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Increased IL-17A Levels Secreted by Adipose Derived Stem Cells Extracted from Geriatric Burn Patients

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Abstract

Background: Burn injuries in the elderly population pose a difficult clinical dilemma. This population is commonly frail with impaired wound healing capabilities and dysregulation of cytokines. Adipose derived stem cells (ADSCs) play a major role in wound healing. The objective of this study was to determine if there was an alteration in the ADSC cytokine profile of geriatric burn patients.

Methods: Adipose tissue was collected from burn patients at their initial excision. ADSCs were extracted, and the supernatant was collected. Cytokine analyses were performed with a multiplex assay. Patients were stratified into two groups: Non GeriBurn (<65 years old) and GeriBurn (≥ 65 years old). Mann-Whitney U test was used to compare the groups.

Results: Thirteen patients were included (GeriBurn n=6). There was a significantly higher median concentration of interleukin-17 (IL-17) in the GeriBurn group (p=0.015).

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Conclusions: This study demonstrated a significantly higher concentration of the pro-inflammatory cytokine IL-17A in the GeriBurn group. This cytokine is associated with increased susceptibility to infections. Further studies are needed to investigate the clinical consequences of this finding.

Keywords

Geriatric; Burn; IL-17.

Introduction

Approximately 180,000 deaths annually are attributed to burn injuries [1]. Geriatric burns account for approximately 5% of all burns and up to 20% of all burns in socioeconomically disadvantaged populations [2]. Due to a higher incidence of comorbid conditions, this population is at two times higher risk of in-hospital mortality after burn injuries [3]. These patients often have less mobility and more frailty resulting in less resiliency to heal following burn injury.

During the aging process, the immune system also undergoes changes that impact the way the body responds to stressors such as trauma or infection. There is an overall decrease in the thymic T cell production as well as a decrease in humoral immunity resulting in an impaired ability to respond to infections [4]. Additionally, many studies have noted a chronic pro-inflammatory state in the geriatric population [5].

Adipose tissue is considered a multifunctional organ that is capable of regeneration and repair [6]. It contains a variety of immune cells including lymphocytes, mast cells, macrophages, and adipose-derived stem cells (ADSCs) [6]. They play an important role in the inflammatory response and wound healing by interacting with surrounding immune cells by releasing cytokines and chemokines which act on nearby cells. [7,8,9].

Previous research demonstrated that inflammatory disease states affect the function of stem cells [10,11]. In an animal model, impaired ADSC function after burn injuries resulted in increased pro-inflammatory cytokines.10 ADSC function is also impacted by aging. The proliferation rate is decreased and cytokine production profile is altered [8,12]. Geriatric patients are at high risk of morbidity and mortality due to burn injuries. The impact of major burn injury on the cytokine profile of ADSCs is not known. We hypothesized there will be an alteration in the ADSC cytokine profile of geriatric burn patients compared to non-geriatric burn patient.

Methods

Patient Selection

This was a prospective study conducted at an American Burn Association verified burn center over a two-year period from 2021-2023. The study was approved by the Institutional Review Board of Louisiana State University Health Sciences Center (IRB #1975). Patients aged 18 years old or older who were admitted with burn injuries (chemical, electrical, or thermal) were eligible for enrollment in this study. Patients had at least one surgical intervention. Members of vulnerable populations including prisoners and pregnant women were excluded from this study. Prior to participation in the study, written informed consent was

obtained by the patient or a legally authorized representative if the patient was not able to provide consent.

Demographics and clinical characteristics

Demographics including patient gender, age, co-morbid conditions, and BMI were collected at the time of admission. Clinical data including initial laboratory values, percent total body surface area (TBSA), type of burn injury, hospital length of stay (LOS), and mortality data were collected. Sepsis was determined using an institutional specific protocol (**Figure 1**). Time of injury was determined using ambulance records and time of initial contact with Emergency Medical Services. Time of presentation was defined as time of arrival to the Emergency Department. Initial resuscitation was performed according to an established guideline as depicted in (**Figure 2**).

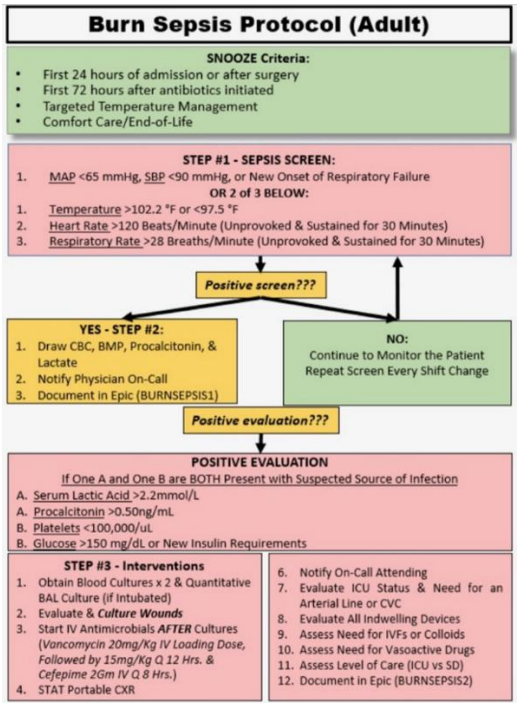

Figure 1. Institutional burn sepsis protocol.

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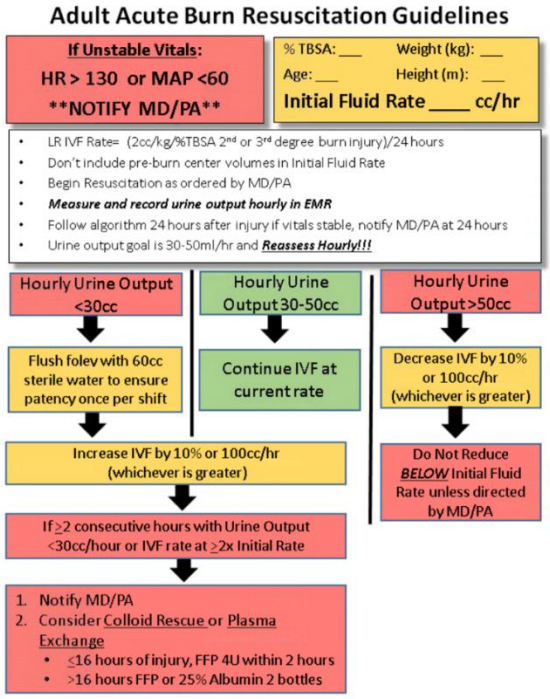

Figure 2: Institutional adult acute burn resuscitation guidelines.

Extraction of adipose-derived stem cell

Adipose tissue was collected from patients with burn injuries at their initial excision. Adipose tissue was weighed and washed with a 1:1 trypsin solution on a shaker for 30 minutes. The sample was then centrifuged at 1500 rpm for five minutes at room temperature. The pellet was resuspended in media, strained through a filter, and centrifuged at 1500rpm for five minutes at room temperature. The pellet was resuspended in five milliliters of ammonium/chloride/potassium (ACK) lysis buffer solution and cells pipetted for five minutes. Fifteen milliliters of phosphate buffer saline (PBS) solution was added and centrifuged at 1500rpm for five minutes. This was resuspended in media and plated. Cells were washed with PBS solution 16 hours after plating. Supernatant from cell cultures were collected 40 hours after plating and stored at -80°C. The presence of ADSCs was confirmed using flow cytometry and cell surface markers CD 90, CD 105, and CD 73.

Cytokine analysis

Supernatant samples were thawed to room temperature. A MilliporeTM Milliplex® map cytokine analysis kit (Milliplex® Human Cytokine/Chemokine/Growth Factor Panela A, reference code HCYTA-60K-10; MilliporeTM, Burlington, MA) was used to determine cytokine concentration levels of each sample in accordance with the manufacturer's recommendations. Kits analyzed for interferon interleukin 1 (IL-1), interleukin 4 (IL-4), interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 10 (IL-10), interleukin 17A (IL-17A), and interferon gamma (IFN-γ). All samples were run in triplicate.

Statistical Analysis

The patients were stratified into two groups: subjects greater than or equal to 65 years old (GeriBurn) and

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subjects less than 65 years old (Non GeriBurn). Continuous data are presented as median with interquartile range and compared using Mann-Whitney test. Categorical data were compared using Fisher exact test. All tests were two-tailed with a p value < 0.05 considered significant. Data was analyzed using Statistical Package for Social Sciences, version 29.0.1.0 for Macintosh (IBM Inc, Armonk, NY).

Results

Patient Characteristics

A total of 13 patients were included in the study with six in the GeriBurn cohort. The median age in the GeriBurn group was 73.5 years and 52.0 years in the Non GeriBurn group (p=0.003) as shown in (**Table 1**). There was a significant difference in the median percent total body surface area burned between the two groups (TBSA; non GeriBurn=34.0%, GeriBurn=14.5; p=0.01) but there was no significant difference in percentage of partial or full thickness burns. Pre-operative values such as lactic acid, hemoglobin, and creatinine did not differ significantly between the two groups. Similarly, there was no significant different in comorbidities such as hypertension, diabetes, or smoking status between the two groups. The meidum time from injury or presentation to hospital to operating room did not differ between the two groups.

	Non GeriBurn	GeriBurn	p value
	n=7	n=6	
Age (median, IQR, years)	52.0, 17.0	73.5, 4.0	0.003*
BMI (median, IQR)	25.2, 8.2	25.2, 16.2	0.72
TBSA (median, IQR, percent)	34.0%, 12.0	14.5%, 17.3	0.01*
Second degree (median, IQR, percent)	3.0%, 19	0.0%, 3.5	0.09
Third degree (median, IQR, percent)	25.0%, 19.0	12.0%, 16.5	0.053
Hypertension (n, percent)	2, 28.6%	3, 50.0%	0.41
Diabetic (n, percent)	1, 14.3%	0, 0%	0.54
Current smoker (n, percent)	5, 71.4%	5, 83.3%	0.56
Lactic acid median, IQR, mmol/L)	1.4, 0.4	1.1, 0.4	0.39
Hemoglobin (median, IQR, g/dL)	13.4, 3.3	11.0, 2.9	0.15
Creatinine (median, IQR, mg/dL)	0.87, 0.85	0.94, 0.55	0.83
Preoperative pRBC (median, IQR, units)	0, 0	0, 0	0.36
Intraoperative pRBC (median, IQR, units)	4.0, 7.0	1.5, 2.5	0.17
Time from injury to OR (median, IQR, hours)	111.8, 83.9	102.5, 60.7	0.57
Time from presentation to OR (median, IQR, hours)	111.1, 87.8	96.0, 30.3	0.89
Hospital LOS (median, IQR, days)	34.0, 19.0	22.5, 16.0	0.17
Sepsis (n, percent)	4, 57.1%	2, 33.3%	0.32
Mortality (n, percent)	1, 14.3%	2, 33.3%	0.5

Table 1: GeriBurn versus Non Geriburn Demographics and Clinical Data

Abbreviations: IQR, interquartile range; TBSA, total body surface area; BMI, body mass index; n, number; pRBC, packed red blood cells; OR, operating room; LOS, length of stay. Asterisks indicates significant difference (p<0.05).

Cytokine Analysis

Median cytokine concentrations are depicted in (**Figure 3**). There was a significantly higher concentration of interleukin-17A (IL-17A) in the GeriBurn group compared to the Non GeriBurn group (**Figure 3A**, p<0.05). All other cytokines analyzed were not significantly different between the two groups (p>0.05).

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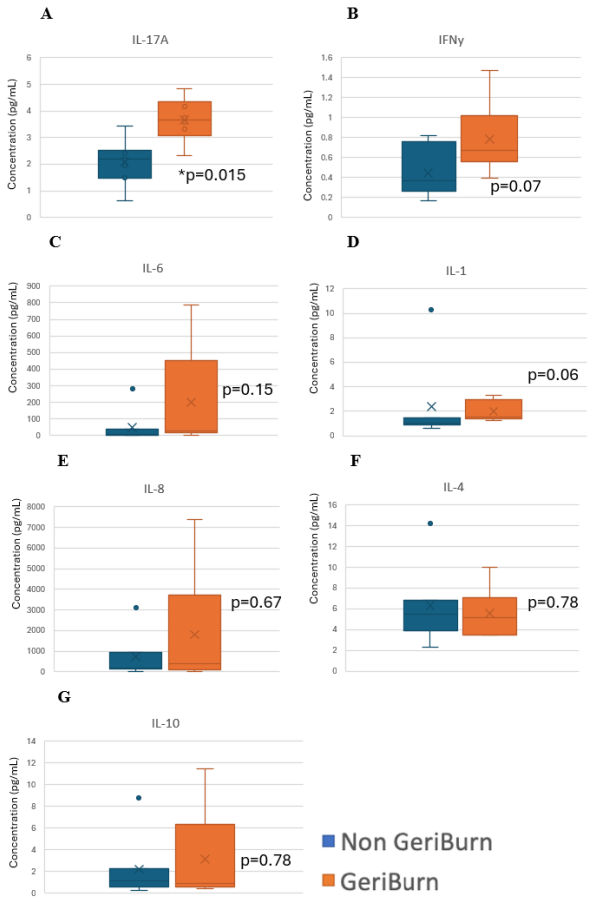

Figure 3: GeriBurn versus Non GeriBurn median cytokine concentrations with interquartile range indicated by box. Median represented by horizontal line in the middle of the box. "X" indicates mean. Asterisks indicate significant difference ($p<0.05$).

Discussion

The geriatric burn population is subject to worse outcomes due to pre-existing pro-inflammatory state and fragility. Our study demonstrated a significantly higher concentration of IL-17A in the geriatric burn population. Interleukin-17A is part of a larger family of cytokines that range from IL-17A to IL-17F.13 Interleukin-17A is the most widely studied of the six and has been shown to demonstrate pro-inflammatory functions by recruiting neutrophils to the area of injury [13]. Although it is produced by a wide array of cell types, Th17 cells are the principle source [3]. It is known to initiate a potent inflammatory response when acting synergistically with other proinflammatory cytokines such as tumor necrosis factor [14]. This cytokine also plays a critical role in maintaining the mucosal barrier integrity and the remodeling of tissue such as epithelium of the airways and cardiac myocytes in response to injury [13].

Several disease processes involving IL-17A have been previously studied. Ahmed and colleagues reported that a high level of this cytokine at the time of admission in patients with polytrauma was associated with an increased risk for the development of septic complications [15]. Interestingly, IL-17A has also demonstrated protective effects against bacterial infections such as those caused by Staphylococcus,

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Streptococcus, and Pseudomonas [13,16]. The exact mechanism for these findings is unknown but this may be due to genetic variations in the IL-17A gene leading to increased susceptibility to infections, as well as higher risk of complications due to sepsis [17]. In a murine model of sepsis, inhibition of IL-17A resulted in decreased recruitment of T cells and neutrophils to the site of methicillin resistant Staphylococcus aureus (MRSA) cutaneous infections. Furthermore, these mice also exhibited more severe abscesses and bacterial density at the site of infection suggesting the protective role of IL-17A against MRSA infections [18]. However, aberrant levels can have harmful effects due to an exaggeration of the immune response [13]. Flierl et al. performed a sepsis murine model using a cecal ligation and puncture technique. The authors found that neutralization of IL-17A resulted in decreased severity of bacteremia and decreased levels of proinflammatory cytokine release [19]. Increased IL-17A levels also play a role in the severity of acute respiratory distress syndrome with higher concentrations associated with increased mortality [20]. Although the exact mechanism underlying the varying effects of IL-17A on the immune response is not fully elucidated, our study demonstrated an increased level of IL-17A in geriatric burn patients. The incidence was of sepsis and in hospital mortality was higher in the GeriBurn group but this was not statistically significant (Table 1). However, the small sample size of our study makes it difficult to interpret these results. Therefore, the clinical significance of the elevated levels of IL-17A on sepsis and mortality in the GeriBurn group remains to be determined.

Interleukin-17A has also been studied in several disease processes closely associated with aging. For example, this cytokine promotes carcinogenesis in prostate epithelial cells leading to prostate cancer [21,22] It is also involved in the pathogenesis of osteoarthritis by promoting cellular pathways that result in chondrocyte senescence and synovial inflammation [23]. In a study conducted by Solá et al., the authors performed en vivo blockade of IL-17A in an aged murine model which resulted in a delay in the appearance of age-related traits [24]. Mechanistically, this is through prevention of downstream activation of nuclear factor κB (NF- κB), a major proinflammatory transcription factor and main effects of IL-17A [21]. There are hundreds of genes under the control of NF- κB with the functions ranging from proinflammatory to cell adhesion molecules [25]. It also regulates apoptosis by inhibiting this process in proinflammatory cells such as macrophages, dendritic cells, T-cells, B-cells and neutrophils [25]. It is very important to the inflammatory response and is an essential mediator of the innate and adaptive immune response.26 Due to its major functions as a mediator in the inflammatory process, NF- κB therefore plays a role in the dysregulation of the immune system during the aging process [26,25]. The fibroblastic nuclear concentration of NF- κB in organs such as the brain, liver, and kidney increases with increasing age [27]. Additionally, chronic inflammation associated with persistent NF-κB activation leads to telomere shortening, a cellular indication of aging and senescence [27]. This transcriptional factor is also involved in the aging of skin via activation by reactive oxygen species induced by ultraviolet light which ultimately leads to increased production of proinflammatory cytokines [28]. This suggests an underlying weakened defense in geriatric patients due to the NF- κB induced aging and senescence of the immune system. The elevated level of IL-17A in the GeriBurn population exhibited in our study may result in a higher degree of proinflammatory response in an immune system already under a chronic proinflammatory state.

The levels of IL-17A have been studied in burn patients with data demonstrating significantly higher concentrations in burn patients [29]. There are also age related differences with pediatric patients having

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a higher concentration after burn injuries when compared to adults [29]. Our results support this finding but in the geriatric burn population. Several murine burn models are also consistent with the findings seen in clinicals studies. Levels of IL-17A in these models are seen to be elevated at the site of the burn injury as well as remote organs such as cardiac myocytes but not in the lung, liver, or small intestines [30, 31]. Although the clinical consequences of these findings have not been fully investigated, this does suggest a derangement in the post burn immune response skewing towards a pro inflammatory response in tissue specific manner.

This study has several limitations that warrant discussion. This is a pilot study with a small sample size. Additionally, it is retrospective and single center. One of the major limitations is the difference in TBSA affected between the two groups. The GeriBurn group had a significantly lower median TBSA burned compared to the Non GeriBurn group. The hyper inflammatory response as a result of a burn injury is proportional to the extent of the burn [32]. Interleukin-17A is a proinflammatory cytokine and increased in the setting of burn injuries. This would suggest that the levels of IL-17A should be proportional to the size or extent of a burn injury. Consequently, if the TBSA were not significantly different between the two groups, this may result in a more significant difference of IL-17A between the two groups. This potential confounder will be further investigated in the future with propensity score matching as well as a larger sample size.

Conclusions

Our study demonstrated significantly higher concentrations of IL-17A in geriatric burn patients. This pro-inflammatory cytokine is implicated in several age-related disease processes. This finding may be associated with increased risk of cardiac and septic complications when compared to the younger population. More studies are needed to investigate the clinical consequences of this observation.

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