# Patellar tendon biomechanical and morphologic properties and their relationship to serum lipids in persons with prediabetes and type 2 diabetes

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**INTRODUCTION:** Type 2 diabetes (T2D) is a multifactorial and progressive disease affecting over 38 million Americans, with an estimated 98 million more having prediabetes. T2D is characterized by insulin resistance, hyperglycemia, and dyslipidemia, which negatively impact the musculoskeletal system. Tendons are particularly affected by diabetes. Individuals with T2D exhibit a 3–4-fold increased risk of tendon injuries compared to individuals without diabetes. Further, clinical imaging has revealed disorganized tendon fibers in up to 89% of patients with diabetes. Such structural disruptions contribute to degenerative tendon disorders, which are challenging to treat in the context of diabetes. These injuries prolong rehabilitation, reduce quality of life, and impose a significant economic burden. Furthermore, impaired tendon health can prevent individuals from maintaining an active lifestyle, exacerbating cardiometabolic risk, and further diminishing quality of life.

**METHODS:** Serum samples from individuals without diabetes, (n=12, 2 males and 10 females, age: 49 yrs, Body Mass Index (BMI): 24, Hemoglobin A1c (HbA1c): 5.3%), prediabetes (n=8, 4 males and 4 females, age: 57 yrs, BMI: 28, HbA1c: 5.8) or type 2 diabetes (n=18, 11 males and 7 females, age: 63, BMI: 32, HbA1c: 7.8) underwent lipid extraction using the Bligh and Dyer method. This project was approved by the Purdue University IRB (#IRB-2025-721). The extracts were analyzed using a triple quadrupole mass spectrometer (Agilent 6410)**,** employing a multiple reaction monitoring profiling approach. In the same subjects, short echo-time enhanced $T_2$-star ($T_2$*) was completed on the patellar tendon using a 3T Siemens MAGNETOM Prisma system with a 3T Tx/Rx 15 Channel Knee Coil to determine $T_2$* relaxation time. A lower $T_2$* relaxation time reflects highly organized collagen, while higher $T_2$* values indicate disruption of fibers. Patellar tendon tangent modulus was assessed using ultrasound methodologies and by plotting the relationship between *in vivo* stress and strain. Lipid samples were matched to their respective donors' *in vivo* patellar tendon properties. Statistical analysis included calculation of relative fold changes and t-tests to determine significance. Lipids showing significant alterations underwent lipid ontology enrichment analysis. Identified lipids were correlated to previously collected *in vivo* patellar tendon measures. We also used elastic net regularization to identify serum biomarkers that best explain variations in tendon properties. The magnitude of associations between biomarkers and tendon properties was interpreted using regression coefficients, with $R^2$ values indicating the variance explained by each model.

**RESULTS:** We identified lipid species unique to the nondiabetic (n=4), prediabetic (n=11), and diabetic (n=10) populations (**Fig. 1**). Direct group comparisons revealed nine upregulated lipids in the prediabetic group and 71 lipids in the diabetic group compared to the nondiabetic group. Additionally, there were 39 differentially expressed lipids when comparing the diabetic group to the prediabetic group. The top five over expressed lipids in the diabetic group compared to the nondiabetic where phosphatidylcholine 42:10, triglyceride (TG) 52:10 neutral lipid (NL) 18:1, diglyceride (DG) 36:3, TG 51:12 NL 18:0, and acylcarnitine 18:0 (**Fig. 2A.**). The top five lipids when comparing the prediabetic and diabetic group were DG 36:3 NL 18:1, TG 52:19, DG 40:5, TG 46:2 NL18:2, TG 49:7 (**Fig. 2B.**). The elastic net regularization of all lipids found that accounting for TG 46:2 NL 18:2, TG 48:3 NL 18:1, and DG 36:3 NL 18:1 and their 2-way interactions explained 18% of variation in tendon modulus. The elastic net regularization identified 13 unique lipid pairs, which, when found in abundance, accounted for 22-36% of the variation in $T_2$* values.

**DISCUSSION:** The identified lipids regulate cellular function, fatty acid transport, lipid storage, energy transport, and insulin sensitivity, playing a crucial role in regulating pathways that likely contribute to tendon complications. Furthermore, these paired lipid interactions appear to contribute to some of the variance in tendon modulus and collagen fibril organization. As we identify lipids or other serum molecules associated with tendon properties, future work using cell culture and animal models can explore the role of these compounds in regulating tenocytes.

**SIGNIFICANCE/CLINICAL RELEVANCE:** The identification of these key lipids will enable a rigorous characterization of their influence on tendon cell signaling and proliferation. Furthermore, this will serve as the foundation to drive clinical interventions towards specified lipid pharmacological regulators to improve tendon health and patient outcomes.

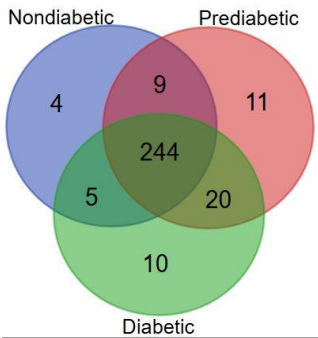


*Figure 1:* Venn Diagram of lipids unique and shared between nondiabetic, prediabetic, and diabetic groups.

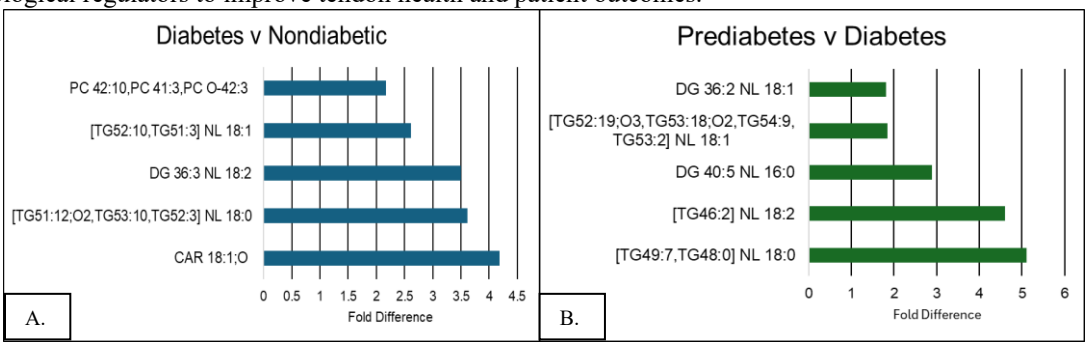


*Figure 2:* Top 5 differentially expressed lipids between the diabetic and nondiabetic groups (A.) and the prediabetic and nondiabetic groups (B.). Liquid chromatography-mass spectrometry generated absolute intensity values for each sample and used them to calculate the fold difference of lipid species between groups. These lipids represent the highest fold difference among significant lipids $p<0.05$.
Phosphatidylcholine (PC), Triglyceride (TG), Diglyceride (DG), Neutral Lipid (NL), Acylcarnitine (CAR).