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

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Abstract

This cross-sectional study aimed to show the potential of oxylipins in the cytochrome p450-soluble epoxide hydroxylase pathway measured from the peripheral serum as a potential biomarker for depression in patients with Type II Diabetes Mellitus. These findings would have significant clinical value as diabetic patients are upto two-fold as likely to experience depressive symptoms which hampers their treatment and long-term health outcomes. Some recent clinical and animal studies have shown that soluble epoxide hydrolase derived oxylipin metabolites of omega-3 and omega-6 polyunsaturated fatty acids may mediate this relationship. These oxylipins are associated with neurovascular, neuroendocrine, and neurodegenerative pathophysiology. We conducted self-report questionnaires to assess patients' mood to determine their state and severity of depression. Additional mood assessments served to indicate anhedonia, stress response and perception of pleasure as exploratory measures. We analysed the relationship between symptoms of depression and their severity with individual serum oxylipin values and ratios of sEH derived diols to CYP450 derived epoxides in 20 depressed and 20 non-depressed individuals. Our results support a lipidemic profile of oxylipin biomarkers: worsening depressive symptoms with increased diols and reduced epoxides. We also discuss the potential of soluble epoxide hydrolase inhibition as a therapy against mood deterioration.

Background and Relevance

Diabetes is a severe metabolic disease that affects an individual throughout their lifetime, requiring chronic care and management. It occurs when the pancreas does not produce enough insulin or when the body cannot effectively make use of the insulin it produces. As of 2014, it is estimated 422 million people have diabetes and this number is on the rise (1). Diabetes is delineated into two groups: Type I Diabetes Mellitus (T1DM) which is an autoimmune condition that destroys pancreatic cells and Type II Diabetes Mellitus (T2DM) which results from somatic cells becoming insulin insensitive. There are broad range economic and social impacts of diabetes. Moreover, the individual and clinician level consequences are not insignificant.

Diabetes can cause complications in systems across the body and increase the chance of early mortality significantly (2). Diagnosing, treating and managing diabetes is a significant burden to both patients, caregivers and clinicians. There is vast research in these areas and somatic interventions are becoming available and diverse. However, there is a psychiatric comorbidity that is not very well understood but whose newly uncovered statistics tells a harrowing story.

People with Type II Diabetes Mellitus (T2DM) are almost twice as likely develop symptoms of depression than non-diabetics (3-6). 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 (4), inflammatory (7), neuroendocrine (8) and neurovascular (9) pathophysiology are being pursued.

T2DM involves widespread lipid dysmetabolism (10-12) 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 (14) – fit neatly into the inflammation model of diabetes and depression comorbidity. It stands to reason that these may be potential candidates for disease biomarkers.

There is some research into the association of sEH and psychiatric diseases, however human studies are sparse. In patients who experience winter depression state, they have elevated soluble epoxide hydrolase diols and one epoxide substrate is decreased in plasma levels compared to their summer non-depressed state (15). Patients with Anorexia Nervosa exhibited higher CYP derived oxylipin products and diol to epoxide ratios, which suggests that sEH activity is elevated, compared to control and recovered anorexia nervosa patients (16). Post-Morten studies have also shown that patients with MDD and other psychiatric disorders have elevated sEH expression and sEH derived oxylipins (17).

Without strong evidence of the role of oxylipins in psychiatric disorders in human models, we cannot identify potent, standardised diagnostic biomarkers. Elucidating the role of these specific bio markers may help address the mood symptoms of psychiatric disorders and their comorbidities such as diabetes. Moreover, they will solidify sEH inhibitors as potential prophylactic and treatment of depression and other psychiatric disorders.

The past two summers, I have worked under the supervision of Dr. Walter Swardfager of the Hurvitz Brain Sciences Program at the Sunnybrook Research Institute in Toronto, Canada, towards identifying associations amongst sEH derived lipid biomarkers and depressive symptoms in diabetic patients.

Hypothesis and Objective

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.

Biochemical Background

Oxylipins are small lipophilic signaling molecules derived from the oxidation of poly-unsaturated fatty acids. They can be short lived and long lived, found in tissue such as liver, adipose and kidney, as well as blood and urine. There are various enzyme catalyzed pathways that produce the diverse array of oxylipins, most significantly the pathways including lipoxygenases (LOX), cyclooxygenase (COX) and the cytochrome-soluble epoxide hydroxylases (CYP-sEH). The last of these is the focus of this paper.

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. This is shown in more detail in **Supplementary Biochemical Figures (14).**

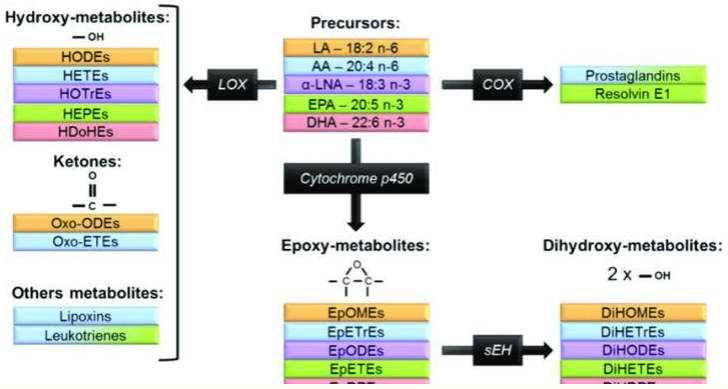

Figure 1. Enzymatic oxylipin synthesis pathways. Oxylipins are synthetized from fatty acids, such as linoleic acid (LA), arachidonic acid (AA), α-linolenic acid (α-LNA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) through three main enzymatic pathways. The cyclooxygenase pathway (COX) produces prostaglandins and resolvins from AA and EPA. The lipoxygenase (LOX) pathway produces hydroxy - metabolites, such as hydroxyoctadecadienoic acids (HODEs), hydroxyeicosatetraenoic acids (HETEs), hydroxyoctadecatrienoic acids (HOTrEs) and hydroxydocosahexaenoic acid (HDOHEs). Leukotrienes, lipoxins and ketones, such as oxo-octadecadienoic acids (oxo-ODEs) and oxo-eicosatetraenoic acids (oxo-ETEs), are also synthetized through the LOX pathway. Finally, the cytochrome p450 pathway generates epoxy-metabolites, such as epoxyoctamonoemoic acids (EpOMEs), epoxyeicosatrienoic acids (EpETrEs), epoxyoctadecadienoic acids (EpODEs), epoxyeicosatetraenoic acids (EpETEs) and epoxydocosapentaenoic acids (EpDPEs). These epoxy-metabolites can be converted via the soluble epoxide hydrolase (sEH) to their respective diols, dihydroxyoctadecamonoenoic acids (DiHOMEs), dihydroxyeicosatrienoic acids (DiHETrEs), dihydroxyoctadecadienoic acids (DiHODEs), dihydroxyeicostetraenoic acids (DiHETEs) and dihydroxydocosapentaenoic acids (DiHDPES). On this figure, precursors and their respective metabolites share the same color code. Adapted from Zivkovic et at. (2012).(18)

These oxylipins, thereby, act as signatures of PUFA metabolism, intake and fluctuations in the body.

Research Methodology

Over the course of two six-week periods in the summer of 2019 and 2020, I and my fellow students in the lab built a database of patient assessment results which included mood and cognitive assessments, medical history, drug charts and blood lipid profiles. Once compiled, the database was analysed to select our participants based on their depression and other demographic criteria.

Participants and Exclusion Criteria: Sunnybrook Type 2 Diabetes study participants experiencing a major depressive episode were matched 1:1 for age, gender and body mass index to participants with T2DM patients without a current depressive episode. During assessments, patients who have type 1 diabetes, prior diagnoses of schizophrenia or bipolar disorder, neurodegenerative diagnoses, pregnancy, active cancer, or a current or past substance use disorder (within the last five years, excluding nicotine), and/or inability to give consent were excluded. In the end we had a research cohort of 20 depressed and 20 non-depressed patients.

Serum Measurements: Blood plasma concentrations of sEH derived oxylipin products of dietary omega-3 and omega-6 fatty acids were measured using UPLC-MS/MS following solid-phase extraction. Fasting blood glucose (FBG) was measured via glucometer (Bayer, Mississauga, ON, Canada). Insulin was measured using an enzyme-linked immunosorbent assay or ELISA (Toronto, ON, Canada).

Depression Criteria: The presence of a depressive episode at the time of study participation was identified using the Structured Clinical Interview for DSM-5 criteria, Research Version (SCID-5-RV). This structured interview is a widely used diagnostic tool, and exhibits moderate to excellent validity and reliability (19-20). To be classified as currently depressed, patients had to exhibit two key symptoms of depression: diminished mood or decreased interest/pleasure (anhedonia).

Additionally, patients needed to have at least four of the following symptoms, lasting nearly every day for a period of at least two weeks:

- weight or appetite changes (unrelated to diet or exercise)
- hypersomnia or insomnia
- psychomotor agitation or retardation
- energy or ability to think
- difficulty concentrating or making decisions
- feelings of worthlessness or guilt
- recurring thoughts of death, suicidal ideation, planned or attempted during the last month.

Depression Severity and Symptom: Using several self-report mood questionnaires, we were able to correlate worsening mood outcomes with measures of individual oxylipins in the blood and ratios of sEH product and substrate. We investigated using the following assessments:

- Beck Depression Inventory 2nd Edition (BDI-II): this is a 21-question self-report questionnaire that assesses the cognitive, somatic, and affective symptoms of depression, such as indecisiveness, guilt, worthlessness, loss of pleasure and suicidal thoughts (21). It has been shown to be an effective and reliable measure of depression symptom severity in patients with T2DM (22)
- Perceived Stress Scale (PSS-10): this is a 10-question self-report questionnaire and most widely used survey that assesses the perception of stress and identifies how unpredictable, uncontrollable, and overloaded respondents experience their daily lives (23). PSS-10 is validated and reliable in T2DM populations (24)
- Behavioral Inhibition Scale/ Behavioral Approach Scale (BIS/BAS): this is a 20-item scale assessing both Gray's Behavioral Inhibition Scale (BIS) and Behavioral Activation Approach Scale Systems (BAS) (25). These items produce a global BIS score and three BAS subscales assessing drive, fun seeking, and reward responsiveness. BIS/BAS has been used as a measure of mood decline and sensitivity in diabetic populations (26).
- Temporal Experience of Pleasure Scale (TEPS): this is an 18-question self-report questionnaire that captures anticipatory and consummatory facets of pleasure, although in recent studies, we have seen that in non-Western populations specifically in Chinese populations, TEPS may capture four factors (consummatory contextual, consummatory abstract, anticipatory contextual, and anticipatory abstract pillars of pleasure) (27-28).

Statistical Analysis: Differences in demographic and clinical characteristics between groups with and without a current depressive episode were tested with independent samples t-tests for continuous variables and chi-squared tests for dichotomous variables. Serum oxylipin measures were compared between depressed and non-depressed matched cohorts by their effect sizes (Cohen's d). Differences in serum oxylipin measures were evaluated by independent samples t-tests. If skewness or kurtosis was detected, oxylipins were log-transformed prior to analyses. Correlations between oxylipins and depressive symptoms were explored using Spearman's rho. All values that are described as significant are significant at an uncorrected p-value of less than 0.05. All analyses were conducted using IBM SPSS Version 24, 25, 26 and 27.

Results

Our comparison of the means of individual oxylipin serum measures in the CYP450-sEH pathway between depressed and non-depressed groups showed a consistent pattern: diols in the depressed group were elevated compared to the non-depressed and the epoxides were reduced. Eight of these diols and five of these epoxides had a Cohen's d modulus value higher than 0.2. 17,18-DiHETE was statistically significant in this difference. The sEH product and substrate ratios all showed a positive equilibrium shift towards product in the depressed group compared to the non-depressed group. Five out of the eight detected had a Cohen's d modulus value higher than 0.2.

The bivariate correlations of the BDI scores and individual oxylipin serum measures demonstrated a similar trend to the means comparison: diols have a positive and epoxides have a negative Spearman's Rho values when comparing depressed to non-depressed. This means as BDI scores increase, i.e. worsening depression symptom severity, diols are elevated in the peripheral serum and epoxides are reduced. Three of the diols and six of the epoxides have Spearman's Rho modulus values higher than 0.2. 10,11-EpDPE and 12,13-EpOME, both epoxides, are significant. sEH product and substrate ratios show a positive correlation with BDI scores, four of which have Rho values greater than 0.2. It should be noted 12,13-DiHOME/EpOME has the highest positive rho and is statistically significant. However, notably 11,12-DiHETrE/EpETrE is negatively correlated with BDI scores.

The scatter plot curves of BDI scores (y) against individual epoxides (x) has either negative slopes with R values exceeding 0.3 (but not 0.4) or weakly positive or stagnant slopes. Most notably 14,15-EpETrE, 13,14-EpDPE and both EpOMEs show moderate strength slopes. In the case of individual diols (x), the slopes are either positive with R values exceeding 0.3 (but not 0.4) or weakly negative or stagnant slopes. Two diols with stronger curves are 16,17-DiHDPA, 17,18-DiHETE. In the non-depressed curves, the slopes of the vast majority were in the same direction but not as strong as its partner depressed curve. Notably, the 13,14-EpDPE non-depressed slope had a comparable R value as its depressed. The scatter plots of the ratios showed a positive slope for most of the depressed curves. The strongest to note would be 14,15-DiHETrE/EpETrE, 16,17-DiHDPA/EpDPE and both the DiHOME/ EpOME ratios. The non-depressed showed weak slopes.

The bivariate correlations of the 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. The highest positive rho value and one of the few that crosses 0.2 is of 16,17-EpDPE. In the depressed group, there is not a noticeable trend demarcating diols and epoxides;14,15-EpETrE is the significant value and has the highest positive rho. But it is the only AA metabolite that is negatively correlated. In the non-depressed group, the ratios show mostly negative correlations. In the depressed group, the correlations are less distinct, however, there are two statistically significant values:14,15-DiHETrE/EpETrE and 19,20-DiHDPA/EpDPE. Interestingly, the former has a positive correlation and the latter a negative correlation.

The PSS (y) scatter plots against individual serum oxylipin measures (x) and ratios (x) did not have any notable differences between epoxides and diols. Amongst the depressed curves, there were four slopes with R values above

0.3: 19,20-EpDPE, 16, 17-DiHDPA, 14,15-DiHETrE/EpETrE and 5,6-DiHETrE/EpETrE. One depressed curve had a slope with R value above 0.4: 19,20-DiHDPA/EpDPE. Interestingly, 19,20-EpDPE, 16, 17-DiHDPA, 14,15-DiHETrE/EpETrE are upward sloping and the remaining two are downward sloping.

The bivariate correlations of TEPS values and individual serum oxylipin measures are comparatively consistent in both non-depressed and depressed groups: both diols and epoxides are negatively correlated with scores. However, 9,10-DiHOME has a positive correlation in the non-depressed group of rho value approximating 0.4. 5,6-DiHETrE and 13,14-EpDPE are significant in non-depressed with rho values between -0.5 and -0.6. Depressed correlations seem to be more consistent with only three very weak negative correlations. The correlations of ratios do not indicate any consistent trends but the interestingly 5,6-DiHETrE/EpETrE is positive (rho>0.2) in the depressed group and negative (rho<-0.2) in the non-depressed group.

The scatter plots for TEPS scores (y) against individual serum oxylipin measure (x) and product/substrate ratios (x) show several moderate strength R values in both depressed and non-depressed. The below tables are a summary of the most notable ones:

Oxylipin individual measure or ratio	Curve	Slope
5,6-EpETrE	Depressed	Negative
11,12-EpETrE	Depressed	Negative
19,20-EpDPE	Non-depressed	Positive
16,17-EpDPE	Non-depressed	Negative
13,14-EpDPE	Non-depressed	Negative
11,12-DiHETrE	Non-depressed	Negative
11,12-DiHETE	Depressed	Negative
14,15-DiHETE	Depressed	Negative
5,6-DiHETrE/EpETrE	Depressed	Positive
11,12-DiHETrE/EpETrE	Depressed	Positive
9,10-DiHOME/EpOME	DEpressed	Negative

Table 1. Description of the TEPS scatter plot curves with R value exceeding 0.3.

Oxylipin individual measure or ratio	Curve	Slope
5,6-DiHETrE	Non-depressed	Negative
5,6-DiHETrE/EpETrE	Depressed	Negative

Table 2. Description of the TEPS scatter plot curves with R value exceeding 0.4.

The bivariate correlation graphs of the Inhibition score of the BIS/BAS, i.e. the global BIS score, 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. In the depressed group, there is some suggestion of positive correlation of BIS scores with epoxide serum levels. Overall, the ratios exhibit a negative correlation with BIS scores meaning reduced diol production from epoxides is associated with increased inhibition scores.

The scatter plots of global BIS scores (y) against individual oxylipins (x) and ratios (x) provide a more exploratory view of their relationships. The below table are a summary of the most notable of these:

Oxylipin individual measure or ratio	Curve	Slope
14,15-EpETrE	Depressed	Positive

14,15-DiHETrE/EpETrE	Depressed	Negative
14,15-EpETE	Depressed	Positive
14,15-EpETE	Non-depressed	Positive
14,15-DiHETE/EpETE	Depressed	Negative
11,12-EpETrE	Depressed	Negative
11,12-DiHETrE	Non-depressed	Negative
19,20-EpDPE	Non-depressed	Positive
16,17-DiHDPA/EpDPE	Non-depressed	Positive (R=0.4)
9,10-EpOME	Non-depressed	Positive

Table 3. Description of the BIS scatter plot curves with R values exceeding 0.3.

Most of the scatter plot curves of epoxides show a positive trend with BIS scores. Notably, 8,9-DiHETrE had a negative sloping non-depressed curve with an R value exceeding 0.4.

The bivariate correlations of the Activation scores or BAS scores of the BIS/BAS exhibited very consistent trends; overwhelmingly, the individual oxylipin measures had positive correlations with BAS. However, the depressed group had many more oxylipin correlations of Rho exceeding 0.2 than non-depressed. The ratios showed mostly weak negative correlations. It should be noted, 11,12-DiHETrE/EpETrE shows an uncharacteristically large positive correlation (Rho ~ 0.4) in non-depressed group. In the depressed group only two show a positive correlation but they are the only ones that exceed Rho = 0.2: 19,20-DiHDPA/EpDPE and 5,6-DiHETrE/EpETrE.

The scatter plots reflect the trends of the Spearman's tests: almost all diols and epoxides have a positive slope. The ratios that have a moderate R value rather than a weak value are the positive values although the majority of the ratio lopes are negative.

Oxylipin individual measure or ratio	Curve	Slope
19,20-EpDPE	Non-depressed	Positive
19,20-DiHDPA/EpDPE	Depressed	Positive
5,6-DiHETrE	Non-depressed	Positive
5,6-DiHETrE/EpETrE	Non-depressed	Positive
11,12-DiHETrE	Non-depressed	Positive
11,12-DiHETE	Depressed	Positive
16,17-DiHDPA	Non-depressed	Positive

Table 4. Description of the BAS scatter plot curves with R values exceeding 0.3.

Oxylipin individual measure or ratio	Curve	Slope
16,17-EpDPE	Depressed	Positive
19,20-DiHDPA	Depressed	Positive
8,9-DiHETrE	Non-depressed	Positive
11,12-DiHETrE/EpETrE	Non-depressed	Positive

Table 4. Description of the BAS scatter plot curves with R values exceeding 0.4.

To view the completed document of the results, please download these documents:

1. Comparison of means and BDI data (correlation and scatterplots), Supplementary tables describing data
2. Bivariate Correlation presented as graphs for PSS, TEPS, and BIS/BAS
3. Scatterplots for PSS, TEPS, and BIS/BAS

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. Moreover, this study explores the possible associations of these oxylipin with the anhedonia, reward seeking, pleasure and stress perception aspects of depression. Seven diol and five epoxide pairs have shown promise as potential diagnostic serum biomarkers for depressive state in both non-depressed and depressed cohorts. These potential biomarkers are also involved in the different mood aspects of depression explored here.

In our analysis, we found that 17,18-DiHETE, 16,17-DiHDPA, 14,15-DiHETrE, 11,12-DiHETrE are elevated and 12,13-EpOME and 14,15-EpETrE are reduced in the peripheral serum of depressed patients compared to non-depressed patients. The ratios of 12,13-DiHOME/EpOME, 9,10-DiHOME/EpOME, 14,15-DiHETrE/EpETrE and 16,17-DiHDPA/EpDPE have a positive association with worsening depressive symptoms. 19,20-DiHDPA/EpDPE and 11,12-DiHETrE/EpETrE show a negative association with worsening depressive symptoms. Our exploration into the various mood facets of depression such as anhedonia, stress perception and activation/inhibition responses strengthen the role of these oxylipins and ratios as potential mediators of the link between diabetes and depression and diagnostic serum biomarkers of depression. It is not, however, an individual indicator that reveals these links or determines mood outcomes: this study is joining recent studies in shaping an oxylipin and enzyme action profile of patient bloodwork that can act as a signature of disease state.

Shifts in oxylipin mixtures in the blood can account for inflammatory response changes and sensitivity to other pro-inflammatory markers. 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 (29). Moreover, we have seen that Epoxides limit the accumulation of pro-inflammatory chemicals and are actively involved in the resolution of inflammation via autocrine/paracrine action:14,15-EpETrE and 11-12-EpETrE have been highlighted as such as anti-inflammatories (30). In the same study, 9,10-EpOME and 12,13-EpOME fluctuations in concentrations at site of inflammation suggest that sEH substrate utilisation may play a role in inflammation resolution that is not yet understood. These oxylipin roles are elucidating an inflammation model of diabetes-depression lipidemic link.

Recent preclinical data suggest that sEH-derived oxylipins may be involved in microvascular complications of T2DM and microangiopathic changes in older patients can be related to depression (31). 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 (9). This is a particularly important avenue for follow-up and Nuclear Magnetic Resonance Imaging studies are required to confirm this association.

A recent mouse study with both in vitro and in vivo analysis showed the potential of decreased epoxide clearance by sEH as a prevention of Blood Brain Barrier (BBB) injury. 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. 14,15-EpETrE diminishes Reactive Oxygen Species (ROS) formation which protects against mitochondrial dysfunction and oxidative stress(32), two biochemical shifts that are linked to depression (33)

A recent nature paper discussed the progression of blindness associated with 19,20-DIHDPA in patients with diabetic retinopathy. DHA conversion to 19,20-DiHDPA leads to endothelial junction disruption in the retina. This

paper too associated disease progression with over-expression of sEH and prevented by sEH inhibition (34). Our study exhibited association of this specific diol with more activation responses to novel stimulus in depressed patients. 19,20-EpDPE, contrary to the expected functionality of epoxides, is associated with worsening stress perception and inhibition response to novel stimulus. The diol/epoxide ratio showed a significant and strong negative correlation to stress perception. This unexpected result may be due to the diabetic dyslipidemia leading to diverting the diol towards the eye's vasculature; substrate utilization prevents the diols cytotoxic effects that lead to severe depressive symptoms.

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 oxyilipns especially those involved in inflammation and oxidative stress (37-38).

The clinical targets of this paper were to provide evidence for the potential of sEH inhibition as a therapy for deteriorating mood outcomes and depressive symptoms in T2DM patients. Moreover, 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. It is difficult to build a somatic diagnostic profile of depression and in vulnerable patients such as diabetics; these difficulties lead to many people suffering from this comorbidity to remain undiagnosed and untreated. Our study included some oxylipins with promising effect sizes and correlations however to fully build a lipidemic profile of depression in diabetic patients and identify pharmacological targets, more clinical research into larger populations is required and with controls to account for confounders such as diet and exercise.

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