardment of chronic pain stimuli from the affected area. Massage may reduce pain by control activating the neural-gating mechanism in the spinal cord.

3. **Releasing of endogenous opiate substances.**

   The pain receptors in the corresponding segment of the spinal cord (Watson 1982; Goats and Keir, 1991) are activated by the massage strokes "initiate reflex activity that stimulate the nuclei within the midbrain, which regulate the release of endogenous opiates (inhibitory neurotransmitters) (Andersson and Lundeberg, 1995) within the spinal segment receiving the painful input (Goats and Keir, 1991). This diminishes the intensity of pain transmitted to the higher centers. Massage cause much greater release of opiates and achieve more profound pain suppression.

   Massage can also increase serotonin levels (Leivadi et al 1999; Field et al, 1996; Ironson et ai, 1996; Field, 1997), a neurotransmitter that plays a role in reducing pain (Guyton, 2000), by inhibition of the transmission of noxious nerve signals to the brain (Field, 1998). This pain control concept appears to be mediated in large
part by the "descending pain suppression mechanism" (Goats, 1994). The endocrine involvement of the encephalin serotonin explains the benefits derived from stress management programs, physical exercise and massage (Cailliet, 1988).

The restorative sleep hypothesis holds that because **substance P**, a neurotransmitter associated with pain is released in the absence of deep sleep, the ability of massage to increase restorative sleep reduces substance P and consequent pain (Sunshine and Field, 1997).

**Muscle Spasm**

**Musculoskeletal nervous system** respond to sensory stimulus, like stretch, touch, pain, or those stimuli produced in the massage therapy. The muscle spindle organ and the Golgi tendon organ act as a stretch receptors to trigger the stretch reflex when a muscle in stretched. Massage stimulates skin mechanoreceptors inhibiting the stimulatory signal of muscle contraction at the spinal level, and reducing the synaptic release of acetylcholine (Goicoechea, 2009). Reduction of Ach inhibits the signal transmission to the spindles, causing the muscle relaxation (Moore, 2007). The responses of muscle spindles to changes in length also play an important role in regulating the contraction of muscles, by activating motoneurons via the stretch reflex to resist muscle stretch. Massage also leads to a decreased of muscle tone by motoneuronal inhibition (Chauviers, 2002) and pain reduction (Leivadi et al 1999; Hernandez-Reif, 2001; Poe et al, 1994).

**Neuromuscular Excitability and the Hoffman Reflex**

Massage on the muscle is expected to increase or decrease **neural excitability** as measured by the Hoffman reflex.

Massage stimulate sensory receptors and can decrease muscle tension by reducing neuromuscular excitability as measured by changes in the Hoffman reflex (H-reflex) amplitude (Morelli et al, 1990; Morelli et al, 1999). **Pain** can be conducted from the peripheral receptors to the spinal cord and brain (CNS). The stimulation of ending nerve terminals or a mechanoreceptor by massage leads to its transmission by the sensory neuron, to the medullar level in the **spinal cord** where is produced the **reflex arc** and a response by the motor neuron that induces changes in the neural excitability (Hoffman reflex) (Palmieri et al, 2004, Goldberg et al, 1992; Lidbeck, 2002; Brouwer and Sousa de Andrade, 1995; Newham and Lederman, 1997; Roberts, 2011). The H-reflex is considered to be the electrical analogue of the muscle stretch reflex (Weerapong et, 2005; Morelli et al, 1990; Zehr, 2002) possibly due to a reduction in (or inhibition) of motor neuron activity with massage. Massage may also result in a
generalized neurophysiologic response where its effects may extend beyond the muscle being massaged.

The potential inhibitory effects of massage on neuromuscular excitability may be one of the explanations for the reduction of muscle tension or spasm following massage treatment (Sullivan et al, 1991).

**Mechanism of action at Psychophysiological level**

Massage can be an effective choice of treatment for a number of psychological issues (Bost and Wallis, 2006):

- **Promotes Relaxation:** Massage stimulate mechanoreceptors causing a reflex relaxation (Moyer et al, 2004). Physical relaxation can improve blood flow, reduce muscle tone and tension in connective tissue, and thus accelerate physical repair (Longworth, 1982; Valentine, 1984).

- **Reduces Anxiety and depression:** Massage stimulate mechanoreceptors causing a reflex relaxation, reducing the anxiety, tension, stress, depression and increase mood and quality of life (Moyer et al, 2004), all of which may contribute to enhancing athletic performance (Hemmings et al, 2000).

- **Promotes Recovery from Fatigue:** Massage produce a positive mood enhancement with a significant decrease in tension, confusion, fatigue, anxiety, depression and anger while maintaining high levels of vigor, which is representative of positive mental health (Weinberg et al, 1988).