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Triglycerides, to target or not to target in DKD - basic point of view

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In contrast to a discrete metabolite such as glucose, plasma lipids are composed of dozens of distinct molecules. For example, combinations of various acyl chains esterified to a glycerol backbone generate numerous unique triacylglycerols (TAGs). We previously found that lipid HUFA content can change rapidly, increasing in plasma TAGs within two hours of various glycolytic stimuli, including oral glucose ingestion, sulfonylurea administration, and exercise (Rhee et al., 2011). The delta-5 desaturase (D5D) and delta-6 desaturase (D6D), encoded by *FADS1* and *FADS2* respectively, are required for the synthesis of highly unsaturated fatty acids (HUFAs) which are then esterified into cellular lipids. D5D and D6D are located in the endoplasmic reticulum membrane and have cytosol- facing catalytic domains; they are highly expressed in the kidney and liver. Our recent findings advance knowledge of metabolism along several axes. First, they show that polyunsaturated fatty acid desaturation increases in response to a reduction in the cytosolic NAD^+/NADH ratio. Second, they characterize this response as a novel mechanism for glycolytic NAD^+ recycling that operates in parallel with lactate fermentation and is acutely adaptive *in vivo* when aerobic respiration is impaired. In this role, the importance of polyunsaturated fatty acid desaturation expands beyond the downstream biologic roles of HUFA end-products. Third, our results provide mechanistic insight on how variants in the monocarboxylate transporter SLC16A11 may impact cellular HUFA production, and thus contribute to the pathogenesis of type 2 diabetes.

Rhee, E.P., Cheng, S., Larson, M.G., Walford, G.A., Lewis, G.D., McCabe, E., Yang, E., Farrell, L., Fox, C.S., O'Donnell, C.J., et al. (2011). Lipid profiling identifies a triacylglycerol signature of insulin resistance and improves diabetes prediction in humans. *J. Clin. Invest.* 121, 1402-1411.