Development of deep tissue injury: inside out or outside in?

KEY WORDS
- Deep tissue injury
- Mechanism of injury
- Pressure ulcers
- Review

Pressure ulcers (PUs) have been described as painful, slow-healing wounds that can develop over bony prominences in individuals experiencing periods of prolonged immobility (Jagannathan and Tucker-Kellogg, 2016). However, new theories are emerging regarding how PUs develop. This article explores and reviews the evidence on the suggested mechanisms of deep tissue injury (DTI) development. DTI is caused by a number of mechanisms. Further research is required to clarify the key differences between mechanisms of injury between DTI and superficial PUs.

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PUs adversely affect quality of life and impose a substantial financial burden on healthcare services both in terms of prevention and management (Demarré et al, 2015).

Traditionally it was hypothesised that PU developed from the "outside in" (Brand, 1973), with pressure, shear, friction and moisture being the main external causative factors (Reuler and Cooney, 1981). However, according to Berlowitz and Brienza (2007), there are four commonly hypothesised pathophysiological explanations for PU development, ischaemia due to capillary occlusion, reperfusion injury (RI), impaired lymphatic function and prolonged mechanical deformation of tissue cells. Yet, Oomens et al (2014) suggested these mechanisms do not completely explain why deep wounds can develop rapidly, often with undermining of intact skin.

Ankrom et al (2005) undertook a systematic review and suggested severe PUs evolve differently, involving the development of significant pressure related damage under intact skin. These injuries, referred to as DTI, are not seen as readily as superficial ulcers (SU) and therefore are associated with necrosis and severe tissue loss (Gefen, 2009). Indeed, various researchers (Bouten et al, 2003; Berlowitz and Brienza, 2007) have questioned whether PUs that only involve superficial tissue should be labelled as a PU at all. Brienza et al (2015) argued that PU by definition develop due to pressure, but superficial lesions not related to prolonged pressure should not be called a PU. Indeed, Berlowitz and Brienza (2007) suggest that most truly superficial skin lesions are as a result of friction and moisture. Brienza et al (2015) postulate that superficial friction wounds can occur in the same locations as PU but that friction is not a sole cause of PU development.

DTI has been defined by the National Pressure Ulcer Advisory Panel (NPUAP), European Pressure Ulcer Advisory Panel (EPUAP) and Pan Pacific Pressure Injury Alliance (PPPIA) (2014: p.13) as a,

"Purple or maroon localised area of discoloured intact skin or blood-filled blister due to damage of underlying soft tissue from pressure and/or shear."

According to Sui et al (2009a), DTI arise in muscle tissues overlying bony prominences. Prolonged mechanical loads leading to reduced blood flow and poor removal of waste products in soft tissues resulting in tissue necrosis have been proposed as causes (Ankrom et al, 2005).

Salcido (2007) and Smart (2013) both proposed different terms for DTI, myosubcutaneous infarct and hypoxic reperfusion ulcer, respectively, based on proposed processes, by which, DTI occurs.

PU DEVELOPMENT — AN OVERVIEW

Berlowitz and Brienza (2007) suggested that superficial skin loss over bony prominences can develop from friction and shear forces when moving an immobile patient in bed. Reger et al (2010) suggested that shear stress occurs due to

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the application of a force parallel to the surface of an object whilst the base of the object remains stationary; shear stresses typically arise in combination with pressure. Furthermore, Reger et al (2010) identified friction force occurs when two objects rub against each other. However, Berlowitz and Brienza (2007) and Brienza et al (2015) postulated that due to the misinterpretation of the original literature in this area (Husain, 1953; Kosiak, 1959), SUs are often misdiagnosed as a PU as they occur in patients who are deemed at risk. Subsequent studies have lead to new hypotheses (Lachenbruch et al, 2013; Stekelenburg et al, 2007). Lachenbruch et al (2013) utilised Doppler flowmetry to measure reactive hyperaemia in the epidermis of the sacrum in humans. Their results suggested shear force did not deform blood vessels in the top 1 to 2 mm of the skin. Therefore, whilst it has been proposed that friction may play a role in creating shear strain in deeper tissues, it does not appear to contribute to PU in the superficial layers of the skin (Brienza et al, 2015).

The dermis was initially considered the most susceptible skin structure to extrinsic pressure (Salcido et al, 2007). Early studies explored the effects of the intensity and duration of external pressure on the development of tissue injury (Husain, 1953; Kosiak, 1959; 1961). Husain (1953) applied pressures of 100–800 mmHg for one to ten hours to the hind legs of rats and guinea pigs. The compressive forces caused vascular occlusion leading to hypoxia, lack of nutrients in the tissues, cell damage and interstitial oedema. Myofibrillar degeneration, infiltration of macrophagic immune cells, capillary haemorrhages and localised oedema in muscle tissue were also noted. Husain suggested that 100 mmHg pressure applied for two hours was the threshold for skeletal muscle. Furthermore, Husain (1953) observed that localised interface pressures (IP) destroyed more vessels in the skin and subcutaneous tissue than in muscle. Yet the muscle was severely damaged whereas the skin and subcutis was not, suggesting damage may originate in the deep muscle layers.

Kosiak (1959; 1961) supported Husain's (1953) findings, demonstrating an inverse trend between magnitude and duration of pressures in animal models. Pressures of 190 mmHg were applied continuously and intermittently for one hour, the results showed this did not cause any macroscopic changes, whereas 70 mmHg applied for two hours caused irreversible tissue damage. On application of 60 mmHg for one hour oedema, cellular infiltration and extravasation occurred. Kosiak (1961) noted these changes were similar to the pathology associated with a bruise.

A later study by Reswick and Rogers (1976) utilised the concept of the inverse trend between magnitude and duration of pressures to formulate their pressure (mmHg) x time (hour) curve. More recently, however, Gefen (2009) highlighted that whilst this formula was appropriate for a few hours of exposure to pressure it was incorrect for extreme ends of the timescale.

According to Nix and Mackey (2016), IP is the force per unit that acts perpendicularly between the skin and support surface. Gefen and Levine (2007) used bovine muscle and computer modelling to demonstrate that internal tissue loads could not be predicted using IP. They found compression stresses in the area of muscle closest to the replica bone used were between five and eleven times higher than the area of muscle at the interface with the support surface. Therefore, based on this evidence, use of IP in the development and prevention of DTI is not appropriate.

Mak et al (2010) suggested that in order to understand DTI aetiology, and therefore whether DTI is an appropriate term, it may be important to comprehend the proposed mechanisms of how forces externally applied on the skin affect the muscle tissues internally.

IN VITRO STUDIES

Bruels et al (2003) developed an *in vitro* model system of engineered murine skeletal muscle tissue (MSMT) enabling them to study the relationship between compressive tissue straining and the initiation of muscle cell damage within a controlled environment. Muscle cells were compressed and studied following staining. Cell death (CD) was noted immediately, significantly increasing with time up to four hours with strains of 30% and 50% (p = 0.001). They noted CD was uniformly distributed under the indenter and concluded that cell deformation was the cause of CD.

Gawlitta et al (2006) also used MSMT. They hypothesised that both deformation and hypoxia

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influence tissue viability but at different time points. They studied the cells under different compressions both in normal oxygen tension (20%) and in hypoxic conditions (<6%) and found tissue compression resulted in immediate CD. Furthermore hypoxia alone or in addition to compression up to a level of 40% had a minimal effect over 22 hours on CD. However, after 48 hours significantly more cells were damaged in hypoxic conditions when compared to controls ($p< 0.05$), suggesting that cells appear to be able to remain viable under hypoxic conditions for more than a day.

Subsequently, Gawlitta et al (2007) hypothesised that hypoxia would stimulate the tissue to anaerobic metabolism. As in previous studies (Bruels et al, 2003; Gawlitta et al, 2006), it was found that deformation initially caused damage. However, hypoxia, with or without deformation, resulted in decreased glucose utilisation and elevated lactic acid production creating an acidic environment leading to a significant reduction in tissue viability by day five ($p< 0.001$). These results suggest a change to anaerobic metabolism over time that may explain why similar effects were not seen in the Bruels et al (2003) study.

Elevated intracellular levels of reactive oxygen species (ROS) that cause damage to cells and DNA is known as oxidative stress (OS) (Schieber and Chandel 2014). OS can affect myoblast cytoskeleton and stimulate cell apoptosis (Sui et al, 2009b; Sun et al, 2014). In terms of DTI development, this is important as it has been proposed that reperfusion of blood to an area that was occluded can result in a cascade of harmful events including release of ROS (Pieper, 2016). A study by Yao et al (2015) indicated that OS weakened the ability of murine myoblasts to resist compressive damage. They postulated this may be due to depolymerisation of actin filaments which are a major component of the cytoskeleton suggesting that where RI is present less time would be needed for initial damage to occur.

IN VIVO STUDIES

Animal models are required to further understand the aetiology and pathophysiology of PUs, however, there are differences in the microvasculature between animal and human skin and muscle, with human being much more complex (Salcido et al, 2007). Yet there is a paucity of studies involving humans possibly due to ethical issues. Nevertheless, Witowski and Parish (1982) studied the PU aetiology of 59 patients by performing punch biopsies over various anatomical locations. Some (n=22) were deemed to have non-blanching erythema which would be consistent with the current NPAUP, EPUAP, PPPIA (2014) category one PU. However, Witowski and Parish found dermal capillary and venule engorgement and necrosis within the subcutaneous fat but normal epidermis was evident. Black et al (2016) suggested that DTI is not evident until the damage has evolved to mid-dermal tissue. Therefore, Witowski and Parish could have been describing DTI that in time may have become evident.

The impact of RI has been explored (Pierce et al, 2000; Bonheur et al, 2004; Tsuji et al, 2005). Each identified an increase in tissue damage when more reperfusion cycles took place. Tsuji et al (2005) analysed the microcirculation of 16 mice comparing continuous compression of 500 mmHg for eight hours with intermittent compression of 500 mmHg, two hours of compression and one hour of release for a total of eight hours. The intermittent group suffered a significantly greater ratio of microcirculatory injury as compared to the continuous group (p=0.002694). Tsuji et al (2005) concluded that RI may significantly contribute to the development of PU. Whilst this study demonstrates the possibility that continuous and intermittent compression create different responses in the skin, it does not offer insight into what may be occurring within deeper tissues over bony prominences where DTI is thought to be initiated. Indeed body site is important when exploring DTI development. Smart (2013) highlighted areas such as the heel and sacrum have a single blood vessel supply and smaller collateral circulation, therefore making them more prone to DTI.

The results of these studies may be cause for concern, given that current guidance (NICE, NPUAP, EPUAP and PPPIA, 2014) suggests the use of alternating air mattresses (AAM) to aid in providing pressure relief. According to Bouten et al (2003), whilst AAM may boast low IP it is not known if pressures are intermittently higher at a deeper level. Therefore, further research is required to assess the effects of AAM in deep muscle tissue.

Using a rat model, Stekelenburg et al (2007)

explored the role of ischaemia and deformation in the onset of DTI. Results supported those of the previous studies (Bruels et al, 2003; Gawlitta et al, 2006), with immediate damage to muscle tissue seen on deformation. In addition, Stekelenburg et al (2007) discovered that two hours of deformation with associated ischaemia caused highly localised areas of irreversible muscle damage. Whereas with ischaemia alone reversible changes such as oedema and disruption of small membranes were seen suggesting deformation is the key stimulus for severe muscle damage. Subsequently, Stekelenburg et al (2008) suggested that compression of tissues may also adversely affect lymphatic flow and movement of interstitial fluid resulting in lack of nutrient delivery to tissues and an increase in toxic metabolites contributing to further CD.

Sari et al (2010) explored the involvement of hypoxia in DTI development using hypoxia-inducible factor-1α (HIF-1α) as a marker. Elevated expression and activation of HIF-1α was seen in both the low and high pressure groups with a greater increase in the high pressure group when compared to controls. Previously, Bruick (2000) found that HIF-1α can induce hypoxia-mediated apoptosis and Zhang et al (2008) demonstrated that HIF-1α increases in ischaemic wound tissue. Therefore, the results suggested ischaemia and hypoxia induced CD play a role in the development of DTI. However, prior to loading, the rat skin utilised in the Sari et al (2010) study, was excoriated using sandpaper in order for the researchers to study exudate. Thus skin damage was already present. It is not known if this had any effect on deeper tissues when loading was applied. Sari et al (2010) claimed that all wounds healed without ulceration, yet the illustrations in the paper do not appear to support this claim casting some doubts on the results.

More recently, Sari et al (2015) inserted metal plates sub-peritoneally in 51 rats. Three groups, indenter with prominence plus soft felt pad (deterioration group), indenter, no prominence, no felt pad (control) and prominence, no felt pad (prominence group) were subjected to 10 kg/3cm2 loading to the overlying skin for eight hours. By day three, post-wounding collagen fibres were noted to be severely denatured but no epidermal lesions were seen in the prominence and flat groups. By day seven, inflammation was seen in deep muscle layers of the deterioration group but extended to the dermis in the other two groups suggesting the felt pad offered some protection to the superficial layers. Importantly, differences were seen in skin colour immediately following compression. The prominence group displayed a darker red skin when compared with the deterioration group. The researchers speculated this was due to bleeding in the skin due to tissue damage.

CONCLUSION

It appears that DTI is caused by a number of mechanisms. Deformation in conjunction with ischaemia appears to play a major role, however ischaemia alone does not cause DTI (Stekelenburg et al, 2007). Therefore, myosubcutaneous infarct, as proposed by Salcido (2007) may not fully describe the mechanisms involved in DTI development. RI has also been demonstrated, not only to be a cause of DTI but also as a mechanism by which any existing damage is exacerbated (Tsuji et al, 2005). Whilst Smart (2013) argued that the term DTI is not specific enough; hypoxic reperfusion ulcer does not acknowledge the role of deformation in DTI development. It also appears that DTIs have a different mechanism of injury to the SU that only involve the superficial tissues. Therefore, Brienza et al's (2015) suggestion that superficial lesions not related to prolonged pressure should be categorised differently may have some merit. Further research is required to clarify the key differences between mechanisms of injury between DTI and superficial PU to enable clinicians to implement strategies to prevent and treat patients appropriately. WUK

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