Biobran (MGN-3) Concurrently Reverses Lipopolysaccharide-Induced Elevation of CD14 and Impairment of Macrophage-Mediated Bacterial Clearance in a Model of Diabetic Wound Biofilms.

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Hyperglycaemia found in type 2 diabetic patients can lead to several complications including a type of chronic wound called a diabetic foot ulcer (DFU). Diabetic foot ulcers are associated with elevated inflammatory markers but defective immune responses that can lead to microbial infection, often characterised by biofilm formation. Cereal-derived fibres called arabinoxylans have shown increased immune function in both the adaptive and innate immune responses in animal models. A cereal-derived fibre called Biobran (MGN-3) has been shown to stimulate immune cells including macrophages, T cell and dendritic cells suggesting it may be of therapeutic benefit to fight infections. This study investigated whether MGN-3 can stimulate the clearance of wound-associated bacterial biofilms under hyperglycaemic conditions and modulate levels of the pattern recognition receptor CD14 on the cell surface of M1 macrophages. Host-pathogen biofilm investigations (n=12) were performed to assess the effect of MGN-3 (0.5, 1.0 and 2.0 mg/ml for 24 hours) on the phagocytosis of both Gram-positive Methicillin resistant *Staphylococcus aureus* (MRSA) and Gram-negative *Pseudomonas aeruginosa* (PA01) biofilms by U937-derived M1 macrophages cultured in glucose-supplemented (11, 15, 20, 30mM) medium. CD14 on the cell surface of M1 macrophages was assessed by confocal microscopy and flow cytometry (n=4).

Findings showed glucose-supplementation significantly ($P<0.05$) inhibits the M1 macrophage-mediated phagocytosis of both MRSA and PA01 biofilms in a dose-dependent manner. Moreover, hyperglycaemia significantly ($P<0.05$) enhanced lipopolysaccharide (LPS)-induced M1 macrophage CD14 surface levels. Treatment of M1 macrophages with MGN-3 (0.5, 1.0 and 2.0 mg/ml) for 24 hours significantly ($P<0.05$; n=12) promoted the clearance of both MRSA and PA01 biofilms in a dose-dependent manner. Moreover, this is the first study to demonstrate MGN-3 reverses the detrimental effects of hyperglycaemia in a dose-dependent manner, significantly ($P<0.05$) increasing M1-mediated clearance of bacterial biofilms and reducing LPS-induced CD14 levels (n=4). CD14 levels significantly ($P < 0.05$; n=4) decreased after dual treatment with LPS and MGN-3 compared to just LPS treatment alone, suggesting competition was taking place between MGN-3 and LPS at the CD14 receptor on M1 macrophages. The findings of this project suggest MGN-3 may be of potential therapeutic benefit for the treatment of DFU patients with wound biofilm infections.