RESEARCH LETTER

# Changes in serum oxylipin profile after one anastomosis gastric bypass

Alicja Pakiet[1], Paulina Łukaszewicz[1], Monika Proczko-Stepaniak[2], Łukasz Kaska[2], Adriana Mika[1,3]

1 Department of Environmental Analysis, Faculty of Chemistry, University of Gdansk, Gdańsk, Poland
2 Department of General, Endocrine and Transplant Surgery, Faculty of Medicine, Medical University of Gdansk, Gdańsk, Poland
3 Department of Pharmaceutical Biochemistry, Faculty of Pharmacy, Medical University of Gdansk, Gdańsk, Poland

**Introduction** Polyunsaturated fatty acids (PUFAs) are precursors of oxylipins, which are involved in the regulation of inflammation, epithelial function, vasoconstriction, blood clotting, adipogenesis, lipolysis, and insulin secretion[1]. This makes them interesting when studying diseases associated with impairment of the abovementioned functions. Obesity is characterized by a state of low-grade chronic inflammation that contributes to further metabolic dysfunction.

Oxylipin levels can be affected by dietary interventions that directly increase the amount of precursors available for n-3 oxylipin synthesis.[2] Modifications of oxylipin profiles are also observed after introducing diets that are not specifically aimed at modulating PUFA levels, for example, low-calorie or low-fat diet.[3] There is also a small number of studies showing changes in the oxylipin profile after a bariatric intervention.[4] Considering the regulatory effects of oxylipins, it is possible that they contribute to metabolic changes observed after bariatric surgery.

In this study, we analyzed the profile of non-esterified oxylipins in the serum of patients with obesity who underwent laparoscopic one anastomosis gastric bypass (OAGB) surgery for the first time.

Correspondence to:
Adriana Mika, PhD,
Department of Pharmaceutical Biochemistry, Faculty of Pharmacy, Medical University of Gdansk,
ul. Dębinki 1, 80-211 Gdańsk,
Poland, phone: +48 58 523 51 90,
email: adrianamika@tlen.pl
Received: August 2, 2023.
Revision accepted: November 15, 2023.
Published online: November 20, 2023.
Pol Arch Intern Med. 2023; 133 (12): 16610
doi:10.20452/pamw.16610


**Patients and methods** **Standards and consumables** All oxylipin standards were purchased from Santa Cruz Biotechnology (Dallas, Texas, United States), with the exception of Mar1, Mar2, PDX, $RvE_1$, and deuterated oxylipins obtained from Cayman Chemical Company (Ann Arbor, Michigan, United States). Nomenclature for all the compounds is given in Supplementary material, *Table S1*, and analyte structures are presented in Supplementary material, *Figure S1*. Standards for gas chromatography-mass spectrometry (GC-MS) analysis (37 FAME MIX and 19-methylarachidic acid) were purchased from Sigma-Aldrich (Saint Louis, Missouri, United States). Solid phase extraction (SPE) of oxylipins was carried out on a 12-port vacuum manifold using Strata C18-E cartridges (3 ml, 200 mg of sorbent) from Phenomenex (Torrance, California, United States).

**Patients** This study was conducted according to standards set in the Declaration of Helsinki, and the study protocol was approved by the local Bioethics Committee at the Medical University of Gdansk (NKBBN/493/2016). Written informed consent was obtained from all patients upon enrolment.

This single-center study included 15 bariatric patients (3 men and 12 women) who underwent OAGB at the Department of General, Endocrine and Transplant Surgery, Medical University of Gdansk, Poland, between 2016 and 2018. Metabolic characteristics of the patients are included in Supplementary material, *Table S2*. The patients were treated when their body mass index (BMI) was above 35 kg/m$^2$ with comorbidities or above 40 kg/m$^2$ without comorbidities. Inclusion criteria followed the Interdisciplinary European Guidelines on Metabolic and Bariatric Surgery.[5] Patients with diseases of the gastrointestinal tract, known autoimmune, inflammatory, or infectious diseases, cancer or tumor regression less than 5 years ago, known kidney disease, or excessive alcohol consumption, and pregnant women were excluded. Before surgery, the patients followed a low-calorie, high-protein, low-fat, and low-carbohydrate reduction diet. After OAGB, they were prescribed vitamin D supplementation. No specific n-3 PUFA supplements were recommended.

Fasting blood was obtained from all 15 patients before the surgery (pre-OAGB), at 2-week

follow-up (FU1) and at 6–9-month follow-up (FU2). After centrifugation, serum was aliquoted into 2-ml polypropylene tubes and stored at –80 °C until extraction of oxylipins using SPE and analysis with liquid chromatography-tandem mass spectrometry (LC-MS/MS).

**Solid-phase extraction procedure** Prior to extraction, each 300-µl serum aliquot was spiked with 10 µl of butylated hydroxytoluene (0.2 mg/ml in methanol) to minimize oxidization, and with 10 µl of 1 µg/ml internal standard stock solution. The extraction of oxylipins from serum was carried out using a method described by Galvão et al.[6] Briefly, 1.5 ml of cold acetonitrile-methanol mixture (1:1, v/v) was added to spiked serum samples, vortexed, and incubated at 4 °C for 30 minutes. The samples were centrifuged (20 min, 4 °C, 1800 rpm), and supernatant was collected into soda-lime glass tubes and diluted with 17 ml of ultrapure water. The solutions were loaded onto SPE cartridges preconditioned with 2 ml of methanol, followed by 2 ml of 0.1% acetic acid. The sorbent bed was washed with 2 ml of 0.1% acetic acid and the compounds of interest were eluted with 2 ml of 0.1% acetic acid in methanol. The solvent was evaporated under nitrogen stream and oxylipins were diluted in 50 µl of methanol supplemented with 0.1% acetic acid (3:1, v/v). The samples were immediately placed in a cooled autosampler (4 °C) and analyzed within 12 hours from preparation.

**Liquid chromatography-tandem mass spectrometry** Analyses were performed using a Shimadzu LCMS-8050 analyzer (Kyoto, Japan) in a negative ionization mode. Working parameters were optimized individually for each standard in direct infusion experiments, and are summarized in Supplementary material, *Table S3*. Instrument conditions are given in Supplementary material, *Table S4*. Injection volume was 10 µl. Chromatographic separation was carried out on a Hypersil GOLD column (100 × 2.1 mm, 3-µm particle size) equipped with a guard column (Thermo Fisher Scientific, San Jose, California, United States). The column oven was set at 35 °C. Binary gradient consisted of solvent A (0.1% formic acid in water) and solvent B (methanol) at a flow rate of 0.3 ml/min. The gradient started from 50% solvent B maintained for 2 minutes, then the amount of solvent B was linearly increased to 60% at 12 minutes, to 70% at 13 minutes, to 80% at 16 minutes, to 85% at 24 minutes, and then lowered back to 50% at 25 minutes. The column was equilibrated with 50% solvent B for 5 minutes. The MS/MS instrument operated in a multiple transition monitoring mode (MRM), and transitions with the highest intensity were used for quantification. The analytical method was characterized and validated in terms of linearity, intra- and interday precision and accuracy, method detection limit (MDL), lower method quantification limit (MQL), and SPE recoveries. The method validation details are given in Supplementary material, and final method characterization is presented in Supplementary material, *Tables S5* and *S6*.

**Fatty acid analysis with gas chromatography-mass spectrometry** For GC-MS analysis, lipids were extracted from 300 µl of serum (with 40 µg of 19-methylarachidic acid added as an internal standard), using 15 ml of chloroform-methanol mixture (2:1, v/v). The lipid extracts were hydrolyzed to release free FAs, which were then derivatized into FA methyl esters (FAMEs) with 0.5 ml of 10% boron trifluoride in methanol. FAMEs were analyzed with a GCMS-QP 2010SE analyzer (Shimadzu), and chromatographic separation was performed on the Zebron ZB-5MSi capillary column (Phenomenex, Torrance, California, United States), as described previously.[7] FA identification was performed using FAME reference standards and the NIST/EPA/NIH Mass Spectral Library (NIST 11) - 2012 Mass Spectral Database for Windows, Standard Reference Data Program (United States Department of Commerce, National Institute of Standards and Technology, Gaithersburg).

**Data handling** Chromatographic peak integration was done with LabSolutions 5.99 software (Shimadzu). Univariate statistical analysis was performed using SigmaPlot 14.5 package (Systat, Software Inc., San Jose, California, United States). For variables with normal distribution, confirmed by the Shapiro–Wilk test, repeated measure 1-way analysis of variance was performed, while for non-normally distributed variables the Friedman test was executed instead; these were followed by a post hoc test with the Holm–Sidak method. For all tests, $\alpha$ was set at 0.05, and for each numerical $P$ value given, the minimal test power was above 0.800. If the power of the test was below 0.800, the post hoc tests were not performed. Values in tables are means (SD) or medians (interquartile range [IQR]), if not normally distributed. The Pearson product moment correlation coefficient was calculated for normally distributed variables, and the Spearman rank order correlation was employed for variables that did not follow normal distribution. Principal component analysis (PCA) was performed using MetaboAnalyst 4.0 software (https://www.metaboanalyst.ca/), with the Hotelling T2 range of 95%. Prior to the analysis, the data were log-transformed and scaled by mean centering and divided by SD of a given variable.

## Results

**Quantification of serum oxylipins in one anastomosis gastric bypass patients** The SPE-LC-MS/MS method enabled detection of 19 serum oxylipins in the bariatric patients. Quantification was possible for 10 metabolites of arachidonic acid (ARA), 3 metabolites of linoleic acid (LA), and 1 metabolite of dihomo-γ-linoleic acid (DGLA). Mean concentrations of the quantified serum oxylipins are given in Supplementary material, *Table S7*. Concentration of the only PUFA

n-3 oxylipin, 18-hydroxyicosapentaenoic acid (18-HEPE), was determined. The calculated concentrations of oxylipins were in line with their previously reported serum concentrations,[2,3,8,9] and ranged from below 0.4 nmol/l (lipoxin A4) to around 32 nmol/l (12-hydroxyeicosatetraenoic acid [12-HETE]). Apart from ARA-derived 12-HETE, other hydroxyeicosatetraenoic acids did not exceed the level of 5 nmol/l. The patients had also high serum concentrations of LA oxylipins, that is, 9- hydroxyoctadecadienoic acid (9-HODE) and 13-HODE (up to around 12.2 nmol/l and up to around 18.6 nmol/l, respectively), in comparison with the other analytes.

**Influence of one anastomosis gastric bypass on serum oxylipin concentration** Next, we performed the analysis of variance for 2 follow-ups to detect changes in serum oxylipin concentration in bariatric patients who underwent OAGB. The *P* values for all oxylipins studied are given in Supplementary material, *Table S6*. Concentrations of oxylipins that differed significantly depending on blood collection time, together with concentrations of respective FA precursors are summarized in FIGURE 1. Two weeks after OAGB, the patients exhibited significantly higher levels of 2 ARA-derived hydroxyeicosatetraenoic acids (20-HETE, 12-HETE), 12-hydroxyheptadecatrienoic acid (12-HHT), and thromboxane B2 (TXB2) than before the operation (FIGURE 1A). At FU2, serum concentrations of the majority of affected ARA oxylipins, similarly to the concentration of ARA itself, were lower than at FU1 and close to preoperative values. Notably, at FU2, serum 12-HHT and TXB2 concentrations were still higher than before the surgery. Among LA-derived oxylipins, no significant differences were detected (Supplementary material, *Table S7*). The mean serum concentration of 13-HODE was significantly higher at FU2 than at FU1, as was the serum content of its precursor, LA. A significant decrease in the serum concentration of DGLA metabolite, 15-hydroxyeicosatrienoic acid (15-HETrE), was also detected at FU2 (FIGURE 1B), and this correlated with a decrease in BMI ($r = 0.526$; $P = 0.008$).

Concentrations of oxylipins that were 50% above the MDL, calculated from the calibration curve or extrapolated and replaced by constant if below lower MQL, were analyzed jointly, in order to establish if the entire profile of analyzed oxylipins differentiates the patients before and after the treatment. The PCA of the data showed separation between the study groups, and the strongest separation was observed between pre-OAGB and post-OAGB patients along the PC1 (Supplementary material, *Figure S3A*), with no clear separation of FU1 and FU2 patients. Surprisingly, despite a more than 2-fold decrease in 12-HETE concentration at FU2 vs its pre-OAGB levels, this variable's contribution to the model was not crucial (Supplementary material, *Figure S3C*). In the PCA, the variables with the strongest contribution to the PC1, which explained 25.1% of variance, were ARA metabolites: prostaglandins (15d-PGJ2, PGE2, PGD2), TXB2, and 12-HHT. The second component (PC2) explained 14.6% of variance in the dataset, and 13-HODE and 20-HETE had the largest effect on this component (Supplementary material, *Figure S3C*).

Lastly, we calculated correlations between inflammatory parameters (C-reactive protein [CRP]) and 2 measures of weight loss in bariatric surgery, that is, percentage of total weight loss (%TWL) and excess weight loss (%EWL). Correlation analysis results are presented in Supplementary material, *Table S8*. CRP level correlated negatively with 13-HODE concentration. Both %TWL and %EWL showed a significant negative correlation with 5-HETE and 20-HETE. Moreover, there was a weak positive correlation between %EWL and 9,10-epoxy-12-octadecenoic acid (9(10)EpOME). 15-HETrE also negatively correlated with %EWL.

**Discussion** SPE-LC-MS/MS allowed for quantitative analysis of 20 serum oxylipins, with MQL ranging from 2 to 395 pg. For most analytes, the extraction efficiency was between 80% and 120%, consistent with other studies.[10] In the serum samples, we quantified 13 analytes and identified further 5. Data visualization using the PCA revealed the heterogeneous nature of oxylipin profiles, which was reported before.[3,4,8,9] The direction of changes in the concentration of specific oxylipins at FU2 was similar to that previously reported in studies on the blood oxylipin profile after weight reduction[4,8,11] or described for patients with obesity and individuals with normal BMI.[9] In the case of 15d-PGJ2 and PGE2, the measured concentrations were higher than those obtained in other studies.[8] 15d-PGJ2 is a peroxisome proliferator-activated receptor γ agonist and was detected in vivo during resolution of inflammation.[12] Two of our patients exhibited higher than expected concentrations of this oxylipin before OAGB. However, we suspect this is not typical for a wider obese population and was probably due to inflammation in these specific patients, which is why that result should be interpreted with caution. High concentration of PGE2, which is an inflammatory mediator and a stimulant of leptin secretion in adipose tissue, was also previously associated with obesity.[13] The concentration of 15-HETrE described in this study correlated positively with BMI, which supports the results of other studies on a link between oxylipin levels and obesity indexes.[14]

The bariatric patients exhibited proinflammatory oxylipin profile before OAGB. Across the study, the patients displayed relatively high levels of hydroxy-ARA metabolites (5-, 12-, and 20-HETE), commonly observed in conditions associated with an inflammatory state.[15] When considering the effect of OAGB on oxylipin levels, we noticed that most of the changes followed the fluctuations in the levels of their precursors, FAs. However, oxylipin concentration did not necessarily correlate significantly with FA content,

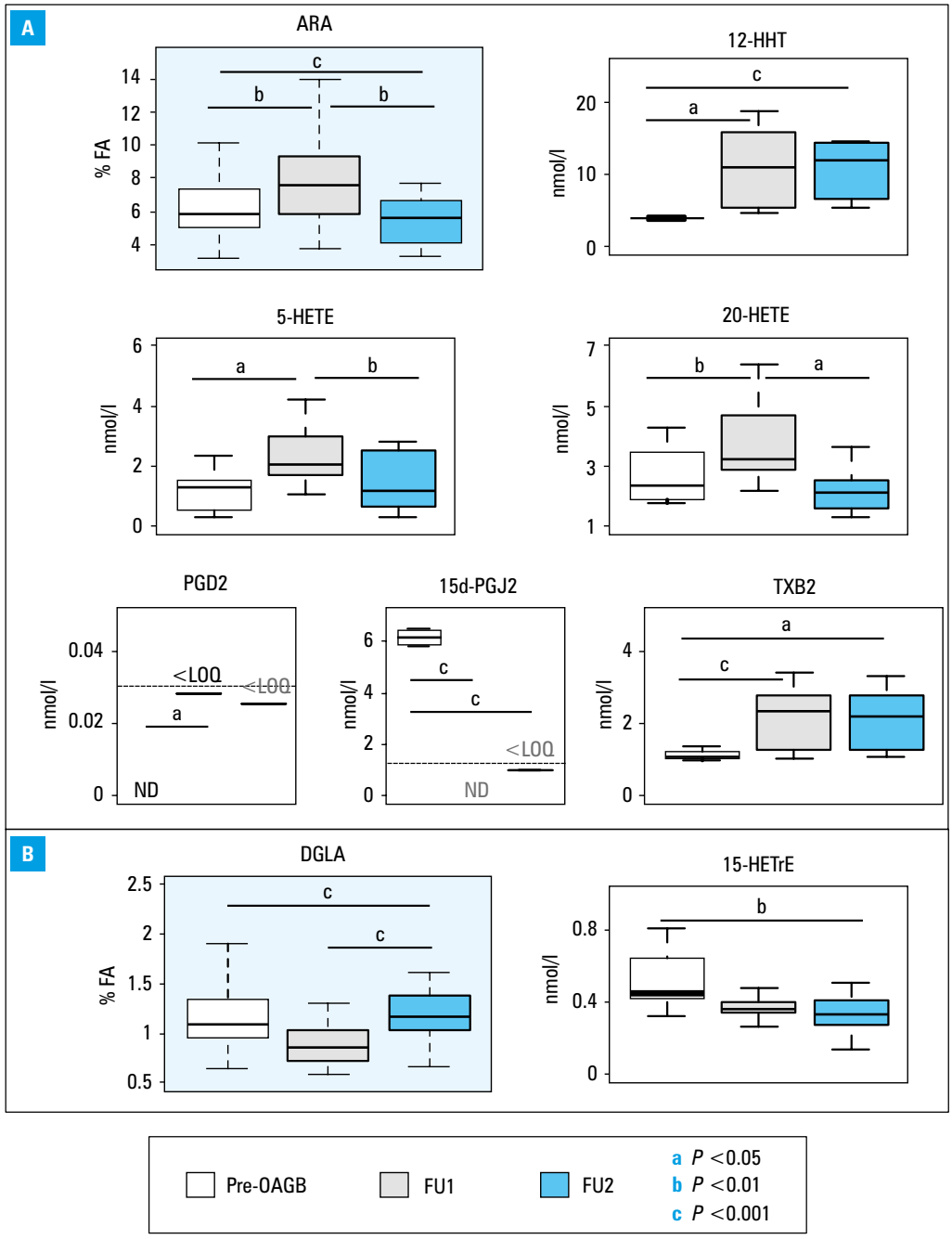


**FIGURE 1** Serum concentration of significant oxylipins in bariatric patients before (pre-one anastomosis gastric bypass [OAGB]), 2 weeks after (follow-up 1 [FU1]), and 6–9 months after (FU2) OAGB surgery.
Values are presented as box plots, where bold horizontal line represents the median, box hinges represent the 1st and 3rd quartile, whiskers are 1.5 interquartile range. Plots with shaded background represent serum parent fatty acid content (%, as measured with gas chromatography-mass spectrometry) of ARA-derived oxylipins (**A**) and dihomo--γ-linoleic acid-derived oxylipins (**B**). Dotted line represents the method quantification limit (MQL). *P* values were derived from repeated measure 1-way analysis of variance followed by a post hoc test with the Holm–Sidak method. The concentrations of oxylipins were calculated only if above 50% of the serum samples were above the MQL.
For details on the number of samples refer to Supplementary material, *Table S7*.
Abbreviations: ARA, arachidonic acid; DGLA, dihomo-γ-linoleic acid; HETE, hydroxyeicosatetraenoic acid; HETrE, hydroxyeicosatrienoic acid; HHT, hydroxyheptadecatrienoic acid; LOQ, limit of quantification; ND, nondetected; PG, prostaglandin; TX, thromboxane

which was also noted by Schuchardt et al.[16] This highlights the need for a direct analysis of oxylipins instead of relying on inference from respective FA levels. At FU1, the concentrations of 5-HETE and 20-HETE were higher than before OAGB. High serum 5-HETE levels were previously reported shortly after bowel resection.[17] This oxylipin is synthetized by 5-lipoxygenase (5-LOX). Upregulated expression of 5-LOX was observed before in adipose tissue of patients with obesity.[18] The activity of 5-LOX is important in chronic and acute inflammation,[18] therefore a high concentration of 5-HETE in OAGB patients can be a marker of short-term escalation of

inflammation after surgery. Apart from 5-HETE, we also saw a tendency for increased concentration of another 5-LOX downstream oxylipin, leukotriene B4, at FU1. After OAGB, there was an increase in 12-HHT, a ligand of leukotriene B4 receptor 2 (BLTR2). The 12-HHT/BLTR2 axis is involved in regeneration and repair of intestine endothelium, and thus it is possible that 12-HHT increase may counteract the surgical trauma inflicted on the gastrointestinal tract. Similar trauma can be the reason for increased concentration of 20-HETE, the production of which is connected with endothelial dysfunction.[15] Some HETEs (5-HETE, 12-HETE) were indicated as factors activating neutrophil chemotaxis, essential in wound healing.[17] Notably, the levels of these analytes strongly and negatively correlated with %TWL and %EWL, which indicates them as potential markers of weight loss, however, this speculation needs further studies. In murine models, 20-HETE increased significantly in animals on high-fat diet, suggesting that higher levels of this compound contribute to obesity.[19] In contrast with the results obtained for 5-HETE, we did not observe significant differences in 12-HETE levels between pre-OAGB and FU1, however, elevated concentration of 12-HETE was demonstrated 1[20] and 4[17] days after the surgery, suggesting that specific HETE concentrations may fluctuate depending on the time span.

OAGB affected also serum concentrations of oxylipins involved in regulation of the vascular endothelium and blood coagulation, that is, TXB2, 15d-PGJ2, and HODEs. TXB2 is a stable product of TXA2, which is an important platelet agonist. Therefore, the observed increase in TXB2 concentration at FU1 may reflect ongoing healing. At this time point, we detected an expected, given the healing process, decrease in the level of 15d-PDJ2, which inhibits angiogenesis,[15] and a declining trend in LA oxylipins (9-HODE, 9(10)-EpOME and 13-HODE). These LA-derived metabolites play a role in angiogenesis and vasoconstriction.[15] At FU1, we found a nonsignificant decrease in the 13-HODE concentration, which is consistent with the observation of short-term changes in oxylipin profile after laparoscopic bowel surgeries.[17]

We were unable to detect so-called special pro-resolving mediators (SPMs) comprising resolvins, maresins, and protectins, present at very low concentrations.[10] Several SPMs were previously detected in the serum of people with obesity.[18] Therefore, considering ongoing healing and inflammation resolution at FU1, we suspected significant changes in the SPM concentrations. This expectation was not confirmed, since the levels of SPMs did not exceed MDLs. Recently, Shebb et al[10] claimed that several research groups did not detect SPMs in biological materials despite optimal experimental conditions. Nonetheless, it must be noted that the oxylipin profile is affected by numerous conditions, such as age, sex, medications, or diet, which could contribute to discrepancies in SPM analysis.

The oxylipin profile was further used in PCA models to visualize the influence of OAGB on the serum oxylipin concentrations. In contrast with the FA profiles,[7] the quantified oxylipins allowed us to discriminate the results of the pre-OAGB patients from those at follow-up.

In this study, we aimed to characterize the serum oxylipin profile in patients with obesity and to analyze the influence of OAGB on the levels of these metabolites. To our knowledge, this is the first study in which the MS-based oxylipin profiling was performed after OAGB. The most surgery-affected compounds were ARA hydroxy-metabolites, which are associated with regulation of the endothelial function. The study has some limitations, the main of which is the small sample size. As we did not include a healthy, lean control group, we could only describe changes in the oxylipin profile following the surgical treatment. Expanding the study group size would provide an opportunity to account for additional factors such as sex, diet, medications, level of physical activity, compliance with pre- and post-surgery recommendations, etc. All of these factors may potentially affect the oxylipin profile, which hampers generalization of the study results to the wider population. Our analyses clearly indicate that oxylipin profiling might be useful in monitoring the effects of bariatric treatment and possibly helpful in developing new treatment regimes. In our panel, the levels of 3 oxylipins, 5-HETE, 20-HETE, and 9(10)-EpOME, correlated with weight loss. Although the exact reason for these associations needs to be elucidated, these oxylipins might influence the degree of post-OABG weight loss.

Monitoring the oxylipin profile to provide new insights into the patients' inflammatory and oxidative stress status, vascular tone, or endothelial function, may lead to, for example, minimizing obesity complications and better understanding of effective treatment strategies on an individual level. Future studies should focus on expanding the panel of assessed analytes by adding more metabolically relevant oxylipins. The MS-based metabolomics allows for robust and reproducible profiling of oxylipins, and the available methods are continuously improved in order to facilitate translation of preliminary studies into clinical practice. It would be also interesting to include a healthy, lean control group, which would help elucidate the association between oxylipins and obesity. And lastly, implementation of longer follow-ups and/or additional weight loss strategies, such as diet of physical activity regimens could certainly be useful in terms of assessing the efficacy of bariatric surgery.

## SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

## ARTICLE INFORMATION

**ACKNOWLEDGMENTS** We would like to thank Shim-POL A.M. Borzymowski for making the Shimadzu LCMS-8050 analyzer available for our research.

**FUNDING** This research was funded by the National Science Centre of Poland, Grant Number NCN 2016/21/D/NZ5/00219; to AM. Financial support was also provided by Polish Ministry of Research and Higher Education under Grant DS 531-T010-D690-23.

**CONFLICT OF INTEREST** None declared.



**HOW TO CITE** Pakiet A, Łukaszewicz P, Proczko-Stepaniak M, et al. Changes in serum oxylipin profile after one anastomosis gastric bypass. Pol Arch Intern Med. 2023; 133: 16610. doi:10.20452/pamw.16610

## REFERENCES

1 Gabbs M, Leng S, Devassy JG et al. Advances in our understanding of oxylipins derived from dietary PUFAs. Adv Nutr. 2015; 6: 513-540.

2 Shearer GC, Walker RE. An overview of the biologic effects of omega-6 oxylipins in humans. Prostaglandins Leukot Essent Fatty Acids. 2018; 137: 26-38.

3 Möller K, Ostermann AI, Rund K, et al. Influence of weight reduction on blood levels of C-reactive protein, tumor necrosis factor-α, interleukin-6, and oxylipins in obese subjects. Prostaglandins Leukot Essent Fatty Acids. 2016; 106: 39-49.

4 Schulte F, Asbeutah AA, Benotti PN, et al. The relationship between specialized pro-resolving lipid mediators, morbid obesity and weight loss after bariatric surgery. Sci Rep. 2020; 10: 20128.

5 Fried M, Yumuk V, Oppert JM, et al. Interdisciplinary European guidelines on metabolic and bariatric surgery. Obes Surg. 2014; 24: 42-55.

6 Galvão AF, Petta T, Flamand N, et al. Plasma eicosanoid profiles determined by high-performance liquid chromatography coupled with tandem mass spectrometry in stimulated peripheral blood from healthy individuals and sickle cell anemia patients in treatment. Anal Bioanal Chem. 2016; 408: 3613-3623.

7 Pakiet A, Haliński ŁP, Rostkowska O, et al. The effects of one--anastomosis gastric bypass on fatty acids in the serum of patients with morbid obesity. Obes Surg. 2021; 31: 4264-4271.

8 Grapov D, Fiehn O, Campbell C, et al. Impact of a weight loss and fitness intervention on exercise-associated plasma oxylipin patterns in obese, insulin-resistant, sedentary women. Physiol Rep. 2020; 8: e14547.

9 Pauls SD, Du Y, Clair L, et al. Impact of age, menopause, and obesity on oxylipins linked to vascular health. Arterioscler Thromb Vasc Biol. 2021; 41: 883-897.

10 Schebb NH, Kühn H, Kahnt AS, et al. Formation, signaling and occurrence of specialized pro-resolving lipid mediators—what is the evidence so far? Front Pharmacol. 2022; 13: 838782.

11 Möller K, Ostermann AI, Rund K, et al. Influence of weight reduction on blood levels of C-reactive protein, tumor necrosis factor-α, interleukin-6, and oxylipins in obese subjects. Prostaglandins Leukot Essent Fatty Acids. 2016; 106: 39-49.

12 Straus DS, Pascual G, Li M, et al. 15-Deoxy-delta 12,14-prostaglandin J2 inhibits multiple steps in the NF-kappa B signaling pathway. Proc Natl Acad Sci U S A. 2000; 97: 4844-4849.

13 Osborn O, Gram H, Zorrilla E, et al. Insights into the roles of the inflammatory mediators IL-1, IL-18 and PGE2 in obesity and insulin resistance. Swiss Med Wkly. 2008; 138: 665-673.

14 Jurado-Fasoli L, Di X, Kohler I, et al. Omega-6 and omega-3 oxylipins as potential markers of cardiometabolic risk in young adults. Obesity. 2022; 30: 50-61.

15 Du Y, Taylor CG, Aukema HM, Zahradka P. Role of oxylipins generated from dietary PUFAs in the modulation of endothelial cell function. Prostaglandins Leukot Essent Fatty Acids. 2020; 160: 102160.

16 Schuchardt JP, Schmidt S, Kressel G, et al. Modulation of blood oxylipin levels by long-chain omega-3 fatty acid supplementation in hyper- and normolipidemic men. Prostaglandins Leukot Essent Fatty Acids. 2014; 90: 27-37.

17 Wolfer AM, Scott AJ, Rueb C, et al. Longitudinal analysis of serum oxylipin profile as a novel descriptor of the inflammatory response to surgery. J Transl Med. 2017; 15: 83.

18 Liakh I, Janczy A, Pakiet A, et al. One-anastomosis gastric bypass modulates the serum levels of pro- and anti-inflammatory oxylipins, which may contribute to the resolution of inflammation. Int J Obes. 2022; 46: 408-416.

19 Gilani A, Pandey V, Garcia V, et al. High-fat diet-induced obesity and insulin resistance in CYP4A14 −/− mice is mediated by 20-HETE. Am J Physiol Regul Integr Comp Physiol. 2018; 315: R934-R944.

20 Strassburg K, Huijbrechts AML, Kortekaas KA, et al. Quantitative profiling of oxylipins through comprehensive LC-MS/MS analysis: application in cardiac surgery. Anal Bioanal Chem. 2012; 404: 1413-1426.