

Association of tryptophan/kynurenine metabolites with healing in chronic venous leg ulcers

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Background

- Chronic venous leg ulcers (CVLUs) affect 2 million persons annually, including 4% of people over age 65 years.
- Chronic wound healing is a complex process of metabolomics pathway that is still not well understood.
- The tryptophan (TRP)-L-Kynurenine (KYN) pathway increased scrutiny in wound healing.
- Indoleamine 2,3-dioxygenase (IDO) which mediates Tryptophan catabolism is highly active during pathological conditions including chronic wounds.
- We utilized metabolomics to investigate the biomarker involved in the TRP-L- KYN pathway in chronic venous leg ulcers (CVLUs) healing.

Objectives

The study aims to apply metabolomics to elucidate the tryptophan (TRP)-L-Kynurenine (KYN) pathway associated with CVLUs wound healing.

Methods

Study design

- We conducted a prospective, longitudinal, and observational study.
- A total of 30 subjects who received weekly sharp debridement at a wound clinic were enrolled. We collected clinical data every two weeks during the 8 weeks of the study period.
- 60 serum samples collected from 30 older adult patients with CVLUs at baseline, week 4, and week 8 until wound closure.

Study variables

- We characterized patient-host demographic characteristics (age, sex, race/ethnicity, marital status, educational level); general health characteristics (BMI, comorbidities, antibiotics and pain medication).
- Wound factors (wound area, wound diameter, and wound days) were characterized overtime and examined their associations.

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Methods continued

Measurements

- Host factors, general health information, wound days, wound area were collected from electronic health records.
- Liquid chromatography-mass spectrometry (LC-MS) metabolomics was utilized to examine targeted metabolites.

Statistical analysis

- Distributions for each variable were examined with descriptive statistics appropriate for measurement level.
- A robust Bayesian approach was employed to examine correlations between change of metabolites and linear healing slope.

Results

- A total of 11 participants had healed wounds during the study period.
- The mean age was 71.13 (± 9.46).
- The healing group (n=23) demonstrated higher levels of mean TRP at baseline and overtime compared to the non-healing group.
- There was moderate support for a negative association between kynurenic acid and a steeper linear healing slopes ($r = -0.36$, Bayes factor: 3.70, 95% Credibility Interval = -0.62, -0.06).

Table 2. Robust Bayes correlations between change metabolomics and linear healing slope

	rho	95% CrI	Probability of Direction	% In ROPE ¹	Bayes Factor
Kynurenine*	-0.07	(-0.40,0.25)	65%	42%	0.43
Tryptophan*	0.17	(-0.13,0.50)	85%	28%	0.69
Serotonin*	-0.08	(-0.43,0.22)	68%	40%	0.45
Xanthurenic Acid*	-0.11	(-0.42,0.22)	72%	37%	0.48
Kynurenic Acid*	-0.36	(-0.62,-0.06)	99%	5%	3.70
100*(Kynurenine/Tryptophan)*	-0.23	(-0.51,0.11)	91%	19%	1.00

Note: *delta value: the difference between last and first visits, that is, last visit – first visit.

Results continued

Table 1. Sample Characteristics at baseline (N=30)

Variable	n (%)	Mean (SD)	Range
Age		71.13 (9.46)	(55,89)
CCI		5.23 (1.76)	(2,9)
BMI		35.59 (14.79)	(16.6,83.4)
Wound areas	29 (96.7%)	2823.54 (6002.93)	(35,25500)
Wound diameter	29 (96.7%)	42.8 (42.7)	(6.7,180.2)
Wound duration (days)		341.67 (538.29)	(23,2783)
Sex			
	Male	15 (50.0%)	
	Female	15 (50.0%)	
Race			
	White	25 (83.3%)	
	African American	5 (16.7%)	
Antibiotic Use			
	No	11 (37%)	
	Yes	19 (63%)	
Smoking			
	Never Smoked	13 (43.3%)	
	Used to Smoke	14 (46.7%)	
	Current Smoker	3 (10.0%)	
Healed During Study Period			
	No	19 (63%)	
	Week 4	2 (7%)	
	Week 6	5 (17%)	
	Week 8	4 (13%)	
Linear Healing Slope < 0 (Decreasing Wound Size)			
	Yes	23 (77%)	
	No	7 (23%)	

Note: Wound area: mm²

Discussion & Conclusion

- Gaining a better understanding of the associations between the TRP-L- KYN pathway and the healing of CVLUs could help to clarify the links of inflammation with the rate and success of wound healing.
- Biomarker development focused on the TRP-L- KYN pathway could be pursued, if the associations are further supported by focused research studies.
- Serum tryptophan may serve as a candidate biomarker for predicting wound healing trajectories, which can guide clinicians in making treatment decisions.
- Specifically, decreasing metabolites associated with the downstream activity of the kynurenine pathway, a pathway for tryptophan metabolism may be an indicator of healing under sharp debridement in CVLUs.