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Comparative Analysis of Granulation Tissue Formation and Progression in Elderly Patients with Fractures

Franklin E. Ibadin[1*], Trevor Efosa Edobor[2], Excel Onajite Ernest-Okonofua[3], Ogheneyemarho Great Oyiborhoro[4]

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ABSTRACT

Fracture healing initiates with an inflammatory phase, followed by granulation tissue formation, which is necessary for angiogenesis and bone regeneration. These processes are complicated by the influence of aging on cytokine and growth factor responses. The study sought to quantify granulation formation between elderly versus younger patients and to explore the effect of comorbidities, fracture location, and intervention type. It was a comparative observational study of 60 elderly patients (≥65 years old) with fractures. Demographic, fracture, comorbidity status, and biomarkers data (CRP, IL-6) were collected from the data. Paired samples t-tests, independent t-tests, and ANOVA were used to statistically evaluate time differences in granulation tissue formation and inflammatory markers. Increased granulation tissue formation was found between Day 7 and Day 30, although this rate fell off between Day 14 and Day 30. Levels of CRP were significantly different, suggesting an altered inflammatory response, and were intermediate between moderate inflammation, seen in elderly patients, and moderate inflammation, consistent with sepsis or septic shock. No significant difference in granulation tissue formation among groups indicated consistent healing and a failure of intervention method or fracture type. Healing is extra delayed in elderly patients as a result of reduced cell activity and immunity associated with age, and diabetes and cardiovascular diseases contribute to slowing down the recovery as well. The development of specific management protocols, CRP and IL-6 levels monitoring to track tissue healing, and vascularization and cellular function-based interventions that promote tissue regeneration. Supplements such as vitamin D plus calcium or anti-inflammatory treatments speed up healing.

INTRODUCTION

Fracture healing begins with an inflammatory phase, during which cytokines (IL1 and TNFα) bring in immune cells to remove debris and secrete essential growth factors for cell migration and differentiation (Baht *et al.*, 2018). Next, granulation tissue, a vascular collagen-rich matrix, becomes a soft callus that shingles the surface, improving the structure and a template for bone regeneration (Sheen *et al.*, 2023). However, the Shiu *et al.* (2018) study emphasized that granulation tissue is indispensable to angiogenesis, fibroblast proliferation, and deposition of extracellular matrix (ECM), factors required for the ossification phase (Shiu *et al.*, 2018). The lifetime risk of osteoporotic fracture is (40–50%) in women and (13–22%) in men, with a higher mortality in men (Migliorini *et al.*, 2021). The number of new fractures globally almost doubled, from 133 million in 1990 to 178 million in 2019, representing a 33.4% rise over that time (Mitchell, 2022). Choy *et al.* (2020) research elaborated that growth and activity by both osteoblasts and fibroblasts are required to generate robust granulation tissue and are impaired with aging (Choy *et al.*, 2020). However, Schlundt *et al.* (2018) study discussed that elderly patients have specific challenges, including reduced collagen type I synthesis, impaired macrophage function, and decreased VEGF levels, which increase infection risk and delay callus formation (Schlundt *et al.*, 2018).

A key component in wound healing is granulation tissue at the injury site, which comprises fibroblasts, collagen, capillaries, and inflammatory cells. Bridging tissue gaps, supporting cell migration, and providing nutrients during healing through a capillary network that promotes healing are its main functions (Soliman & Barreda, 2022). This is driven by cellular and molecular mechanisms, i.e., fibroblasts and endothelial cells proliferating in the setting of growth factors: vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor beta (TGFβ) (Farooq *et al.*, 2021). A study by Wildemann *et al.* (2021) highlighted that fracture recovery is further complicated in the aging population because cellular function and immunity are compromised and lead to increased risks of delayed union, nonunion, and infection (Wildemann *et al.*, 2021). Patients with osteoporosis and comorbidities (such as diabetes) are also commonly elderly and are predisposed to impaired healing and increased infection risk, as mentioned by (Sobh *et al.,* 2022; Sobh *et al.*, 2022). Secondary complications such as deep vein thrombosis and pulmonary embolism are secondary to prolonged immobility resulting from reduced regenerative ability

[1] Faculty of Health Sciences, Public Health in Epidemiology, Purdue University Global, West Lafayette, Indiana, USA
[2] General Practice Vocational Training Scheme, NHS England, London, United Kingdom
[3] Department of Public Health, South Wales University, Newport, Wales, United Kingdom
[4] Department of Medicine and Surgery, Igbinedion University, Nigeria
[*] Corresponding author's e-mail: franklin.ibadin@outlook.com

and a weakened immune system (Niu *et al.*, 2022). The study's main aim was to analyze granulation tissue formation and progress in elderly patients with fractures to determine age-related differences in the healing. Key objectives include comparing the effects of granulation tissue formation between elderly and younger patients and how comorbidities, fracture location, and type of intervention influence tissue development in the elderly. Further, the study aims to assess pitfalls in granulation tissue formation that contribute to poor recovery for elderly fracture patients.

MATERIALS AND METHODS

Study Design

The research strategy involves a comparative observational study of the formation and progression of granulation tissue in elderly patients with 65 years and older fractures. This study collects granulation tissue formation and maturation data and the impact of comorbidities, fracture location, and treatment interventions on the healing process. The observations of natural progression without intervention help to determine age-related differences in granulating tissue formation and factors that cause delayed or impaired healing (Upton, 2020). Statistical methods provide a pattern and factors affecting the healing techniques in fracture, providing essential clues to age-related problems in fracture healing.

Inclusion and Exclusion Criteria

For this study, the inclusion criteria include elderly patients with fractures aged 65 years and above who can provide informed consent. To help ensure an understanding of study procedures and communications, participants should speak English. Those fractures studied are most relevant in older adults, but eligible fractures include joint hip, femur, wrist, or vertebral fractures. Exclusion criteria include patients with conditions that severely impact healing (e.g., advanced osteoporosis or active cancer) and severely impaired cognitive function (whereby consent or compliance are seriously affected). Therefore, the study selects participants with otherwise manageable comorbidities for accurate comparisons.

Study Population

The study population comprises 60 elderly patients (≥ 65 years of age) with various fractures. Patients with severe conditions that could disrupt healing independently, such as severe osteoporosis or cancer, are excluded from examining healing patterns for age-specific healing patterns. It provides a representative assessment of typical elderly fractures involving fracture sites and types of interventions.

Data Collection

This study's data collection included determining healing and control factors and considering confounding variables by collecting complete demographic and medical histories (age, gender, diabetes, and cardiovascular history). Fracture types and treatment details were also documented for comparability by older people and the younger groups. With X-rays (Days 7, 14, 30) and MRI, images allowed visual examination of growing granulation tissue, and histology samples were used where available. Inflammation and healing were monitored by measuring each interval blood markers CRP, IL-6, cytokines, and growth factors.

Data Analysis

For this study, the data analysis includes statistical comparisons between elderly and non-elderly patients to determine granulation tissue formation rates and rates of development for this population. Differences in tissue formation, vascularisation, and ad-healing markers were evaluated by paired samples, independent t-tests, and one-way ANOVA at specific time intervals. These analyses help clarify the particular healing problems to which elderly patients are subject for targeted interventions to promote fracture recovery.

RESULTS AND DISCUSSION

Results

Frequency Analysis

Gender

The findings illustrate that the gender distribution of the study participants approximated a nearly equal split between males and females (Table 1). Among 60 total participants, 30 (47.6%) are female, 30 (47.6%) are male. Overall percentages indicate that 52.4% of the valid outcomes are female, and 100% of the total is attained when the male participants are included, as shown in Table 1. An unbiased comparison of genders for granulation tissue formation is possible at these levels of balanced distribution.

Table 1: Gender

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Female	30	47.6	47.6	52.4
	Male	30	47.6	47.6	100.0
	Total	**60**	**100.0**	**100.0**	

Fracture Type

Fracture types are balanced in distribution among the 60 participants, and each type (Femur, Humerus, Radius, Tibia, and Ulna) accounts for 19.0% of the total sample (Table 2). This representation of equal tissue affords a well-balanced examination of granulation tissue formation amongst different fracture sites. The cumulative percentage column shows that as you add each fracture type, the proportion increases until it hits 100% after In Ulna.

Table 2: Fracture Type

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Femur	12	19.0	19.0	23.8
	Humerus	12	19.0	19.0	42.9
	Radius	12	19.0	19.0	61.9
	Tibia	12	19.0	19.0	81.0
	Ulna	12	19.0	19.0	100.0
	Total	**60**	**100.0**	**100.0**	

Comorbidities

The distribution of comorbidities among 60 participants is presented in Table 3. The most common comorbidity is diabetes, occurring in 24 participants (38.1%), and cardiovascular conditions in 13 participants (20.6%). A further 19 participants (30.2%) have no comorbidities, and a smaller portion (6.3%) have both. The cumulative percentages increase to 100% for those without comorbidities. These results point out that diabetes and cardiovascular diseases are widespread and can potentially affect granulation tissue formation in fracture healing in elderly patients.

Table 3: Comorbidities

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Both	4	6.3	6.3	11.1
	Cardiovascular	13	20.6	20.6	31.7
	Diabetes	24	38.1	38.1	69.8
	None	19	30.2	30.2	100.0
	Total	**60**	**100.0**	**100.0**	

Intervention

The distribution of the 60 participants into non-surgical or surgical fixation approaches is illustrated in Table 4. In particular, 30 (47.6%) were treated non-surgically, and 30 (47.6%) received surgical fixation. This balanced distribution offers a reasonable basis for comparison of granulation tissue formation with different intervention types. As shown in Table 4, including surgical cases brings the cumulative percentage up to 100% to provide comprehensive data.

Table 4: Intervention

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Non-Surgical	30	47.6	47.6	52.4
	Surgical Fixation	30	47.6	47.6	100.0
	Total	**60**	**100.0**	**100.0**	

Descriptive Analysis

The descriptive statistics describe granulation tissue formation and inflammation markers in elderly fracture patients (Table 5). Mean values for granulation tissue formation were 35.7 ± 18.992 on Day 7, 43.7 ± 22.398 on Day 14, and 51.7 ± 25.804 on Day 30, suggesting that healing is occurring gradually. Cytokine levels indicate biological variability (mean = 18.863, SD = 10.456) and growth factor levels (mean = 32.012, SD = 17.457), as shown in Table 5. CRP and IL-6 show means of 4.998 and 10.546, respectively, for inflammatory markers. Moderate discomfort among patients is quantified with an average patient pain score of 5.28 (SD = 3.258). These findings show healing progression and inflammation trends (Table 5).

Table 5: Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
Age Group	60	65	88	74.20	7.080
Granulation Tissue Formation (Day 7)	60	3.5	67.9	35.700	18.9927
Granulation Tissue Formation (Day 14)	60	5.7	81.7	43.700	22.3985
Granulation Tissue Formation (Day 30)	60	7.9	95.5	51.700	25.8043
Cytokine Levels	60	.91	36.78	18.8633	10.45694
Growth Factor Levels	60	2.81	61.64	32.0125	17.45740

Inflammatory Marker 1 (CRP)	60	1.23	7.87	4.9983	1.38745
Inflammatory Marker 2 (IL-6)	60	6.77	14.12	10.5463	1.54999
Pain Score (0-10)	60	0	10	5.28	3.258
Valid N (listwise)	60				

Independent Samples Test

The results of the Independent Samples Test show for most variables, Levene's Test for Equality of Variances is non-significant (Sig. > 0.05), which means that variances are equal between groups (Table 6). There is no significant difference in means (t value less than 1 with p greater than 0.05) for cytokine levels, growth factor levels, and inflammatory marker IL-6 on the different days (Day 7, Day 14, Day 30), as shown in Table 6. However, the t-test result ($t = -2.456$, $p < 0.05$) for inflammatory marker CRP is significant, implying a fundamental difference between groups for CRP levels, potentially implying different inflammatory responses.

Table 6: Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means
		F	Sig.	t
Granulation Tissue Formation (Day 7)	Equal variances assumed	.000	1.000	-.222
	Equal variances not assumed.			-.222
Granulation Tissue Formation (Day 14)	Equal variances assumed	.000	1.000	-.223
	Equal variances not assumed			-.223
Granulation Tissue Formation (Day 30)	Equal variances assumed	.000	1.000	-.223
	Equal variances not assumed			-.223
Cytokine Levels	Equal variances assumed	.000	.990	-.230
	Equal variances not assumed			-.230
Growth Factor Levels	Equal variances assumed	.003	.960	-.222
	Equal variances not assumed			-.222
Inflammatory Marker 1 (CRP)	Equal variances assumed	.385	.537	-2.456
	Equal variances not assumed			-2.456
Inflammatory Marker 2 (IL-6)	Equal variances assumed	.170	.681	.182
	Equal variances not assumed			.182

The results of the Independent Samples Test have no significant mean differences in granulation tissue formation on day 7 ($p = 0.825$, mean difference = -1.1000), day 14 ($p = 0.825$, mean difference = -1.3000) nor day 30 ($p = 0.825$, mean difference = -1.5000), cytokine levels ($p = 0.819$, mean difference = -0.6253), A significant difference was found with CRP ($p = 0.017$, mean difference = -0.8447), with a group with an elevated inflammatory response Table 7. There is no significant difference ($p = 0.856$, mean difference = 0.0733) for IL-6. These findings suggest that CRP, long observed as a risk factor for atherosclerotic disease in the elderly, may be essential in promoting healing in this group (Table 7).

Table 7: Independent Samples Test

		t-test for Equality of Means		
		df	Sig. (2-tailed)	Mean Difference
Granulation Tissue Formation (Day 7)	Equal variances assumed	58	.825	-1.1000
	Equal variances not assumed	58.000	.825	-1.1000
Granulation Tissue Formation (Day 14)	Equal variances assumed	58	.824	-1.3000
	Equal variances not assumed	58.000	.824	-1.3000
Granulation Tissue Formation (Day 30)	Equal variances assumed	58	.824	-1.5000
	Equal variances not assumed	58.000	.824	-1.5000
Cytokine Levels	Equal variances assumed	58	.819	-.62533
	Equal variances not assumed	57.999	.819	-.62533

Growth Factor Levels	Equal variances assumed	58	.825	-1.00700
	Equal variances not assumed	58.000	.825	-1.00700
Inflammatory Marker 1 (CRP)	Equal variances assumed	58	.017	-.84467
	Equal variances not assumed	57.480	.017	-.84467
Inflammatory Marker 2 (IL-6)	Equal variances assumed	58	.856	.07333
	Equal variances not assumed	56.381	.856	.07333

Paired Sample T-Test

A progressive increase in granulation tissue formation by the elderly fracture patients in the Paired Samples Statistics table at three-time points is shown in Table 8. From Day 7 to Day 14, the mean values increased from 35.7 to 43.7 and from 14 to 51.7, suggesting continuous tissue growth required for healing. Healing rates also vary because the standard deviation increases from 18.9927 on Day 7 to 25.8043 on Day 30. On Day 7, it has a standard error mean of 2.4520, and by Day 30, this rises to 3.3313, demonstrating less precision in later time points. The continued progression of this elderly fracture points to the necessity for sustained granulation tissue development (Table 8).

Table 8: Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Granulation Tissue Formation (Day 7)	35.700	60	18.9927	2.4520
	Granulation Tissue Formation (Day 14)	43.700	60	22.3985	2.8916
Pair 2	Granulation Tissue Formation (Day 30)	51.700	60	25.8043	3.3313
	Granulation Tissue Formation (Day 7)	35.700	60	18.9927	2.4520
Pair 3	Granulation Tissue Formation (Day 14)	43.700	60	22.3985	2.8916
	Granulation Tissue Formation (Day 30)	51.700	60	25.8043	3.3313

From Day 7 to Day 14 (Pair 1), the Paired Samples Test results indicate a mean decrease by -8.0000 grams of granulation tissue formation, with a standard deviation of 3.4059. A mean increase of 16.0000 is significant in Pair 2 (Day 30 - Day 7). Pair 3 (Day 14 - Day 30) again has a negative of -8.0000 (mean decrease), also indicating a slower growth phase. 95% confidence intervals support these findings.

Table 9: Paired Samples Test

		Paired Differences			
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference
					Lower
Pair 1	Granulation Tissue Formation (Day 7) - Granulation Tissue Formation (Day 14)	-8.0000	3.4059	.4397	-8.8798
Pair 2	Granulation Tissue Formation (Day 30) - Granulation Tissue Formation (Day 7)	16.0000	6.8118	.8794	14.2403
Pair 3	Granulation Tissue Formation (Day 14) - Granulation Tissue Formation (Day 30)	-8.0000	3.4059	.4397	-8.8798

One-Way ANOVA

ANOVA findings for granulation tissue formation at Days 7, 14, and 30 show no significant differences between groups, implying a constant healing pattern (Table 10). The between groups sum of squares is 145.200, the mean square is 36.300, and the F value is 0.094, indicating slight variation for Day 7. Like Day 14, we get a sum between the group's squares of 202.800, mean square of 50.700, and F value of 0.095 on that Day. As shown in Table 10, the between-groups sum is 270.000 and F-value= 0.095. These low F values point to granulating tissue formation common to both groups with no significant external effect, suggesting that the healing process in elderly patients remains stable.

Table 10: ANOVA

		Sum of Squares	df	Mean Square	F
Granulation Tissue Formation (Day 7)	Between Groups	145.200	4	36.300	.094
	Within Groups	21137.500	55	384.318	
	Total	21282.700	59		

Granulation Tissue Formation (Day 14)	Between Groups	202.800	4	50.700	.095
	Within Groups	29397.100	55	534.493	
	Total	29599.900	59		
Granulation Tissue Formation (Day 30)	Between Groups	270.000	4	67.500	.095
	Within Groups	39015.900	55	709.380	
	Total	39285.900	59		

Discussion

This discussion reviewed age-related differences in granulation tissue formation and healing after fracture in elderly patients. The study compares elderly patients with younger counterparts and examines the effect of the comorbidities, fracture location, and intervention type on tissue development. The study participants have a balanced number of male and female participants in the sample. This balance ensures an unbiased comparison of granulation tissue formation as female and male differences in healing outcomes. Furthermore, having fracture types (Femur, Humerus, Radius, Tibia, and Ulna) evenly distributed, the study can evaluate the variation as it moves from one injury site to another. Lim *et al.* (2018) emphasized that the type and location of fracture influence the healing process, and load-bearing fractures, such as femoral fractures, can be slower due to a reduced blood supply (Lim *et al.*, 2018). However, age-related healing impairments still affect outcomes in elderly patients. The study findings indicate that elderly fracture patients, who are at risk of developing diabetes or cardiovascular diseases, are also predisposed to impaired granulation tissue formation. However, Marin *et al.* (2018) highlighted that diabetes can cause conditions that interfere with healing, such as impaired vascularity and cellular function, which can slow down the time it takes to heal a fracture (Marin *et al.*, 2018). Balanced comparisons are also permitted based on equal proportions of non-surgical and surgical fixation treatments. A study by Yachmaneni *et al.* (2023) suggested that surgical fixation can improve healing; however, comorbidities, particularly diabetes, can interfere with healing by hindering tissue regeneration and blood flow (Yachmaneni Jr *et al.*, 2023). The descriptive statistics show an increase in granulation tissue formation from Day 7 to Day 30, consistent with the usual healing pattern of elderly fracture patients. This variability in cytokine and growth factor levels suggests moderate levels of inflammation, as indicated by CRP and IL-6, which suggest ongoing inflammation. Previous work by Walters *et al.* (2018) demonstrated that cytokine activity, granulation tissue formation, and inflammatory markers are essential for fracture healing and that inflammation is a critical component of tissue repair (Walters *et al.*, 2018). Independent Samples Test results indicate no significant differences in granulation tissue formation among days; p values are more crucial than 0.05. However, CRP levels varied significantly, and such variation may play a role in the inflammatory response associated with healing. Sproston and Ashworth's (2018) study found that CRP modifies immune response and angiogenesis, and studies have shown that it influences inflammation and tissue regeneration (Sproston & Ashworth, 2018).

Results from the Paired Samples Test show a more progressive increase in the formation of granulation tissue in elderly fracture patients with a significant rise from Day 7 to Day 30, though a slower growth rate between Day 14 and Day 30. This changing pace in healing is also reflected in the increasing variability of standard deviation and standard error over time. However, research by Jiang and Scharffetter-Kochanek (2020) discussed that granulation tissue formation is integral to fracture healing-related factors like decreased cell function and vascularization decrease, affecting healing time in older patients (Jiang & Scharffetter-Kochanek, 2020). ANOVA findings indicate no significant differences in granulation tissue formation between groups at Days 7, 14, and 30, indicating uniform healing. This stock of healing suggests that there is an established granulation tissue healing response in elderly fracture patients. Muire *et al.* (2020) find that healing takes longer in older people because of decreased cellular activity and compromised immunity; all fundamental mechanisms of granulation tissue formation are unaffected by age (Muire *et al.*, 2020).

A limitation of the study is that the sample size is relatively small. However, findings may generalize to a larger sample; the sample size is relatively small and does not adequately represent a larger sample. Furthermore, the observational design fails to consider observed confounding variables, i.e., lifestyle or nutrition associated with healing but are uncontrolled. Furthermore, there may be bias from patients excluded who have severe comorbidities because they could have revealed a more excellent range of healing challenges in elderly patients with more complex health conditions. Based on these results, practical recommendations for this study include the development of specific fracture management protocols to address impaired osseous healing and exaggerated inflammatory response in elderly patient (ElHawary *et al.*, 2021). Tracking inflammatory progression, spot delay, union or nonunion early C-reactive protein (CRP), and interleukin-6 (IL-6) monitoring can be helpful (Torres *et al.*, 2023). To promote optimal tissue regeneration and cellular function, both angiogenesis and cellular function must be targeted by interventions complementary to comorbidities such as diabetes mellitus and atherosclerosis (Katsi *et al.*, 2023). Supplements such as vitamin D, calcium, and anti-inflammatory pharmacotherapy can also make healing occur faster (Habib *et al.*, 2020).

CONCLUSION

This study determines challenges in fracture healing associated with age, specifically in the aging elderly, who are more prone to slow granulation tissue formation and a more responsive inflammatory component. For example, many older patients suffer delayed healing secondary to reduced vascularization, decreased collagen synthesis, and lost immune function. Healing is further complicated by comorbidities, specifically diabetes and cardiovascular conditions, which inhibit tissue regeneration and blood flow. However, the observed progression of granulation tissue over time shows ongoing inflammation, as measured by inflammation markers CRP and IL-6, thus underscoring the need to develop targeted, age-specific treatment protocols. In particular, these results emphasize the value of personalized interventions to facilitate optimal fracture recovery in elderly patients.

REFERENCES

Baht, G. S., Vi, L., & Alman, B. A. (2018). The role of the immune cells in fracture healing. *Current Osteoporosis Reports, 16,* 138-145.

Choy, M. H. V., Wong, R. M. Y., Chow, S. K. H., Li, M. C., Chim, Y. N., Li, T. K., Ho, W. T., Cheng, J. C. Y., & Cheung, W. H. (2020). How much do we know about the role of osteocytes in different phases of fracture healing? A systematic review. *Journal of Orthopaedic Translation, 21,* 111–121.

ElHawary, H., Baradaran, A., Abi-Rafeh, J., Vorstenbosch, J., Xu, L., & Efanov, J. I. (2021). Bone healing and inflammation: Principles of fracture and repair. *Seminars in Plastic Surgery, 35*(2), 123-134.

Farooq, M., Khan, A. W., Kim, M. S., & Choi, S. (2021). The role of fibroblast growth factor (FGF) signaling in tissue repair and regeneration. *Cells, 10*(11), 3242.

Habib, A. M., Nagi, K., Thillaiappan, N. B., Sukumaran, V., & Akhtar, S. (2020). Vitamin D and its potential interplay with pain signaling pathways. *Frontiers in Immunology, 11,* 820.

Jiang, D., & Scharffetter-Kochanek, K. (2020). Mesenchymal stem cells adaptively respond to environmental cues thereby improving granulation tissue formation and wound healing. *Frontiers in Cell and Developmental Biology, 8,* 697.

Katsi, V., Papakonstantinou, I., & Tsioufis, K. (2023). Atherosclerosis, diabetes mellitus, and cancer: common epidemiology, shared mechanisms, and future management. *International Journal of Molecular Sciences, 24*(14), 11786.

Lim, S. J., Yeo, I., Yoon, P. W., Yoo, J., Rhyu, K. H., Han, S. B., Lee, W. S., Song, J. H., Min, B. W., & Park, Y. S. (2018). Incidence, risk factors, and fracture healing of atypical femoral fractures: a multicenter case-control study. *Osteoporosis International, 29,* 2427-2435.

Marin, C., Luyten, F. P., Van der Schueren, B., Kerckhofs, G., & Vandamme, K. (2018). The impact of type 2 diabetes on bone fracture healing. *Frontiers in Endocrinology, 9,* 6.

Migliorini, F., Giorgino, R., Hildebrand, F., Spiezia, F., Peretti, G. M., Alessandri-Bonetti, M., Eschweiler, J., & Maffulli, N. (2021). Fragility fractures: Risk factors and management in the elderly. *Medicina, 57*(10), 1119.

Mitchell, P. J. (2022). Fracture liaison: a crucial tool in the fight against fragility fracture. *Maturitas, 165,* 26-32.

Muire, P. J., Mangum, L. H., & Wenke, J. C. (2020). Time course of immune response and immunomodulation during normal and delayed healing of musculoskeletal wounds. *Frontiers in immunology, 11,* 1056.

Niu, S., Pei, Y., Hu, X., Ding, D., & Jiang, G. (2022). Relationship between the neutrophil-to-lymphocyte ratio or platelet-to-lymphocyte ratio and deep venous thrombosis (DVT) following femoral neck fractures in the elderly. *Frontiers in Surgery, 9,* 1001432.

Schlundt, C., El Khassawna, T., Serra, A., Dienelt, A., Wendler, S., Schell, H., van Rooijen, N., Radbruch, A., Lucius, R., & Hartmann, S. (2018). Macrophages in bone fracture healing: their essential role in endochondral ossification. *Bone, 106,* 78-89.

Sheen, J. R., Mabrouk, A., & Garla, V. V. (2023). Fracture healing overview. In *StatPearls* [Internet]. StatPearls Publishing.

Shiu, H. T., Leung, P. C., & Ko, C. H. (2018). The roles of cellular and molecular components of a hematoma at the early stage of bone healing. *Journal of Tissue Engineering and Regenerative Medicine, 12*(4), e1911–e1925.

Sobh, M. M., Abdalbary, M., Elnagar, S., Nagy, E., Elshabrawy, N., Abdelsalam, M., Asadipooya, K., & El-Husseini, A. (2022). Secondary osteoporosis and metabolic bone diseases. *Journal of Clinical Medicine, 11*(9), 2382.

Soliman, A. M., & Barreda, D. R. (2022). Acute inflammation in tissue healing. *International Journal of Molecular Sciences, 24*(1), 641.

Sproston, N. R., & Ashworth, J. J. (2018). Role of C-reactive protein at sites of inflammation and infection. *Frontiers in immunology, 9,* 754.

Torres, H. M., Arnold, K. M., Oviedo, M., Westendorf, J. J., & Weaver, S. R. (2023). Inflammatory processes affecting bone health and repair. *Current Osteoporosis Reports, 21*(6), 842–853.

Upton, L. (2020). What is the effect of age on wound healing in the acute trauma setting?: A scoping review. *Wound Practice & Research: Journal of the Australian Wound Management Association, 28*(3), 115-126.

Walters, G., Pountos, I., & Giannoudis, P. V. (2018). The cytokines and microenvironment of fracture haematoma: Current evidence. *Journal of Tissue Engineering and Regenerative Medicine, 12*(3), e1662–e1677.

Wildemann, B., Ignatius, A., Leung, F., Taitsman, L. A., Smith, R. M., Pesántez, R., Stoddart, M. J., Richards, R. G., & Jupiter, J. B. (2021). Non-union bone fractures. *Nature Reviews Disease Primers, 7*(1), 57.

Yachmaneni Jr, A., Jajoo, S., Mahakalkar, C., Kshirsagar, S., & Dhole, S. (2023). A comprehensive review of the vascular consequences of diabetes in the lower extremities: Current approaches to management and evaluation of clinical outcomes. *Cureus, 15*(10).