ACTIVATED COLLAGEN ACCELERATES WOUND REPAIR AND MODULATES CYTOKINE PRODUCTION IN WHOLE BLOOD AND PBMC CULTURES.

Gregory B. Pott1,2, K. Scott Beard1,2, Matthew Regulski3, and Leland Shapiro1,2

1Department of Medicine, Denver Veterans Affairs Medical Center, Denver, CO, USA. 2Department of Medicine, University of Colorado Denver, Aurora, CO. 3Wound Care Center of Ocean County, NJ.

Abstract

Several reports have shown that exogenous collagen fragments enhance wound repair through poorly understood mechanisms. CollenextrinK is an activated (fragmented) product derived from Type I Collagen that is applied topically as gel or powder to open wounds that have been infected or colonized with bacteria. In these earlier studies, topical CollenextrinK in conjunction with standard therapy accelerated wound closure more rapidly than standard therapy alone. We conducted an interim analysis of 16 patients with lower extremity diabetic ulcers. Eight patients received CollenextrinK in addition to standard treatment, and 8 received standard treatment alone. A quantitative analysis of wound healing at 14 weeks showed that CollenextrinK-treated wounds were 100% healed compared to 59.3% healing in control just-wound treatments. To examine possible mechanisms by which CollenextrinK enhances wound healing, cytokine production was assessed in 24 hours of cultures of whole blood and peripheral blood mononuclear cells (PBMC) from 10 healthy subjects. These cultures were conducted in the absence or presence of stimulation with heat-killed Staphylococcus epidermidis (S.epi) or lipopolysaccharide (LPS). In whole blood, CollenextrinK significantly increased spontaneous production of IL-1α, IL-8, IL-6, IL-10, and significantly reduced TNF-α concentrations of IL-8 (Δ) and IL-6 (○).TNF-α (○) decreased in both PBMC and whole blood. IL-10 (△) increased in both PBMC and whole blood. IL-1α (□) increased in PBMC and decreased in whole blood. CPG-induced IL-1α, IL-6 and IL-10 (△) increased in PBMC.

Background

The innate immune response is activated in wounds and includes cytokine biological effects, which are rapid and highly regulated. Cytokines act important for physiological wound healing include effects on coagulation, inflammation, epithelialization, angiogenesis, matrix and tissue remodeling, and pathogen control. CollenextrinK, comprised primarily of proteolytically cleaved collagen, is thought to accelerate wound healing by incompletely understood mechanisms. We investigated the effect of CollenextrinK on cytokine production and anti-inflammatory cytokine levels in whole blood and PBMC cultures from healthy volunteers.

Methods

Wound healing in diabetic ulcers

Sixteen patients with below-knee diabetic ulcers were treated with CollenextrinK. Eight patients (CollenextrinK group) were treated with an application of 1-0.15 g CollenextrinK powder (Wound Care Devices, LLC Florida) in addition to the standard therapy. Wounds were treated with a hydrocolloid dressing, and wound areas were quantified using analog measurement. Whole blood was harvested by venous puncture and centrifuged over Ficoll-Hypaque, and the peripheral blood mononuclear cells (PBMC) were isolated and cultured in the absence (CollenextrinK=0) or presence of CollenextrinK. After 7 days of incubation, cytokines were quantified as cytokine concentration in both whole blood and PBMC cultures. Cytokine activities important for physiological wound healing include effects on coagulation, inflammation, epithelialization, angiogenesis, matrix and tissue remodeling, and pathogen control. CollenextrinK significantly increased spontaneous production of IL-1α, IL-8, IL-6, IL-10, and IL-1β. TNF-α was suppressed. CPG-induced IL-1β, IL-6 and IL-10 (△) increased in PBMC.

Results

Diabetes-related lower extremity infections are a major clinical problem. In the U.S., 6-10% of all diabetic patients experience lower extremity ulcer infections, which result in over 50,000 amputations each year. Lower extremity diabetic ulcer care costs an estimated 1.2 billion dollars in the United States ($S) annually for treatment alone. Improved treatments for diabetic foot infections are urgently needed to prevent progression to gangrene and amputation. We treated 16 diabetic and non-diabetic patients in conjunction with standard care with CollenextrinK to assess the biological relevance of our previous clinical studies to the general wound healing process.

Discussion

Diabetes-related lower extremity infections are a major clinical problem. In the U.S., 6-10% of all diabetic patients experience lower extremity ulcer infections, which result in over 50,000 amputations each year. Lower extremity diabetic ulcer care costs an estimated 1.2 billion dollars in the United States ($S) annually for treatment alone. Improved treatments for diabetic foot infections are urgently needed to prevent progression to gangrene and amputation. We treated 16 diabetic and non-diabetic patients in conjunction with standard care with CollenextrinK to assess the biological relevance of our previous clinical studies to the general wound healing process.