Serum non-esterified fatty acid (NEFA) composition and longitudinal changes in beta-cell function

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Background

- Elevated NEFA concentrations are associated with incident type 2 diabetes (T2DM)(1–3), however NEFA are comprised of physiologically diverse species.
- Limited longitudinal data exist on total and individual NEFA in the progression of metabolic disorders underlying diabetes.
- Our **objective** was to study the longitudinal associations of NEFA concentrations and individual NEFA species with 6-yr changes in insulin sensitivity (IS), beta-cell function, and insulin clearance.

Methods: Prospective Metabolism and Islet Cell Evaluation cohort

- Adults at-risk for diabetes were recruited from Toronto and London, ON and followed every 3-yrs. A total of 3 visits were collected (6-yrs follow-up)
- An OGTT was conducted at each visit (3 blood samples: 0, 30, 120 min) to measure glucose, insulin, and fasting NEFA (n=477).
- NEFA were quantified at baseline using thin layer chromatography and gas chromatography, and both mol% and concentration values were analyzed.
- The primary outcomes were computed from the glucose and insulin from the OGTT: 1/HOMA-IR and ISI (Matsuda Index) for IS (4,5); Insulinogenic index over HOMA-IR (IGI/IR) and Insulin Secretion-Sensitivity Index-2 (ISSI-2) for beta-cell function (6,7).
- A secondary outcome was insulin clearance (IC), using insulin-to-C-peptide ratio based on all values from the OGTT.
- Generalized estimating equations was used adjusted for waist, sex, ethnicity, baseline age, family history of diabetes, and ALT.
- P-values were adjusted using the False Discovery Rate to correct for multiple testing.

Results: Brief overview

- Over the 6-yr period, the primary outcomes decreased between 8.7% to 19.5%
- Of the NEFA, palmitic acid, oleic acid, and linoleic acid comprised the majority (74.1%) of the pool (Figure 1).
- Strong correlations were seen between certain NEFA (e.g. 16:0, 16:1n-7, 14:0, and 14:1n-7 were all strongly correlated with each other; Figure 2).
- From the GEE analysis (Figure 3), no fatty acids were associated with IS; associations were only seen with beta-cell function. Palmitic acid, linoleic acid, and total NEFA were negatively associated with beta-cell function. Only docosahexaenoic acid was negatively associated with IC, though weakly. No associations were seen for NEFA as a mol%.
- There were *no time-by-NEFA* interactions with any of the outcome variables.
- The lowest tertile of total NEFA concentration had consistently the highest beta-cell function over the 6-yrs (Figure 4).

Results: Distribution of NEFA

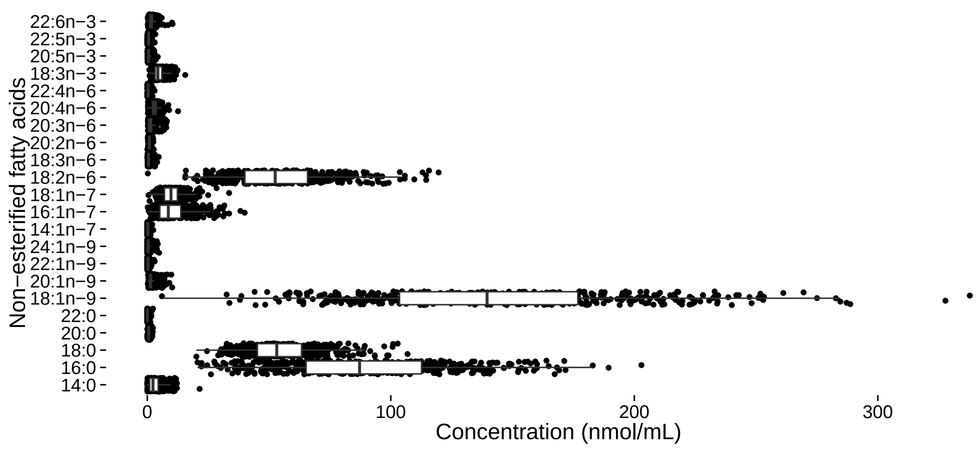

Figure 1: Distribution of non-esterified fatty acid species in absolute concentrations. Dots represent individual data points, while the boxes represent the median and interquartile range.

Results: Correlations of fatty acids within NE fraction

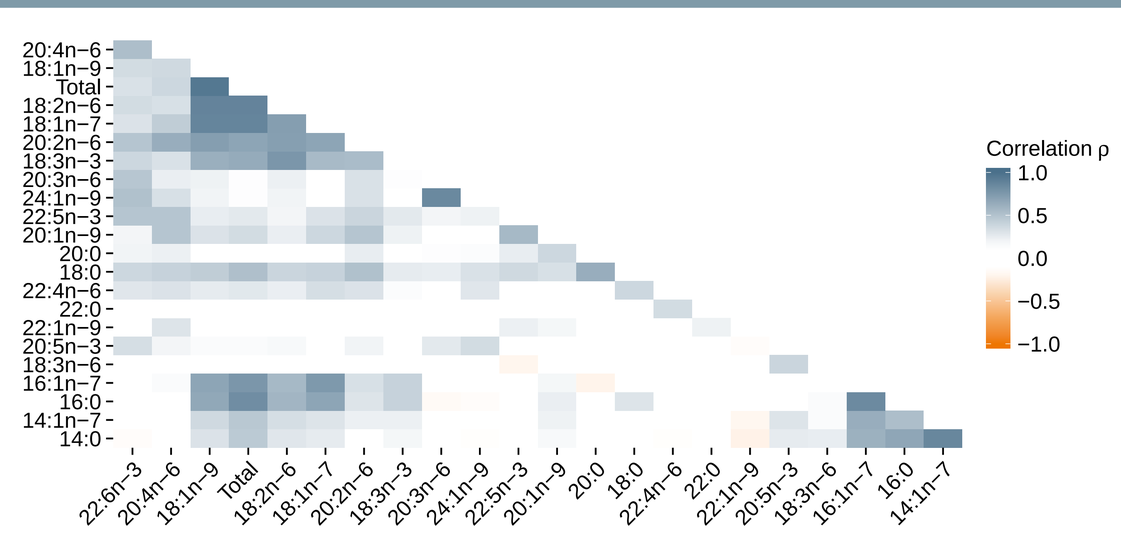

Figure 2: Heatmap of Pearson correlations between individual NEFA.

Conflict of Interest Disclosure:

This poster does not contain trade names. It also does not cover any unapproved uses of specific drugs, other products or devices.

Results: GEE analysis

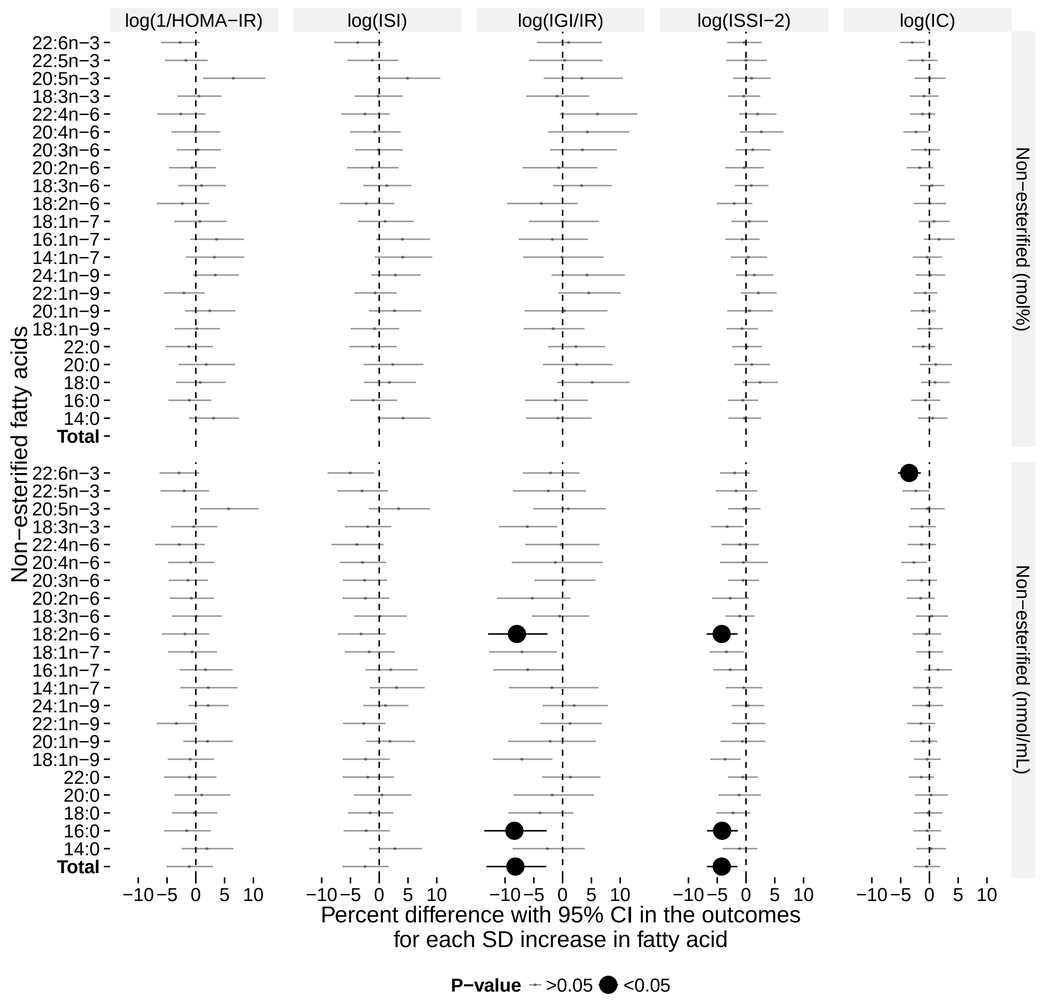

Figure 3: Longitudinal associations of non-esterified fatty acids with insulin sensitivity, beta-cell function, and insulin clearance over a 6-yr period. GEE models adjusted for sex, ethnicity, waist, baseline age, ALT, and family history of diabetes. P-values were adjusted for multiple testing using the False Discovery Rate.

Results: GEE results of total NEFA with beta-cell function

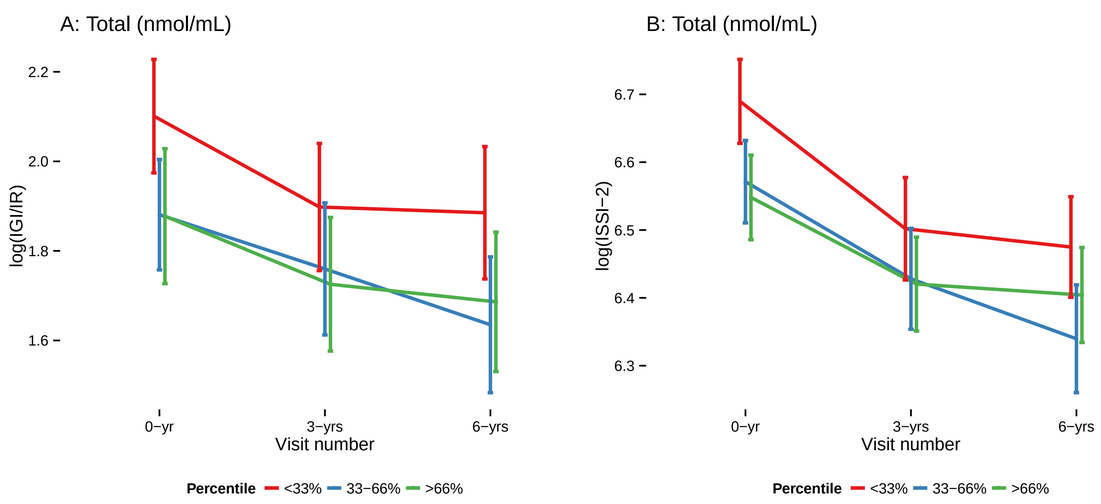

Figure 4: Predicted marginal means (lsmeans) of total NEFA with beta-cell function from the adjusted GEE models. Coloured lines represent tertiles of total NEFA concentration.

Discussion

- While palmitic acid and linoleic acid as a concentration had a negative association with beta-cell function, these associations were likely driven by the negative association seen with total NEFA and beta-cell function. This is confirmed in light of the mol% results.
- Our novel findings emphasize that higher total NEFA, irrespective of the FA composition, associate with lower beta-cell function and that this observation is consistent longitudinally. The role of NEFA on beta-cell function is consistent with literature suggesting that beta-cells are particularly sensitive to lipotoxicity (2).

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