



## **UWL REPOSITORY**

**repository.uwl.ac.uk**

The influence of anaemia on pressure ulcer healing in elderly patients

Tuz, Mariusz Adam and Mitchell, Aby (2021) The influence of anaemia on pressure ulcer healing in elderly patients. *British Journal of Nursing*, 30 (15). S32-S38. ISSN 0966-0461

10.12968/bjon.2021.30.15.S32

This is the Accepted Version of the final output.

UWL repository link: <https://repository.uwl.ac.uk/id/eprint/8210/>

**Alternative formats:** If you require this document in an alternative format, please contact: [open.research@uwl.ac.uk](mailto:open.research@uwl.ac.uk)

### **Copyright:**

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

**Take down policy:** If you believe that this document breaches copyright, please contact us at [open.research@uwl.ac.uk](mailto:open.research@uwl.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.

## **The influence of anaemia on pressure ulcers (PU) healing in elderly individuals**

### **Abstract**

Anaemia is a common and multifactorial blood disorder in the elderly individuals. This condition may be a significant barrier to pressure ulcers healing as it is associated with decreased level of oxygen being supplied to body tissues. Some nutritional deficiencies such as iron, cobalamin and folate may also cause anaemia and have negative impact on pressure ulcer healing. An increased iron demand in chronic pressure ulcers is a significant factor associated with the risk of anaemia of chronic disease in elderly patients. Anaemia screening and correction may need to be considered as well as iron supplementation if required in pressure ulcer prevention and management.

**Key words:** anaemia, pressure ulcers, elderly.

### **Introduction**

Anaemia is a common condition in the elderly patients (Beghé, Wilson & Ershler, 2004; Gaskell et al, 2008; McCormick and Stott, 2007; Rivilla Marugán et al, 2019) and its prevalence is strongly associated with an individuals socioeconomic status, psychological state and available support (Gupta et al, 2020; Lamba et al, 2019; Styszynski et al, 2018; Andreev et al, 2020; Hosseini et al, 2018). Anaemia in elderly patients is often multifactorial; however, the most common cause of this condition is iron deficiency due to malnutrition, decreased iron absorption, chronic gastrointestinal blood loss and chronic inflammatory conditions (Andrès et al, 2008; Cappellini, Musallam & Taher, 2020; Thomas, 2017; Girelli, Marchi & Camaschelli, 2018; Thomas, 2017).

The prevalence of pressure ulcers (PU) is significantly increased in the elderly individuals and is also related to other factors such as dementia, socioeconomic status, long term conditions, malnutrition low oxygen level and tissue ischemia (Jaul et al, 2018; Børsting et al, 2018; Margolis, 2002; Olivo et al, 2020; Azevedo Macena

et al, 2017; Liao et al, 2019; Galivanche et al, 2020; Lenche et al, 2016; Neloska et al, 2016; Kim et al, 2019 ).

Anaemia and decreased haemoglobin levels have been identified as significantly associated with PU development in the elderly population (Bailey et al, 2011; Gengenbacher et al, 2002; Jaul et al, 2018; Nadukkandiyil et al, 2019). There is a need to investigate the impact of anaemia on the process of PU healing and consider possible improvements in PU management as the current guidelines do not directly include any measures and actions associated with anaemia and only consider the impact of oxygenation deficits and impaired nutritional status on the risk of PU as a recommendation (European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel, 2019; Fletcher & Hall, 2018; NICE, 2014, 2015, 2020; Stansby et al, 2014).

### **A significance of aetiology and pathophysiology of anaemia in the PU development and healing**

Anaemia is defined by the World Health Organisation as a blood disorder in which haemoglobin levels are below 120 g/l in females and 130 g/l in males (WHO, 2011). This is a condition associated with a decreased ability of erythrocytes to transport oxygen from lungs to body's tissues (Cappellini & Motta, 2015). Erythrocytes accommodate an iron – containing protein – haemoglobin, which is able to bind oxygen molecules to heme groups (Kosmachevskaya & Topunov, 2018; Marengo-Rowe, 2006). A diminished oxygen supply to body's tissues due to a low concentration of haemoglobin may lead to local hypoxia which has a destructive impact on certain tissues depending on their metabolic activity and oxygen demand (Hare et al, 2013; McLellan & Walsh, 2004; Thomas & Lumb, 2012). A significant decrease of oxygen concentration may also cause tissue continuity disruption and cell necrosis which can result in PU initiation. The prevalence of this is higher in the elderly population due to altered skin elasticity and increased fragility (Blackburn et al, 2020; Gefen, 2008; Sree et al, 2019).

A PU caused by sustained pressure decreases the oxygen supply to the tissue which leads to tissue ischemia and necrosis (Edsberg et al, 2016; Lumbers, 2019; Mervis & Phillips, 2019). The significant factor is the length of time pressure is applied during specific occurrences. For example, when a patient needs to be in the same position such as proning (Stephen-Haynes & Maries, 2020) or positioning for surgical purposes (Walton-Geer, 2009). Anaemia in patients can significantly increase the development of a PU as oxygen concentration is already lower due to diminished haemoglobin and oxygen supply, resulting in tissue hypoxia (Thomas & Lumb, 2012; Sree et al, 2019).

A decreased level of oxygen at cellular level caused by anaemia has a negative impact on the PU healing rate. Oxygen plays specific roles in all of the stages of the wound healing process (Gordillo & Sen, 2003; Hopf & Rollins, 2007; Kimmel, Grant & Gitata, 2016) and is essential in the cell metabolism which may be altered in the elderly (Catic, 2018; Giorgi et al, 2018). Oxygen is also converted into ROS (reactive oxygen species) in the mitochondrial oxidative phosphorylation process which reduces as the person gets older (Ray et al, 2012; Lesnefsky & Hoppel, 2006). ROS regulates different cellular signalling pathways associated with each phase of the healing process (Gordillo & Sen, 2003; Kimmel, Grant & Gitata, 2016; Ray, Huang & Tsuji, 2012). For example platelet aggregation and vasoconstriction in the haemostasis phase (Masselli et al, 2020; Peters et al, 2000). Vasodilation, chemotaxis for phagocytic cells, and anti-inflammatory response in the inflammatory phase and angiogenesis, proliferation and differentiation of cells, and extracellular matrix formation in the proliferation phase. ROS also regulates formation and maturation in the remodelling phase (Mittal et al, 2014; Staiculescu et al, 2014; Day & Suzuki, 2006; Staiculescu et al, 2014; Saxena et al, 2019 ). Additionally, the PU healing process is compromised by both intrinsic and extrinsic factors as a result of the ageing process (Mitchell, 2020).

Anaemia may also affect PU healing differently in each individual. Some difficulties and problems may depend on the PU aetiology and pathophysiology, the staging of the PU damage and physical, psychological and socio – economic factors. These

need to also be considered according to the biopsychosocial model as the PU impact on patient's quality of life is always multidimensional (Mervis & Phillips, 2019; Morton & Phillips, 2016; European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel, 2019; Kurtz and Silverman, 1996),.

There are the following three groups of anaemia on the basis of the mean corpuscular volume (MCV) of erythrocytes (table 1).

#### Groups of anaemia

Group	Example
<b>Microcytic</b>	Iron deficiency, thalassaemia or some chronic diseases such as (MCV is decreased to below 82 fL);
<b>Macrocytic</b>	Megaloblastic, B12 and folate deficiency, liver disorders or alcohol related (MCV is increased to above 98 fL
<b>Normocytic</b>	renal insufficiency, haemolytic or related to some chronic diseases (MCV is within normal range of 82 fL – 98 fL)

(Moreno Chulilla et al, 2009; Thomas, 2017)

The classification of anaemia may also be based on pathogenic mechanisms related to production and loss of red blood cells (RBC) which allows to divide anaemia into the two groups (table 2)

<b>Hypo-regenerative</b> (bone marrow production of appropriate RBC is diminished which may be caused by lack of iron, B12 or folic acid)
<b>Regenerative (production of RBC is increased by an appropriate respond by bone marrow to low RBC level)</b>

(Moreno Chulilla et al, 2009).

There can be some dissimilarity in the influence of specific types of anaemia on PU healing and the appropriate treatments may need to be considered depending on the aetiology of anaemia as many factors can affect the wound healing process (Guo & Dipietro, 2010).

#### Anaemia associated with nutritional deficiencies and PU healing

Iron deficiency anaemia (IDA) is the most common form of anemia in the elderly (Cappellini, Musallam & Taher, 2020; Halawi, Moukhadder & Taher, 2017). This is microcytic anaemia caused by a reduced value of MCV (Thomas, 2017) and is associated with a decreased ability of haemoglobin production due to an insufficient level of iron in the body (absolute iron deficiency) or diminished iron supply to bone

marrow (functional iron deficiency) (Lopez et al, 2016). This can affect PU healing differently than other types of anaemia. Iron deficiency is an additional factor that negatively influences wound healing. Iron is required to assist with various molecular mechanisms in the skin such as oxidative stress processes and ultraviolet induced damages in the skin, cell apoptosis. In the wound healing process iron deficiency can affect cellular proliferation and differentiation, protein synthesis, and regulation of macrophage function during the inflammatory phase (Recalcati, Gammella & Cairo, 2019; Soares & Hamza, 2016; Wright, Richards & Srail, 2014; Kurz et al, 2008; Wlaschek et al, 2019; Wright, Richards & Srail, 2014).

Iron concentration is elevated in damaged tissue when a wound is healing (Coger et al, 2019) and there is an increased local iron deposition in chronic wounds (Tchanque-Fossuo et al, 2017). This specifically increased iron demand may also be a contributing factor to anaemia in patients with a chronic PU. Fuoco et al., (1997) found a significant association of anemia patients with PU during the inflammatory phase of wound healing which disappeared after healing. In addition, chronic PU (an inflammatory condition) may lead to anaemia of chronic disease (ACD) (Fraser, 2010).

There are other significant nutritional deficiencies which may cause anaemia such as a vitamin B12 (cobalamin) and a vitamin B9 (folate). Both are common nutritional disorders in the elderly caused by malnutrition, malabsorption, some chronic conditions and medication and may lead to macrocytic anaemia associated with an increased value of MCV and an impaired development of abnormally large erythrocytes - megaloblasts (Thomas, 2017; Marchi et al, 2020; Vadakattu et al, 2019; Watson, Lee & Garcia-Casal, 2018; Nagao & Hirokawa, 2017 ). However, macrocytic anaemia may also be non-megaloblastic if caused by specific conditions such as liver dysfunction, hypothyroidism or myelodysplastic syndrome but not by cobalamin or folate deficiency (Nagao & Hirokawa, 2017). PU healing may be specifically affected by cobalamin and folate deficiencies in addition to a negative influence by impaired oxygen transportation to tissues in patients with megaloblastic anaemia. These vitamins play important roles in vascular functions such as cellular

homocysteine metabolism, nitric oxide bioavailability and vasodilation (Stanhewicz & Kenney, 2017; Blom & Smulders, 2011; Gilfix, 2005). Cobalamin and folate deficiencies may lead to vascular dysfunction and occlusions (Haloul et al, 2020; Haynes, 2002). Psychological functions of the elderly individuals may also be affected in terms of cognitive deficits, depression, and pain (Julian et al, 2020; Baroni et al, 2019; Khosravi et al, 2020).

### **Recommendations for practice**

A full holistic assessment is necessary to effectively treat elderly patients and nurses need a good understanding of the causes and implications of anemia on pressure ulcer healing to inform long-term management. Risk assessments for pressure ulcers should be carried out as soon as possible (within a maximum of eight hours) of the patient admitted to hospital or community caseload and repeated as often as required based on patient acuity (Epuap, 2014) or if a change occurs in the patient's condition (Mitchell, 2018). There are several validated risk assessment tools used, the Waterlow score is the most commonly used in the UK, despite the lack of conclusive evidence of one score over another (Anthony et al., 2008, Mitchell, 2018). These tools are not directly associated with anaemia or risk assessment of anemia. The Waterlow assessment tool involves haemoglobin level only as the one of many risks factors of PU development (Waterlow, 2005). The Malnutrition Universal Screen Tool (MUST) which is an accurate and valid malnutrition assessment tool for the elderly (Pouliou et al, 2012) concentrates on the body mass index (BMI) and the weight loss over time than significant nutritional deficiencies associated with anaemia (Bapen, 2011).

The prevention and management of PU in the elderly patients needs to involve anaemia assessment and correction in addition to diet supplementation and repositioning according to (Nadukkandiyil et al, 2019); however, a holistic risk assessment on admission and at any significant change in patient's condition always should be carried out according to the NICE guidelines (NICE, 2014). This may also need to involve any risks associated with anaemia and an approach based on the

biopsychosocial model by considering all the physical, psychological and social factors associated with anaemia as early recognition and management of this blood disorder can have a great impact on an elderly individual's health condition (Burney, Ahmad & Masroor, 2016; Kurtz & Silverman, 1996)).

### **Recommendations summary**

- More primary research is needed on associations between anaemia and PU development and healing;
- Anaemia screening and correction may need to be implemented in PU prevention and management;
- An iron supplementation may need to be considered in elderly patients with PU as they are at risk of ACD due to increased iron demand.

### **Conclusion**

The elderly individuals are at an increased risk of anaemia of multifactorial aetiology and a higher risk of ACD due to an increased iron demand associated with PU. This blood condition influences negatively PU healing. Anaemia screening and correction, as well as an iron supplementation, may need to be considered in the prevention and management of PU in elderly individuals. Physical, psychological and social factors are significant in association between anaemia and pressure ulcer healing based on the biopsychosocial model (Kurtz & Silverman, 1996) (Fig. 1).

**Declaration of interests:** none.

### **References**

Andreev A, Erdinc B, Shivaraj K, Schmutz J, Levochkina O, Bhowmik D, Farag F, Money KM, Primavera LH, Gotlieb V, Sahni S. The association between anemia of chronic inflammation and Alzheimer's disease and related dementias. *J Alzheimers Dis Rep.* 2020; 4 (1):379–391.

Andrès E, Federici L, Serraj K, Kaltenbach, G. Update of nutrient-deficiency anemia in elderly patients. *Eur J of Intern Med.* 2008; 19 (7):488–493.

Azevedo Macena MS, da Costa Silva RS, Dias Fernandes MIDC, Almeida Medeiros AB, Batista Lúcio KD, Carvalho Lira ALB. Pressure ulcer risk evaluation in critical patients: clinical and social characteristics. *Open Nurs J.* 2017; 11:91–97.



Bailey RA, Reardon G, Wasserman MR, McKenzie RS, Hord RS, Kilpatrick B. Association of anemia with pressure ulcers, falls, and hospital admissions among long-term care residents. *Health Outcomes Res Med*. 2011; 2 (4): e227-e240.

Bapen. Malnutrition Universal Screening Tool. 2011; [https://www.bapen.org.uk/pdfs/must/must\\_full.pdf](https://www.bapen.org.uk/pdfs/must/must_full.pdf) (accessed 25 November 2020).

Baroni L, Bonetto C, Rizzo G, Bertola C, Caberlotto L, Bazzera G. Association between cognitive impairment and vitamin B12, Folate, and Homocysteine status in elderly adults: a retrospective study. *J Alzheimer's Dis*. 2019; 70 (2): 443–453.

Beghé C, Wilson A, Ershler WB. Prevalence and outcomes of anemia in geriatrics: a systematic review of the literature. *Am J Med*. 2004; 116 (Suppl 7A): 3S-10S.

Black JM, Cuddigan JE, Walko MA, Didier LA, Lander MJ, Kelpel MR. Medical device related pressure ulcers in hospitalized patients. *Int Wound J*. 2010; 7 (5):358–365.

Blackburn J, Ousey K, Taylor L, Moore B, Patton D, Moore Z, Avsar P. The relationship between common risk factors and the pathology of pressure ulcer development: a systematic review. *J Wound C*. 2020; 29 (Suppl 3): S4-S12.

Blom HJ, Smulders Y. Overview of homocysteine and folate metabolism. With special references to cardiovascular disease and neural tube defects. *J Inher Metab Dis*. 2011; 34 (1): 75–81.

Børsting TE, Tvedt CR, Skogestad IJ, Granheim TI, Gay CL, Lerdal A. Prevalence of pressure ulcer and associated risk factors in middle- and older-aged medical inpatients in Norway. *J Clin Nurs*. 2018; 27 (3-4):e535-e543.

Burney S, Ahmad S, Masroor R. Anaemia in elderly: a benign condition or an early warning? A hospital based study. *PAFMJ*. 2016; 66 (3):400–406.

Cappellini MD, Motta I. Anemia in clinical practice-definition and classification: does hemoglobin change with aging? *Semin Hematol*. 2015; 52 (4):261–269.

Cappellini MD, Musallam KM, Taher AT. Iron deficiency anaemia revisited. *J Intern Med*. 2020; 287 (2):153–170.

Catic A. Cellular metabolism and aging. *Prog Mol Biol Transl Sci*. 2018; 155:85–107.

Coger V, Million N, Rehbock C, Sures B, Nachev M, Barcikowski S, Wistuba N, Strauß S, Vogt PM. Tissue concentrations of Zinc, Iron, Copper, and Magnesium during the phases of full thickness wound healing in a rodent model. *Biol Trace Elem Res*. 2019; 191 (1):167–176.

Day RM, Suzuki YJ. Cell proliferation, reactive oxygen and cellular glutathione. *Dose Response*. 2006; 3 (3): 425–442.

Edsberg LE, Black JM, Goldberg M, McNichol L, Moore L, Sieggreen M. Revised National Pressure Ulcer Advisory Panel Pressure Injury Staging System: revised pressure injury staging system. *JWOCN*. 2016; 43 (6):585–597.

European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel. Prevention and treatment of pressure ulcers/injuries: quick reference guide. 2019. [Online], Emily Haesler (Ed.). EPUAP/NPIAP/PPPIA. <https://guidelinesales.com/page/EPUAP> (accessed 11 November 2020).

Fletcher J, Hall J. New guidance on how to define and measure pressure ulcers. *Nurs Times*. 2018; 114 (10): 41–44. <https://www.nursingtimes.net/clinical-archive/tissue-viability/new-guidance-on-how-to-define-and-measure-pressure-ulcers-10-09-2018/> (accessed 11 November 2020).

Fraser C. The identification of barriers to pressure ulcer healing. *Wound Care Can*; 2010; 8 (2):20–25.

Fuoco U, Scivoletto G, Pace A, Vona VU, Castellano V. Anaemia and serum protein alteration in patients with pressure ulcers. *Spinal Cord*. 1997; 35 (1): 58–60.

Galivanche AR, Kebaish KJ, Adrados M, Ottesen TD, Varthi AG, Rubin LE, Grauer JN. Postoperative pressure ulcers after geriatric hip fracture surgery are predicted by defined preoperative comorbidities and postoperative complications. *J Am Acad Orthop Surg*. 2020; 28 (8):pp. 342–351.

Gaskell H, Derry S, Andrew Moore R, McQuay HJ. Prevalence of anaemia in older persons: systematic review. *BMC Geriatr*, 2008; 8:1.

Gefen A. How much time does it take to get a pressure ulcer? Integrated evidence from human, animal, and in vitro studies. *Ostomy Wound Manag*. 2008; 54 (10): 26-8, 30-5.

Gengenbacher M, Stähelin HB, Scholer A, Seiler WO. Low biochemical nutritional parameters in acutely ill hospitalized elderly patients with and without stage III to IV pressure ulcers. *Aging Clin Exp Res*. 2002; 14 (5): 420–423.

Gilfix BM. Vitamin B12 and homocysteine. *CMAJ*. 2005; 173 (11):1360.

Giorgi C, Marchi S, Simoes ICM, Ren Z, Morciano G, Perrone M, Patalas-Krawczyk P, Borchard S, Jędrak P, Pierzynowska K, Szymański J, Wang DQ, Portincasa P, Węgrzyn G, Zischka H, Dobrzyn P, Bonora M, Duszyński J, Rimessi A, Karkucinska-Wieckowska A, Dobrzyn A, Szabadkai G, Zavan B, Oliveira PJ, Sardao VA, Pinton P, Wieckowski MR. Mitochondria and reactive oxygen species in aging and age-related diseases. *Int Rev Cell Mol Biol*, 2018; 340: 209–344.

Girelli D, Marchi G, Camaschella C. Anemia in the elderly. *HemaSphere*, 2018; 2 (3):e40.

Gordillo GM, Sen CK. Revisiting the essential role of oxygen in wound healing. *Am J Surg*. 2003; 186 (3): 259–263.

Gosain A, DiPietro LA. Aging and wound healing. *World J Surg*. 2004; 28 (3):321–326.

Guo S, DiPietro LA. Factors affecting wound healing. *J Dent Res*. 2010; 89 (3):219–229.

Gupta A, Ramakrishnan L, Pandey RM, Sati HC, Khandelwal R, Khenduja P, Kapil U. Risk factors of anemia amongst elderly population living at high-altitude region of India. *J Family Med Prim Care*. 2020; 9 (2):673–682.

Halawi R, Moukhadder H, Taher A. Anemia in the elderly: a consequence of aging? *Expert Rev Hematol*. 2017; 10 (4): 327–335.

Haloul M, Vinjamuri SJ, Naquiallah D, Mirza MI, Qureshi M, Hassan C, Masrur M, Bianco FM, Frederick P, Cristoforo GP, Gangemi A, Ali MM, Phillips SA, Mahmoud AM. Hyperhomocysteinemia and low folate and vitamin B12 are associated with vascular dysfunction and impaired nitric oxide sensitivity in morbidly obese patients. *Nutrients*. 2020; 12 (7):2014.

Hare GMT, Tsui AKY, Ozawa S, Shander A. Anaemia: can we define haemoglobin thresholds for impaired oxygen homeostasis and suggest new strategies for treatment? *Best Pract Res Clin Anaesthesiol*. 2013; 27 (1): 85–98.

Haynes, W. G. (2002) 'Hyperhomocysteinemia, vascular function and atherosclerosis: effects of vitamins', *Cardiovascular drugs and therapy*, vol. 16, no. 5, pp. 391–399.

Hopf HW, Rollins MD. Wounds: an overview of the role of oxygen. *Antioxid Redox Signal*. 2007; 9 (8):1183–1192.

Hosseini SR, Zabihi A, Ebrahimi SH, Jafarian Amiri SR, Kheirkhah F, Bijani A. The prevalence of anemia and its association with depressive symptoms among older adults in north of Iran. *JRHS*. 2018; 18 (4):e00431.

Jaul E, Barron J, Rosenzweig JP, Menczel J. An overview of co-morbidities and the development of pressure ulcers among older adults. *BMC Geriatr*, 2018; 18 (1):305.

Jaul E, Factor H, Karni S, Schiffmiller T, Meiron, O. Spasticity and dementia increase the risk of pressure ulcers. *Int Wound J*. 2019; 16 (3): 847–851.

Julian T, Syeed R, Glasgow N, Angelopoulou E, Zis, P. B12 as a treatment for peripheral neuropathic pain: a systematic review. *Nutrients*, 2020; 12 (8): 2221.

Khosravi M, Sotoudeh G, Amini M, Raisi F, Mansoori A, Hosseinzadeh, M. The relationship between dietary patterns and depression mediated by serum levels of Folate and vitamin B12. *BMC Psychiatry*. 2020; 20 (1):63.

Kim J, Lee JY, Lee E. Risk factors for newly acquired pressure ulcer and the impact of nurse staffing on pressure ulcer incidence. *J Nurs Manag*. 2019. doi: 10.1111/jonm.12928.

Kimmel HM, Grant A, Ditata, J. The presence of oxygen in wound healing. *Wounds*. 2016; 28 (8):264–270.

Kosmachevskaya OV, Topunov A F. Alternate and additional functions of erythrocyte hemoglobin. *Biochemistry (Mosc)*. 2018; 83 (12):1575–1593.

Kurtz SM, Silverman JD. The Calgary-Cambridge Referenced Observation Guides: an aid to defining the curriculum and organizing the teaching in communication training programmes. *Med Educ*. 1996; 30 (2):83-89.

Kurz T, Terman A, Gustafsson B, Brunk, UT. Lysosomes in iron metabolism, ageing and apoptosis. *Histochem Cell Biol*. 2008; 129 (4): 389-406.

Lamba R, Agarwal A, Rana R, Agarwal V. Prevalence of Anemia and its correlates among elderly population of an urban slum in Meerut. *J Indian Acad Geriatr*. 2019; 15 (3):109-114.

Lenche N, Katerina D, Nikolchev A, Lidija P, Biljana PZ, Milenko, K. The influence of comorbidity on the prevalence of pressure ulcers in geriatric patients. *Glob Dermatol*. 2016; 3 (3):319-322.

Lesnefsky EJ, Hoppel CL. Oxidative phosphorylation and aging. *Ageing Res Rev*. 2006; 5 (4): 402-433.

Liao X, Ju Y, Liu G, Zhao X, Wang Y, Wang Y. Risk factors for pressure sores in hospitalized acute ischemic stroke patients. *J Stroke Cerebrovasc Dis*. 2019; 28 (7): 2026-2030.

Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. *Lancet*. 2016; 387 (10021):907–916.

Lumbers M. An overview of pressure ulcers: revised definition and measurement. *Br J Community Nurs*. 2019; 24 (5): 216-223.

Makrantonaki E, Wlaschek M, Scharffetter-Kochanek K. Pathogenesis of wound healing disorders in the elderly. *J Dtsch Dermatol Ges*. 2017; 15 (3):255–275.

Marchi G, Busti F, Zidanes AL, Vianello A, Girelli D. Cobalamin deficiency in the elderly. *Mediterr J Hematol Infect Dis*. 2020; 12 (1): e2020043.

Marengo-Rowe AJ. Structure-function relations of human hemoglobins. *Proc (Bayl Univ Med Cent)*. 2006; 19 (3): 239–245.

Margolis D. The incidence and prevalence of pressure ulcers among elderly patients in general medical practice. *Ann Epidemiol*. 2002; 12 (5):321–325.

Masselli E, Pozzi G, Vaccarezza M, Mirandola P, Galli D, Vitale M, Carubbi C, Gobbi G. ROS in platelet biology: functional aspects and methodological insights. *Int J Mol; Sci*. 2020; 21(14):4866.

McCormick L, Stott DJ. Anaemia in elderly patients. *Clin Med (Lond)*. 2007; 7 (5): 501–504.

McLellan SA, Walsh TS. Oxygen delivery and haemoglobin. *CEACCP*. 2004; 4 (4):123–126.

Mervis JS, Phillips T J. Pressure ulcers: pathophysiology, epidemiology, risk factors, and presentation. *J Am Acad Dermatol*, 2019; 81 (4): 881–890.

Mittal M, Siddiqui MR, Tran K, Reddy SP, Malik AB. Reactive oxygen species in inflammation and tissue injury. *Antioxid Redox Signal*. 2014; 20 (7):1126–1167.

Mitchell. A, 2018 Adult pressure area care: preventing pressure ulcers. *British Journal of Nursing*. Vol 27, issue 18

Mitchell. A, 2020 Assessment of wounds in adults. *British Journal of Nursing*. Tissue Vaibility Supplement. Vol 29. No. 20

Moreno Chulilla JA, Romero Colás MS, Gutiérrez Martín M. Classification of anemia for gastroenterologists. *World J Gastroenterol*. 2009; 15 (37):4627–4637.

Morton LM, Phillips TJ. Wound healing and treating wounds: differential diagnosis and evaluation of chronic wounds. *J Am Acad Dermatol*. 2016; 74 (4):589-605.

Nadukkandiyil N, Syamala S, Saleh HA, Sathian B, Ahmadi Zadeh K, Acharath Valappil S, Alobaidli M, Elsayed SA, Abdelghany A, Jayaraman K, Al Hamad H. Implementation of pressure ulcer prevention and management in elderly patients: a retrospective study in tertiary care hospital in Qatar. *Male*. 2019; 1–7.

Nagao T, Hirokawa M. Diagnosis and treatment of macrocytic anemias in adults. *J Gen Fam Med*. 2017; 18 (5):200–204.

Neloska L, Damevska K, Nikolchev A, Pavleska L, Petreska-Zovic B, Kostov M. The association between malnutrition and pressure ulcers in elderly in long-term care facility. *Open Access Maced J Med Sci*. 2016; 4 (3): 423–427.

NICE. Pressure ulcers: prevention and management. Clinical guideline. 2014. <https://www.nice.org.uk/guidance/cg179> (accessed 11 November 2020).

NICE. Pressure ulcers. Quality standard [QS89]. 2015. <https://www.nice.org.uk/guidance/qs89> (accessed 11 November 2020).

NICE. Pressure ulcers overview. 2020. <https://pathways.nice.org.uk/pathways/pressure-ulcers> (accessed 11 November 2020).

Olivo S, Canova C, Peghetti A, Rossi M, Zanotti R. Prevalence of pressure ulcers in hospitalised patients: a cross-sectional study. *J Wound Care*. 2020; 29 (Sup3):S20-S28.

Peate I, Stephens M. *Wound care at a glance*. Hoboken, NJ, USA, Wiley Blackwell 2020.

Peters SL, Mathy MJ, Pfaffendorf M, van Zwieten PA. Reactive oxygen species-induced aortic vasoconstriction and deterioration of functional integrity. *Naunyn-Schmiedeberg's Arch Pharmacol*. 2000; 361 (2):127–133.

Poulika KA, Yannakoulia M, Karageorgou D, Gamaletsou M, Panagiotakos DB, Sipsas NV, Zampelas A. Evaluation of the efficacy of six nutritional screening tools to predict malnutrition in the elderly. *Clin Nutr*. 2012; 31 (3):378–385.

Ray PD, Huang BW, Tsuji Y. Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signalling. *Cell Signal*. 2012; 24 (5):981–990.

Recalcati S, Gammella E, Cairo G. Ironing out macrophage immunometabolism. *Pharmaceuticals (Basel)*. 2019; 12 (2):94.

Rivilla Marugán L, Lorente Aznar T, Molinero Rodriguez M, García-Erce JA. Anciano y anemia: revisión crítica de su definición y prevalencia. *Rev Esp Geriatr Gerontol*. 2019; 54 (4):189–194.

Rodrigues M, Kosaric N, Bonham CA, Gurtner GC. Wound healing: a cellular perspective. *Physiol Rev*. 2019; 99 (1):665–706.

Saxena S, Vekaria H, Sullivan PG, Seifert AW. Connective tissue fibroblasts from highly regenerative mammals are refractory to ROS-induced cellular senescence. *Nat Commun*. 2019; 10 (1):4400.

Soares MP, Hamza I. Macrophages and iron metabolism. *Immunity*. 2016; 44 (3): 492–504.

- Sree VD, Rausch MK, Tepole AB. Linking microvascular collapse to tissue hypoxia in a multiscale model of pressure ulcer initiation. *Biomech Model Mechan*. 2019; 18 (6): 1947–1964.
- Staiculescu MC, Foote C, Meininger GA, Martinez-Lemus L. A. The role of reactive oxygen species in microvascular remodelling. *Int J Mol Sci*. 2014; 15 (12): 23792–23835.
- Stanhewicz AE, Kenney W. L. Role of folic acid in nitric oxide bioavailability and vascular endothelial function. *Nutr Rev*. 2017; 75 (1):61–70.
- Stansby G, Avital L, Jones K, Marsden G. Prevention and management of pressure ulcers in primary and secondary care: summary of NICE guidance. *BMJ*. 2014; 348:2592.
- Stephen-Haynes J, Maries M. Pressure ulcers and the prone position. *Br J Nurs*. 2020; 29 (12):S6.
- Styszynski A, Mossakowska M, Chudek J, Puzianowska-Kuznicka M, Klich-Raczka A, Neumann-Podczaska A, Szybalska A, Wieczorowska-Tobis K. Prevalence of anemia in relation to socio-economic factors in elderly Polish population: the results of PolSenior study. *J Physiol Pharmacol*. 2018; 69 (1):75–81.
- Tchanque-Fossuo CN, Dahle SE, Buchman SR, Isseroff RR. Deferoxamine: potential novel topical therapeutic for chronic wounds. *Br J Dermatol*. 2017; 176 (4):1056–1059.
- Thomas A. Investigation and management of anaemia. *Medicine*. 2017; 45 (4):209–213.
- Thomas C, Lumb AB. Physiology of haemoglobin. *CEACCP*. 2012; 12 (5):251–256.
- Vadakattu SS, Ponday LR, Nimmathota A, Nagalla B, Kondru DS, Undrajarapuram P, Banavath BR, Kommula SR, Punjal R, Palla S. Prevalence of nutritional anemia and hyperhomocysteinemia in urban elderly. *Indian J Clin Biochem*. 2019; 34 (3):330–335.
- Walton-Geer PS. (2009) 'Prevention of pressure ulcers in the surgical patient', *AORN*. 2009; 89 (3):538-48; 549-51.
- Waterlow J. From costly treatment to cost-effective prevention: using Waterlow. *Br J Community Nurs*. 2005; 10 (9):S25-6, S28, S30.
- Watson J, Lee M, Garcia-Casal MN. Consequences of inadequate intakes of vitamin A, vitamin B12, vitamin D, Calcium, Iron, and Folate in older persons. *Curr Geriatr Rep*. 2018; 7 (2):103–113.
- WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. 2019. Geneva. World Health Organisation. <https://www.who.int/vmnis/indicators/haemoglobin/en/> (accessed 17 October 2020).
- Wlaschek M, Singh K, Sindrilaru A, Crisan D, Scharffetter-Kochanek K. Iron and iron-dependent reactive oxygen species in the regulation of macrophages and fibroblasts in non-healing chronic wounds. *Free Radic Biol Med*. 2019; 133:262–275.
- Wright JA, Richards T, Srani SKS. The role of iron in the skin and cutaneous wound healing, *Front Pharmacol*. 2014; 5:156.

