# ROS and Pressure Ulcer Formation

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Contributor: Thomas Theis

During the reperfusion phase, oxygen is reintroduced to the tissue, which leads to an oxidative burst that produces an extensive amount of ROS. After oxygen returns to the tissue, xanthine oxidase generates superoxide and hydrogen peroxide, which causes tissue injury, activation of phagocytic cells, and damage to membrane lipids, proteins, and DNA. In addition, the return of oxygen into the tissue leads to a dramatic increase in mitochondrial activity.

Keywords: spinal cord injury ; brain injury ; pressure ulcer ; reactive oxygen species ; oxidative stress ; wound healing

## 1. Introduction

Pressure ulcers (PUs) are skin injuries primarily caused by prolonged pressure on the skin and underlying tissue. Skin wound healing is a multi-stage process that aims to restore the integrity and function of the skin after injury but is often impaired in patients with underlying diseases or other medical conditions, including traumatic brain injury (TBI) and spinal cord injury (SCI). TBI and SCI result in sensory (lack of sensation) and motor loss (paralysis). Affected patients are at risk of PU development because they do not feel the pain that would normally signal excessive and prolonged pressure in one area and lack mobility to alter position to relieve that pressure. PUs are prone to reoccur and may lead to rehospitalization, which increases the cost of care and burdens the families of patients both financially and emotionally.

In the United States, 1–3 million people per year develop PUs [1]. It causes enormous costs to the healthcare system, with an average of over $124,000 per patient to treat a stage 4 PU [2] and a total annual cost of up to $11 billion [3]. The severity of PUs is scored using different stages (stages 1–4). Stage 1 is the mildest form of PU and, in many cases, it can transform into a severe stage such as stage 4. Stage 4 is the most severe form of PU with full-thickness skin loss and extensive destruction of the tissue that affects also an underlying muscle, bone, and/or supporting tissue [4]. From nursing home admissions, 10–13% have PU ratings if in stages 2 to 4 [5]. PUs are caused by immobility and lack of protective sensory perception after any neurological injury; 28.3% of patients that suffer from SCI and 18.8% of patients with TBI develop PUs during their hospitalization [3][6]. In the lifetime of SCI patients, up to 95% may develop advanced stages 3 or 4 PUs [7]. Patients with a cervical or thoracic SCI have a three-fold greater risk to develop a PU compared to patients with a lumbar or sacral SCI [8]. The severity of TBI can be scored with the GCS scale [9]. The percentage of TBI patients with PU development varies from mild to severe TBI. As mild TBI patients are lower in the number who develop PU compared to moderate and severe TBI patients. Severe TBI patients with PU had a five times higher mortality [10], as compared to mild and moderate TBI.

## 2. Spinal Cord Injury and Pressure Ulcers

One of the major reasons for the rehospitalization of SCI patients who are over 25 years old is due to the development of PUs [11]. The European Pressure Ulcer Advisory Panel, the Pan Pacific Pressure Injury Alliance, and the National Pressure Ulcer Advisory Panel jointly published international clinical practice guidelines to prevent and treat PUs [12]. Coleman and colleagues suggest that there are three direct causal factors of developing a PU: (1) Immobility; (2) general health condition of the skin and if the patient has a history of developing PUs; (3) how well the tissue is perfused. They also identified several indirect causal factors, including moisture, sensory perception, diabetes, age, low albumin, and poor nutrition [13].

Ischemia-reperfusion leads to a transient ROS spike in the tissue. ROS are products of cellular metabolism that contain radical and non-radical derivatives of oxygen. Oxygen radicals contain one or more unpaired electrons and thus, are the most unstable and highly reactive; these include superoxide, hydroxyl, peroxyl, and hydroperoxyl. Non-radicals include hydrogen peroxide and peroxynitrite. An increase of ROS in the cell might lead to inappropriate oxidation of DNA, proteins, and lipids, which might lead to loss of function and potentially to an additional increase of ROS levels. To regulate ROS levels in the cell, antioxidant mechanisms have evolved. Excessive ROS levels and ensuing oxidative stress arise if the production of ROS increases and/or when antioxidants are depleted [14][15].

The epidermis of the skin provides major protection from oxidative damage. Hydrophilic, lipophilic, and enzymatic antioxidants are present at higher concentrations in the epidermis than in the dermis layer of the skin [16]. In the epidermis, there is a concentration gradient of antioxidants [17][18]. The uppermost tissue layer, which is exposed to the environment, has the lowest concentration of antioxidants, and this concentration increases with the increasing depth of the epidermis. Additionally, antioxidant levels can be enhanced by exogenous antioxidant treatments, such as vitamin C acetate and/or vitamin E [17][18].

In patients with SCI, major risk factors to developing a chronic PU with impaired healing are the immobility of the patient together with impaired sensation as well as the general condition of the skin. The risk is exacerbated by increasing age and by metabolic disorders such as diabetes. Following the primary mechanical injury, excessive humidity, immunodeficiency, and diabetes may result in an increased likelihood of bacterial infection of the skin. Such infections trigger an immune response that further increases ROS levels due to secretion from host phagocytes with ensuing additional tissue damage [19][20][21].

## 3. Brain Injury and Pressure Ulcers

Traumatic and non-traumatic brain injuries result in patients that are bedridden depending upon the severity of the injury and the related functional impairment. Both in acute and chronic care settings, these patients have been seen to develop PUs [8]. PUs increase the length of hospital stay, extend nursing care, and raise the total treatment cost; they also affect morbidity and mortality, especially in the young [22]. It is reported that immobility is an independent risk factor for PU development besides nutrition, age, gender, associated systemic injury, surgical intervention, and enteral feeding [23]. The role and mechanism of ROS and oxidative stress are likely similar to that discussed for SCI-induced PU formation, although there are no reported studies on the role of ROS and oxidative stress in the context of brain injury. The tools and scales for predicting and reporting the development of PUs are very important in terms of their specificity and sensitivity. The scale of PU prediction after TBI during the acute care setting is very important to provide the proper care for affected patients. According to the GCS score in a different population of mild to severe TBI patients, more patients develop PUs with severe TBI [9] as compared to mild to moderate TBI patients. A study related to Norton and Braden scale estimation/prediction sensitivity and specificity of patients developing PUs suggested that the Braden Scale compared well with the Norton Scale regarding sensitivity, while the specificity was greater for the Norton than for the Braden Scale (64% versus 36%, respectively). This difference is critical to provide the proper care for these patients [24] and assess the overall role of injury in the development of PUs.

Montalcini et al. (2015) studied the brain injury population meeting the minimal conscious state (MCS) criteria and they found that low albumin concentration (<3.1 g/dL) predicted PU formation and mortality. Besides, a low level of hemoglobin was also significantly associated with PU formation in these patients [25]. Dhandapani et al. (2014) found that 16% of TBI patients developed PUs within 21 days of admission despite taking all the measures for PU prevention [10]. TBI-related delayed enteral feeding, >10% decrease in hemoglobin and albumin had a significant impact on PU development with severe TBI. They also reported an association of PUs with recovery status at three months and mortality at 21 days. A study also suggested that patient's history about their formal life, if it involved planning daily care according to health professionals, had an encouraging effect on PU prevention [26]. A study of TBI patients in long-term palliative care centers (2013–2016) suggested no difference between TBI patients in at-home care vs. rehabilitation centers and intensive care units, and death in respect to mobilization and PUs. PU formation significantly increased the length of stay in TBI patients and had higher GCS scores [27]. Overall, it is not only intrinsic metabolic and physiological changes that are responsible for the formation of PUs after brain injury, but also external factors such as acute primary care and the patient's history.

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