**Diabetes-derived circulating factors alter macrophage polarization and wound healing *in vitro***

**Aims:**

Diabetes-related foot ulcers (DFUs), a major complication with high recurrence rates, remain poorly understood in their tissue pathogenesis, including how diabetes affects macrophage polarization during wound healing. This study aimed to investigate the impact of circulating factors from individuals with DFUs or diabetes-related complications on macrophage differentiation and polarization, and its subsequent influence on wound healing *in vitro*.

**Methods:**

THP-1 cells, a monocyte cell line, and THP-1-differentiated macrophages (PMA+THP-1) were cultured with plasma from individuals with DFU exhibiting different healing outcomes, and from individuals with diabetes, either with (Dcomp+) or without (Dcomp-) retinopathy complications. Cell viability, differentiation and polarisation were analysed using flow cytometry. The impact of plasma-treated THP-1 or PMA+THP-1 cells on wound healing was assessed using an *in vitro* wound model and monitored with IncuCyte.

**Results:**

Plasma from individuals with diabetes, especially from the unhealed DFU group, reduced THP-1 cell viability. Compared to untreated cells, plasma from Dcomp+ significantly increased THP-1 cell maturation (CD68+, *p*<0.05), while plasma from individuals with DFUs, regardless of healing status, increased cell activation (CD11b+, *p*<0.0001), skewing the population toward the CD206+ M2 phenotype (*p*<0.01), particularly in the unhealed DFU group (*p*<0.05). However, opposite effects in PMA+THP-1 macrophages treated with plasma, particularly from DFUs, resulted in reduced activation, maturation, and CD163+ M2 phenotype than untreated PMA+THP-1. The plasma-treated THP-1 or PMA+THP-1 reduced *in vitro* wound closure, regardless of complications status or healing outcomes, under both normal and high glucose conditions, all compared with untreated cells (*p*<0.05).

**Conclusion:**

This study draws attention to the importance of circulating factors from people with diabetes, particularly those with complications and DFUs, when considering the impact on monocyte and macrophage profiles, and their subsequent influence on wound healing dynamics. This emphasises the potential of targeting the contrasting effects of diabetes-derived plasma on monocytes vs macrophages, warranting further investigation.