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A cross-sectional study on antioxidant status in trauma patients with wound healing disorders

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Abstract
Background: Disorders in wound healing (DWH) are common in trauma patients, the reasons being not completely understood. Inadequate nutritional status may favour DWH, partly by means of oxidative stress.
Objective: To investigate the status of markers of anti-oxidant in patients with DWH within routine setting.
Methods: a cross-sectional study was conducted in 44 trauma patients with DWH in addition to markers of pro-/antioxidant balance (antioxidant capacity, peroxides, and malondialdehyde). Epi-info was used as software. Statistical significance was set at $P < 0.05$.
Results: Mean concentrations of β-carotene (0.6± 0.4 μmol/L), selenium (0.79±0.19 μmol/L) were relatively low. Most patients showed levels of selenium (≤ 94 μmol/L; 71%) and β-carotene (<0.9 μmol/L; 86%) below the reference range. Plasma antioxidant capacity was decreased, whereas peroxides and malondialdehyde were increased compared to normal values. Inverse correlations were found between CRP and albumin ($P<0.05$) and between CRP and prealbumin ($P<0.01$).
Conclusions: Trauma patients with DWH frequently suffer from protein malnutrition and reduced plasma concentrations of anti-oxidant and oxidative burden. Thus, adequate nutritional measures are strongly recommended to trauma patients.

Keywords: disorders in wound healing, inflammation, oxidative stress, trauma patients

Introduction
Disorders in wound healing (DWH) are frequently observed post-surgically in patients with vascular diseases and soft tissue trauma [1]. DWH are associated with a prolonged hospital stay and essentially contribute to high morbidity and mortality [2]. Thus, apart from the individual burden, DWH generate enormous costs in the health care system. The pathophysiological mechanisms leading to DWH are not completely understood. Recent studies in patients with pressure ulcers [3] support the hypothesis that general protein/energy malnutrition can considerably increase the risk for DWH by several mechanisms. An insufficient intake of micronutrients may lead to intra-/extracellular deficiencies resulting in an imbalance between pro-/and antioxidants which exerts cytotoxic effects and, consequently, may impair WH as shown in a small patient group for selenium [4]. However, representative cross-sectional studies focusing on the assessment and evaluation of general and specific nutritional status in a variety of patients with DWH are scarce. Therefore, the aim of this cross-sectional study was to assess concentration of selected biomarkers of pro-/ antioxidative balance in trauma patients with DWH in a routine clinical setting.

Material and Methods
Study design- cross-sectional design
Study population- 44 adult trauma patients with DWH (defined as failure to heal, i.e. wound not closed or persisting secretion within ten days after trauma or surgery) were consecutively recruited between May and December 2018 at the Department of Orthopaedics and Trauma Surgery, Birla Hospital.
Exclusion criteria- parenteral and enteral nutrition, exclusive implant removal, pressure ulcers as primary diagnosis, HIV infection, chronic inflammatory bowel diseases, liver diseases, drug abuse, known pregnancy, lactation, stay in the intensive care unit and sepsis.
After enrolment, data on main diagnosis, comorbidities and medication were obtained and the individual injury severity score[5] was determined. The time between trauma/surgery and enrolment was documented. All patients provided written, informed consent prior to enrolment.
Methodology- On the day after enrolment, blood samples were collected after an overnight fast in EDTA or lithium coated tubes and in tubes without anticoagulant. Plasma and serum were obtained within two hours by centrifugation at 2000 × g, 4°C for 10 min. C-reactive protein (CRP; nephelometry, Siemens Health- care Diagnostics, Eschborn, Germany) was analyzed by routine clinical chemistry. The reference value for CRP was obtained from the Department of Bio-Chemistry. Plasma concentrations of β-carotene (CV 3.2%) were measured in EDTA-plasma by HPLC [6, 7]. selenium by atom absorption spectrometry (CV 3%; Biosyn, Fellbach, Germany). The trolox equivalent antioxidant capacity (TEAC) assay [8] was used to determine antioxidant capacity (CV1.2%) in EDTA-plasma. MDA was measured in plasma by photometry (CV 7.4%) [9]. An ELISA kit was used to determine the concentration of peroxides.

Statistical Analysis
Data on TEAC, peroxides, and MDA were comparison between patients and healthy subjects was done by Mann–Whitney U test. Statistical significance was assumed for $P<0.05$. Epi-info version 7 was used for analysis.

Results

Table 1: Demographic details of study subject (N=44)

Parameters		N
Sex	Male	29
	Female	15
Age		60±21
Diagnosis	Long bone fracture	10
	Pelvic fracture	6
	Joint fracture	14
	Miscellaneous fracture	14
Injury severity score		14±6
Infection		32
Morbidities	Diabetes mellitus	8
	Vascular disease	13
Smoker		11
Hospital stay duration (days)		27±4

Table 1 shows demographic details of study subjects. The study was male preponderance with mean age was 60±21 years. Joint fractures were the highest. More than 80% of subjects has infection. Around 25% has vascular disease. And 15% were smoker. Duration of hospital stay was 27 days as mean.

Table 2: Micronutrients status in Plasma

Micronutrients	Patients	Range of reference
β- carotene	0.5±0.4	0.9-4.6
Selenium	0.80±0.20	>0.94
Albumin	31.8±7.8	As per age
Pre-albumin	23.2±8.9	15-36

The concentrations of β-carotene, and selenium were relatively low, and in most of the subjects below the reference range. A deficiency was also observed for albumin and, partly, for prealbumin but that was not found to be significant.

Table 3: Markers of antioxidant balance and oxidative stress

Markers	Cases	Controls	p-value
Teac	1.22±0.18	1.58±0.16	<0.05
Peroxides	0.88±-0.21	0.70±0.10	>0.05
Malondialdehyde	81.7±32.4	12.4±4.3	<0.05

Table 3 predicts patients with DWH, TEAC was lower (P <0.05), and the concentrations of peroxides (P >0.05) and MDA (P <0.05) were higher compared to healthy controls. This can be due to several endogenous factors.

Discussion

Mean plasma concentrations of β-carotene and selenium were below the reference values and 59 - 86% of the patients had a deficiency. Since post-traumatic and post-surgical metabolic events, such as inflammation [10, 11] and oxidative stress[12], may generally contribute to lower plasma levels of β-carotene low plasma status of these micronutrients in trauma patients with DWH may be a concomitant phenomenon considering increased levels of CRP, MDA, and peroxides. While it may not be the reason for the development of DWH, it nevertheless should be considered that the plasma level of micronutrients does not necessarily reflect the micronutrient status in the wounded tissue with respect to substrate fluxes to the wound area. Such fluxes have been observed in rats for free amino acids during early wound healing period, leading to a relative lack of arginine in whole body [13]. However, as a cofactor of glutathione peroxidase, selenium may reduce oxidative stress in patients with DWH [14]. Disturbances in the redox state are discussed to be risk factors for delayed WH [4]. Since direct measurements of the short-lived reactive oxygen species require laborious and expensive techniques, such as electron paramagnetic resonance, indirect methods are used in routine clinical setting to detect an imbalance between pro- and antioxidants [15]. This includes analysis of peroxidation products, such as MDA and peroxides, analysis of single antioxidants (e.g., ascorbic acid, α-tocopherol, β-carotene) [16] and analysis of total antioxidant capacity reflecting the synergistic action between endogenous (albumin, uric acid) and nutritive (ascorbic acid, α-tocopherol and β-carotene) antioxidants [17]. Oxidative stress in patients with DWH was indicated by increased concentrations of peroxides compared to healthy adults. TEAC was lower in patients with DWH than in healthy controls, probably due to lower concentrations of several endogenous (e.g., albumin) and exogenous antioxidants like ascorbic acid with a high contribution to plasma antioxidant capacity. Despite the relatively low specificity of MDA [18], the increased values of MDA suggest an increased lipid peroxidation in patients with DWH, which is in line with increased peroxides and reduced TEAC.

Conclusions

Trauma patients with DWH frequently suffer from biochemical deficiency in several ways probably due to inflammation, increased requirement and oxidative burden. Thus, tailored nutritional measures and early supplementation with selected micronutrients are strongly recommended to hospitalized trauma patients.

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