Identifying Diagnostic Serum Biomarkers For Depression in Patients with Type 2 Diabetes

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Background

People with Type II Diabetes Mellitus (T2DM) are almost twice as likely develop symptoms of depression than nondiabetics(1-4). This statistic is reflected in studies completed all over the world crossing cultural, ethnic, and regional lines. The aim now is to find the link between these diseases. Studies have shown shared psychosocial (2), inflammatory (5), neuroendocrine (6) and neurovascular (7) pathophysiology are being pursued.

T2DM involves widespread lipid dysmetabolism (8-10) and depression is strongly associated with the lipid composition of diet (13). This includes the altered fluctuations in omega-6 and omega-3 polyunsaturated fatty acids that we acquire from our diet and especially in the cytochrome p450 epoxygenase - soluble epoxide hydrolase (sEH) metabolism pathway. sEH derived oxylipins – small signalling lipid molecules that can be found in the plasma (11) – fit neatly into the inflammation model of diabetes and depression comorbidity. It stands to reason that these may be potential candidates for disease biomarkers.

Oxylipins are formed from the both omega-6 and omega-3 fatty acids. These PUFAs are initially broken down to their acid metabolites (e.g. arachidonic acid, linoleic acid) and, these, in turn are converted to smaller epoxides, ketones, diols and other oxygenated molecules.

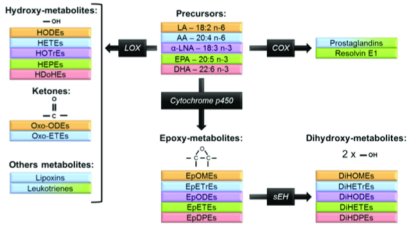

Figure 1. Enzymatic oxylipin synthesis pathways. Oxylipins are synthetized from fatty acids, such as linoleic acid (LA), arachidonic acid (AA),α-linolenic acid (α-LNA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) through three main enzymatic pathways.

Hypothesis

I hypothesize that there will be higher fatty acid diols and lower fatty acid epoxides will be found in the blood of T2DM patients experiencing a depressive episode than those who are not, and that sEH derived oxylipin concentrations will be associated with the severity of depressive symptoms.

Methods

- **Study design:** Cross-sectional observational study of participants enrolled in the Sunnybrook Type 2 Diabetes Study (S2DS)
- **Participants:** Participants from the Sunnybrook Type 2 Diabetes Study (NCT04455867) experiencing a major depressive episode (n=20) were matched 1:1 for age, sex, and body mass index to participants without a current depressive episode
- **Depression status:** Measured using the Structured Clinical Interview for DSM-5, Research Version (SCID-5-RV)
- **Depression severity:** Beck Depression Inventory, 2ndedition (BDI-II) questionnaire

Methods Continued

- **Exploratory Mood Questionnaires:** Perceived Stress Scale (PSS-10), Behavioral Inhibition Scale/ Behavioral Approach Scale (BIS/BAS), and Temporal Experience of Pleasure (TEPS).
- **Oxylipin quantification:** Unesterfied serum oxylipins assayed from fasting blood by ultra-high pressure liquid chromatography tandem mass spectrometry
- **Statistics:** Effect sizes (Cohen's *d*) were calculated for differences in oxylipin concentrations between participants with and without a depressive episode, and they were compared using t-tests. Correlations between oxylipins and depression severity were assessed using Spearman's rho.

Results

Our results support a lipidemic profile of oxylipin biomarkers of **worsening depressive symptoms with increased diols and reduced epoxides.**

Demographics	Current Depressive Episode (n=20) M±SD or N (%)	No Current Depressive Episode (n=20) M±SD or N (%)	*p*
Age (years)	57.2± 9.4	60.6± 7.3	0.209
Sex (%women)	13 (65%)	13 (65%)	0.999
BMI (kg/m²)	32.8 ± 6.1	31.3 ± 5.9	0.438
Weight (kg)	92.1 ± 22.9	86.0 ± 19.7	0.371
Diabetes Duration (years)	78 ± 12.4	8.5 ± 12.4	0.871
Antidepressant Use	10 (50%)	4 (20%)	**0.047**
Aspirin Use	5 (25%)	3 (15%)	0.429
Statin Use	11 (55%)	11 (55%)	0.999
Fasting Glucose (nmol/L)	6.8 ± 1.8	7.0 ± 1.8	0.723
Fasting Insulin (pmol/L)	61.9 ± 73.4	58.6 ± 28.2	0.857
HbA1c (%)	7.0 ± 1.0	7.1 ± 0.8	0.807
HOMA-IR	3.0 ± 4.4	2.7 ± 1.6	0.810

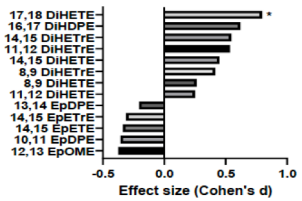

Figure 2. Differences in oxylipins between patients with and without a depressive episode (n=40), expressed as effect sizes (Cohen's *d*). Only oxylipins with *d* >| 0.2 | are shown. Bars marked with an asterisk (*) were significant at an uncorrected p-value <0.05.

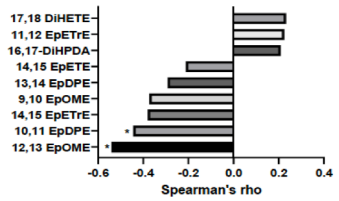

Figure 3. Spearman's rho for correlations between oxylipins and total BDI-II scores in the depressed group (n=20), where rho > |0.2| are shown. Correlations marked with an asterisk (*) were significant at an uncorrected p-value <0.05.

Results Contd.

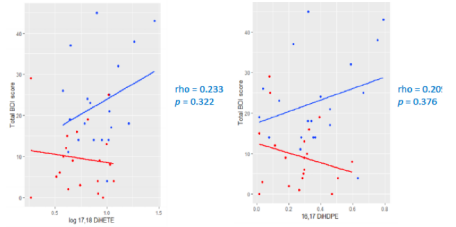

Figure 4. Correlations between depression severity (BDI-II scores) and select sEH-derived diols in T2DM patients. (Blue: with depressive episode; red: without depressive episode.)

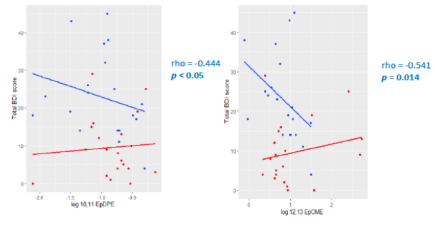

Figure 5. Correlations between depression severity (BDI -II scores) and select CYP450-derived epoxides in T2DM patients. (Blue: with depressive episode; red: without a depressive episode.)

- PSS scores and individual serum oxylipin measures do not show as a consistent story, however, in the non-depressed group epoxides are positively correlated with scores.
- TEPS correlations are comparatively consistent in both non-depressed and depressed groups: both diols and epoxides are negatively correlated with scores. TEPS scatterplots had several R values exceeding 0.4 including 5,6-DiHETrE and 5,6-DiHETrE/EpETrE.
- BIS correlations did not exhibit particularly consistent or strong rho values. In the non-depressed group, 8,9-DiHETrE is negatively correlated with a rho value exceeding |0.2| and statistically significant.
- BAS exhibited very consistent trends; overwhelmingly, the individual oxylipin measures had positive correlations with BAS. The scatter plots reflect the trends of the Spearman's tests: almost all diols and epoxides have a positive slope.

Discussion

- This cross-sectional study showed that oxylipins in the cytochrome p450-soluble epoxide hydroxylase pathway measured from the peripheral serum have a possible association with depression state and severity of depressive symptoms.
- sEH inhibition has also been effective in reducing inflammation.In a recent Nature paper, epoxide 11,12-EpETrE was associated with vascular relaxation. 12,13-DiHOME and 9,10-DiHOME were linked to a shift towards a pro-inflammation state (15).
- Elevated 12,13-DiHOME/EpOME and 9,10-DiHOME/EpOME is associated with White Matter Hyperintensities in the brain and vascular cognitive impairment. This suggests that the worsening of depressive symptoms in our patients as 12,13-DiHOME and 9,10-DiHOME are elevated may be mediated through the widely hypothesized neurovascular degeneration. There is significant evidence to suggest neurovascular dysfunction as the basis of Major Depression (7).
- The over-expression of sEH in the liver, where it is the most abundant in humans, is positively associated with depressive symptoms in mice. The enhanced breakdown of 14,15-EPETrE into its diol means many of its protective functions are lost (15).
- We were able to exhibit several potential diagnostic biomarkers which are easily collected and assayed to improve the management and treatment – both pharmacological and non-pharmacological – outcomes of depression.
- Our results do reflect the limited current human and animal studies that surround soluble epoxide hydrolase and mood, however, this study is limited by the lack of dietary PUFA intake data which we know can affect serum levels of their metabolites (35-36). Moreover, exercise can affect the lipidemic profile by mobilising oxyilpns especially those involved in inflammation and oxidative stress (16-17).

Reference Link