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Deep tissue injury: a narrative review on the aetiology of a controversial wound.

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Corresponding Author:	Matthew Oliver Wynn University of Salford Salford, UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of Salford
Corresponding Author's Secondary Institution:	
First Author:	Matthew Oliver Wynn
First Author Secondary Information:	
Order of Authors:	Matthew Oliver Wynn
Order of Authors Secondary Information:	
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Abstract:

Deep tissue injuries (DTI) were first introduced to pressure ulcer grading systems in 2009. Since then they have been associated with the same aetiological processes as other forms of pressure injuries (PI). This is despite notable clinical differences in presentation along with variations in their natural history suggesting that they are the consequence of processes distinct from those that cause other PI.

Understanding the aetiology of DTI is essential to guide clinical prevention and treatment efforts in addition to ensuring healthcare governance processes deeply tied to pressure injury are effective and efficient.

Current understanding of the aetiology of DTI has significant gaps, with several key challenges impeding progress in this area of pressure injury research including inconsistent reporting by healthcare services, the limitations of animal and computer models in addition to the ethical barriers to conducting studies on human subjects. Synthesis of early studies with studies undertaken pre 2009 is also limited by the various definitions of DTI used prior to the definition published by the NPUAP and EPUAP in full at first use in 2009.To date few prospective clinical studies have been conducted.

This article presents a narrative review on the clinical and animal study evidence indicating contemporary understanding DTI.

Key Words

Pressure injury, PI, deep tissue injury, DTI, aetiology, pressure ulcer

Highlights:

- Controversies remain as to the aetiological features of DTI
- Currently there are no major studies investigating the impact of co-morbidities on tissue responses to pressure in humans
- Future studies should focus on the aetiological differences between normal PI and DTI
- Consistent reporting and follow up of DTI may ultimately help provide a data set from which to better establish the epidemiological features of DTI

Reflective questions:

- How does your understanding of deep tissue injury impact your nursing interventions for primary/secondary prevention?
- Are your route cause analysis processes evidence based with regards to pressure injury?
- How do you think current understanding of deep tissue injury impacts patients experience of receiving care?

Introduction

DTI became a distinct classification of PI in 2009 following the recognition of the unique clinical presentation and pathogenesis of these injuries compared with normal PI (Bader et al 2017). DTI have been defined as

> *"purple or maroon localized area of discoloured intact skin or blood-filled blister due to damage of underlying soft tissue from pressure and/or shear. The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer or cooler as compared to adjacent tissue"*
>
> (NPIAP/EPUAP/ PPPIA, 2019).

The epidemiology of deep tissue injury remains to be fully elucidated however the clinical impact of these injuries can be significant. Recent retrospective studies have indicated that full thickness tissue loss is expected in between 9-14% of DTI cases indicating the potentially significant impact of DTI on patients physical and psychological health in addition to the potential economic burdens on healthcare services (Sullivan 2013, Tescher et al 2018). Current understanding of PI pathology does not explain why some PI, specifically 'deep tissue injury' (DTI) can develop rapidly and undermine viable tissues, whereas 'normal' PI such as those defined within the I-IV grading system initially created by Shea in 1975, in many cases affect only superficial tissues despite the higher vulnerability of deeper muscle tissues to pressure (Oomens et al 2015).

A recent retrospective review of pressure ulcer route cause analyses (RCA) challenged the previous consensus that 95% of grade II-IV PI are avoidable, instead reporting that only 43% of grade II-IV PI are likely to have been avoidable if best practice had been followed Downie et al (2013). A later analysis conducted following the ending of

reimbursement of hospitals for costs associated with hospital acquired PI in the US found that the incidence of grade III and IV PI reduced following the ending of reimbursement payments (Padula et al (2015). Notably, neither of these analyses included DTI as a distinct category of injury, it is possible however that DTI that evolved may have been re-graded as grade III or IV PI and subsequently included in these analyses. This indicates the potential financial impact that evolved DTI may have on healthcare services even though it remains unclear why some DTI become deep wounds and others do not. It is also possible that the avoidability of DTI may be wrongly included in statistics describing non-DTI grade III-IV PI making it difficult to determine if clinical outcomes associated with DTI can be influenced by preventative intervention.

It is also unclear if DTI is an appropriate name for injuries which often do not result in full thickness tissue loss (Tescher et al 2018). Overall, these issues indicate the controversial nature of DTI from epidemiological, clinical and economic perspectives.

This article will discuss the current understanding of the aetiologies associated with deep tissue injury in contrast to normal PI based on evidence from clinical studies.

Animal studies

One of the earliest studies investigating the nature of pressure related injuries was conducted by Husain (1953) and focussed on the relationship between PI and bacterial infections rather than focussing primarily on the aetiology of the injury. Hussain (1953) made two key observations which challenged the understanding of PI and indicated a potential explanation for the nature of DTI which was not defined until much later in 2009 (Bader et al 2017). These observations were that; dermal tissues suffered more vascular damage compared to skeletal muscle when subjected to pressure; however, skeletal muscle suffers more structural damage because of pressure compared to dermal tissue. This study utilised murine models however, potentially limiting extrapolation of these observations to human subjects due to structural differences between murine and human tissues (Ansell et al 2012).

A review by Bouten et al (2003) investigated whether PI start in muscle tissues or can be only ‘skin deep’ as suggested by the most recent guidelines (EPUAP/NPIAP/PPPIA 2019). The review established four key pathologies associated with PI which include occlusion of capillaries and lymph vessels, mechanical deformation and reperfusion injury. Bouten et al

(2003) suggested that muscle may be more susceptible to PI due to the higher metabolic activity of skeletal muscle compared to dermal tissue. The metabolic requirements would make the tissue more prone to damage following a restriction of blood supply and amplify the accumulation of metabolic waste created by lymphatic occlusion (Bouten et al 2003). The authors concluded that future studies should adopt a 'hierarchic' approach utilising a combination of computer model and *in vivo* methodologies to yield more information on the nature of PI on deeper tissues; this is in recognition of the limitations of animal models and the ethical challenges inherent in testing on live subjects.

This review was later supported by Berlowitz and Brienza (2007) who reviewed both computer model and animal studies as well as human punch biopsy studies on PI aetiology. According to the authors stress (force applied per unit area) and strain (amount of tissue deformation) were demonstrably higher at the interior bone-buttock interface than at the skin surface suggesting that deeper muscle structures were more susceptible to the mechanical deformation damage as described by Bouten et al (2003). It was also reported in porcine models that increased heat may lead to increases in metabolic activity generating an increased strain on the muscle tissues due to effects of vascular occlusion (Berlowitz and Brienza 2007). Despite the known limitations of animal models, porcine tissue is widely considered to be most like human and therefore most indicative of how human tissues may react to any given clinical phenomena (Vlig et al 2019). This may indicate a potentially increased risk of DTI in human patients experiencing pyrexia in which the muscle tissue may be prone to more damage due to the metabolic consequences of increased temperature combined with the lack of lymphatic draining and oxygen supply to dermal tissues caused by pressure. However, pyrexia is not currently recognised as a risk for PI in contemporary risk assessments tools (Coleman et al 2013). Finally, a punch biopsy study by Berlowitz and Brienza (2007) reported that grade 1 PI (as per EPUAP grading 2019) showed necrosis in subcutaneous tissues and sub-dermal haemorrhage indicating that deeper damage may already be present in PI considered clinically to be superficial. Ultimately Berlowitz and Brienza concluded that superficial lesions commonly associated with pressure may be more likely to be caused by friction or moisture. Although this review supports the developing concept that pressure universally creates damage in deeper tissues, it does not explain the differences in clinical presentation of deep PI compared to DTI as per the NPUAP/EPUAP/ PPPIA (2019)

definition. Specifically, the variation in skin colour changes and the ability of DTI to either ‘resolve’ or ‘evolve’; a phenomenon not observed in non-DTI PI.

A primary study conducted by Stekelenburg et al (2008) adopted the hierarchic approach recommended by Bouten et al (2003). This study utilised a combination of *in vitro* and *in vivo* techniques to model the effects of pressure at a cellular and a tissue level. According to Stekelenburg and colleagues tissue necrosis was observed as an apparent consequence of tissue acidification due to ischaemia and glucose depletion. This study utilised a murine model which have been criticised in clinical studies investigating muscle function due to the different mechanical structures of the tissues between murine and humans (Hu et al 2017). However, a primary *in vitro* study by Jacobs et al (2012) comparing the metabolic function of murine muscle and human muscle reported no statistically significant difference in mitochondrial function between the species. This suggests that although the effects of mechanical deformation on murine tissues may not be comparable to the effects it has on human muscle the impact of pressure on the metabolic processes within muscle cells may be similar in mice and humans. Notably, Jacobs et al (2012) did not compare differences in cellular function between murine and human dermal tissues making it unclear if the observed deeper tissue damage observed in murine models is reflective of the patterns of damage which may occur in human subjects exposed to the same pressures. Overall, the Stekelenburg et al (2008) study reinforces the concept of metabolic stress and subsequent tissue necrosis as a central mechanism associated with the development of DTI and suggests that patients with impaired glucose metabolism may be at increased risk of deeper tissue damage. Although diabetes and malnourishment are recognised as risk factors, other conditions potentially affecting glucose metabolism such as high melatonin levels (Garaulet et al 2020), reductions in physical activity (Von Ah Morano et al 2019) or dietary fat-induced impairments in glycaemic control (Parry et al 2019) are not currently considered in current PI risk assessment tools (Coleman et al 2013) which may impact their clinimetric sensitivity by underestimating risk in patients with genuine risk for DTI.

Compartment syndrome theory of DTI development

According to Smart (2013) skeletal muscle is more vulnerable to reperfusion injuries. Smart (2013) illustrates this concept with data indicating that most DTI occur on the heel (41%) and to a lesser extent the sacrum (19%). These are areas that have no distinct main blood supply but rely on dense collateral capillaries for their perfusion (Anderson

1978). Smart (2013) argued that due to the small and stiff musculature surrounding the sacrum and heel covering a rigid underlying fascia in both cases, these areas are prone to compartment syndrome following swelling caused by ischaemia and vascular occlusion. Ultimately it is suggested that DTI should be referred to as 'hypoxic reperfusion ulcers' based on the proposed aetiology, with the outcome of pressure applied over the affected areas being entirely dependent on the metabolic situation of the patient (Smart 2013). Although the impact of the pathologies associated with PI e.g. vascular occlusion, metabolic changes and increased mechanical strain in deeper tissues suggest that deep damage to muscle and deeper tissues is inevitable in cases of prolonged exposure to pressure (Bouten et al 2003, Stekelenburg 2008). Smart's (2013) conclusion that suggests that all DTI are unavoidable from a nursing perspective and may be avoided only by medical intervention to create changes in the metabolic state of the patient. However, this does not explain why normal PI can occur in the same anatomical locations (heel or sacrum) or following the use of medical devices in anatomical locations that do not fit the compartment syndrome theory of DTI (Kayser et al 2018). Notably, according to a review by Downie et al (2013) on whether PI are avoidable, the authors argued that DTI are often categorised as grade 3 ulcers or not reported until a wound bed is clinically visible which does not always develop in cases of DTI. For example, a retrospective study by Sullivan (2013) reported that in a sample of n=128 patients with DTI only 9.3% (n=12) resulted in full thickness tissue loss. This means that current incident reporting data is unlikely to support the view of Smart (2013) that DTI are largely unavoidable if the patient's metabolic status is not optimised, due to inconsistencies and potentially inappropriate reporting of DTI as other types of PI. Inconsistencies in reporting will confound data indicating the proportion of DTI considered 'avoidable'. In addition to this, root cause analyses for PI are often inconsistent in design and likely poor indicators of patterns in clinical presentation and outcomes due to their widely perceived function as a mechanism to apportion blame for clinical events (Samuriwo 2015).

Animal Model of DTI Deterioration

A murine study by Sari et al (2015) produced the first model of DTI deterioration. The authors used a hierarchic approach, using a murine model in combination with a computer finite element model (FEM) in which the distribution of pressure through tissues was simulated and measured. Notably, the FEM results demonstrated the higher levels of shear stress in deeper tissues at a simulated bone-tissue interface supporting the early observations that deeper tissues are more vulnerable to pressure (Hussain 1953). Results

from histological analysis and observation of the deterioration of induced DTI as per the EPUAP/EPUAP/ PPPIA (2019) definition suggested that these wounds showed little infiltration of inflammatory cells or denaturation of dermal collagen (Sari et al 2015). These findings are consistent with damage starting within the deeper tissues. However, Sari et al (2015) reported that 100% of the DTI produced in the murine models deteriorated to produce deep wounds. This is inconsistent with the retrospective study by Sullivan (2013) in which only 9.3% of DTI deteriorated to form wounds. This may be reflective of variations in clinical assessments of PI which is most often carried out by nurses who often have inconsistent training and understanding of PI (Aydin et al 2019, De Mayer et al 2019). Alternatively, the clinical appearance of the injuries created in the Sari et al (2015) study may be a result of bruising due to the use of loose skinned murine models (Vlig et al 2019) which are more prone to bleeding into tissues when compressed (Vanezis 2001). Notably, Sari et al (2015) concluded that the darker appearance of DTI was likely due to bleeding into the tissues due to the shearing of blood vessels. Ultimately it is unclear if the wounds created by the Sari et al (2015) model are representative of the pathology involved in DTI in humans which have been hypothesised to be related to metabolic stresses (Berlowitz and Brienza 2007) or a potential compartment syndrome effect (Smart 2013), or if they are more comparable to the simpler pathology of traumatic bruising (Vanezis 2001). Current consensus on the development of DTI suggests that tissue damage is not typically visible for 24-72 hours after the exposure to pressure (Bader et al 2017), this is in contrast to the Sari et al (2015) study in which ‘superficial ulcers’ were reported in all of the test animals from the day of wounding. This is more suggestive of a traumatic injury than the pathology typically associated with DTI.

Novel Approaches

More recent studies have adopted other methodologies to demonstrate the aetiology of DTI including the use of magnetic resonance imaging (MRI) (Nelissen et al 2018) and using biomarkers to indicate the source and magnitude of tissue damage (Traa et al 2019). Notably, Nelissen et al (2018) demonstrated that damage to deep muscle is visible on MRI for up to two weeks following mechanical deformation periods of only two hours. This was later supported by a study by Traa et al (2019) who demonstrated that concentrations of myoglobin and troponin in blood and urine samples are increased following mechanical compression providing strong evidence of damage to muscle tissues even in the absence of clinically visible tissue damage at the skin surface. However, in both studies no prospective observation of changes in the superficial tissues was

conducted, making it difficult to conclude that the damage to muscle tissues observed or determined by biomarkers is unique to DTI or inevitable in all mechanically loaded tissues.

Challenges in DTI Diagnosis

Issues associated with the unique clinical appearance of DTI and how this may relate to their aetiology was investigated in a case series by Solmos et al (2019). Solmos et al (2019) highlighted the significant number of potential alternative diagnoses to DTI consistent with the purpura type lesions described by the EPUAP/EPUAP/ PPPIA (2019) definition of DTI including vasculitis, warfarin induced necrosis and calciphylaxis. Solmos et al (2019) concluded that lesions caused by non-pressure related pathologies may frequently be confused for DTI due to a lack of effective assessment methods to differentiate between DTI and other lesions due to the poor understanding of DTI aetiology. This reflects current methodologies adopted to investigate DTI, relying on FEM or animal models which seek to demonstrate damage in deep tissues caused by mechanical deformation, vascular shearing or metabolic stresses without demonstrating any clear differences in aetiology between ‘normal’ PI and DTI due to a lack of concurrent observation of changes in the skin or use of human subjects (Nelissen et al 2018, Traa et al 2019).

Conclusion

Clear aetiological processes have been described, observed and measured in cases of PI (Bouten et al 2003, Stekelenburg et al 2008, Traa et al 2019). These processes include the mechanical deformation of cells with concurrent occlusion of vascular structures creating additional metabolic and biochemical strain on tissues leading to inflammation and necrosis (Berlowitz and Brienza 2007). However, controversies remain as to the aetiological features of DTI. More recent reviews have suggested the unique clinical presentation of DTI may be due to a compartment syndrome effect created by the increased metabolic requirements of deep muscle tissue combined with a limited vascular supply and stiff fascia surrounding areas DTI are commonly found (heels and sacrum) (Smart 2013). However, this does not explain DTI caused by medical devices which may occur at any location on the body (Kayser et al 2018).

Primary studies aiming to elucidate the aetiology of DTI currently rely heavily on animal models and FEM to demonstrate the distribution of pressure (Sari et al 2015, Traa et al 2019). This may ultimately prevent extrapolation of results from these studies to human subjects due to the structural differences in tissues between animals and humans (Ansell et al 2012). Notably, the loose skin of mice creates a higher risk of bruising (Vanezis 2001), murine models may therefore mimic the clinical appearance of DTI when exposed to pressure explaining the early observation of DTI in studies modelling DTI deterioration (Sari et al 2015).

Currently there are no major studies investigating the impact of co-morbidities on tissue responses to pressure in humans and DTI may consequently be diagnosed inappropriately in cases where other pathologies are the cause of similar purpuric lesions (Solmos et al 2019). Future studies should focus on the aetiological differences between normal PI and DTI taking into consideration the presence of co-morbidities not included in FEM or animal studies. It is also notable that prior to the 2009 definition and inclusion of DTI by the EPUAP in the widely used PI grading system (Bader et al 2017), varying definitions of DTI were used in studies investigating DTI aetiology potentially limiting the value of these studies and whether they were investigating injuries consistent with the current definition of DTI. Consistent reporting and follow up of DTI may ultimately help provide a data set from which to better establish the epidemiological features of DTI to help guide future prospective studies investigating potential aetiologies of these unusual injuries.

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Authors:

1. Corresponding author:
   Matthew Wynn – Lecturer, Adult Nursing
   University of Salford
   Mary Seacole Building, M6 5ST
   m.o.wynn@salford.ac.uk

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