Force Related Tissue Damage: A White Paper

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Key words: pressure injury, force related tissue damage, tissue, manual handling, mechanical handling, patient care, ergonomic, biomechanical

Overview: The intention of this white paper is to challenge and explore existing thinking around force related tissue damage or pressure injury.

Summary

Current evidence suggests there are many contributing factors that work together to cause a pressure injury. These contributing factors in the underlying aetiology can more accurately be described as force related tissue damage. This is therefore the term adopted throughout the paper.

Force related tissue damage can occur at any point in the body, where the body is unable to maintain its innate tissue protection and homeostasis. These forces may affect the skin, but can also radiate and have an effect in the deeper tissue layers of the body and trigger many marginal contributing factors within the body, which when combined, can surpass a threshold beyond which cells die or tissues rupture.

Under normal healthy circumstances the body's tissues work jointly to manage both external and internal forces. The body protects and repairs its internal environment by using both physiological and biomechanical mechanisms (biotensegrity) to maintain homeostasis. Force related tissue damage occurs when the threshold of the tissue integrity is surpassed or reduced. This can be caused by forces, physiological events or behaviour which either surpass or reduce the tissue threshold for one or more parameters. This damage can occur from the micro level in the form of stress up to the level of a visible lesion.

This is an expansion of current thinking which relates to (internal) lesions due to a vessels collapse or tissue ruptures. It is necessary because it addresses the parameters needed for diagnosis, prognosis, treatment and prevention of force related damage. It allows a detailed description of the way a patient differs from a healthy subject who will not acquire force related lesions. Expanding from the description of the lesion towards a description of the biomechanical and physiological state of the tissue involved will make caregivers aware of the preventable causes and practical treatment options.

Attention to forces will raise awareness that instead of pressure, a force has dimensions of magnitude, direction and time. This can explain why a low magnitude force can be more damaging than a large magnitude force or vice versa depending on the time and direction it is applied to the body.

Attention to physiology will explain why it is incorrect to think of a lesion as being unavoidable and raise awareness to diagnostic and therapeutic approaches that have the ability to reduce the number of lesions that occur.

Attention to behaviour will reduce the generation of unnecessary external forces which surpass the body's innate protection mechanisms as a result of manual or mechanical handling of patients.

The diagnosis of factors related to the tissue threshold will help in discovering and managing individuals prone to acquiring a force related lesion. The type of forces that results from both manual and mechanical handling of

patients can cause damage in tissue, when they are of an intensity and dissipation that cannot be handled by the body's homeostatic and biotensegrity mechanisms.

Therefore, this paper identifies that the major causes of force related tissue damage are twofold and results from a combination of the methods used to move patients and/or the way in which the patient is stabilised on resting/support-interfaces.

Both the major causative and the marginal contributing factors must be assessed at all organisational levels to predict and prevent the occurrence of force related tissue damage and resultant pathological lesions. This will allow for a desired safer trajectory for patients and their carers, by the adoption of preventative strategies that design out the major causes of force related tissue damage and induced lesions.

Introduction

Following NPUAP 2016 guidelines[1], pressure injuries are areas of localised damage to the skin and underlying tissue, caused by pressure, shear or friction. Pressure injuries are historically called pressure ulcers, pressure sores, bed sores/ulcers, decubitus ulcers and other names. With growing understanding of the aetiology underlying the damage to the tissue a more accurate description may be force related tissue damage.

Healthy individuals do not develop force related tissue damage; this results instead from a number of events caused by damaged or impaired tissues and/or systems. Force alone is not sufficient to explain the occurrence of the force related injury seen in current clinical practice. It therefore makes sense to have a deeper look into the aetiology of lesions commonly described as 'pressure injury", to allow for more tailored diagnostic, curative and preventive interventions. This allows for defining marginal factors, factors allowing for a lesion to occur and causing factors, which are the cause of the lesion. Usually marginal factors are a prerequisite for a causal factor to lead to a lesion.

Normally, tissues are continuously submitted to forces as a result of maintaining body posture, gravity and movement. Due to these forces, tissues and cells are frequently and recurrently damaged. So even in a healthy subject, homeostatic and regeneration processes are always active [2,3]. Living organisms maintain their homeostasis by handling forces and damage [4] by the continuous replacement or repair of cells and tissues[5,6].

The amount of damage incurred depends on the way forces are applied and also on the cells, tissue and processes involved. Damage occurs when the tissue involved is not able to withstand the applied force. Therefore, the amount of force any given tissue can handle, is defined by its specific characteristics; the tissue threshold. If the tissue threshold is surpassed, damage will occur. Initially there are only two parameters: the applied forces and included tissues. This applied force and the tissue involved are complex, dynamic and interrelated phenomena.

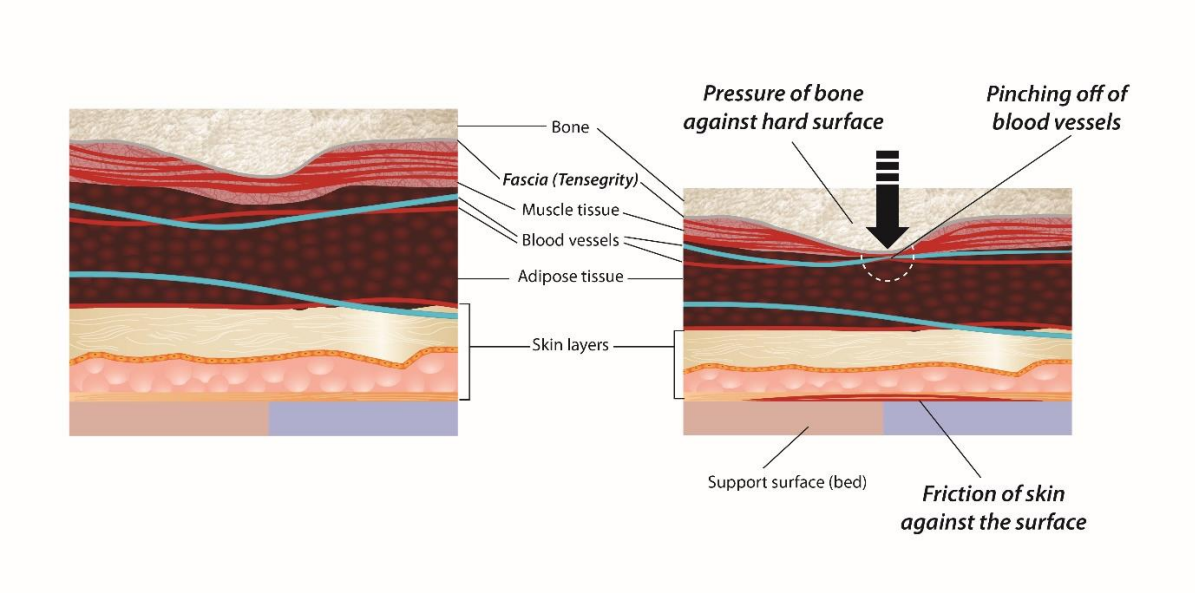

Figure 1: Classic representation of events related to force related tissue damage.

The common concept of pressure damage (pressure ulcers) states it results from vessel collapse and cell death due to compressing tissue between bone and a hard surface (figure 1). This is an oversimplification of the processes involved. It focuses on passing the tissue threshold whilst ignoring the reasons the threshold has been passed. Research on the subject is of high quantity and usually of low quality as highlighted in a recent review on support surfaces for pressure ulcer prevention, which revealed that few studies were of sufficient quality to be evaluated [7,8]. Most studies relate to pressure exerted on tissue; some address shear; few address tension and none address the interrelation and dynamics of force exerted on tissue. Also, most studies focus on lesions or necrosis, but prior to necrosis; cells will be stressed, injured and damaged. Forces exerted on tissue have several direct and indirect effects on all levels of organisation. Events may occur at molecular, cellular, tissue and/or body level [9] and may be of a chemical, physical, biological or mathematical nature or combination thereof. Since the main lesions occur due to biomechanical events, the effect of forces on tissue is relevant. It is important therefore to consider the direct and indirect way forces influence tissue and in what way the tissue threshold can be altered or lowered.

Force

External force (a major causal factor) acting on tissues has primary, secondary and tertiary effects. The primary effects of forces are compression, shear and tension leading to deformation, damage and possible rupture of cells and tissues.

The primary effects of external force on tissue cause problems in perfusion leading to secondary events such as hypoxia, lack of nutrients and waste accumulation. Usually, these effects then cascade into further events such as reperfusion injury, chronic immune response, nerve damage etc. which result from the effects of applying forces to tissues for a longer period of time.

Finally, significant loss of tissue and tissue integrity due to the combination of primary and secondary effects, usually triggers the formation of forces on other places in the tissue; a house-of-cards like

tertiary effects which result in further spreading of damage. A telling example is the removal of skin, which decreases the shear threshold of skeletal muscle by 50% [10].

Pulling or pushing forces are usually expressed in pascal (1Pa= 1N/m^2), describing how much force (newton) is applied per surface (m^2). The amount of energy a cell or tissue can handle depends on the force applied and the tissue(s) involved. The way tissue responds to force depends on its resilience - part of this is described by its response to mechanical strain and stress by its elasticity or Young's modulus [11]. However, the resilience of tissue to withstand force depends on the combination of the tissues and structures involved. For several tissue types this has been established [12–14]. This means, for example, adipose tissue has a different response to forces applied than epidermal or muscle tissue. The structure and cooperation of cells and tissues form a complex system, allowing for the management of larger forces than a single cell could handle alone. Reversely, damage to one type of tissue will influence other tissues' threshold.

If and when applied forces lead to a lesion depends upon the circumstances. Every type of cell or tissue has a certain amount of energy it can absorb; beyond this, it will be damaged to the extent that it fails. Fibrin networks are able to handle damage, but this ability can be compromised due to mechanical or metabolic events [15,16] .

It is commonly known the skin has an inhomogeneous response to force applied[17]. Most cells and tissues are anisotropic; the ability to withstand compression, shear and tension is not the same in all directions and depends upon the angle at which it is applied[18]. Therefore, the amount of damage also depends on the angle of forces applied. This is usually not taken into account and this is illustrated by the way ulcers are classified: they are now called pressure injury a classification which tends to ignore other causative factors.

Damage also depends on the tissues involved and how much force they can withstand, i.e. the tissue threshold. The pathological damage may originally start in muscle, adipose tissue, the dermis or other tissue types and spread from there. Deep tissue damage is the common denominator for this group of pathological phenomena. The tissue threshold is defined by the amount of force, chemical events (including redox) and/or radiation (including temperature) any given tissue can handle. Generally, it makes sense to discern "normal force" – in other words, events surpassing the tissue threshold of healthy tissue causing trauma, but within the limits of normal homeostasis. The only way force related damage occurs in a healthy subject is when force is applied at abnormal magnitude, angle and/or time: i.e. trauma. Apart from trauma, pathological lesions develop when tissues and/or systems are compromised. Therefore, the characteristics of a force applied to tissue have three elements: the magnitude, the time and the angle to which it is applied.

Direct and indirect cellular responses to forces

Under normal circumstances, cells and tissues are constantly challenged and damaged, leading to not only mechanical stress but also to other kinds of stress such as regulatory and metabolic stress[19]. Tissues, and cells within tissues, co-operate to handle these stresses, strains and their secondary effects[20,21].

At cellular level, compressing, tension and/or shear will lead to deformation. Tissue damage therefore starts at the cytoskeletal level of a single cell[22,23]. Further deformation of cells leads to increased membrane permeability, which will cause intracellular metabolic stress[24]. Dermal and muscle cells, as well as neural cells, respond in this way to damage[25]. Damaging the cell membrane leads to an influx of extracellular Ca^{2+}. This influx is regarded as an immediate danger signal for the cell, which will quickly repair the membrane[26] . But even limited pressure can lead to a breakdown of cell organelles[27], triggering programmed cell death or apoptosis. Even though large magnitude forces can lead to necrosis, apoptosis appears to be the main cause for tissue damage[28]. Cells also respond to other events resulting from applying force. For example, stiffness of the tissue, which increases under an applied force, has effect on the cells involved[29].

Oxygen depletion leads to changes in energy and redox potentials and causes cells to switch to different metabolic routes to maintain redox homeostasis[30]. A first step is that the mitochondria produce reactive-oxygen and -nitrogen species. This causes oxidation in the cell [31], leading to further damage and eventually apoptosis [32]. Prolonged hypoxia causes cells to produce stress signals leading to vasodilatation [33,34]. The same factors leading to vasodilatation also switch on angiogenesis [35], senescence, apoptosis and autophagy [36]. Depending on the type of cell involved, hypoxia also leads to different responses of, for example, stem cells [37,38].

Apart from hypoxia, the lack of nutrients can lead to reduced vitality and reduced mitogenic capacity. Eventually, it will lead to cell death, for instance by endoplasmic reticulum stress where the production of proteins is disturbed. This leads to the unfolded protein response (UPR), which entails several actions to restore homeostasis, and, if they fail, to apoptosis [39]. Accumulation of waste products also causes problems for individual cells [40,41].

Not only do hypoxia and lack of nutrients cause metabolic stress, the accumulation of waste and the accumulation of ‘cell remains’ in the tissue causes further problems in the mitochondrion and the endoplasmic reticulum [42,43]. Stress also makes cells more susceptible to other events such as reperfusion damage [44] and inflammation [45].

Regulatory signals can force a cell to proliferate or (partially) kill itself[46,47]. For example, increased or prolonged stress causes cells to reduce the need for oxygen and nutrients by apoptosis or autophagy.

At some point, the number of dying cells triggers an active immune response as a result of circulating stress signals and cell remains; damage associated molecular patterns (DAMPs)[48–50]. Damaged cells and molecular debris is considered a main trigger of the post-traumatic danger response [51]. Accumulating neutrophils may further increase local pressure leading to damage induced damage.

Generally, the preferred way of cells to die is by apoptosis because necrosis generates massive danger signals and the remains of the cell cannot be “recycled” efficiently[52–54]. Repair at the cellular level involves local cells, stem cells, macrophages[55] and fibroblasts[56]. Therefore at the level of the cell, even if there is no cell death, many complex events occur as a result of forces applied to tissue[57]. The resulting molecular and cellular events impact the threshold level of the tissue involved.

Direct and indirect tissue response to forces

Lesions usually develop in tissue between the body and a surface. Deformation of tissue can block vessels but also has an effect of other structures like fascia and nerves[58]. Typically, the tissue involved is organised in layers; dermis, subcutis, fat tissue, muscle tissue and bone. In and around these are fascia, blood vessels, lymph vessels and nerves. Tissues have an individual and an interdependent role in homoeostasis and regeneration[59].

Homeostasis handles primary and secondary effects in tissues [60,61] by monitoring tissue and systems quality and by replacing compromised cells and structures. Repair of damage as a result of "living"[62] is a straightforward well controlled process, involving vascular, lymphatic, immunologic, neural and endocrinological systems at local and systemic level[63]. In areas where more damage is to be expected, like the plantar regions, the metabolic speed is somewhat upregulated to allow the homeostatic process to resolve excess damage.

To prevent damage, the body has several ways to detect local deformation[64] and its symptoms[65,66]. The neural, fascial and vascular systems play a central role in detecting and responding to force, hypoxia, acidification, cell and/or tissue damage[67,68]. The usual response to force induced damage signals, is to reposition the body.

Mechanical force causes perfusion problems when compressing arterial, venous or lymphatic vessels [69]. Perfusion problems are wider than just preventing transport by compressing capillaries[70]. Collapsing of capillaries causes hypoxia[71] and leads to upregulation of hypoxia signals[66,72] and organelle dysfunction[73]. But the application of force on tissue also compromises the lymphatic system[74] were for instance, the lymph flow is reduced[75] due to and leading to oedema[76]. Compressed vessels have a recovery time in which they restore the original lumen. This means that after compression the perfusion is not fully restored immediately[77]. The time needed for recovery is a second parameter influencing damage[78]. Finally, the endothelial quality of the dilated vessel will dictate improvement of further damage as a result of pressure induced vasodilatation. In studies with spinal cord injury (SCI) patients it was observed that recovery time was necessary to prevent injury[79]. It seems that there is a sweet spot in recovery time to allow for pressure induced vasodilatation but prevent reperfusion injury. This could also explain tissue damage during repeated stress-compression cycles[80,81].

The combination of perfusion collapse and following reperfusion is, in itself, a cause of cell death as a result of reperfusion injury[44]. Refilling blocked blood vessels is not without consequences. Due to the lack of perfusion, the endothelium becomes very permeable [82]. The renewed influx of blood will cause significant leakage, which results in local oedema as well as an increased influx of neutrophils also due to the influence of the neural system[83].

The lymphatic system has a very complex role in handling forces in tissue. In general it depends on oscillating pressures in the tissue for its transport[84]. In adipose tissue it plays a role in initial force handling by allowing for interstitial fluid transport away from an area of high internal pressure[13]. It does so by opening up its lumen under a medium applied force, however, if the forces are larger, the vessel will collapse leading to oedema due to accumulating fluid consisting of metabolic waste products and other compounds [85].

Nerves have several important roles in tissue homeostasis and regeneration [86]; as understood from regeneration studies with SCI patients where wounds above the lesion heal better compared to wounds below the lesion. Nerves sense hypoxia[87], ischaemic pain and play a role in pressure induced vasodilatation [88]. Longer term effect of nerves comes from their role in maintaining the redox balance in tissue[89]. Aging also influences the sensory neurons leading to a decline in vasodilatory response upon hypoxia[90].

Despite its strength [91], the epidermis is usually the first place where the effects of the vessel collapse becomes visible [92]; in the form of skin reddening and blister formation [93]. Visible reddening of the skin is the result of vasodilatation due to the NOX (nitric oxide) generated[94]. This response is meant to increase the blood flow to ischemic areas and it starts at pressures above 32mmHg[95,96]. The integrity of the skin is also influenced by moisture, which causes increased friction and a reduced tissue quality. Being on the outer perimeter of the body the skin is susceptible to climatic events [97,98].

The dermis has a higher viscoelasticity compared to the epidermis [99] in that it can extend up to 25% and compress in a similar manner. This effect is caused by the adipose tissue in the subcutis. The role of adipose tissue, in relation to exerted force, is to absorb energy and redistribute lower forces to the surrounding tissue. Adipose tissue can suffer from damage due to direct strain and from damage due to hypoxia. However, the biomechanical properties of adipose tissue are different. It can deform much more than other tissue layers and has, like muscle [100], a anti-thixotropic effect. Under pressure it deforms but under prolonged pressure it stiffens [101]. In adipose tissue the fascia handles most of the force and as such it protects the vessels and cells in the tissue[102]. The connective tissue in the adipose tissue ensures that increased pressure is handled by a combination of fibres and adipose cells while the vessels and nerves are not compressed [103]. Apparently, if the pressure in one part is too high, more adipose cells are involved in the process. This is how the amount of force applied relates to the volume of adipose tissue with an increased pressure. This allows the adipose tissue to withstand higher pressures without damage. It is not clear what causes this effect. The mechanical function of adipose tissue can be impaired by prolonged exposure to NOX which leads to fibrosis [104].

The role of muscle in force related damage is well investigated [105]. It absorbs pressure by deforming whilst remaining able to function. Deformation has a negative impact on interstitial transport. This is one of the main reasons muscle tissue is more prone to compression-induced injury [106]. The impaired diffusion of large molecules in muscle tissue [107] not only hampers the oxygenation of individual cells but also disables the transport of metabolites in and out of the tissue and the surrounding blood and lymph vessels. So, there are two ways in which muscle tissue is damaged. Firstly, direct force causing tissue strain, which is greatest near a bony prominence and leads to fast occurring damage. Secondly, due to hypoxia, leading to anaerobic metabolism - which for a short period of time is well tolerated but during prolonged periods leads to tissue acidification and cell death.

All layers, from the epidermis to the muscles, are well able to handle forces. The bone functions as a hard structure to counterbalance powers from outside and as an anchor point for tissues.

Where bone delivers rigidity to the body mass, the dermis envelops and the fascia handles all the mechanical issues in between. Fascia has several, sometimes conflicting functions: to separate, to allow movement [108], to connect, to hold together and/or to transfer forces [109]. It consists of tissue sheets

(fascia profunda), septa, capsules, the epimysium, skin fascia, endomysium, perimysium, periosteum, ligaments and tendons etc.

Fascia and connective tissue play a vital central role in force handling [110]. It forms a continuous network, connecting each individual cell to the entire body in a reciprocal way [111,112]. Every tissue type has its own specific type of fascia [113]. Its role extends beyond the level of the cell, as it forms a mechanical link between a cell nucleus and the entire body [114–116]. It is clear that the fascia integrates the mechanical functionality of all tissues involved [117]. In its specific role in the force distribution in and between tissues [105], it has a large impact on the Young's modulus where it allows for the combination of tissues to handle far more force than each tissue type could in isolation. . It is not clear in what way fascia dysfunction [118] influences force transmission in tissue nor is its role clear in damage, regeneration [119] and wound healing[120]. General issues with fibrin and collagen however, directly impact the quality and function of the fascia.

Healthy tissue can normally withstand 2-4 hrs of static mechanical forces causing local reduced perfusion (occlusion). Sitting, for instance, causes non-pathological ischaemia in the subcutaneous tissue [121]. The reaction of tissue to pressure is not static but relies on the characteristics of the force applied. Brief periods of load relief during a 2 hour loading period did not have any significant effect on the damage progress [122]. It also appears that, over time, the relative softness of, for example, a sitting cushion becomes less important[123].

The integrated biomechanical and physiological properties of tissue allow the body to handle forces far beyond normal biological values.

Biomechanics and biotensegrity

Each tissue type responds differently to force applied. Forces applied on a complex structure like a body, will not only compress tissue, but also cause shearing and even pulling forces. Shearing and pulling forces cause tension. Logically, shear and tension usually act at a different location than compression forces[124].

Tissue is not homogeneous[125]. The parts cooperate to absorb and/or handle energy from forces applied from outside of the body, by stretching, absorbing force and/or deformation. Complex processes are involved in transferring forces between tissues whilst maintaining homeostasis. The body needs to allow stretching of the skin, handle pressure increase in the adipose tissue and also allow free movement of the muscle whilst not obstructing perfusion of blood and lymph or hindering neural function[126].

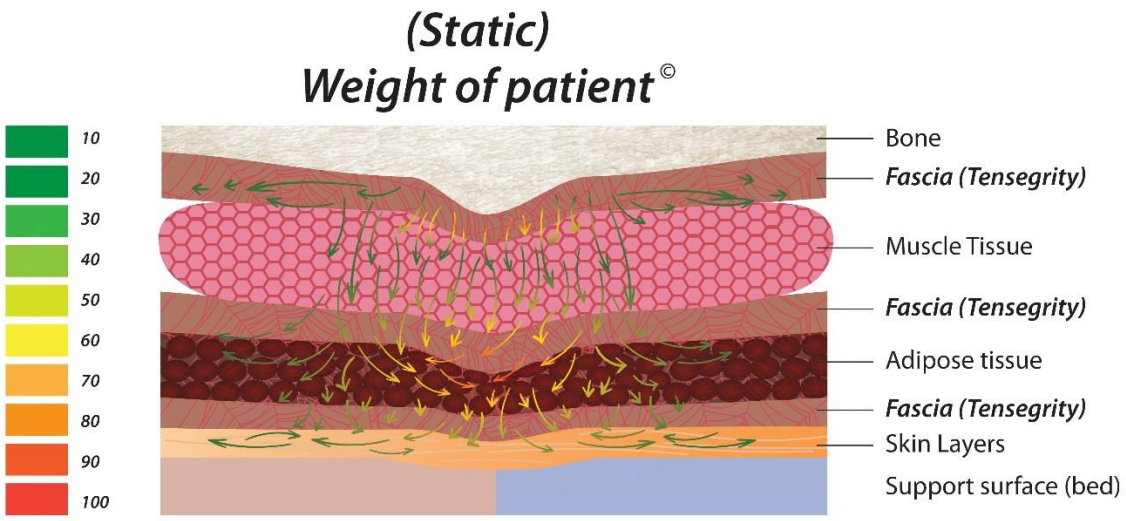

Figure 2: Schematic representation of force distribution in tissue under the influence of gravitational forces.

To be able to maintain tissue integrity and mechanical stability, fascia plays a pivotal role. It has a complex structure from macro to micro[127] and is very well adapted to sensing and transferring static and dynamic forces in the body[112]. This system functions in a continuum at the molecular[128], cellular, tissue[129] and body level[130]. Therefore, it can sense, transfer and withstand forces in a continuous way from the skin up to the atomic level of an individual cell nucleus and vice versa [131].

Tissue, bones and fascia cooperatively functions like a flexible pole and guy rope structure. This means that the combination of tension in the fascia and rigidity of the bones, combined provide a strong but flexible structure. This system, based upon tension to maintain tissue integrity, is called biotensegrity[132]. In this system, the muscles function as an actor, the bones as an anchor and the fascia as connecting rope. This system also exists at the level of tissue and cells. It enables the formation of compartments in, around and between tissues. The connective tissue then functions as a force handling structure (figure 2). Its function may be more than to act as a rope because it functions in a moist environment where hydraulic or hydrodynamic mechanisms come into play [133].

The biotensegrity system also implies that the ability to withstand external forces depends on the direction the forces are applied. The "design" of the human body is made for a "normal" and "self-supporting" life. This means that the tissue is anisotropic [134]. The ability to handle forces is not the same for all angles and starting points. There are indications that shear stress is more causative for tissue damage when compared to pressure stress [124,135]. Therefore, if force applied is too large or from an odd angle, it may cause ruptures in tissue[136.] Mostly due to changes in the collagen structure[137,138]. The Morel-Lavallée lesion, a posttraumatic haemolymphatic collection related to shearing injury and disruption of interfascial planes between subcutaneous soft tissue and muscle[139], is not a part of usual pressure damage theory, whilst it should be since 40% percent of these lesions are on the hip, gluteal or lumbosacral region [140]. Reversibly it is unclear how many deep tissue injuries are in reality a

traumatic lesion with a very different aetiology (patient transfer)[141]. This also has implications for diagnosis and treatment [142].

Damage in tissue as a result of mechanical stresses can occur at several levels, from blistering of the skin if the dermo-epidermal junction [143]is damaged; to necrosis of the subcutis due to the adipose tissue; to necrosis of muscles because they have a small low threshold for mechanical stress; to local necrosis due to extreme high forces (Laplace law) near bony structures [144]. If and which type of tissue will fail will depend on the characteristics of the mechanical forces exerted and on the quality of the tissues or body systems involved [145]. This may involve more than one tissue type as damage to a tissue can affect the threshold of other tissues. The interdependent function of tissues in force handling means that events on one point have an impact on the entire system. Problems may not manifest at the site of origin. Even at a superficial ulcer, the microcirculation can be compromised at a depth of 10mm[146].

It is not unlikely that a structural problem in a tissue manifests itself at a different location, making it hard to discover exactly what is causing injury.

The amount of force is negatively correlated with the time it is applied in relation to damage. However, this is not the entire story. Thixotropy of tissue causes it to have a tissue response time, its deformation can only begin when the tissue has become more viscoelastic. In a very short time frame lesser force can cause damage due to the inert and, slightly thixotropic nature of tissue [147]. These properties are the reason tissue needs some time to respond to a force. Forces applied faster than the "tissue response time" cause trauma. This means tissue will need time to adapt to an incoming force. Logically, this means that pushing very fast will also cause bruises in the tissue. Similarly, pulling on a body may cause unanticipated tissue damage [148]. This is well in line with findings that deep tissue damage develops in a short time frame and ischemia is likely not the only causative factor [149].

This also explains why manual handling techniques for moving patients can cause Morel-Lavallée like trauma which later is categorised as pressure damage (pressure sore). So not only relatively low but prolonged forces may cause injury, also short but high forces damage tissues. Therefore, we must adapt the time-force graph in order to reflect trauma induced by short peak forces (figure 3).

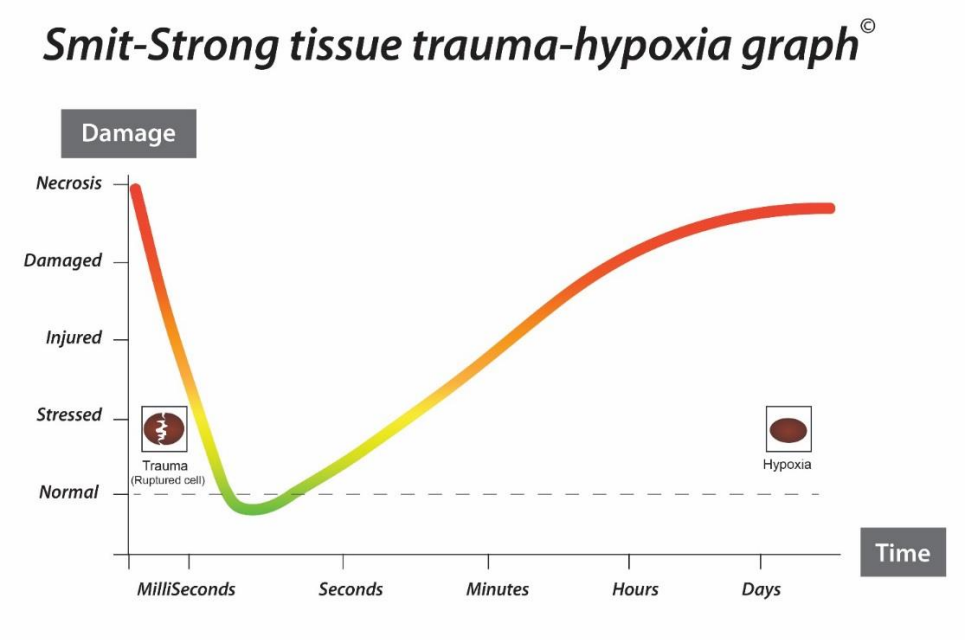

Figure 3. Representation of force over time, surpassing the tissue threshold in a very short or a long period

Any patient movement can be both intentional and unintentional. Similarly, any movement can be gross or micro movement. Some of the patients' movements can be made by themselves and other movements can be initiated by their carers manually (manual handling) or using mechanical aids. These types of movements when combined together with the identified complexities of the body's internal systems for preventing and repairing tissue damage, leads to a reasoned conclusion that, the most effective preventative trajectory to maintaining the patient's optimum tissue integrity is to control the two major factors that are within their external environment: Both the resting/support surface interface and ways that patients are rested/supported, moved and stabilised.

Differences between health and disease

In a healthy subject, lesions at the body-surface interface rarely develop. Lesions occur when the tissue involved is not able to withstand the force applied. In order to develop force-induced damage in patients, it is required that a) the forces cannot be evaded, b) the tissue quality is reduced and/or c) homeostatic and/or regeneration processes are impaired. Patients suffering from generic, structural or systemic issues may qualify by having less opportunity to counter, recover or bypass the effects of forces on or in the tissue compared to a healthy subject.

General risk factors for acquiring pressure ulcers are summed up in the Braden scale: which addresses both causative external factors: pressure and friction and disabling factors (tissue threshold reducing): sensory perception, activity, mobility, nutrition, skin moisture. Table 1 provides more detail and examples in which the tissue threshold may be impaired by factors in the entire body, its systems, its structures and/or local factors.

The fastest source of damage is trauma, which results from extreme forces on tissue – for instance, due to pulling the body to reposition a patient, or non-suitable contact surfaces (shoes). Connective tissue and interfaces between tissue types are especially prone to this type of injury. If the connective tissue or collagen structures are compromised, even a light force can cause pathological ruptures[150,151]. However vigilant patient carers are, manually handling a patient generates peak forces that easily lead to the rupture of compromised tissue. Laplace Law dictates the generated force will maximise at bone-tissue interfaces, causing deep tissue injury.

The quality of the dermis can be influenced by moisture - changes in its collagen and elastin and flattening of the dermal-epidermal junction - all leading to a decrease in its energy absorbing capacity and increasing the chances of force related damage [93,152] . The same applies for a degradation of the epidermal-dermal junction.

Adipose and muscle tissue have thixotropic properties; if it is not moved, it becomes stiff. This can be understood by the combined effect of adipose cells and the fascia. However, this means that abrupt application of force on static tissue has an effect on muscle and adipose tissue that may cause microscopic ruptures in the compromised tissue [102]. Generally, collagen will not deteriorate gradually but it is more likely to rupture. The mechanical integrity of the tissue can be further reduced by lipid position in fascia [153] and stiffening [154],[155].

Behavioural issues, the position of the body in time and space, are usually summarised as mobility problems. Immobility causes vessels to be occluded for a longer period than the tissue can handle.

TABLE 1: POSSIBLE CAUSES FOR REDUCTION OF TISSUE THRESHOLD ©

Generic factors
1. Mobility issues which compromise the ability to reposition the body.
2. Ageing [156–158].
3. Co-morbidity (diabetes, spinal cord injury).
4. Nutritional problems, patients can be cachexic which means that they simply do not have the energy available to run the necessary processes[159160].
5. Endocrinological issues like diabetes[161].
6. Slow metabolic processes leading to slower cell generation[162].
7. Stress [158,163].
Systemic factors
8. Sensory disability due to neural system impairment. Compromising detection of local pressure and/or ischaemia.
9. Neural problems reducing the homoeostatic capacity of the tissue.
10. Metabolic problems which hamper the homoeostatic capacity of the tissue[159,164,165].
11. Endothelial disability; due to endothelial problems, the exchange of metabolites in the tissue is impaired, local energy balance is disturbed and oedema can occur.
12. Non-resolving inflammation is not a primary cause, but it contributes significantly to the pathogenesis[166].
13. Vasopressors [cox].
Structural factors
14. Atrophy functionally compromising tissue[167].
15. Tissue stiffening, which also leads to problems in force distribution[168].
16. Lymphatic sclerosis[169].
17. Perfusion problems like vascular disease where vessels easily collapse or have impaired recovery ability[170,171].
18. Fascial dysfunction[150,172,173].
19. Local metabolic capacity, wounds in areas with a high metabolic activity like hands and face usually heal faster than wounds in areas with a lower metabolic rate
20. Biotensegrity issues.
Local factors
21. Moisture[174,175].
22. Time issues (See figure 3).

Lack of oxygen causes cells to die. Normally, hypoxic signalling leads to repositioning of the body. Repositioning is compromised when the body cannot be timely repositioned. This is usually caused by an inability to move – as in the case of very ill or weak persons, or co-morbidity due to spinal cord injury. There is a trade-off in surface type – in terms of the positioning is easy on a relatively hard surface whilst a high conforming surface may increase the energy needed to reposition the body. This becomes even more important when it is understood that aged muscle in itself is "stuck in gear", and is not able to produce the force needed to reposition the body [176]. Another possibility is that the body is not detecting forces and/or hypoxia, usually as a result of neural pathology. Damage can also occur without obvious ischaemia, which makes it hard for the body to detect.

Immobility for longer than a few days causes numerous changes such as increased skin temperature, hyperaemia and increased trans epidermal water loss[177] of which reduced bone density and muscle atrophy[178] are the most well-known[179]. Tissue deformation can be macro: muscle deformation[180] and micro: thinning, stiffening, deformation of several tissue types and changes in collagen and elastine type and function[181,182]. Micro changes in tissue, especially stiffening, alter the cellular response. In as little as fourteen days of bed rest, a healthy middle-aged subject will develop significant muscle damage[183]. Apart from immobility, there are more marginal factors for reduced tissue quality. Atrophy compromises the force handling ability of muscle tissue[184]. Impaired force handling ability of muscle and other tissues may lead to numerous small, sublytic lesions. Repair will lead to a gradual fibrosis and further loss of tissue quality[185]. Ageing also impacts the ability to regenerate injured tissue like muscle[186]. The main cause for this is tissue fibroblast and macrophage senescence.

The role of the arterial system in force related injuries has been discussed above. However, any age or disease-related change to the vascular system will have an immediate effect on the reaction to force and the ability to handle hypoxia, due to issues such as reduced elasticity and or endothelial dysfunction[187]. Different pathologies require different measures, where the quality of the vessel wall is compromised [188]. Reduced vessel quality can dramatically increase the time needed for recovery from minutes to days. The key factor is to prevent indentation and maximise recovery time. For example, in spinal cord injured patients, the vessel walls are not compromised and here, alternating pressure has a better outcome[189].

If the tissue reperfusion is not optimal, tissue will be hypoxic for a longer period. Adipose, muscular, dermal and neural tissues are not equally sensitive to hypoxia. This may be another explanation why damage does not always occur at the location of the highest force, notwithstanding better resistance to hypoxia. The short-term and the mechanical properties of adipose tissue are negatively influenced by fibrosis as a result of long-term hypoxia[190], which is another cause of connective tissue degradation reducing tear resistance.

A prominent issue in tissue damage is inappropriate inflammation. In essence, this is damage-induced damage. It is conceivable that a small number of dead cells, combined with failing inflammation or sensory failure, triggers a snowball effect[191], leading to larger defects to which a response does not necessarily solve problems [192].

This is because the inflammatory response in itself can be a cause of nervous and muscular damage, eventually leading to nerve damage and rhabdomyolysis[193]. Further, immune senescence[194] can lead

to a reduced immune response and this inflammation[195] is considered a major cause of age-related events.

Apart from the obvious hardship to reposition, the paraplegic person also faces the direct and indirect results of the spinal lesion[196,197] which impacts movement, but also tissue (including bone) itself [198,199]. Nerve fibres degrade over time, compromising the pivotal role that the neural system plays in tissue homeostasis and repair. Skin/tissue failure might be misdiagnosed as being force related tissue damage. Critically ill patients may develop acute skin/tissue failure[200,201], which appears as force related tissue damage but has a different aetiology[202]. Failing skin loses normal temperature control and cannot prevent transdermal loss of fluid, electrolyte and protein[203]. It is an indicator of body system failure.

The body uses complex systems of cells for homeostasis and repair. The impact/effect that forces have on the biotensegrity system at one point may manifest elsewhere in the system. The many ways that forces can exceed thresholds, and tissues comprised, makes typing ulcerations difficult[204]. Critically ill patients suffer from serious system malfunction where the neural and muscular system are deteriorating[205].

Patients may help us to not only distinguish between skin/tissue failure that is due to body system failure of both critically ill and end of life patients (last 5 days approx.) and that of force related tissue damage (pressure injury), but also help discover what is age-related and what is disease-related marginal factors in pressure related tissue damage. So not only factors related to force and tissue threshold but also behavioural factors play a role in force related tissue damage.

Conclusion and Recommendations

There is a common concept that force related tissue damage (presently referred to as pressure injury, historically called pressure ulcers etc.) results from vessel collapse and cell death due to compressing (pressure theory) tissue between bone and a hard surface (figure 1). This is an oversimplification of the processes involved as it focuses on passing the static tissue pressure threshold. However, it ignores the interrelation and dynamics of many forces exerted on tissue and the reasons why tissue thresholds have been passed.

Force related tissue damage occurs when events lead to stress and damage at a molecular, cellular, tissue, organ and organism level, well in advance of the skin being broken. Sublytic damage at one point can cascade via mechanical, physiologic, chemical or systemic pathways into pathological lesions. Present wound care science struggles to diagnose and cure lesions due to the complexity and processes involved regarding tissue homoeostasis, damage and regeneration. This paper identifies in table 1 over 22 internal marginal influencing factors. These include generic (such as stress), systematic, structural and local factors, that can contribute to the loss of optimum tissue integrity (i.e. that can cause/contribute to both a reduction in the tissue resistance threshold and/or a reduction in tissue recovery).

A predictive approach will require a greater use of available standard medical procedures which are applicable for wound care and would include current diagnostic tools for assessing and grading deep tissue injury (DTI), endothelial status and reperfusion injury. Incorporating the use of classical diagnostic tools such as medication screening [206,207], laboratory values[208,209], biomarkers[210,211], tissue

sampling[212,213] and imaging[106,123] guidelines. Together with available advanced diagnostic tools such as (epi) genetic[212,214–216], proteomic[217] and metabolomic[218,219] screening they will allow us to predict, prevent and treat individuals at risk in the near future.

Some patients are more prone and of a higher risk to tissue damage, screening tools can overlook patients who don't show tell-tale signs but are nevertheless prone and are at risk to tissue damage when the body's threshold of resistance and/or ability to recover from damage, is reduced and/ or surpassed. Unnecessary external forces can be generated by the practices used to rest the patient, by how they are moved and how they are re-stabilised, during and after their body mass has been re-orientated. They are an undesirable result from having to work against gravity and can be directly linked to the manual and/or mechanical handling practices being used to overcome the downward gravitational forces that are keeping the patient stable.

Any patient movement and stability should be controlled in a way, which requires working with gravity. Allowing the body to move and be re-orientated safely, further compliments and supports the body's innate homeostasis to keep the patients skin and tissues within its natural threshold of resistance and repair. Thereby, maintaining its optimum tissue integrity. Ideally a patient should be rested, repositioned and stabilised by using gravity without the need for manual and/or mechanical handling. It should allow repositioning and stabilising to be at a sufficiently slow controlled rate and allowing the bodies homeostatic and biotensegrity processes to safely dissipate any potential related tissue damaging forces.

This paper proposes a future trajectory that is both desirable and achievable and would bring wound care prevention, diagnosis and assessment up to date. A trajectory that consigns statements such as: ***"Off-loading the area still offers the best chance for tissue that is ischemic or injured, but not infarcted"*** [220] to be logical at first sight but in reality non-sufficient for practical application. The evidence base for this approach to safer care demonstrates that force related tissue damage prediction and prevention, rather than treatment, is always the preferred approach to maintaining the patient's optimum tissue integrity.

Categorising force related tissue damage using terms like inflammation, amount of tissue lost or necrosis does not fully address events leading to force related tissue damage. Recognising parameters of force, behaviour and tissue threshold in the events leading to ulceration may impact the way we prevent and treat force related tissue damage. Clearer guidelines are required that not only recognise, identify, and incorporate the exact tissues and systems involved but also make sure the latest up to date options for prevention, diagnosis, assessment and treatment are available and used.

Statement regarding conflict of interest:

Phil Strong: designer and supplier of related health care products

Harm Smit: none

Signed:

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References:

1. Npuap. NPUAP Position Statement on Staging – 2017 Clarifications. *http://www.npuap.org/wp-content/uploads/2012/01/NPUAP-Position-Statement-on-Staging-Jan-2017.pdf* (2017).
2. Vriz, S., Reiter, S. & Galliot, B. *Cell Death. A Program to Regenerate. Current Topics in Developmental Biology* 108, (Elsevier Inc., 2014).
3. Merino, M. M. *et al.* Elimination of unfit cells maintains tissue health and prolongs lifespan. *Cell* 160, 461–476 (2015).
4. Rubin, B. P. *et al.* A dynamic architecture of life. *F1000Research* 4, 1–17 (2015).
5. Neves, J., Demaria, M., Campisi, J. & Jasper, H. Of flies, mice, and men: evolutionarily conserved tissue damage responses and aging. *Dev. Cell* 32, 9–18 (2015).
6. Karin, M. & Clevers, H. Reparative inflammation takes charge of tissue regeneration. *Nature* 529, 307–315 (2016).
7. Lockyer, S., Hodgson, R., Dumville, J. C. & Cullum, N. 'Spin' in wound care research: the reporting and interpretation of randomized controlled trials with statistically non-significant primary outcome results or unspecified primary outcomes. *Trials* 14, 371 (2013).
8. McInnes, E., Cullum, N. A., Bell-Syer, S. E., Dumville, J. C. & Jammali-Blasi, A. Support surfaces for pressure ulcer prevention. in *Cochrane Database of Systematic Reviews* (ed. McInnes, E.) (John Wiley & Sons, Ltd, 2008). doi:10.1002/14651858.CD001735.pub3
9. Enyedi, B. & Niethammer, P. Mechanisms of epithelial wound detection. *Trends Cell Biol.* 25, 398–407 (2015).

10. Yoshitake, Y., Miyamoto, N., Taniguchi, K., Katayose, M. & Kanehisa, H. The Skin Acts to Maintain Muscle Shear Modulus. *Ultrasound Med. Biol.* 42, 674–682 (2016).

11. Guz, N., Dokukin, M., Kalaparthi, V. & Sokolov, I. If Cell Mechanics Can Be Described by Elastic Modulus: Study of Different Models and Probes Used in Indentation Experiments. *Biophys. J.* 107, 564–575 (2014).

12. Agache, P. G., Monneur, C., Leveque, J. L. & Rigal, de J. Mechanical properties and Young's Modulus of human skin in vivo. *Arch. Dermatol. Res.* 269, 221–232 (1980).

13. Comley, K. & Fleck, N. A. A micromechanical model for the Young's modulus of adipose tissue. *Int. J. Solids Struct.* 47, 2982–2990 (2010).

14. Kim, O. V. *et al.* Foam-like compression behavior of fibrin networks. *Biomech. Model. Mechanobiol.* 15, 213–228 (2016).

15. Kurniawan, N. A. *et al.* Fibrin Networks Support Recurring Mechanical Loads by Adapting their Structure across Multiple Scales. *Biophys. J.* 111, 1026–1034 (2016).

16. Piechocka, I. K. *et al.* Multi-scale strain-stiffening of semiflexible bundle networks. *Soft Matter* 12, 2145–2156 (2016).

17. Meijer, R., Douven, L. F. a. & Oomens, C. W. J. Characterisation of Anisotropic and Non-linear Behaviour of Human Skin In Vivo. *Comput. Methods Biomech. Biomed. Engin.* 2, 13–27 (1999).

18. Nolan, D. R., Gower, A. L., Destrade, M., Ogden, R. W. & McGarry, J. P. A robust anisotropic hyperelastic formulation for the modelling of soft tissue. *J. Mech. Behav. Biomed. Mater.* 39, 48–60 (2014).

19. Rau, K. K. *et al.* Cutaneous tissue damage induces long-lasting nociceptive sensitization and regulation of cellular stress- and nerve injury-associated genes in sensory neurons. *Exp. Neurol.* (2016). doi:10.1016/j.expneurol.2016.06.002

20. Canović, E. P., Zollinger, A. J., Tam, S. N., Smith, M. L. & Stamenović, D. Tensional homeostasis in endothelial cells is a multicellular phenomenon. *Am. J. Physiol. - Cell Physiol.* 311, C528–C535 (2016).

21. Das, A. *et al.* Monocyte and Macrophage Plasticity in Tissue Repair and Regeneration. *Am. J. Pathol.* 185, 2596–2606 (2015).

22. Jagannathan, N. S. & Tucker-Kellogg, L. Membrane permeability during pressure ulcer formation: A computational model of dynamic competition between cytoskeletal damage and repair. *J. Biomech.* 49, 1311–1320 (2016).

23. Gefen, A. & Weihs, D. Cytoskeleton and plasma-membrane damage resulting from exposure to sustained deformations: A review of the mechanobiology of chronic wounds. *Med. Eng. Phys.* 38, 828–833 (2016).

24. Slomka, N. & Gefen, A. Relationship between strain levels and permeability of the plasma membrane in statically stretched myoblasts. *Ann. Biomed. Eng.* 40, 606–618 (2012).

25. LaPlaca, M. C. & Prado, G. R. Neural mechanobiology and neuronal vulnerability to traumatic loading. *J. Biomech.* 43, 71–78 (2010).

26. Draeger, A., Schoenauer, R., Atanassoff, A. P., Wolfmeier, H. & Babiychuk, E. B. Dealing with damage: Plasma membrane repair mechanisms. *Biochimie* 66–72 (2014). doi:10.1016/j.biochi.2014.08.008

27. Gefen, A., van Nierop, B., Bader, D. L. & Oomens, C. W. Strain-time cell-death threshold for skeletal muscle in a tissue-engineered model system for deep tissue injury. *J. Biomech.* 41, 2003–2012 (2008).

28. Wu, Y., Schaft, D. W. J. van der, Baaijens, F. P. & Oomens, C. W. J. Cell Death Induced by Mechanical

Compression on Engineered Muscle Results from a Gradual Physiological Mechanism. *J. Biomech.* 1–7 (2016). doi:10.1016/j.jbiomech.2016.02.028

29. Trichet, L. *et al.* Evidence of a large-scale mechanosensing mechanism for cellular adaptation to substrate stiffness. *Proc. Natl. Acad. Sci. U. S. A.* 109, 6933–8 (2012).

30. Li, P. *et al.* Redox homeostasis protects mitochondria through accelerating ROS conversion to enhance hypoxia resistance in cancer cells. *Sci. Rep.* 6, 1–13 (2016).

31. Narasimhan, M. & Rajasekaran, N. S. Reductive potential - A savior turns stressor in protein aggregation cardiomyopathy. *Biochim. Biophys. Acta - Mol. Basis Dis.* 1852, 53–60 (2015).

32. Panday, A., Sahoo, M. K., Osorio, D. & Batra, S. NADPH oxidases: an overview from structure to innate immunity-associated pathologies. *Cell. Mol. Immunol.* 12, 5–23 (2015).

33. Krystel-Whittemore, M., Dileepan, K. N. & Wood, J. G. Mast cell: A multi-functional master cell. *Front. Immunol.* 6, 1–12 (2016).

34. Raaz, U. *et al.* Hemodynamic regulation of reactive oxygen species: implications for vascular diseases. *Antioxid. Redox Signal.* 20, 914–28 (2014).

35. Hashimoto, T. & Shibasaki, F. Hypoxia-inducible factor as an angiogenic master switch. *Front. Pediatr.* 3, 33 (2015).

36. Poyton, R. & Hendrickson, M. Crosstalk between nitric oxide and hypoxia-inducible factor signaling pathways: an update. *Res. Reports Biochem.* Volume 5, 147 (2015).

37. Kakudo, N., Morimoto, N., Ogawa, T., Taketani, S. & Kusumoto, K. Hypoxia Enhances Proliferation of Human Adipose-Derived Stem Cells via HIF-1α Activation. *PLoS One* 10, e0139890 (2015).

38. Rios, C. *et al.* Low Oxygen Modulates Multiple Signaling Pathways, Increasing Self-Renewal, While Decreasing Differentiation, Senescence, and Apoptosis in Stromal MIAMI Cells. *Stem Cells Dev.* 1–56 (2016). doi:10.1089/scd.2015.0362

39. Iurlaro, R. & Muñoz Pinedo, C. Cell death induced by endoplasmic reticulum stress. *FEBS J.* n/a-n/a (2015). doi:10.1111/febs.13598

40. Mirtaheri, P., Gjøvaag, T., Worsley, P. R. & Bader, D. L. A review of the role of the partial pressure of carbon dioxide in mechanically loaded tissues: the canary in the cage singing in tune with the pressure ulcer mantra. *Ann. Biomed. Eng.* 43, 336–47 (2015).

41. Reddy, N. P. & Cochran, G. V. Interstitial fluid flow as a factor in decubitus ulcer formation. *J. Biomech.* 14, 879–81 (1981).

42. Kaufman, R. J. Orchestrating the unfolded protein response in health and disease. *J. Clin. Invest.* 110, 1389–98 (2002).

43. Griffiths, H. R., Gao, D. & Pararasa, C. Redox regulation in metabolic programming and inflammation. *Redox Biol.* 12, 50–57 (2017).

44. Cui, F. *et al.* Pressure Combined with Ischemia/Reperfusion Injury Induces Deep Tissue Injury via Endoplasmic Reticulum Stress in a Rat Pressure Ulcer Model. *Int. J. Mol. Sci.* 17, 284 (2016).

45. Guthrie, L. N. *et al.* Attenuation of PERK signaling selectively controls endoplasmic reticulum stress induced inflammation without compromising immunological responses. *J. Biol. Chem.* jbc.M116.738021 (2016). doi:10.1074/jbc.M116.738021

46. Vanden Berghe, T. *et al.* Regulated necrosis: the expanding network of non-apoptotic cell death pathways. *Nat. Rev. Mol. Cell Biol.* 15, 135–47 (2014).

47. Kaczmarek, A., Vandenabeele, P. & Krysko, D. V. Necroptosis: The Release of Damage-Associated Molecular Patterns and Its Physiological Relevance. *Immunity* 38, 209–223 (2013).

48. Niethammer, P. The early wound signals. *Curr. Opin. Genet. Dev.* 40, 17–22 (2016).

49. Tidball, J. G. Mechanisms of muscle injury, repair, and regeneration. *Compr. Physiol.* 1, 2029–2062 (2011).

50. Mi, Q. *et al.* Translational systems biology of inflammation: potential applications to personalized medicine. *Per. Med.* 7, 549–559 (2010).

51. Huber-Lang, M., Ignatius, A. & Brenner, R. E. Role of Complement on Broken Surfaces After Trauma. *Adv. Exp. Med. Biol.* 865, 43–55 (2015).

52. Newton, K. *et al.* Activity of protein kinase RIPK3 determines whether cells die by necroptosis or apoptosis. *Science* 343, 1357–60 (2014).

53. Newton, K. RIPK1 and RIPK3: Critical regulators of inflammation and cell death. *Trends Cell Biol.* 25, 347–353 (2015).

54. Zhang, Q. *et al.* Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature* 464, 104–7 (2010).

55. Lech, M., Gröbmayr, R., Weidenbusch, M. & Anders, H. J. Tissues use resident dendritic cells and macrophages to maintain homeostasis and to regain homeostasis upon tissue injury: The immunoregulatory role of changing tissue environments. *Mediators Inflamm.* 2012, (2012).

56. Elliott, M. R. & Ravichandran, K. S. Clearance of apoptotic cells: Implications in health and disease. *J. Cell Biol.* 189, 1059–1070 (2010).

57. Krafts, K. P. Tissue repair: The hidden drama. *Organogenesis* 6, 225–33 (2010).

58. Fromy, B., Merzeau, S., Abraham, P. & Saumet, J. L. Mechanisms of the cutaneous vasodilator response to local external pressure application in rats: involvement of CGRP, neurokinins, prostaglandins and NO. *Br. J. Pharmacol.* 131, 1161–1171 (2000).

59. Jiang, Y. & Lu, S. Three-dimensional insights into dermal tissue as a cue for cellular behavior. *Burns* 40, 191–199 (2014).

60. Klimczak, A. & Kozlowska, U. Mesenchymal Stromal Cells and Tissue-Specific Progenitor Cells: Their Role in Tissue Homeostasis. *Stem Cells Int.* 2016, 4285215 (2016).

61. Dyment, N. A. & Galloway, J. L. Regenerative biology of tendon: mechanisms for renewal and repair. *Curr. Mol. Biol. reports* 1, 124–131 (2015).

62. Sotiropoulou, P. A. & Blanpain, C. Development and homeostasis of the skin epidermis. *Cold Spring Harb. Perspect. Biol.* 4, 1–9 (2012).

63. Chovatiya, R. & Medzhitov, R. Stress, inflammation, and defense of homeostasis. *Mol. Cell* 54, 281–288 (2014).

64. Tadeo, I., Berbegall, A. P., Escudero, L. M., Alvaro, T. & Noguera, R. Biotensegrity of the Extracellular Matrix: Physiology, Dynamic Mechanical Balance, and Implications in Oncology and Mechanotherapy. *Front. Oncol.* 4, 39 (2014).

65. Waypa, G. B., Smith, K. A. & Schumacker, P. T. O2 sensing, mitochondria and ROS signaling: The fog is lifting. *Mol. Aspects Med.* 47–48, 76–89 (2016).

66. Palmer, B. F. & Clegg, D. J. Oxygen sensing and metabolic homeostasis. *Mol. Cell. Endocrinol.* 397, 51–58 (2014).

67. Ahern, G. P. Transient receptor potential channels and energy homeostasis. *Trends Endocrinol. Metab.* 24, 554–60 (2013).

68. Tóth, B. I., Oláh, A., Szöllősi, A. G. & Bíró, T. TRP channels in the skin. *Br. J. Pharmacol.* 171, 2568–81 (2014).

69. Manorama, A., Meyer, R., Wiseman, R. & Bush, T. R. Quantifying the effects of external shear loads on arterial and venous blood flow: Implications for pressure ulcer development. *Clin. Biomech.* 28, 574–578 (2013).

70. Stekelenburg, A., Gawlitta, D., Bader, D. L. & Oomens, C. W. Deep Tissue Injury: How Deep is Our Understanding? *Arch. Phys. Med. Rehabil.* 89, 1410–1413 (2008).

71. Lei, X. G. *et al.* Paradoxical Roles of Antioxidant Enzymes: Basic Mechanisms and Health Implications. *Physiol. Rev.* 96, 307–364 (2016).

72. Hong, W. X. *et al.* The Role of Hypoxia-Inducible Factor in Wound Healing. *Adv. wound care* 3, 390–399 (2014).

73. Schönenberger, M. J. Hypoxia signaling pathways: modulators of oxygen-related organelles. *Front. Cell Dev. Biol.* 3, 42 (2015).

74. Zolla, V. *et al.* Aging-related anatomical and biochemical changes in lymphatic collectors impair lymph transport, fluid homeostasis, and pathogen clearance. *Aging Cell* 582–594 (2015). doi:10.1111/acel.12330

75. Akl, T. T. J., Nagai, T., Coté, G. L. & Gashev, A. a. Mesenteric lymph flow in adult and aged rats. *Am. J. …* 76504, 1828–1840 (2011).

76. Rahbar, E., Akl, T., Coté, G. L., Moore, J. E. & Zawieja, D. C. Lymph transport in rat mesenteric lymphatics experiencing edemagenic stress. *Microcirculation* 21, 359–67 (2014).

77. Bader, D. L. The recovery characteristics of soft tissues following repeated loading. *J. Rehabil. Res. Dev.* 27, 141–150 (1990).

78. Faber, J. E. *et al.* Aging causes collateral rarefaction and increased severity of ischemic injury in multiple tissues. *Arterioscler. Thromb. Vasc. Biol.* 31, 1748–1756 (2011).

79. Thorfinn, J., Sjoberg, F. & Lidman, D. Perfusion of buttock skin in healthy volunteers after long and short repetitive loading evaluated by laser Doppler perfusion imager. *Scand. J. Plast. Reconstr. Surg. Hand Surg.* 41, 297–302 (2007).

80. Casares, L. *et al.* Hydraulic fracture during epithelial stretching. *Nat. Mater.* 14, 343–351 (2015).

81. Schleip, R. *et al.* Strain hardening of fascia: Static stretching of dense fibrous connective tissues can induce a temporary stiffness increase accompanied by enhanced matrix hydration. *J. Bodyw. Mov. Ther.* 16, 94–100 (2012).

82. Collard, C. D. & Gelman, S. Pathophysiology, clinical manifestations, and prevention of ischemia-reperfusion injury. *Anesthesiology* 94, 1133–8 (2001).

83. Leoni, G., Neumann, P.-A., Sumagin, R., Denning, T. L. & Nusrat, A. Wound repair: role of immune-epithelial interactions. *Mucosal Immunol.* 8, 959–68 (2015).

84. Breslin, J. W. Mechanical forces and lymphatic transport. *Microvasc. Res.* 96, 46–54 (2014).

85. Gray, R. J., Voegeli, D. & Bader, D. L. Features of lymphatic dysfunction in compressed skin tissues - Implications in pressure ulcer aetiology. *J. Tissue Viability* 25, 26–31 (2016).

86. Barker, A. R., Rosson, G. D. & Dellon, a L. Wound healing in denervated tissue. *Ann. Plast. Surg.* 57,

339–342 (2006).

87. Yingjun, G. & Xun, Q. Acid-sensing ion channels under hypoxia. *Channels* 7, 231–237 (2013).

88. Demiot, C., Fromy, B., Saumet, J. L. & Sigaudo-Roussel, D. Preservation of pressure-induced cutaneous vasodilation by limiting oxidative stress in short-term diabetic mice. *Cardiovasc. Res.* 69, 245–252 (2006).

89. Meda, F. *et al.* Nerves Control Redox Levels in Mature Tissues Through Schwann Cells and Hedgehog Signaling. *Antioxid. Redox Signal.* 24, 299–311 (2016).

90. Fromy, B. *et al.* Aging-associated sensory neuropathy alters pressure-induced vasodilation in humans. *J. Invest. Dermatol.* 130, 849–855 (2010).

91. Yang, W. *et al.* On the tear resistance of skin. *Nat. Commun.* 6, 6649 (2015).

92. Moore, Z. *et al.* Pressure ulcer prevalence and prevention practices: a cross-sectional comparative survey in Norway and Ireland. *J. Wound Care* 24, 333–339 (2015).

93. Hatje, L. K., Richter, C., Blume-Peytavi, U. & Kottner, J. Blistering time as a parameter for the strength of dermoepidermal adhesion: a systematic review and meta-analysis. *Br. J. Dermatol.* 172, 323–30 (2015).

94. Ulker, P., Gunduz, F., Meiselman, H. J. & Baskurt, O. K. Nitric oxide generated by red blood cells following exposure to shear stress dilates isolated small mesenteric arteries under hypoxic conditions. *Clin. Hemorheol. Microcirc.* 54, 357–369 (2013).

95. Lyder, C. H. *et al.* Quality of care for hospitalized medicare patients at risk for pressure ulcers. *Arch. Intern. Med.* 161, 1549–54 (2001).

96. Brienza, D. M., Geyer, M. J. & Jan, Y. K. A comparison of changes in rhythms of sacral skin blood flow in response to heating and indentation. *Arch. Phys. Med. Rehabil.* 86, 1245–1251 (2005).

97. Gray, M., McNichol, L. & Nix, D. Incontinence-Associated Dermatitis. *J. Wound, Ostomy Cont. Nurs.* 43, 188–192 (2016).

98. Yusuf, S. *et al.* Microclimate and development of pressure ulcers and superficial skin changes. *Int. Wound J.* 12, 40–46 (2015).

99. Jee, T. & Komvopoulos, K. In vitro investigation of skin damage due to microscale shearing. *J. Biomed. Mater. Res. - Part A* 102, 4078–4086 (2014).

100. Proske, U., Morgan, D. L. & Gregory, J. E. Thixotropy in skeletal muscle and in muscle spindles: a review. *Prog. Neurobiol.* 41, 705–21 (1993).

101. Geerligs, M. Skin layer mechanics. (2009).

102. Alkhouli, N. *et al.* The mechanical properties of human adipose tissues and their relationships to the structure and composition of the extracellular matrix. *Am. J. Physiol. Endocrinol. Metab.* 305, E1427-35 (2013).

103. Sachs, F. & Sivaselvan, M. V. Cell volume control in three dimensions: Water movement without solute movement. *J. Gen. Physiol.* 145, 373–80 (2015).

104. Jang, J. E. *et al.* Nitric Oxide Produced by Macrophages Inhibits Adipocyte Differentiation and Promotes Profibrogenic Responses in Preadipocytes to Induce Adipose Tissue Fibrosis. *Diabetes* 65, 2516–28 (2016).

105. Oomens, C. W. J., Bader, D. L., Loerakker, S. & Baaijens, F. Pressure Induced Deep Tissue Injury Explained. *Ann. Biomed. Eng.* 43, 297–305 (2015).

106. Stekelenburg, A. *et al.* Role of ischemia and deformation in the onset of compression-induced deep tissue injury: MRI-based studies in a rat model. *J. Appl. Physiol.* 102, 2002–2011 (2007).

107. van Nierop, B. J. *et al.* Diffusion of water in skeletal muscle tissue is not influenced by compression in a rat model of deep tissue injury. *J. Biomech.* 43, 570–5 (2010).

108. Purslow, P. P. Muscle fascia and force transmission. *J. Bodyw. Mov. Ther.* 14, 411–417 (2010).

109. van der Wal, J. The architecture of the connective tissue in the musculoskeletal system-An often overlooked functional parameter as to proprioception in the locomotor apparatus. *Int. J. Ther. Massage Bodyw. Res. Educ. Pract.* 2, 9–23 (2009).

110. Li, W. & Ahn, A. C. Subcutaneous fascial bands-a qualitative and morphometric analysis. *PLoS One* 6, (2011).

111. Stecco, C., Macchi, V., Porzionato, A., Duparc, F. & De Caro, R. The fascia: the forgotten structure. *Ital. J. Anat. Embryol.* 116, 127–38 (2011).

112. Bordoni, B. & Zanier, E. Clinical and symptomatological reflections: The fascial system. *J. Multidiscip. Healthc.* 7, 401–411 (2014).

113. Ullah, M., Sittinger, M. & Ringe, J. Extracellular matrix of adipogenically differentiated mesenchymal stem cells reveals a network of collagen filaments, mostly interwoven by hexagonal structural units. *Matrix Biol.* 32, 452–465 (2013).

114. Mok, S. & Moraes, C. Thinking big by thinking small: advances in mechanobiology across the length scales. *Integr. Biol.* 8, 262–266 (2016).

115. Checa, S., Rausch, M. K., Petersen, A., Kuhl, E. & Duda, G. N. The emergence of extracellular matrix mechanics and cell traction forces as important regulators of cellular self-organization. *Biomech. Model. Mechanobiol.* 14, 1–13 (2015).

116. Gyoneva, L. *et al.* Cell-matrix interaction during strain-dependent remodelling of simulated collagen networks. *Interface Focus* 6, 20150069 (2016).

117. Scarr, G. Fascial hierarchies and the relevance of crossed-helical arrangements of collagen to changes in the shape of muscles. *J. Bodyw. Mov. Ther.* 20, 377–387 (2016).

118. Bordoni, B. & Marelli, F. The fascial system and exercise intolerance in patients with chronic heart failure: Hypothesis of osteopathic treatment. *J. Multidiscip. Healthc.* 8, 489–494 (2015).

119. Tyrone, J. W. *et al.* Transforming growth factor beta3 promotes fascial wound healing in a new animal model. *Arch. Surg.* 135, 1154–9 (2000).

120. Lau, F. H. & Pomahac, B. Wound healing in acutely injured fascia. *Wound Repair Regen.* 22, 14–17 (2014).

121. Thorfinn, J., Sjoberg, F. & Lidman, D. Sitting can cause ischaemia in the subcutaneous tissue of the buttocks, which implicates multilayer tissue damage in the development of pressure ulcers. *Scand. J. Plast. Reconstr. Surg. Hand Surg.* 43, 82–89 (2009).

122. Loerakker, S. *et al.* Temporal effects of mechanical loading on deformation-induced damage in skeletal muscle tissue. *Ann. Biomed. Eng.* 38, 2577–87 (2010).

123. Linder-Ganz, E. & Gefen, A. Stress analyses coupled with damage laws to determine biomechanical risk factors for deep tissue injury during sitting. *J. Biomech. Eng.* 131, 11003 (2009).

124. Stucke, S. *et al.* Spatial relationships between shearing stresses and pressure on the plantar skin surface during gait. *J. Biomech.* 45, 619–622 (2012).

125. Shoham, N. & Gefen, A. Deformations, mechanical strains and stresses across the different hierarchical scales in weight-bearing soft tissues. *J. Tissue Viability* 21, 39–46 (2012).

126. Guimberteau, J. C., Delage, J. P., McGrouther, D. a & Wong, J. K. F. The microvacuolar system: how connective tissue sliding works. *J. Hand Surg. Eur. Vol.* 35, 614–622 (2010).

127. Ingber, D. E. Tensegrity-based mechanosensing from macro to micro. *Prog. Biophys. Mol. Biol.* 97, 163–179 (2008).

128. Enyedi, B., Jelcic, M. & Niethammer, P. The Cell Nucleus Serves as a Mechanotransducer of Tissue Damage-Induced Inflammation. *Cell* 165, 1160–1170 (2016).

129. Eckes, B., Krieg, T. & Wickström, S. A. Role of integrin signalling through integrin-linked kinase in skin physiology and pathology. *Exp. Dermatol.* 23, 453–456 (2014).

130. Gohl, K. L., Listrat, A. & Béchet, D. Hierarchical mechanics of connective tissues: integrating insights from nano to macroscopic studies. *J. Biomed. Nanotechnol.* 10, 2464–507 (2014).

131. Gautieri, A., Vesentini, S., Redaelli, A. & Buehler, M. J. Hierarchical structure and nanomechanics of collagen microfibrils from the atomistic scale up. *Nano Lett.* 11, 757–766 (2011).

132. Ingber, D. E., Wang, N. & Stamenovic, D. Tensegrity, cellular biophysics, and the mechanics of living systems. *Rep. Prog. Phys.* 77, 46603 (2014).

133. Fan, D., Creemers, E. E. & Kassiri, Z. Matrix as an interstitial transport system. *Circ. Res.* 114, 889–902 (2014).

134. Amadio, P. C. Gliding resistance and modifications of gliding surface of tendon: clinical perspectives. *Hand Clin.* 29, 159–66 (2013).

135. Takahashi, Y. *et al.* A new concept: 'Relative position between the external force and the bony prominence' explains location-specific occurrence of superficial injury over an undermining lesion. *J. Tissue Viability* 8–11 (2016). doi:10.1016/j.jtv.2016.08.001

136. Huijbregts, P. A. Muscle Injury, Regeneration, and Repair. *J. Man. Manip. Ther.* 9, 9–16 (2001).

137. Depalle, B., Qin, Z., Shefelbine, S. J. & Buehler, M. J. Large Deformation Mechanisms, Plasticity, and Failure of an Individual Collagen Fibril with Different Mineral Content. *J. Bone Miner. Res.* 31, 380–390 (2016).

138. Depalle, B., Qin, Z., Shefelbine, S. J. & Buehler, M. J. Influence of cross-link structure, density and mechanical properties in the mesoscale deformation mechanisms of collagen fibrils. *J. Mech. Behav. Biomed. Mater.* 52, 1–13 (2015).

139. Bonilla-Yoon, I. *et al.* The Morel-Lavallée lesion: Pathophysiology, clinical presentation, imaging features, and treatment options. *Emerg. Radiol.* 21, 35–43 (2014).

140. Vanhegan, I. S., Dala-Ali, B., Verhelst, L., Mallucci, P. & Haddad, F. S. The Morel-Lavallée Lesion as a Rare Differential Diagnosis for Recalcitrant Bursitis of the Knee: Case Report and Literature Review. *Case Rep. Orthop.* 2012, 1–5 (2012).

141. Black, J. M., Brindle, C. T. & Honaker, J. S. Differential diagnosis of suspected deep tissue injury. *Int. Wound J.* 13, 531–9 (2016).

142. Greenhill, D., Haydel, C. & Rehman, S. Management of the Morel-Lavallée Lesion. *Orthop. Clin. North Am.* 47, 115–25 (2016).

143. Aumailley, M. & Rousselle, P. Laminins of the dermo-epidermal junction. *Matrix Biol.* 18, 19–28 (1999).

144. Mimura, M., Ohura, T., Takahashi, M., Kajiwara, R. & Ohura, N. Mechanism leading to the development of pressure ulcers based on shear force and pressures during a bed operation: Influence of body types, body positions, and knee positions. *Wound Repair Regen.* 17, 789–796 (2009).

145. Rausch, M. K., Karniadakis, G. E. & Humphrey, J. D. Modeling Soft Tissue Damage and Failure Using a Combined Particle/Continuum Approach. *Biomech. Model. Mechanobiol.* (2016). doi:10.1007/s10237-016-0814-1

146. Bergstrand, S., Kallman, U., Ek, A.-C., Engstrom, M. & Lindgren, M. Microcirculatory responses of sacral tissue in healthy individuals and inpatients on different pressure-redistribution mattresses. *J. Wound Care* 24, 346–358 (2015).

147. Kroy, K. New and Notable The Inelastic Hierarchy : Multiscale Biomechanics of Weak Bonds. *Biophysj* 111, 898–899 (2016).

148. Honaker, J., Brockopp, D. & Moe, K. Suspected deep tissue injury profile: a pilot study. *Adv. Skin Wound Care* 27, 133-40–2 (2014).

149. Linder-Ganz, E. & Gefen, A. The effects of pressure and shear on capillary closure in the microstructure of skeletal muscles. *Ann. Biomed. Eng.* 35, 2095–2107 (2007).

150. Shindyapina, A. V *et al.* Mineralization of the connective tissue: a complex molecular process leading to age-related loss of function. *Rejuvenation Res.* 17, 116–33 (2014).

151. Cavalcante, F. S. a *et al.* Mechanical interactions between collagen and proteoglycans: implications for the stability of lung tissue. *J. Appl. Physiol.* 98, 672–679 (2005).

152. Fisher, G. J. *et al.* Collagen fragmentation promotes oxidative stress and elevates matrix metalloproteinase-1 in fibroblasts in aged human skin. *Am. J. Pathol.* 174, 101–14 (2009).

153. Adams, C. W., Bayliss, O. B., Baker, R. W., Abdulla, Y. H. & Hunter-Craig, C. J. Lipid deposits in ageing human arteries, tendons and fascia. *Atherosclerosis* 19, 429–40 (1974).

154. Pavan, P. G., Stecco, A., Stern, R. & Stecco, C. Painful connections: densification versus fibrosis of fascia. *Curr. Pain Headache Rep.* 18, 441 (2014).

155. Trindade, V. L. A. *et al.* Experimental study of the influence of senescence in the biomechanical properties of the temporal tendon and deep temporal fascia based on uniaxial tension tests. *J. Biomech.* 45, 199–201 (2012).

156. Demontis, F., Piccirillo, R., Goldberg, A. L. & Perrimon, N. Mechanisms of skeletal muscle aging: insights from Drosophila and mammalian models. *Dis Model Mech* 6, 1339–1352 (2013).

157. Burkhalter, M. D., Rudolph, K. L. & Sperka, T. Genome instability of ageing stem cells-Induction and defence mechanisms. *Ageing Res. Rev.* 23, 29–36 (2014).

158. DuRant, S. E., de Bruijn, R., Tran, M. N. & Romero, L. M. Wound-healing ability is conserved during periods of chronic stress and costly life history events in a wild-caught bird. *Gen. Comp. Endocrinol.* 229, 119–126 (2016).

159. Masoodi, M., Kuda, O., Rossmeisl, M., Flachs, P. & Kopecky, J. Lipid signaling in adipose tissue: Connecting inflammation & metabolism. *Biochim. Biophys. Acta - Mol. Cell Biol. Lipids* 1851, 503–518 (2015).

160. Waters, C. A. & Tredget, E. E. Nutrition and Wound Healing. 47–61 (2012). doi:10.1016/B978-1-4377-0867-7.00005-3

161. Sorci, G., Riuzzi, F., Giambanco, I. & Donato, R. RAGE in tissue homeostasis, repair and regeneration. *Biochim. Biophys. Acta - Mol. Cell Res.* 1833, 101–109 (2013).

162. van Beek, J. H. G. M., Kirkwood, T. B. L. & Bassingthwaighte, J. B. Understanding the physiology of the ageing individual: computational modelling of changes in metabolism and endurance. *Interface Focus* 6, 20150079 (2016).

163. Christian, L. M., Graham, J. E., Padgett, D. A., Glaser, R. & Kiecolt-Glaser, J. K. Stress and wound healing. *Neuroimmunomodulation* 13, 337–346 (2007).

164. Rodríguez A, Ezquerro S, Méndez-Giménez L, Becerril S, F. G. Revisiting the adipocyte: a model for integration of cytokine signaling in the regulation of energy metabolism. *Am J Physiol Endocrinol Metab.* 309, E691-714 (2015).

165. Li, Y. *et al.* Age-Associated Increase in Skin Fibroblast-Derived Prostaglandin E2 Contributes to Reduced Collagen Levels in Elderly Human Skin. *J. Invest. Dermatol.* 135, 2181–8 (2015).

166. Nathan, C. & Ding, A. Nonresolving Inflammation. *Cell* 140, 871–882 (2010).

167. Belizário, J. E., Fontes-Oliveira, C. C., Borges, J. P., Kashiabara, J. A. & Vannier, E. Skeletal muscle wasting and renewal: a pivotal role of myokine IL-6. *Springerplus* 5, 619 (2016).

168. Loerakker, S. *et al.* How does muscle stiffness affect the internal deformations within the soft tissue layers of the buttocks under constant loading? *Comput. Methods Biomech. Biomed. Engin.* 16, 520–9 (2013).

169. Trujillo, A. & Breslin, J. W. Lymphaticosclerosis: a new way of thinking about lymphatic vessel obstruction. *Br. J. Dermatol.* 172, 1184–1185 (2015).

170. Weiss, R. M. Lasting effects of lost vascular elasticity. *Circ. Res.* 100, 604–6 (2007).

171. Ungvari, Z., Kaley, G., De Cabo, R., Sonntag, W. E. & Csiszar, A. Mechanisms of vascular aging: New perspectives. *Journals Gerontol. - Ser. A Biol. Sci. Med. Sci.* 65 A, 1028–1041 (2010).

172. Pavan, P. G., Pachera, P., Stecco, C. & Natali, A. N. Biomechanical behavior of human crural fascia in anterior and posterior regions of the lower limb. *Med. Biol. Eng. Comput.* 53, 951–959 (2015).

173. Fisher, G. J. *et al.* Collagen fragmentation promotes oxidative stress and elevates matrix metalloproteinase-1 in fibroblasts in aged human skin. *Am. J. Pathol.* 174, 101–14 (2009).

174. Gerhardt, L.-C., Strassle, V., Lenz, A., Spencer, N. . & Derler, S. Influence of epidermal hydration on the friction of human skin against textiles. *J. R. Soc. Interface* 5, 1317–1328 (2008).

175. Cutting, K. F. & White, R. J. Maceration of the skin and wound bed. 1: Its nature and causes. *J. Wound Care* 11, 275–8 (2002).

176. Holt, N. C., Danos, N., Roberts, T. J. & Azizi, E. Stuck in gear: age-related loss of variable gearing in skeletal muscle. *J. Exp. Biol.* 219, 998–1003 (2016).

177. Kottner, J. *et al.* Skin response to sustained loading: A clinical explorative study. *J. Tissue Viability* 24, 114–122 (2015).

178. Calvani, R. *et al.* Mitochondrial pathways in sarcopenia of aging and disuse muscle atrophy. *Biol. Chem.* 394, 393–414 (2013).

179. Kalamgi, R. C. & Larsson, L. Mechanical Signaling in the Pathophysiology of Critical Illness Myopathy. *Front. Physiol.* 7, 23 (2016).

180. Ceelen, K. K. *et al.* Compression-induced damage and internal tissue strains are related. *J. Biomech.* 41, 3399–3404 (2008).

181. Humphrey, J. D. Review Paper: Continuum biomechanics of soft biological tissues. *Proc. R. Soc. A Math. Phys. Eng. Sci.* 459, 3–46 (2003).

182. Cyron, C. J., Wilson, J. S. & Humphrey, J. D. Mechanobiological stability: a new paradigm to understand the enlargement of aneurysms? *J. R. Soc. Interface* 11, 20140680 (2014).

183. Arentson-Lantz, E., English, K. L., Paddon-Jones, D. & Fry, C. S. 14 Days of Bed Rest Induces a Decline in Satellite Cell Content and Robust Atrophy of Skeletal Muscle Fibers in Middle-Aged Adults. *J. Appl. Physiol.* 5680, jap.00799.2015 (2016).

184. Wang, H. *et al.* Apoptosis in capillary endothelial cells in ageing skeletal muscle. *Aging Cell* 13, 254–262 (2014).

185. Fisher, G. J., Varani, J. & Voorhees, J. J. Looking older: fibroblast collapse and therapeutic implications. *Arch. Dermatol.* 144, 666–72 (2008).

186. Zhou, Y. *et al.* Age-dependent changes cooperatively impact skeletal muscle regeneration after compartment syndrome injury. *Am. J. Pathol.* 184, 2225–36 (2014).

187. Struck, B. D. & Wright, J. E. Pressure ulcers and endothelial dysfunction: is there a link? *J. Nutr. Elder.* 26, 105–17 (2007).

188. Scioli, M. G., Bielli, A., Arcuri, G., Ferlosio, A. & Orlandi, A. Ageing and microvasculature. *Vasc. Cell* 6, 19 (2014).

189. Jan, Y.-K., Brienza, D. M., Boninger, M. L. & Brenes, G. Comparison of skin perfusion response with alternating and constant pressures in people with spinal cord injury. *Spinal cord Off. J. Int. Med. Soc. Paraplegia* 49, 136–141 (2011).

190. Sun, K., Tordjman, J., Clément, K. & Scherer, P. E. Fibrosis and adipose tissue dysfunction. *Cell Metab.* 18, 470–7 (2013).

191. Vodovotz, Y. Translational systems biology of inflammation and healing. *Wound Repair Regen.* 18, 3–7 (2010).

192. Arnold, C. P. *et al.* Pathogenic shifts in endogenous microbiota impede tissue regeneration via distinct activation of TAK1/MKK/p38. *Elife* 5, e16793 (2016).

193. Gefen, A., Farid, K. J. & Shaywitz, I. A review of deep tissue injury development, detection, and prevention: shear savvy. *Ostomy. Wound. Manage.* 59, 26–35 (2013).

194. Ponnappan, S. & Ponnappan, U. Aging and immune function: molecular mechanisms to interventions. *Antioxid. Redox Signal.* 14, 1551–85 (2011).

195. Hazeldine, J., Lord, J. M. & Hampson, P. Immunesenescence and inflammaging: A contributory factor in the poor outcome of the geriatric trauma patient. *Ageing Res. Rev.* 24, 349–57 (2015).

196. Basson, M. D. & Burney, R. E. Defective wound healing in patients with paraplegia and quadriplegia. *Surg. Gynecol. Obstet.* 155, 9–12 (1982).

197. Stover, S. L., Hale, a M. & Buell, a B. Skin complications other than pressure ulcers following spinal cord injury. *Arch. Phys. Med. Rehabil.* 75, 987–993 (1994).

198. Ruschkewitz, Y. & Gefen, A. Cellular-scale transport in deformed skeletal muscle following spinal cord injury. *Comput. Methods Biomech. Biomed. Engin.* 14, 411–424 (2011).

199. Sopher, R., Nixon, J., Gorecki, C. & Gefen, A. Effects of intramuscular fat infiltration, scarring, and spasticity on the risk for sitting-acquired deep tissue injury in spinal cord injury patients. *J. Biomech. Eng.* 133, 21011 (2011).

200. Levine, J. M. Skin Failure: An Emerging Concept. *J. Am. Med. Dir. Assoc.* 17, 666–669 (2016).

201. Delmore, B., Cox, J., Rolnitzky, L., Chu, A. & Stolfi, A. Differentiating a Pressure Ulcer from Acute

Skin Failure in the Adult Critical Care Patient. *Adv. Skin Wound Care* 28, 514-24–6 (2015).

202. Dubay, D. A. & Franz, M. G. Acute wound healing: The biology of acute wound failure. *Surg. Clin. North Am.* 83, 463–481 (2003).

203. Irvine, C. 'Skin failure'--a real entity: discussion paper. *J. R. Soc. Med.* 84, 412–3 (1991).

204. Russell, L. Pressure ulcer classification: defining early skin damage. *Br. J. Nurs.* 11, S33-4, S36, S38, S40-1 (2002).

205. Friedrich, O. *et al.* The Sick and the Weak: Neuropathies/Myopathies in the Critically Ill. *Physiol. Rev.* 95, 1025–109 (2015).

206. Hill-Taylor, B. *et al.* Effectiveness of the STOPP/START (Screening Tool of Older Persons' potentially inappropriate Prescriptions/Screening Tool to Alert doctors to the Right Treatment) criteria: Systematic review and meta-analysis of randomized controlled studies. *J. Clin. Pharm. Ther.* 41, 158–169 (2016).

207. Levine, J. M. The Effect of Oral Medication on Wound Healing. *Adv. Skin Wound Care* 30, 137–142 (2017).

208. Gould, L. J. *et al.* Spinal Cord Injury survey to determine pressure ulcer vulnerability in the outpatient population. *Med. Hypotheses* 83, 552–558 (2014).

209. Callahan, D. *et al.* Predictors of Severity in Diabetic Foot Infections. *Ann. Vasc. Surg.* (2015). doi:10.1016/j.avsg.2016.01.003

210. Lindley, L. E., Stojadinovic, O., Pastar, I. & Tomic-Canic, M. Biology and Biomarkers for Wound Healing. *Plast. Reconstr. Surg.* 138, 18S–28S (2016).

211. Tegl, G., Schiffer, D., Sigl, E., Heinzle, A. & Guebitz, G. M. Biomarkers for infection: enzymes, microbes, and metabolites. *Appl. Microbiol. Biotechnol.* 99, 4595–4614 (2015).

212. Januszyk, M. & Gurtner, G. C. High-Throughput Single-Cell Analysis for Wound Healing Applications. *Adv. wound care* 2, 457–469 (2013).

213. Voegeli, D. & Lwaleed, B. Back to basics: histological, microbiological and biochemical sampling in wound care. *J. Wound Care* 22, 650–2, 654 (2013).

214. Anderson, A. E. & Galko, M. J. Rapid clearance of epigenetic protein reporters from wound edge cells in Drosophila larvae does not depend on the JNK or PDGFR/VEGFR signaling pathways. *Regeneration* 1, 11–25 (2014).

215. Zhang, S. & Duan, E. Epigenetic regulations on skin wound healing: implications from current researches. *Ann. Transl. Med.* 3, 227 (2015).

216. Cutroneo, K. R. & Chiu, J. F. Comparison and evaluation of gene therapy and epigenetic approaches for wound healing. *Wound Repair Regen.* 8, 494–502 (2000).

217. Förster, Y. *et al.* Microdialysis sampling from wound fluids enables quantitative assessment of cytokines, proteins, and metabolites reveals bone defect-specific molecular profiles. *PLoS One* 11, 1–24 (2016).

218. Zang, T. *et al.* The biochemistry of blister fluid from pediatric burn injuries: proteomics and metabolomics aspects. *Expert Rev. Proteomics* 13, 35–53 (2016).

219. Kalkhof, S. *et al.* Proteomics and Metabolomics for In Situ Monitoring of Wound Healing. *Biomed Res. Int.* 2014, 1–12 (2014).

220. National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel & Pan Pacific Pressure Injury Alliance. *Prevention and Treatment of Pressure Ulcers: Quick Reference Guide*. (2014).