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Impaired innate immune system defenses against pathogenic bacteria in diabetic wound

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Enhanced bacterial infection and microbiome shift towards pathogenic bacteria are major co-morbidities that contribute to impair wound healing in diabetic ulcer. The underlying reasons for the impaired infection control in diabetic wound remain poorly understood. We used the cutaneous full-thickness wound models in STZ-injected type 1 diabetic (T1D) rats and db/db T2D mice, to study the early dynamics of bacterial infection control in normal and diabetic wound tissues. Surprisingly, we have found that unlike chronic diabetic ulcers which suffer from persistent unresolved inflammation, the acute phase of inflammatory response which is needed for counter invading pathogens early after injury is significantly delayed in diabetic wounds, rendering these wounds susceptible to bacterial infection and healing impairment. Importantly, treatment with a pro-inflammatory chemokine jumpstarts inflammatory response and promotes healing in diabetic wound, indicating that inadequate inflammatory response early after injury in diabetic wound is just as harmful as the persistent inflammatory state that dominates these wounds as they become chronic. Our data further suggest that normal wound tissues express pathogen-specific antimicrobial peptides (ps-AMPs) that preferentially target pathogenic bacteria amongst commensals by recognizing specific virulence structure(s) that are only found in pathogenic bacteria. In contrast, pathogen-specific antimicrobial defenses are impaired in diabetic wounds, thus setting the stage for the microbiome shift towards pathogenic bacteria. We further show that the inability to control pathogenic bacteria leads to persistent inflammatory state and impaired healing in diabetic wound. We posit that inadequate chemokine expression in diabetic wound early after injury leads to delayed inflammatory response, which in turn results in reduced ps-AMPs, rendering diabetic wound vulnerable to infection with pathogenic bacteria, which exacerbate wound damage and drive diabetic wound toward persistent unresolved inflammatory state. We further propose that chemokine therapy can be used to jumpstart inflammatory response and restore antimicrobial defenses and stimulate healing in diabetic wound.

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The effect of salsalate on glucose homeostasis

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Evidences indicate that salsalate treatment improves glucose homeostasis. The aim of this study is to evaluate the effect of salsalate on glycemia. We searched PubMed for randomized trials looking at the effect of salsalate on glycemia in adults. A MEDLINE search from 01-2015 to 11-2016 was undertaken using: Salsalate (diabetes, glucose). Only randomized, placebo-controlled studies evaluating salsalate versus placebo were included. Meta-analyses were performed for differences in fasting plasma glucose (FPG) (mmol/l) and hemoglobin A1c (%) between baseline and end-of-study. The outcome was calculated as standardized mean difference (SMD) with 95% confidence interval (CI). The quality of the studies was determined by the Jadad score. The random effects model was used to calculate the combined outcome. Heterogeneity was assessed by I2 statistic. Publication bias was assessed by the trim-and-fill analysis. Literature search, data gathering and quality assessment were performed independently by 2 investigators. All graphs and calculations were obtained using Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ). We included 9 studies (N=933) reporting on fasting FPG or A1c. Salsalate dose ranged from 3 to 4.5 g per day. Study duration ranged from 4 to 120 weeks. Out of 9 studies, 8 were double blinded and 1 was single blinded. Jadad score ranged from 3-5. Salsalate therapy was associated with a greater decrease in the SMD for FPG than placebo with SMD -0.58 (95% CI -0.76 to -0.41; $p<0.001$). Heterogeneity was moderate with I2=30% (p=0.16). Sensitivity analyses by removing one study at a time showed no bias but there was publication bias. By adjusting for the four imputed studies, the difference remains significant SMD: -0.47 (95% CI -0.67 to -0.27). Salsalate was also associated with a greater reduction on the SMD for hemoglobin A1c than placebo with SMD -0.47 (95% CI -0.66 to -0.27; $p<0.001$). Heterogeneity was low with I2=20% and p=0.27. Sensitivity analysis showed no bias and there was no publication bias also. Salsalate has been marketed for pain relief since long time. One must consider these glycemic benefits in relation to potential risks. Larger randomized controlled trials are needed where the population might benefit the most.

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