TRANSIENT EXPOSURE TO ELEVATED GLUCOSE AND FATTY ACIDS CAUSES PERSISTENT CHANGES IN ENDOTHELIAL CELL RESPONSES TO INJURY: EVIDENCE OF METABOLIC MEMORY (191)

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**Introduction:** Effects of hyperglycemia on wound repair processes remain poorly understood. Hyperglycemia contributes to diabetic complications by causing endothelial dysfunction. Unfortunately, some detrimental effects of hyperglycemia persist after glucose level normalization. Compelling evidence from large-scale clinical trials supports this phenomenon commonly known as metabolic memory. Emerging data suggest that epigenetic regulation of gene expression mediates hyperglycemia-induced metabolic memory. The purpose of this study was to determine whether hyperglycemia and hyperlipidemia induce metabolic memory in human dermal microvascular endothelial cells, known participants in angiogenesis during mammalian cutaneous wound repair. We hypothesized that transient hyperglycemia and hyperlipidemia cause sustained alteration of endothelial cell responses to injury and persistent epigenetic changes in gene expression.

**Methods:** Primary human dermal microvascular endothelial cells were seeded on study day -2 at 5x10^3 cells/cm² in Medium 131 with 5mM D-glucose. On day 0, cells were exposed to experimental conditions (GFA) with or without 30mM D-glucose, 40μM linoleic acid and 40μM oleic acid. The Control group was maintained at 5mM D-glucose without fatty acids; the Transient GFA group was exposed to GFA for two days and returned to Control conditions for the duration of the experiment and the Chronic GFA group was exposed to GFA for the duration of the experiment.

**Results:** Transient GFA caused sustained effects on endothelial cell migration, tube formation and TIMP3 gene expression. The effects on TIMP3 expression were associated with persistent changes in histone modification at the 5’ end of the TIMP3 gene, suggesting an epigenetic effect.

**Conclusion:** Overall, these results suggest that hyperglycemia/hyperlipidemia induced metabolic memory contributes to regulation of TIMP3, a key protein involved in angiogenesis after cutaneous injury, and identify a potential molecular target for therapeutic intervention for chronic non-healing diabetic wounds.