Clinical Nutrition 43 (2024) 246–258

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Metabolic adaptations in severe obesity: Insights from circulating oxylipins before and after weight loss

Andrea Jiménez-Franco [a, 1], Helena Castañé [a, 1], Cristian Martínez-Navidad [a], Cristina Placed-Gallego [a], Anna Hernández-Aguilera [b], Salvador Fernández-Arroyo [c], Iris Samarra [c], Marta Canela-Capdevila [a, d], Meritxell Arenas [d], Antonio Zorzano [e, f, g], María Isabel Hernández-Alvarez [e, f, g], Daniel del Castillo [h], Marta Paris [h], Javier A. Menendez [i, j], Jordi Camps [a, *], Jorge Joven [a, **]

[a] Unitat de Recerca Biomèdica, Hospital Universitari Sant Joan, Institut d'Investigació Sanitària Pere Virgili, Universitat Rovira i Virgili, Reus, Spain
[b] Department of Pathology, Hospital Universitari Sant Joan, Institut d'Investigació Sanitària Pere Virgili, Universitat Rovira i Virgili, Reus, Spain
[c] Center for Omics Sciences, EURECAT-Technology Center of Catalonia, Reus, Spain
[d] Department of Radiation Oncology, Institut d'Investigació Sanitària Pere Virgili, Universitat Rovira i Virgili, Reus, Spain
[e] Department de Bioquímica i Biomedicina Molecular, Facultat de Biología, Barcelona, Spain
[f] Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology, Barcelona, Spain
[g] CIBER de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Instituto de Salud Carlos III, Spain
[h] Servei de Cirurgia, Hospital Sant Joan de Reus, Institut d'Investigació Sanitària Pere Virgili. Avinguda, Departament de Medicina i Cirurgia, Universitat Rovira i Virgili, Reus, Spain
[i] Metabolism and Cancer Group, Program Against Cancer Therapeutic Resistance (ProCURE), Catalan Institute of Oncology, Girona, Spain
[j] Girona Biomedical Research Institute, Girona, Spain

ARTICLE INFO

Article history:
Received 26 June 2023
Accepted 4 December 2023

Keywords:
Bariatric surgery
Cyclooxygenase
Lipoxygenase
Metaflammation
Polyunsaturated fatty acids
Weight loss

SUMMARY

Background: The relationship between lipid mediators and severe obesity remains unclear. Our study investigates the impact of severe obesity on plasma concentrations of oxylipins and fatty acids and explores the consequences of weight loss.

Methods: In the clinical trial identifier NCT05554224 study, 116 patients with severe obesity and 63 overweight/obese healthy controls matched for age and sex (≈2:1) provided plasma. To assess the effect of surgically induced weight loss, we requested paired plasma samples from 44 patients undergoing laparoscopic sleeve gastrectomy one year after the procedure. Oxylipins were measured using ultra-high-pressure liquid chromatography coupled to a triple quadrupole mass spectrometer via semi-targeted lipidomics. Cytokines and markers of interorgan crosstalk were measured using enzyme-linked immunosorbent assays.

Results: We observed significantly elevated levels of circulating fatty acids and oxylipins in patients with severe obesity compared to their metabolically healthier overweight/obese counterparts. Our findings indicated that sex and liver disease were not confounding factors, but we observed weak correlations in plasma with circulating adipokines, suggesting the influence of adipose tissue. Importantly, while weight loss restored the balance in circulating fatty acids, it did not fully normalize the oxylipin profile. Before surgery, oxylipins derived from lipoxygenase activity, such as 12-HETE, 11-HDoHE, 14-HDoHE, and 12-HEPE, were predominant. However, one year following laparoscopic sleeve gastrectomy, we observed a complex shift in the oxylipin profile, favoring species from the cyclooxygenase pathway, particularly proinflammatory prostanoids like TXB2, PGE2, PGD2, and 12-HHTrE. This transformation appears to be linked to a reduction in adiposity, underscoring the role of lipid turnover in the development of metabolic disorders associated with severe obesity.

* Corresponding author. Unitat de Recerca Biomèdica, Hospital Universitari Sant Joan, Av. del Doctor Josep Laporte, 2, 43204, Reus, Spain.
** Corresponding author.
E-mail addresses: jorge.camps@salutsantjoan.cat (J. Camps), jorge.joven@urv.cat (J. Joven).
[1] Contributed equally.

https://doi.org/10.1016/j.clnu.2023.12.002

Conclusions: Despite the reduction in fatty acid levels associated with weight loss, the oxylipin profile shifts towards a predominance of more proinflammatory species. These observations underscore the significance of seeking mechanistic approaches to address severe obesity and emphasize the importance of closely monitoring the metabolic adaptations after weight loss.

Abbreviations

AA	arachidonic acid
ACN	acetonitrile
ALA	alpha-linolenic acid
BHT	butylated hydroxytoluene
BMI	body mass index
BS	bariatric surgery
CCL2	C-C Motif Chemokine Ligand 2
COX	cyclooxygenase
CYP450	cytochrome p450
DHA	docosahexaenoic acid
DiHDPE	dihydroxydocosapentaenoic acid
DiHETE	dihydroxyeicosatetraenoic acid
DiHETrE	dihydroxyeicosatrienoic acid
DiHODE	dihydroxyoctadecadienoic acid
DiHOME	dihydroxyoctadecenoic acid
EDTA	ethylenediaminetetraacetic acid
ELISA	enzyme-linked inmunoassay
EPA	eicosapentaenoic acid
EpODE	epoxyoctadecadienoic acid
EpOME	epoxcyoctadecenoic acid
FGF	fibroblast growth factor
HDoHE	hydroxydocosahexaenoic acid
HEPE	hydroxyeicosapentaenoic acid
HETE	hydroxyeicosatetraenoic acid
HHTrE	hydroxyheptadecatrienoate
HODE	hydroxyoctadecadienoic acid
HOMA-IR	homeostatic model assessment-insulin resistance
HOTrE	hydroxyoctadecatrienoic acid
IL-10	interleukin-10
LA	linoleic acid
LDA	linear discriminant analysis
LOX	lipoxygenase
LSG	laparoscopic sleeve gastrectomy
MeOH	methanol
MUFA	monounsaturated fatty acid
NAFLD	non-alcoholic fatty liver disease
NEFAs	non-esterified fatty acids
oxoODE	oxooctadecadienoic acid
PGD	prostaglandin D
PGE	prostaglandin E
PGF	prostaglandin F
PGH	prostaglandin H
HPLA2	phospholipase A2
PLSDA	partial least square discriminant analysis
PUFA	polyunsaturated fatty acid
QqQ/MS	triple quadrupole mass spectrometry
SFA	saturated fatty acid
T2DM	type 2 diabetes mellitus
TriHOME	trihydroxyoctadecenoic acid
TNF-α	tumor necrosis factor-α
TXB2	thromboxane B2
UHPLC	ultra-high pressure liquid chromatography

1. Introduction

A prominent epidemiological challenge in contemporary times is the escalating incidence of obesity, attaining epidemic proportions [1]. Individuals with obesity share a common metabolic foundation, and their clinical status is frequently influenced by environmental factors like an unbalanced dietary regimen or a sedentary way of life [2]. Obesity is intricately linked with the manifestation of chronic diseases, encompassing type 2 diabetes mellitus, nonalcoholic fatty liver disease, cardiovascular disorders, and metabolic syndrome [3]. Several observations support the hypothesis that lipid mediators interact with obesity and influence weight changes [4–8]. Excess body fat can lead to tissue damage, inflammation, and disruptions in lipid metabolism, with higher body mass index (BMI, Kg/m2) exacerbating these complications.

Individuals with severe obesity, characterized by a BMI over 40 kg/m^2, who underwent weight loss surgery provide a unique perspective to investigate these phenomena. Bariatric surgery is a widely used surgical procedure for the treatment of morbid obesity and its associated comorbidities. Patients who benefit from this procedure not only reduce weight but also improve insulin resistance, hepatic alterations, and hypertension.

Lipids are versatile molecules that regulate oxidative and inflammatory stress [9]. Among them, oxylipins are bioactive oxygenated metabolites of fatty acids with similar biochemical transport and are established as essential mediators in inflammatory diseases. Animal studies have shown that oxylipins can contribute to metabolic dysfunction in obesity [10–13]. The analytical limitations and the complex enzymatic and non-enzymatic pathways involved [14] complicate the examination of human oxylipins. To avoid limitations, we propose focusing on a specific subset of plasma oxylipins that are consistently detected, easily quantifiable, and resistant to freezing from the total pool of oxylipins in human blood. By taking this approach, we can reliably assess human oxylipin levels considering their potential source from specific reactions on polyunsaturated fatty acids (PUFAs) catalyzed by cyclooxygenases (COX), lipoxygenases (LOX), and cytochromes P450 (CYP450) [10,15–17].

In this study, we extensively investigated the relationship between plasma oxylipins and various factors that could influence our results. Severe obesity often leads to the accumulation of lipids in alternative tissues, especially the liver, triggering metabolic stress and the abnormal secretion of hormones known as organokines [18–20]. Although the link between oxylipins and organokines has yet to be fully comprehended, animal studies suggest their involvement in inflammation, insulin resistance, and energy balance [21,22]. To scrutinize these effects in humans, we measured specific hormones in the blood, including adiponectin, leptin, fibroblast growth factor (FGF)-19, and FGF-21 [23–26], as well as irisin and galectin-3, both associated with inflammation and fibrosis [27,28].

There exists limited understanding regarding the plasma oxylipin profile in morbid obesity, how this profile relates to pertinent metabolic biomarkers, and how this is changed after patients have undergone bariatric surgery. Consequently, this investigation aimed to delineate the plasma oxylipin profile in individuals afflicted with severe obesity, discern any significant associations between this profile and metabolic markers and comorbidities, and ascertain the impact of weight reduction and metabolic readjustment occurring 12 months post-bariatric surgery.

2. Materials and methods

2.1. Human subjects, study design, and ethical considerations

We conducted a pilot investigation involving individuals afflicted by severe obesity at the Bariatric Surgery Unit of Hospital Universitari Sant Joan, Reus.

Our approach for sample size determination (n = 116) and study design was guided by prior research findings [29,30] and adhered to established protocols. Among eligible participants, either Roux-en-Y gastric bypass (n = 59) or laparoscopic sleeve gastrectomy (LSG) (n = 57) were independently indicated. We did not find differences between both groups, which were combined. By utilizing the results of nonalcoholic fatty liver scores (NAS) on liver biopsies obtained during the procedure, we separated patients with and without nonalcoholic steatohepatitis (NASH) (n = 61 with NAS $\geq$5 and n = 55 with NAS $\leq$2, respectively) to assess the effect of liver lesion in plasma oxylipins. To maximize the differences in liver disease, we excluded patients with intermediate damage (NAS = 3 or 4). We also collected paired, before and one year after surgery, bioelectric impedance data using a Tanita TBF-420 scale. Although not initially designed in the study, we collected under permission paired computerized tomography (CT) scans from several patients retrospectively to assess variations in adiposity observed with imaging techniques. We excluded patients under 18 years of age, those with excessive alcohol consumption, acute illness, malignancies, previous or current major cardiovascular events, and advanced liver disease. Our study received approval from the Institutional Review Board (EPIMET PI21/00510_083 and PL4NASH 112/2021), and all participants provided written informed consent. We collected plasma samples from ongoing research (ClinicalTrials.gov NCT05554224) while adhering to Good Clinical Practice Guidelines and the Declaration of Helsinki. The samples were collected the previous day before surgery, processed within the first 2 h, and frozen (−80 °C) until analysis. We specifically selected patients undergoing LSG to study post-surgery effects in a 1-year follow-up study and plasma was collected equally. It was important to ensure the fasting state for at least 12 h and the lack of physical activity during the previous 30 min. We retained data and paired plasma samples from 44 participants who adhered to the proposed schedules for this period, resulting in an attrition rate of 17.5%. Patients were weight stable in this particular point of observation. Patients usually cease active weight loss approximately 6–8 months after surgery. A few patients may continue this process after 1 year and even some re-gain some weight but none was included in this cohort. Though susceptible to debate, we assume a static picture in the interpretation.

In addition, we obtained age- and sex-matched samples from a cross-sectional survey (GENUP 2021) conducted by the Institut d'Investigació Sanitària Pere Virgili designed to monitor health and nutritional status. We ruled out liver disease in these volunteers through laboratory values and diagnostic medical ultrasonography without liver biopsy. These samples came from 63 otherwise healthy overweight/obese participants who served as controls.

2.2. Biopsies sampling and quantification of cytokines and organokines in plasma

We collected intraoperative hepatic, visceral, and subcutaneous adipose tissue biopsies from the patients that underwent bariatric surgery, as per protocol. We used a standardized method to evaluate the alterations in liver tissue, which involved scoring fibrosis, steatosis, lobular inflammation, and ballooning in liver portions obtained through wedge resection [31–33]. Adipose tissue samples were examined to assess adipocyte size and fibrosis severity [34,35]. We used staining techniques such as Hematoxylin and eosin, Masson's trichrome, and Sirius Red to aid in these evaluations. The scores ranged from 0 to 2 or 3 for liver samples and from 0 to 3 for adipose tissue samples. We diagnosed hyperlipidemia, type 2 diabetes mellitus, and hypertension using established protocols and anthropometric and routine laboratory methods [36,37]. We measured specific cytokines C-C motif chemokine Ligand 2 (CCL2), interleukin-10 (IL-10), and tumor necrosis factor-α (TNF- α)] in plasma samples using ELISAs from Peprotech (London, UK). Additionally, we measured circulating levels of irisin, FGF-19, FGF-21, leptin, adiponectin, and galectin 3 using ELISAs from R&D Systems (Minneapolis, USA).

2.3. Identification and quantification of fatty acids and oxylipin metabolites

We employed previously established procedures to identify and quantify fatty acids and oxylipin metabolites [38–42]. The measurement of oxylipins presented challenges due to their diverse chemical structures and isomers and their susceptibility to degradation and auto-oxidation. We provided access to further experimental data, reference spectra, and analytical procedures through the Metabolights database and repository under the study number MTBLS7758 (www.ebi.ac.uk/metabolights/MTBLS7758). We cross-referenced our obtained concentrations with The Human Metabolome Database to validate their accuracy (https://hmdb.ca/).

The process involved multiple sample preparations and runs in a chromatography system comprising a 1290 Infinity II ultra-high pressure liquid chromatograph (UHPLC) coupled with a 6490 triple quadrupole (QqQ) mass spectrometer (MS) operating in negative electrospray mode. We mixed 100 μL of plasma with 400 μL of methanol for fatty acid measurement, including a mixture of labeled fatty acids as internal standards. After centrifugation and drying 300 μL of the extract on a SpeedVac® vacuum concentrator, we reconstituted it with 100 μL of methanol for chromatographic analysis.

We combined 250 μL of plasma with 100 μL labeled oxylipins as a standard internal mixture and 500 μL of 0.001 M butylated hydroxytoluene in methanol for oxylipin measurement. Labeled internal standards enabled us to account for inter-sample differences resulting from the extraction procedure and analytical signal drift. After protein precipitation and centrifugation, we collected and purified the supernatant onto the SPE cartridge, using acetonitrile: methanol (9:1, v/v) for oxylipin elution. The samples were then dried under N2 flow and reconstituted in water: methanol (1:1, v/v) for chromatographic analysis. To quantify specific oxylipins (Table S1), we utilized materials obtained from Cayman Chemical (Ann Arbor, MI) and generated ten seriated concentrations with good linearity using a standard internal mixture. We used stock standards dissolved in methanol for calibration curves. To ensure measurement reproducibility, we injected lipid extracts from a pool of different samples twice daily and after every 20 analyses as a quality control measure. We followed a semi-targeted approach for molecules without available standards, quantifying them using the most similar oxylipin molecule.

We excluded oxylipins with low concentrations, known variation after storage, and those resulting in more than 10% missing values or outliers. Our analysis encompassed data for 51 omega-3 and omega-6 fatty acid-derived oxylipins (Figure S1). We observed that the proposed plasma signature remained consistent across the measurements, with the time elapsed after venipuncture (<2 h until freezing) and adherence to a strict plasma processing protocol emerging as critical factors.

Our study exclusively examined non-esterified oxylipins and fatty acids without the inclusion of a hydrolysis step. It is important to clarify this point because if we do not avoid an hydrolysis step circulating lipoproteins represent a major source of esterified lipids that become non-esterified in vitro, i.e., artificially. Then, separation between these pools is impossible and adds considerable confusion. This approach allowed us to comprehensively explore metabolic adaptations and the potential use of oxylipins as a biomarker. We did not measure esterified oxylipins and fatty acids in lipoproteins, which would require additional analytical steps irrelevant to our present aim. Furthermore, it is crucial to note that the plasma albumin concentration was average in all fasting state samples.

2.4. Statistical methods and analysis

We utilized various software tools and packages, such as GraphPad Prism 6.01, R program, and related packages (ggplot2, ggpubr, dplyr, ggrepel, corrplot, and Performance Analytics) in our data analysis. We employed parametric or non-parametric tests based on the distribution of our data to determine the appropriate statistical test for bivariate comparisons and correlations. Unless stated otherwise, we presented numerical values as a median with an interquartile range. MetaboAnalyst 5.0 was used for machine learning algorithms, and MassHunter Quantitative Analysis B.07.00 was used for lipid analysis with a calibration curve generated from the corresponding standard. We applied the Benjamini and Hochberg procedure to control the false discovery rate and adjust for multiple comparisons.

3. Results

3.1. Influence of sex and liver disease on plasma oxylipin signature

We found that sex-associated differences in PUFAs and oxylipins in plasma were negligible (Fig. 1A, Table S2). Patients in the cohort were diagnosed with metabolic syndrome using the American Heart Association's criteria. Liver biopsies in patients with severe obesity revealed the potential health implications of ectopic fat accumulation [43,44]. Patients with NASH had more metabolic imbalances than those without NASH. However, we found no significant links between fatty liver disease severity, age, comorbidities, medication, BMI, or other anthropometric measurements (Table 2, Figure S2). Although plasma PUFAs were significantly lower in NASH patients, plasma oxylipin levels did not differ between those with and without NASH (Fig. 1B, Table S3). We also observed that plasma oxylipins were not predictive of NASH, and there were no significant changes in the circulating oxylipin signature across different histologic features (Figure S3). Our data firmly establish that sex and liver disease are not confounding factors in assessing the circulating oxylipin signature.

3.2. Impact of cytokine and organokine levels on the oxylipin signature

Patients with severe obesity exhibit a higher prevalence of low-grade chronic inflammation compared to overweight/obese individuals, as indicated by elevated levels of C-reactive protein, CCL2, and TNF-α, and reduced IL-10 levels in the bloodstream (Table 1). However, these cytokines did not provide insight into plasma fatty acid or oxylipin signatures in severe obesity. It is essential to note that plasma organokine levels do not necessarily reflect interactions within different tissues, but severe obesity can exacerbate abnormal secretion. Compared to overweight or obese individuals, those with severe obesity had higher circulating levels of leptin and lower FGF-19 levels, likely indicating an influence from liver and gut but there were no significant differences in the circulating levels of other selected organokines. Similarly, the impact of metabolic comorbidities on plasma organokine levels was not significant (Figures S4 and S5). Additionally, the relationships between organokines and oxylipins were weak and only exhibited marginal statistical significance (Figures S6 and S7). These findings underscore the complexity of the metabolic phenotype in individuals with severe obesity.

3.3. Elevated oxylipin levels in severe obesity

Our study revealed that patients with severe obesity exhibit significantly higher levels of circulating saturated, monounsaturated, and polyunsaturated fatty acids compared to healthy overweight or less severely obese individuals, with excess adiposity playing a pivotal role. The study observed differences in both ω-6 and ω-3 polyunsaturated fatty acids. Notably, patients with severe obesity exhibited a unique plasma oxylipin profile, with most species showing significantly higher concentrations (Fig. 2 A-C, Table S4). Our analysis showed that lipoxygenase-derived oxylipins are the dominant species in the plasma of patients with severe obesity, with specific metabolites (12-HETE, 11-HDoHE, 14-HDoHE, and 12-HEPE) key in establishing the circulating oxylipins profile, as depicted in Fig. 2 D, E. The Receiver Operating Characteristic (ROC) curve based on comparing these metabolite levels indicated high accuracy in differentiating between the two groups with an Area under the Curve value of 0.937 (Figure S8). Importantly, metabolic comorbidities do not significantly impact the plasma oxylipin profile (Figure S9), indicating that lipoxygenase activity could contribute to lipotoxicity in severe obesity mainly due to inefficient adipose tissue expansion and ectopic lipid accumulation.

3.4. Changes in plasma oxylipin composition one year after weight loss surgery. The potential role of major variations in adiposity

One year after weight loss surgery, patients experienced a significant reduction in excess fat and BMI by 42% and 29.1%, respectively ($p < 0.0001$) (Table 3). The surgery also improved glucose and lipid metabolism, arterial hypertension, and decreased low-grade chronic inflammation, reducing the need for medication. Additionally, transaminase activity decreased, indicating relief in liver damage (Table 3). We observed a consistent decrease in plasma fatty acids after weight loss, likely due to metabolic adaptations (Fig. 3). Furthermore, the levels of plasma oxylipins increased following the surgery. One year after surgery, there was a notable increase in total circulating oxylipin levels, altering the plasma signature. Statistical analysis revealed significant differences between signatures, making before and one year after surgery profiles distinguishable in linear discriminant analysis. However, some differences were inconsistent, and we did not notice any apparent association with improving comorbidities. While plasma levels of individual ω-3 PUFAs-derived oxylipins remained stable or slightly decreased, those derived from ω-6 PUFAs increased. Although plasma levels of oxylipins derived from linoleic acid remained unchanged one year after surgery, those derived from arachidonic acid were significantly overrepresented. The most dominant species identified in the signature were COX-derived oxylipins,

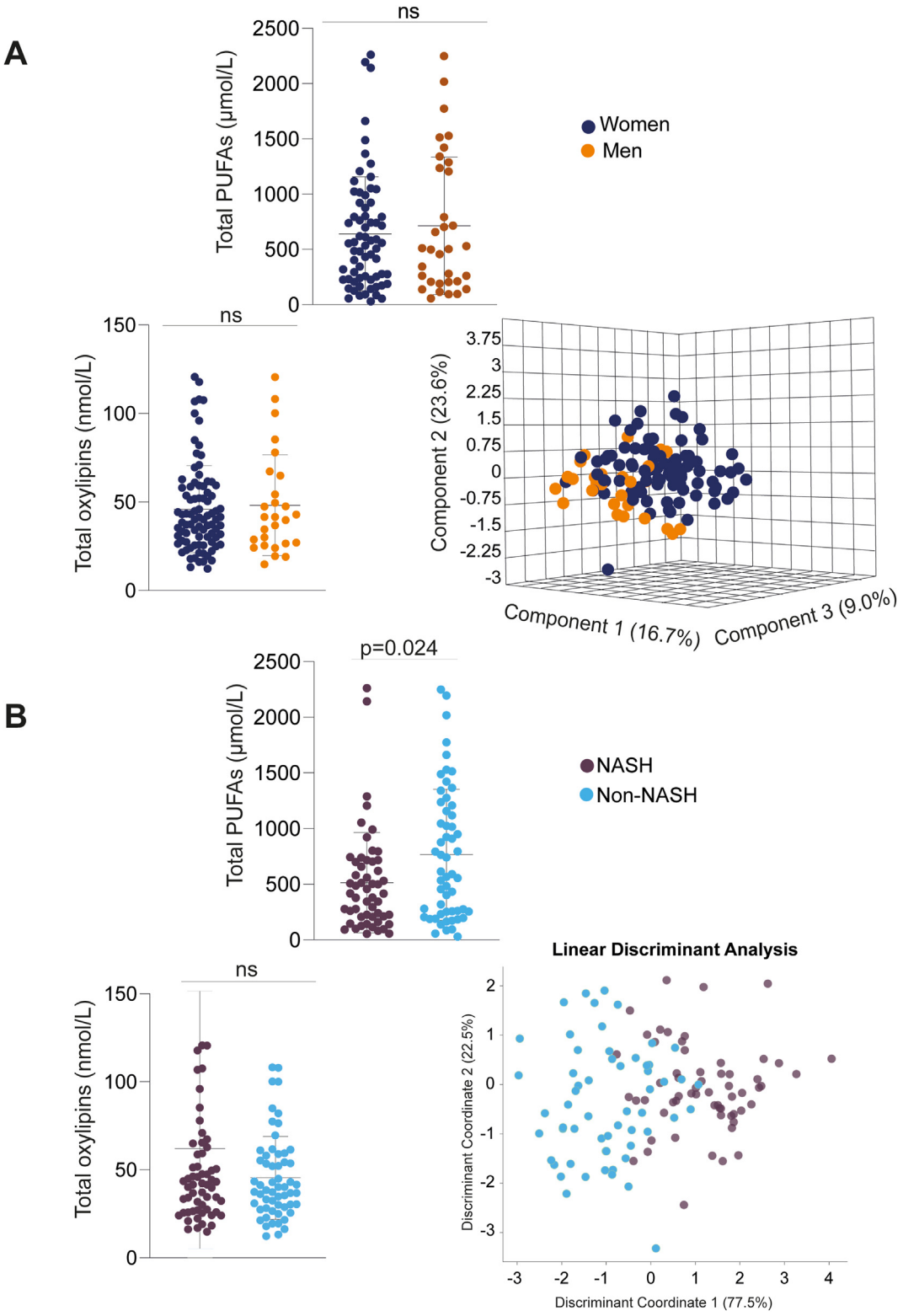

Fig. 1. Plasma levels of polyunsaturated fatty acids and oxylipins in patients with severe obesity: Impact of sex differences and NASH. (A) The results showed that sex was not a significant factor affecting measured variables. (B) In NASH patients, plasma PUFAs showed a significant decrease, whereas plasma oxylipin levels remained unchanged regardless of NASH status.

Table 1
Severe obesity-associated metabolic changes.

	Healthy overweight obese (n = 63)	Severe Obesity (n = 116)
Female, n (%)	50 (79.4)	88 (75.9)
Age (years)	44.5 (38.0–58.8)	50.0 (41.0–56.0)
BMI (kg/m^2)	27.1 (24.9–31.1)	43.4 (40.0–48.7)*
Type 2 diabetes mellitus, n (%)	1 (2.0)	36 (31.0)*
Arterial hypertension, n (%)	14 (28.0)	68 (58.6)*
Dyslipidemia, n (%)	3 (4.8)	40 (34.5)*
Medication		
Sulfonylureas, n (%)	–	4 (3.4)
Insulin, n (%)	–	14 (12.1)
Diuretics, n (%)	7 (11.1)	16 (13.8)
ACEIs, n (%)	3 (4.8)	26 (22.4)*
Biochemical variables		
Glucose (mmol/L)	4.5 (4.3–4.9)	6.7 (5.7–8.5)*
Insulin (mmol/L)	49.4 (30.7–78.9)	82.7 (42.7–121.4)*
HOMA-IR	1.4 (0.9–2.2)	3.5 (1.6–5.9)*
Triglycerides (mmol/L)	1.0 (0.7–1.4)	1.4 (1.1–1.9)*
Total Cholesterol (mmol/L)	4.9 (4.5–5.8)	3.8 (3.5–4.5)*
HDL-cholesterol (mmol/L)	1.5 (1.3–1.8)	0.9 (0.8–1.1)*
LDL-cholesterol (mmol/L)	3.1 (2.5–3.7)	2.2 (1.8–2.9)*
VLDL- cholesterol (mmol/L)	0.4 (0.3–0.6)	0.6 (0.5–0.8)
NEFAs (μmol/L)	234.4 (100.7–466.5)	2339.9 (1083.7–5033.5)*
CCL2 (pg/mL)	21.2 (10.1–36.7)	30.1 (12.4–46.1)*
IL-10 (pg/mL)	450.2 (201.3–854.4)	80.1 (62.3–85.7)*
TNF- α (pg/mL)	3.8 (2.9–7.9)	7.9 (5.7–13.6)*
CRP (mg/dL)	1.1 (0.4–2.3)	9.4 (5.3–14.3)*
Transaminases (μKat/L)		
ALT	0.2 (0.2–0.4)	0.6 (0.4–0.9)*
AST	0.3 (0.3–0.4)	0.6 (0.4–0.8)*
GGT	0.2 (0.1–0.3)	0.4 (0.3–0.6)*

Values are provided as n (percentage) or median (interquartile range). Statistical analyses performed by the Student's t-test (quantitative) or χ-square test (qualitative), *p < 0.05. ACEIs: angiotensin-converting-enzyme inhibitor; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CCL2: CC-chemokine ligand2; CRP: c-reactive protein; GGT: gamma-glutamyl transferase; IL-10: interleukin 10; NEFAs: non-esterified fatty acids; TNF-α: tumor necrosis factor alpha.

Table 2
Hepatic features in patients with severe obesity.

Steatosis, n (%)	
<5%	20 (17.2)
5–33%	62 (53.4)
34–66%	26 (22.4)
>66%	8 (6.9)
Lobular inflammation, n (%)	
No foci	4 (3.5)
<2 foci per 200 × field	68 (59.1)
2–4 foci per 200 × field	41 (35.7)
>4 foci per 200 + field	2 (1.7)
Hepatocellular ballooning, n (%)	
None	32 (27.8)
Few cells	52 (45.2)
Many cells	31 (27.0)
Fibrosis, n (%)	
None (stage 0)	1 (0.9)
Perisinusoidal or periportal (stage 1)	28 (24.6)
Perisinusoidal and portal (stage 2)	53 (46.5)
Bridging fibrosis (stage 3)	30 (26.3)

Values are provided as n (percentage).

including TXB2, PGE2, PGD2, and 12-HHTrE (Fig. 4, Table S5). Whether this response has any pathobiological significance is unclear and requires further research effort and other design study. In particular, we interpret these changes as the result of metabolic dysfunction caused by the accumulation and subsequent reduction in adiposity. As an observational study, paired biopsies after surgery were considered ethically unacceptable but biopies obtained during the procedure revealed major structural changes between subcutaneous and omental visceral adipose tissue. Notably, adipocytes in visceral adipose tissue were more fibrotic and significantly smaller in size. Similarly, CT scans one year after surgery were only indicated in a limited number of patients but illustrated major variations in adiposity (Fig. 5, Figure S10). These findings emphasize the need for further research and consideration in postoperative care.

4. Discussion

Our research underscores the importance of evaluating the impact of severe obesity and weight loss surgery on circulating fatty acids and oxylipins. It is imperative to take early therapeutic actions to prevent severe obesity, which can lead to adipose tissue dysfunction and harm other bodily tissues [30,45]. We carefully examined factors that could have affected our findings and their implications. Previous animal studies have suggested that there may be differences in oxylipin metabolism in males and females in various tissues, including the liver, depending on age, inflammation, and enzyme expression [46–48]. However, we found no evidence that these differences extend to blood plasma levels. Our analysis showed that all patients had at least two features indicating metabolic dysfunction: arterial hypertension, hypertriglyceridemia, low HDL-C, prediabetes, insulin resistance, and subclinical inflammation. However, we found no links between plasma oxylipins and these comorbidities. Sex and liver disease did not affect the plasma oxylipin profile of patients with severe obesity. Nevertheless, the disrupted endocrine patterns in leptin and FGF-19 responsiveness suggest metabolic crosstalk between adipose tissue, liver, and gut dysfunctions. In addition, we found no strong associations between organokines and oxylipins in the

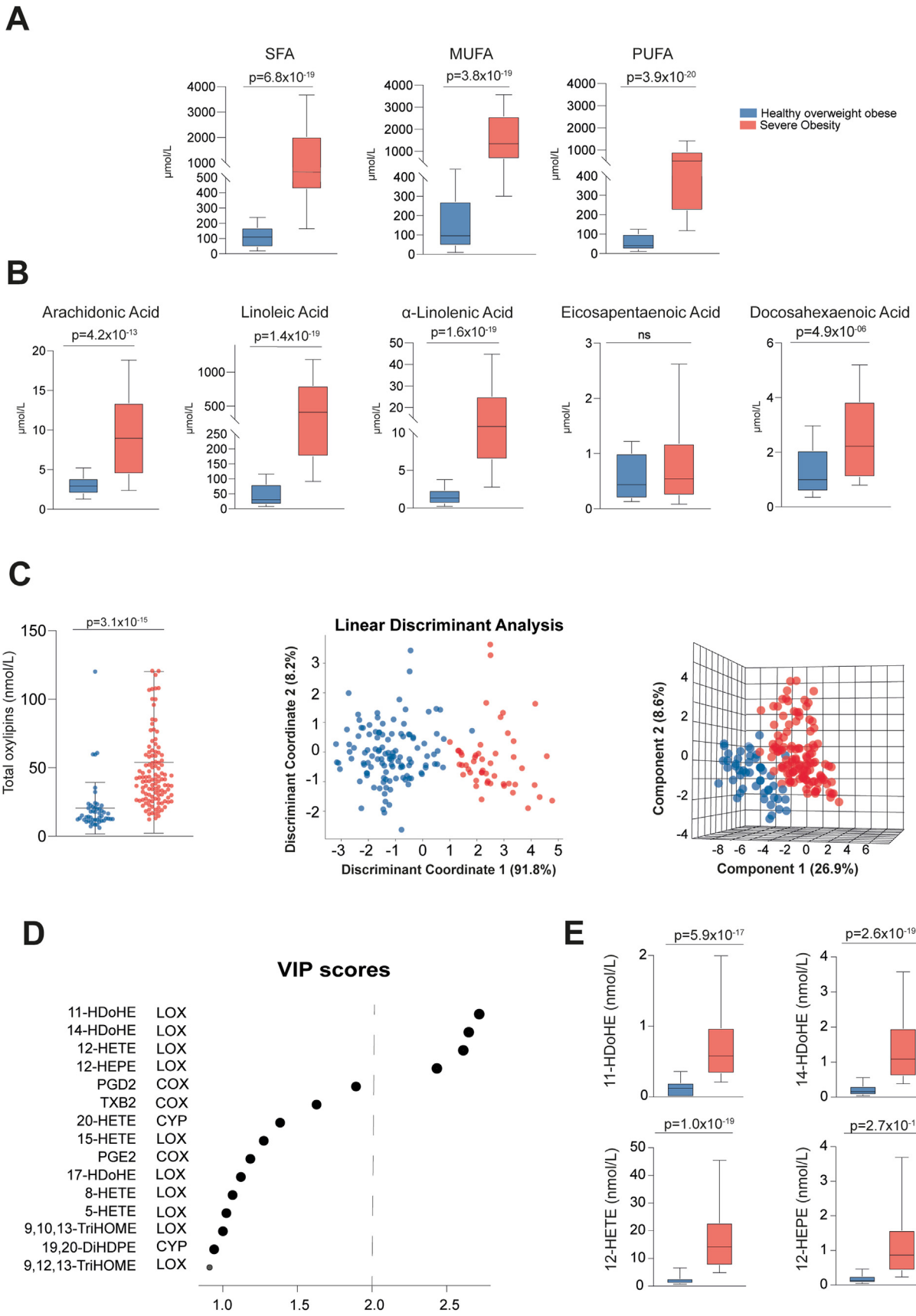

Fig. 2. Severe obesity leads to an elevated concentration of fatty acids and oxylipins into the bloodstream. (A) Plasma levels of saturated, monounsaturated, and polyunsaturated fatty acids were elevated. (B) All five selected PUFAs exhibited an increase in plasma concentration. However, the ω-3 eicosapentaenoic acid level difference was not statistically significant. (C) By performing a specific measurement of plasma oxylipins, we observed a substantial increase in most species (see also Table S4). The discriminant analysis indicated

Table 3
Bariatric surgery-associated metabolic changes.

	Before surgery (n = 44)	One year after surgery (n = 44)
Female, n (%)	31 (70.5)	–
Age (years)	53 (49-61)	–
BMI (kg/m^2)	46.0 (41.7–50.3)	32.6 (30.6–36.4)*
Fat mass (%)	50.3 (48.9–54.3)	33.7 (29.2–42.5)*
Visceral fat rating	18.0 (15.0–21.0)	9.5 (6.0–12.5)*
Type 2 diabetes mellitus, n (%)	18 (40.4)	16 (36.4)*
Arterial hypertension, n (%)	31 (70.5)	26 (59.1)*
Dyslipidemia, n (%)	20 (45.5)	9 (20.5)*
Medication		
Sulfonylureas, n (%)	3 (6.8)	–
Insulin, n (%)	9 (20.5)	2 (4.5)*
Diuretics, n (%)	12 (27.3)	1 (2.3)*
ACEIs, n (%)	15 (34.1)	1 (2.3)*
Biochemical variables		
Glucose (mmol/L)	7.1 (6.1–9.7)	4.7 (4.3–5.4)*
Insulin (mmol/L)	86.1 (52.1–118.8)	50.9 (37.3–74.6)*
HOMA-IR	3.7 (2.4–5.8)	1.6 (1.2–2.2)*
Triglycerides (mmol/L)	1.4 (1.2–2.0)	0.8 (0.7–1.4)*
Total Cholesterol (mmol/L)	3.8 (3.3–4.7)	4.2 (3.7–4.9)*
HDL-cholesterol (mmol/L)	0.9 (0.8–1.0)	1.5 (1.3–1.7)*
LDL-cholesterol (mmol/L)	2.1 (1.7–2.9)	2.0 (1.7–2.3)
VLDL- cholesterol (mmol/L)	0.7 (0.6–0.9)	0.4 (0.3–0.6)*
NEFAs (μmol/L)	2339.9 (1083.7–5033.5)	395.7 (164.4–757.8)*
CCL2 (pg/mL)	30.0 (13.1–15.2)	29.8 (13.4–42.5)
IL-10 (pg/mL)	85.8 (79.8–95.9)	180.2 (150.5–210.0)*
TNF- α (pg/mL)	8.1 (6.3–12.9)	4.1 (3.8–5.7)*
CRP (mg/dL)	9.3 (4.9–12.3)	1.3 (0.3–2.1)*
Transaminases (μKat/L)		
ALT	0.7 (0.5–1.0)	0.2 (0.2–0.3)*
AST	0.7 (0.4–0.9)	0.3 (0.2–0.3)*
GGT	0.4 (0.3–0.6)	0.3 (0.2–0.3)*

Values are provided as n (percentage) or median (interquartile range). Statistical analyses performed by the Student's t-test (quantitative) or χ-square test (qualitative), *p < 0.05.ACEIs: angiotensin-converting-enzyme inhibitor; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CCL2: CC-chemokine ligand2; CRP: c-reactive protein; GGT: gamma-glutamyl transferase; IL-10: interleukin 10; NEFAs: non-esterified fatty acids; TNF- α: tumor necrosis factor alpha.

plasma of patients with severe obesity. This finding indicates that the relationship between organokines and oxylipins observed in animal models and isolated tissues [22–28] may not be apparent in human circulation.

Some of our observations in severe obesity suggest that changes in the amount and function of adipose tissue are likely responsible for the metabolic response of circulating fatty acids and oxylipins. Patients with severe obesity have significantly higher levels of plasma oxylipins and fatty acids than those who are overweight or less severely obese. However, the response to weight loss varies, and while plasma fatty acid levels may return to typical values partially, the same was not valid for plasma oxylipins. The distinct plasma oxylipin signature before surgery may represent an adaptive response to sustained metabolic dysfunction over time. The lipoxygenase-derived oxylipins were the most dominant species. Although their biological significance in different tissues is still unclear, there is evidence that they regulate adipocyte lipid storage and adipokine production [20,49,50]. Moreover, they competitively inhibit metabolic pathways leading to self-limiting factors in inflammation [51–54].

After losing weight, we observed a reversal in the effects of severe obesity, and we confirmed a significant improvement in metabolic dysfunction [55,56]. However, there was an increase in plasma oxylipin levels, and we noted qualitative differences in the plasma oxylipin signature. Following surgery, arachidonic acid derivatives dominated the circulating oxylipin signature, specifically significant increases in prostaglandins and leukotrienes. Although studies in mice have shown that dysfunctional oxylipin metabolism occurs exclusively in adipose tissue, no guidance is available for humans. Our investigation revealed significant alterations in visceral adipose tissue (VAT) following bariatric surgery, underscoring its importance in the context of severe obesity. Post-surgery assessments showed a notable reduction in VAT and a substantial decrease in subcutaneous adipose thickness, resulting in a marked decrease in overall body fat percentage. Further analysis of VAT biopsies exhibited reduced adipocyte size. We could not determine the size of the adipose tissue with CT scan because the image we obtained was not standardized. These findings suggest that bariatric surgery impacts total body fat and induces profound changes in the composition and quality of VAT. These observations emphasize the interplay between VAT alterations and metabolic improvements observed post-bariatric surgery [57,58]. Our findings highlight the contribution of oxylipin trafficking to the metabolic adaptation in adipose tissue after weight loss. We confirm previous data that suggest PGD2 plays a potential role in driving weight gain [13], and the increase in TXB2 levels may indicate adipose tissue remodeling [59]. However, studies on the correlation between plasma levels of primary prostanoid metabolites and

a distinct profile in individuals with severe obesity. (D) Docosanoids and eicosanoids are overrepresented among the measured oxylipins in comparison to octanoids. (E, F) Variable importance in the projection of the partial least squares-discriminant analysis identified the critical role of lipoxygenase-derived metabolites. We used the Mann–Whitney U test to assign statistical significance to comparisons. DiHDPE: dihydroxydocosapentaenoic acid; DiHODE: dihydroxyoctadecadienoic acid; HDoHE: hydroxydocosahexaenoic acid; HEPE: hydroxyeicosapentaenoic acid; HETE: hydroxyeicosatetraenoic acid; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acid; SFA: saturated fatty acid; TriHOME: trihydroxyoctadecanoic acid.

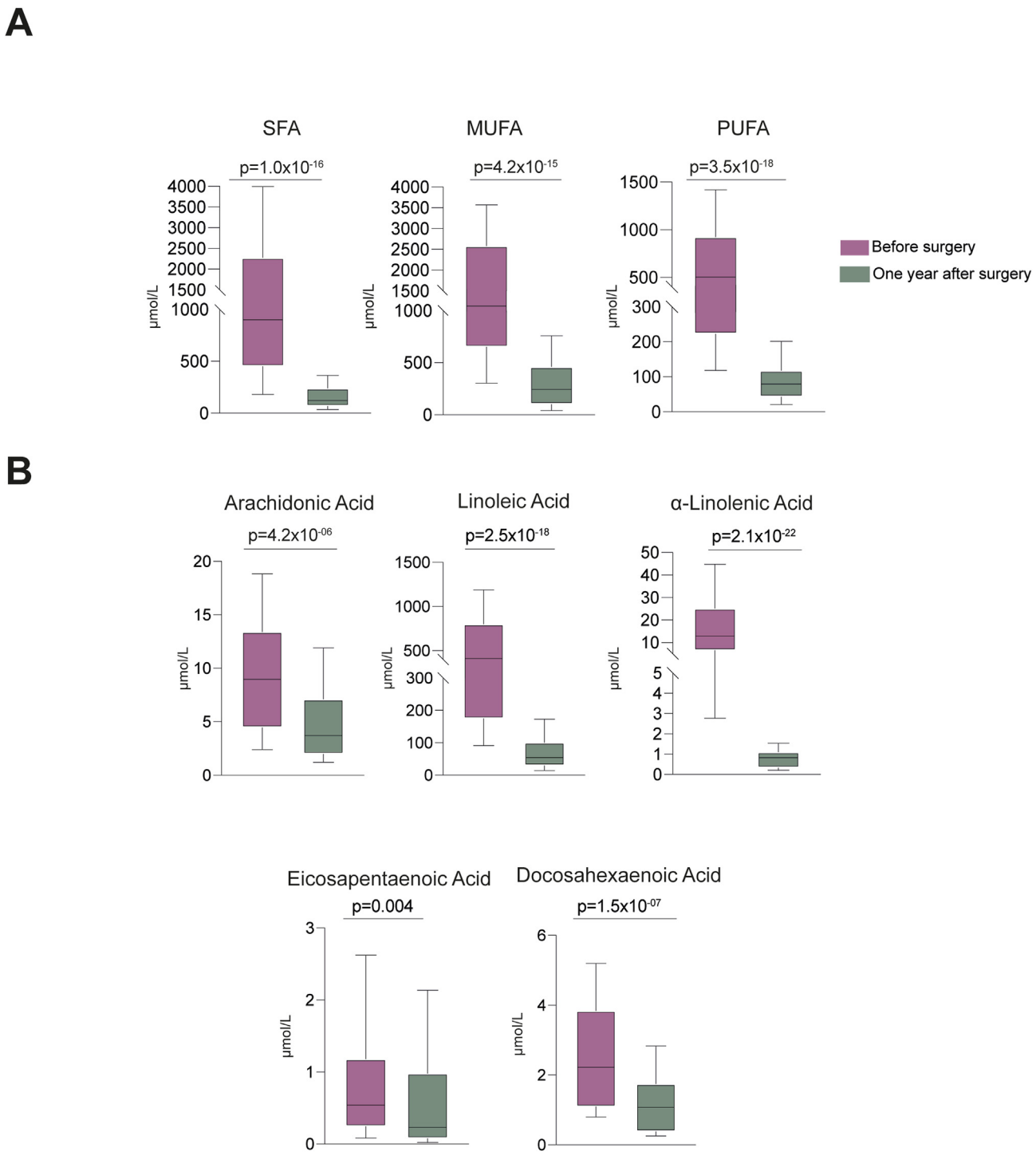

Fig. 3. Plasma fatty acids decreased after weight loss. Although patients remained obese one year after the surgery, plasma fatty acids decreased significantly (A), including those characterized as precursors of oxylipins (B). We utilized the Mann–Whitney U test to determine the statistical significance of the comparisons before and one year after surgery. MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids; SFA: saturated fatty acids.

cardiovascular risk have yielded contradictory results. TXB2 stimulates platelet aggregation [60–62], while PGE2 promotes anti-inflammatory macrophage polarization and reduces atherosclerosis progression [63]. Nevertheless, the necessary research to understand the mechanisms behind these effects in humans is complex and raises considerable ethical concerns.

We identify limitations that may improve the design of future research. The study is observational and solely focuses on patients with severe obesity. Patients remained obese after the one-year observation period, and it is unclear if patients achieved complete metabolic homeostasis. Variations in the gut microbiota may affect the relationship between obesity and metabolic dysfunction. Our findings on oxylipins suggest that patients who have undergone bariatric surgery need monitoring for the long term. Ongoing research will explore the mechanisms contributing to the excessive accumulation and management of adipose tissue metabolism.

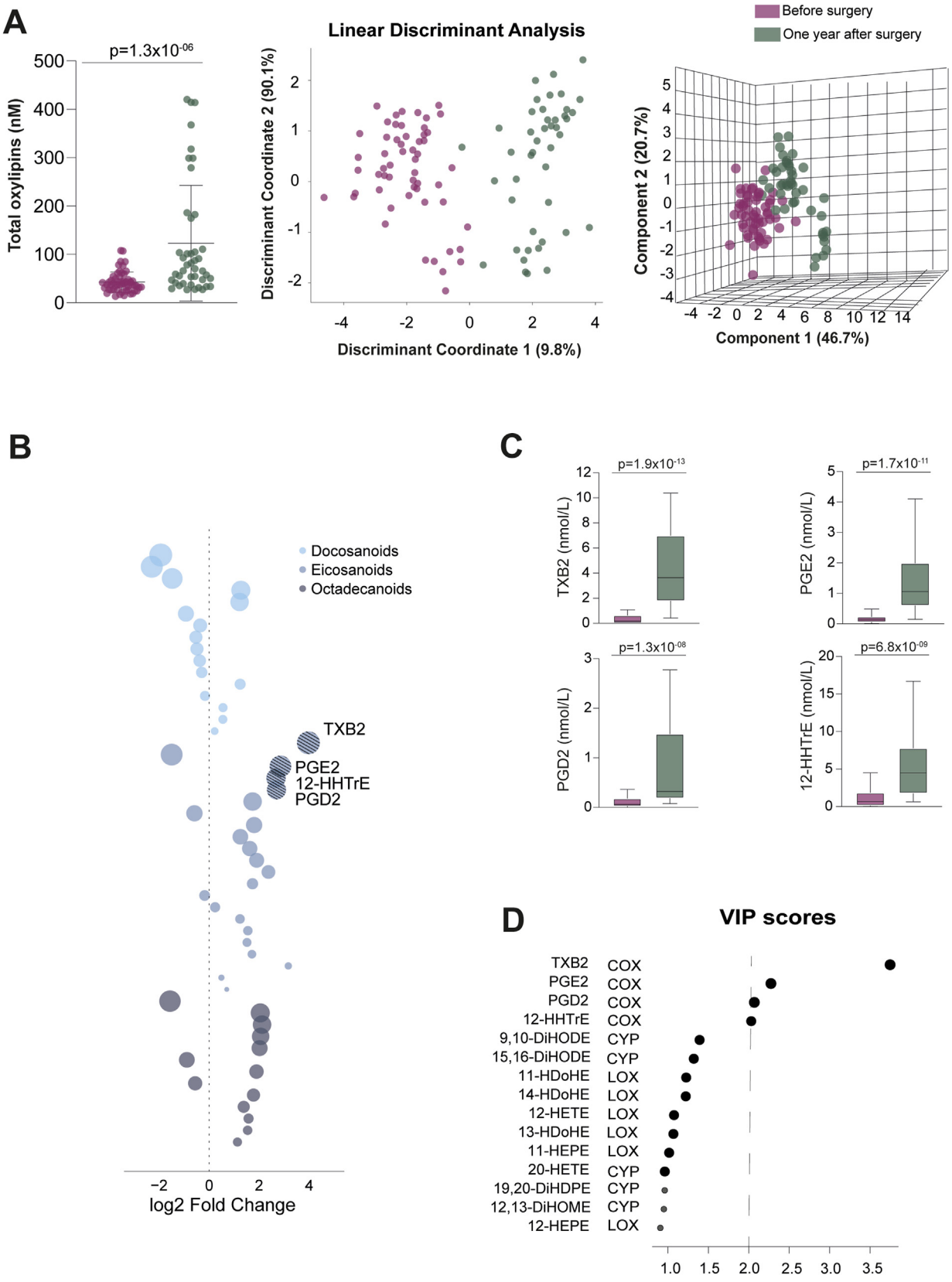

Fig. 4. Surgical weight loss led to an increase in the levels of oxylipins in plasma, which caused changes in the oxylipin profile. The analysis showed a clear separation before and after the surgery (A), with some oxylipin species being decreased, particularly within docosanoids and octadecanoids, while prostaglandins and leukotrienes increased significantly (B). The most dominant species identified by the random forest analysis were cyclooxygenase-derived metabolites from arachidonic acid (C, D). We used the Mann–Whitney U test to determine the statistical significance of the comparisons. HHTrE: hydroxyheptadecatrienoate; PGD2: prostaglandin D2; PGE2: prostaglandin E2; TXB2: thromboxane B2.

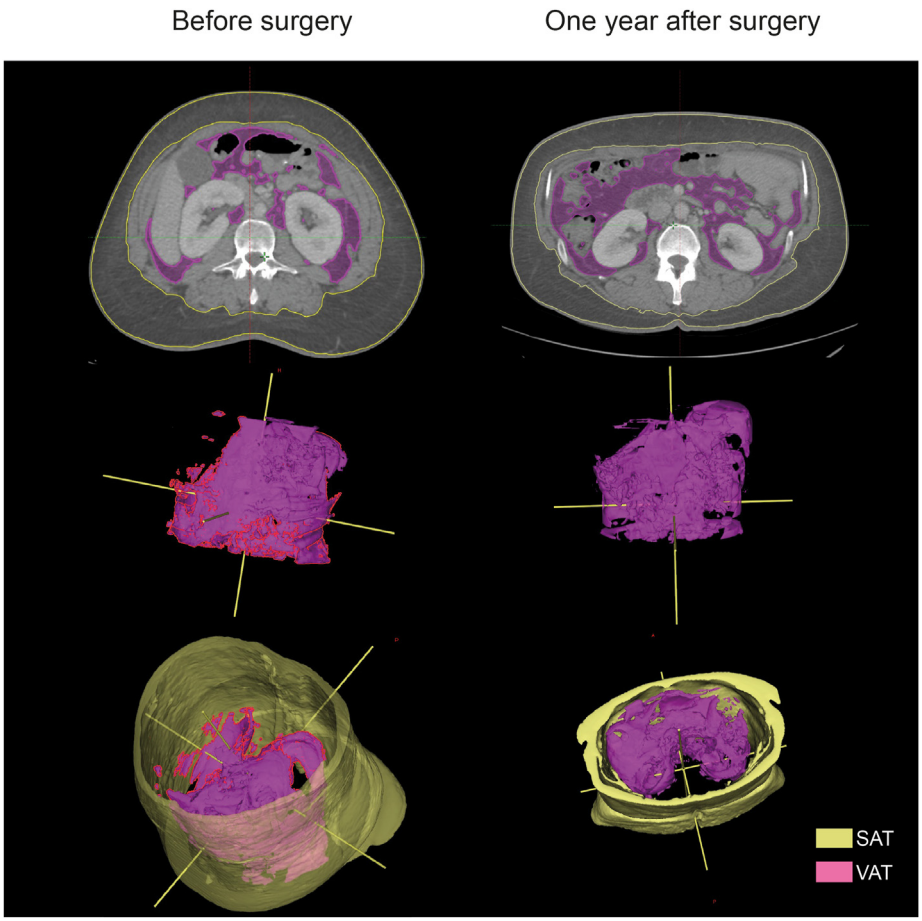

Fig. 5. Computed-tomography scans illustrate the dramatic reduction in adipose tissue one year after surgery.

Other vital questions include why weight loss maintenance becomes easier over time, why macrophage infiltration into adipose tissue does not reverse after weight loss, and how metabolic adaptations persist longer in adipocytes than in other cell types [64–70].

5. Conclusions

Metabolic imbalances are a common consequence of severe obesity. Our research suggests that in patients with this condition, there is an altered balance in circulating fatty acids and oxylipins, leading to higher levels than in overweight/obese individuals who are metabolically healthy. The activity of LOX plays a crucial role in determining the types of oxylipins present in the bloodstream of patients with severe obesity, providing a distinct signature. After weight loss surgery, we observed a shift in the oxylipin signature, with COX-derived species becoming more predominant after one year. This finding was unexpected and requires further investigation to understand the complex changes in metabolic dysfunction in adipose tissue during obesity and weight loss. Effectively addressing metabolic dysfunction in severe obesity is a challenging but essential step in improving the health outcomes of those affected. Future studies aim to address this issue comprehensively.

Funding

Funding for the project leading to these results was obtained from “la Caixa” Foundation, under project code “HR21-00430”, and from the Instituto de Salud Carlos III (ISCIII) through the project “PI21/00510” and co-funded by the European Union. AGAUR provided AJ with the 2023 FI-3 00065 grant. The Generalitat de Catalunya provided HC with the PERIS-SLT017/3501/2020 grant.

Conflict of interest

The authors declare that there are no competing interests in disclosing personal or financial interests, and there are no external factors potentially affecting the objectivity and quality of the information.

Authorship contribution statement

The contributions of the authors to this study are as follows: Andrea Jiménez-Franco and Helena Castañé: Conceptualization, methodology, formal analysis, data curation, and writing drafts. Cristian Martínez-Navidad, Cristina Placed-Gallego, and Marta Canela-Capdevila: Data management, software development, and laboratory tasks. Salvador Fernández-Arroyo and Iris Samarra: Formal analysis and data curation. Meritxell Arenas, Antonio Zorzano, and María Isabel Hernández-Alvarez: Conceptualization and methodology. Daniel del Castillo and Marta Paris: Patient management, supervision, and adherence to ethical standards. Javier A Menendez: Intellectual contribution. Jordi Camps: Supervision, project management, final approval. Jorge Joven: Conceptualization, data curation, revision and editing, and funding.

Acknowledgments

The EURECAT-Technology Center of Catalonia (Reus, Spain) contributed its expertise and advice in lipidomics measurements. The IISPV Biobank provided protocols for EDTA plasma collection and storage. The authors thank Raquel García-Pablo for assistance in analyzing the CT scans.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.12.002.

References

[1] Janssen F, Bardoutsos A, Vidra N. Obesity prevalence in the long-term future in 18 European countries and in the USA. Obes Facts 2020;13:514–27.
[2] Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017-2018. NCHS Data Brief 2020:1–8.
[3] Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, et al. Obesity and cardiovascular disease: a scientific statement from the American Heart association. Circulation 2021;143:e984–1010.
[4] Hernández-Alvarez MI, Sebastián D, Vives S, Ivanova S, Bartoccioni P, Kakimoto P, et al. Deficient endoplasmic reticulum-mitochondrial phosphatidylserine transfer causes liver disease. Cell 2019;177:881–895.e17.
[5] Cabré N, Luciano-Mateo F, Chapski DJ, Baiges-Gayà G, Fernández-Arroyo S, Hernández-Aguilera A, et al. Laparoscopic sleeve gastrectomy in patients with severe obesity restores adaptive responses leading to nonalcoholic steatohepatitis. IJMS 2022;23:7830.
[6] Cabré N, Luciano-Mateo F, Fernández-Arroyo S, Baiges-Gayà G, Hernández-Aguilera A, Fibla M, et al. Laparoscopic sleeve gastrectomy reverses non-alcoholic fatty liver disease modulating oxidative stress and inflammation. Metabolism 2019;99:81–9.
[7] Nudel J, Sanchez VM. Surgical management of obesity. Metabolism 2019;99:81–9.
[8] Arterburn DE, Olsen MK, Smith VA, Livingston EH, Van Scoyoc L, Yancy WS, et al. Association between bariatric surgery and long-term survival. JAMA 2015;313:62.
[9] Hotamisligil GS. Foundations of immunometabolism and implications for metabolic health and disease. Immunity 2017;47:406–20.
[10] Dyall SC, Balas L, Bazan NG, Brenna JT, Chiang N, Da Costa Souza F, et al. Polyunsaturated fatty acids and fatty acid-derived lipid mediators: recent advances in the understanding of their biosynthesis, structures, and functions. Prog Lipid Res 2022;86:101165.
[11] Christie WW, Harwood JL. Oxidation of polyunsaturated fatty acids to produce lipid mediators. Essays Biochem 2020;64:401–21.
[12] Liakh I, Janczy A, Pakiet A, Korczynska J, Proczko-Stepaniak M, Kaska L, 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;46:408–16.
[13] Hernandez-Carretero A, Weber N, La Frano MR, Ying W, Lantero Rodriguez J, Sears DD, et al. Obesity-induced changes in lipid mediators persist after weight loss. Int J Obes 2018;42:728–36.
[14] Pedersen TL, Newman JW. Establishing and performing targeted multi-residue analysis for lipid mediators and fatty acids in small clinical plasma samples. In: Giera M, editor. Clinical metabolomics, vol. 1730. New York, NY: Springer New York; 2018. p. 175–212.
[15] Hartung NM, Ostermann AI, Immenschuh S, Schebb NH. Combined targeted proteomics and oxylipin metabolomics for monitoring of the COX-2 pathway. Proteomics 2021;21:1900058.
[16] Hajeyah AA, Griffiths WJ, Wang Y, Finch AJ, O'Donnell VB. The biosynthesis of enzymatically oxidized lipids. Front Endocrinol 2020;11:591819.
[17] Radmark O. Formation of eicosanoids and other oxylipins in human macrophages. Biochem Pharmacol 2022;204:115210.
[18] De Oliveira Dos Santos AR, De Oliveira Zanuso B, Miola VFB, Barbalho SM, Santos Bueno PC, Flato UAP, et al. Adipokines, myokines, and hepatokines: crosstalk and metabolic repercussions. IJMS 2021;22:2639.
[19] Kojta I, Chacińska M, Błachnio-Zabielska A. Obesity, bioactive lipids, and adipose tissue inflammation in insulin resistance. Nutrients 2020;12:1305.
[20] Zahradka P, Neumann S, Aukema HM, Taylor CG. Adipocyte lipid storage and adipokine production are modulated by lipoxygenase-derived oxylipins generated from 18-carbon fatty acids. Int J Biochem Cell Biol 2017;88:23–30.
[21] Tans R, Bande R, Van Rooij A, Molloy BJ, Stienstra R, Tack CJ, et al. Evaluation of cyclooxygenase oxylipins as potential biomarker for obesity-associated adipose tissue inflammation and type 2 diabetes using targeted multiple reaction monitoring mass spectrometry. Prostagl Leukot Essent Fat Acids 2020;160:102157.
[22] Misheva M, Johnson J, McCullagh J. Role of oxylipins in the inflammatory-related diseases NAFLD, obesity, and type 2 diabetes. Metabolites 2022;12:1238.
[23] Kadowaki T. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest 2006;116:1784–92.
[24] Yadav A, Kataria MA, Saini V, Yadav A. Role of leptin and adiponectin in insulin resistance. Clin Chim Acta 2013;417:80–4.
[25] Guo J-Y, Chen H-H, Lee W-J, Chen S-C, Lee S-D, Chen C-Y. Fibroblast growth factor 19 and fibroblast growth factor 21 regulation in obese diabetics, and non-alcoholic fatty liver disease after gastric bypass. Nutrients 2022;14:645.
[26] Jin L, Yang R, Geng L, Xu A. Fibroblast growth factor–based pharmacotherapies for the treatment of obesity-related metabolic complications. Annu Rev Pharmacol Toxicol 2023;63:359–82.
[27] Dong R, Zhang M, Hu Q, Zheng S, Soh A, Zheng Y, et al. Galectin-3 as a novel biomarker for disease diagnosis and a target for therapy (Review). Int J Mol Med 2018;41:599–614.
[28] Zhu W, Sahar NE, Javaid HMA, Pak ES, Liang G, Wang Y, et al. Exercise-induced irisin decreases inflammation and improves NAFLD by competitive binding with MD2. Cells 2021;10:3306.
[29] Grönroos S, Helmiö M, Juuti A, Tiusanen R, Hurme S, Löyttyniemi E, et al. Effect of laparoscopic sleeve gastrectomy vs roux-en-Y gastric bypass on weight loss and quality of life at 7 Years in patients with morbid obesity: the SLEEVEPASS randomized clinical trial. JAMA Surg 2021;156:137.
[30] Cabré N, Luciano-Mateo F, Baiges-Gayà G, Fernández-Arroyo S, Rodríguez-Tomàs E, Hernández-Aguilera A, et al. Plasma metabolic alterations in patients with severe obesity and non-alcoholic steatohepatitis. Aliment Pharmacol Ther 2020;51:374–87.
[31] Calvo N. Liver fat deposition and mitochondrial dysfunction in morbid obesity: an approach combining metabolomics with liver imaging and histology. WJG 2015;21:7529.
[32] Brunt EM. Nonalcoholic fatty liver disease and the ongoing role of liver biopsy evaluation. Hepatology Communications 2017;1:370–8.
[33] Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. Hepatology 2009;49:1017–44.
[34] Palomäki VA, Koivukangas V, Meriläinen S, Lehenkari P, Karttunen TJ. A straightforward method for adipocyte size and count analysis using open-source software QuPath. Adipocyte 2022;11:99–107.
[35] Bel Lassen P, Charlotte F, Liu Y, Bedossa P, Le Naour G, Tordjman J, et al. The FAT score, a fibrosis score of adipose tissue: predicting weight-loss outcome after gastric bypass. J Clin Endocrinol Metabol 2017;102:2443–53.
[36] Ortega FB, Lavie CJ, Blair SN. Obesity and cardiovascular disease. Circ Res 2016;118:1752–70.
[37] Bertran N, Camps J, Fernandez-Ballart J, Arija V, Ferre N, Tous M, et al. Diet and lifestyle are associated with serum C-reactive protein concentrations in a population-based study. J Lab Clin Med 2005;145:41–6.
[38] Fernández-Arroyo S, Hernández-Aguilera A, De Vries MA, Burggraaf B, Van Der Zwan E, Pouw N, et al. Effect of vitamin D3 on the postprandial lipid profile in obese patients: a non-targeted lipidomics study. Nutrients 2019;11:1194.
[39] Baiges-Gaya G, Fernández-Arroyo S, Luciano-Mateo F, Cabré N, Rodríguez-Tomàs E, Hernández-Aguilera A, et al. Hepatic metabolic adaptation and adipose tissue expansion are altered in mice with steatohepatitis induced by high-fat high sucrose diet. J Nutr Biochem 2021;89:108559.
[40] Castañé H, Iftimie S, Baiges-Gaya G, Rodríguez-Tomàs E, Jiménez-Franco A, López-Azcona AF, et al. Machine learning and semi-targeted lipidomics identify distinct serum lipid signatures in hospitalized COVID-19-positive and COVID-19-negative patients. Metabolism 2022;131:155197.
[41] Samarra I, Masdevall C, Foguet-Romero E, Guirro M, Riu M, Herrero P, et al. Analysis of oxylipins to differentiate between organic and conventional UHT milks. Food Chem 2021;343:128477.
[42] Polinski KJ, Armstrong M, Manke J, Seifert J, Crume T, Yang F, et al. Collection and storage of human plasma for measurement of oxylipins. Metabolites 2021;11:137.
[43] TsatsoulisA, Paschou SA. Metabolically healthy obesity: criteria, epidemiology, controversies, and consequences. Curr Obes Rep 2020;9:109–20.
[44] Vinaixa M, Ángel Rodríguez M, Rull A, Beltrán R, Bladé C, Brezmes J, et al. Metabolomic assessment of the effect of dietary cholesterol in the progressive development of fatty liver disease. J Proteome Res 2010;9:2527–38.
[45] Sun Y, Koh HWL, Choi H, Koh WP, Yuan J-M, Newman JW, et al. Plasma fatty acids, oxylipins, and risk of myocardial infarction: the Singapore Chinese Health Study. J Lipid Res 2016;57:1300–7.
[46] Monirujjaman M, Devssy JG, Yamaguchi T, Sidhu N, Kugita M, Gabbs M, et al. Distinct oxylipin alterations in diverse models of cystic kidney diseases. Biochim Biophys Acta Mol Cell Biol Lipids 2017;1862:1562–74.
[47] Monirujjaman M, Aukema HM. High dietary protein does not alter renal prostanoids and other oxylipins in normal mice or in those with inherited kidney disease. J Nutr 2020;150:1135–43.
[48] Pauls SD, Du Y, Clair L, Winter T, Aukema HM, Taylor CG, et al. Impact of age, menopause, and obesity on oxylipins linked to vascular health. AATVB 2021;41:883–97.
[49] Kuhn H, Thiele BJ. The diversity of the lipoxygenase family. Many sequence data but little information on biological significance. FEBS Lett 1999;449:7–11.
[50] Tan R, Yan B, Wang C, Zhang L. The role of 12/15-lipoxygenase and its various metabolites generated from multiple polyunsaturated fatty acids as substrates in inflammatory responses. BioMed research international2022 2022:1–13.
[51] Powell WS, Rokach J. Biosynthesis, biological effects, and receptors of hydroxyeicosatetraenoic acids (HETEs) and oxoeicosatetraenoic acids (oxo-

ETEs) derived from arachidonic acid. Biochimica et Biophysica Acta (BBA)-Molecular and Cel Biology f Lipids 2015;1851:340–55.
[52] Marbach-Breitrück E, Kutzner L, Rothe M, Gurke R, Schreiber Y, Reddanna P, et al. Functional characterization of knock-in mice expressing a 12/15-lipoxygenating Alox5 mutant instead of the 5-lipoxygenating wild-type enzyme. Antioxidants Redox Signal 2020;32:1–17.
[53] Sexton A, McDonald M, Cayla C, Thiemermann C, Ahluwalia A. 12-Lipoxygenase-derived eicosanoids protect against myocardial ischemia/reperfusion injury via activation of neuronal TRPV1. Faseb J 2007;21:2695–703.
[54] Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediatorsNat. Rev Immunol 2008;8:349–61.
[55] Middleton A-LO, Byrne JP, Calder PC. The influence of bariatric (metabolic) surgery on blood polyunsaturated fatty acids: a systematic review. Clinical Nutrition ESPEN 2022;48:121–40.
[56] Hovland A, Nestvold T, Bohov P, Trøseid M, Aukrust P, Berge RK, et al. Bariatric surgery reduces fasting total fatty acids and increases n-3 polyunsaturated fatty acids in morbidly obese individuals. Scand J Clin Lab Investig 2017;77:628–33.
[57] Després J-P, Lemieux I. Abdominal obesity and metabolic syndrome. Nature 2006;444:881–7.
[58] Tchernof A, Després J-P. Pathophysiology of human visceral obesity: an update. Physiol Rev 2013;93:359–404.
[59] Colson C, Batrow P-L, Dieckmann S, Contu L, Roux CH, Balas L, et al. Effects of fatty acid metabolites on adipocytes britening: role of thromboxane A2. Cells 2023;12:446.
[60] Graziani F, Biasucci LM, Cialdella P, Liuzzo G, Giubilato S, Della Bona R, et al. Thromboxane production in morbidly obese subjects. Am J Cardiol 2011;107:1656–61.
[61] Lei X, Li Q, Rodriguez S, Tan SY, Seldin MM, McLenithan JC, et al. Thromboxane synthase deficiency improves insulin action and attenuates adipose tissue fibrosis. Am J Physiol Endocrinol Metabol 2015;308:E792–804.
[62] Patrono C, Rocca B. Measurement of thromboxane biosynthesis in health and disease. Front Pharmacol 2019;10:1244.
[63] Bi C, Fu Y, Zhang Z, Li B. Prostaglandin E2 confers protection against diabetic coronary atherosclerosis by stimulating M2 macrophage polarization via the activation of the CREB/BDNF/TrkB signaling pathway. Faseb J 2020;34:7360–71.
[64] Lajoie J, Kowatsch MM, Mwangi LW, Boily-Larouche G, Oyugi J, Chen Y, et al. Low-dose acetylsalicylic acid reduces T cell immune activation: potential implications for HIV prevention. Front Immunol 2021;12:778455.
[65] Dalli J, Kitch D, O'Brien MP, Hunt PW, Funderburg N, Moisi D, et al. Pro-inflammatory and pro-resolving lipid mediators of inflammation in HIV: effect of aspirin intervention. EBioMedicine 2023;89:104468.
[66] Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med 2022;387:205–16.
[67] Wing RR, Phelan S. Long-term weight loss maintenance. Am J Clin Nutr 2005;82:222S–5S.
[68] Izquierdo E, Cuevas VD, Fernández-Arroyo S, Riera-Borrull M, Orta-Zavalza E, Joven J, et al. Reshaping of human macrophage polarization through modulation of glucose catabolic pathways. J Immunol 2015;195:2442–51.
[69] Arner P, Bernard S, Appelsved L, Fu K-Y, Andersson DP, Salehpour M, et al. Adipose lipid turnover and long-term changes in body weight. Nat Med 2019;25:1385–9.
[70] Arner P, Bernard S, Salehpour M, Possnert G, Liebl J, Steier P, et al. Dynamics of human adipose lipid turnover in health and metabolic disease. Nature 2011;478:110–3.