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RESEARCH LETTER

WILEY

Plasma leukotriene B₄ decreases after bariatric–metabolic surgery in severe obesity: A prospective observational study

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1 | BACKGROUND

Obesity increases the risk of diabetes and other metabolic disorders.¹ Bariatric–metabolic surgery (BMS) achieves durable weight loss and glycaemic improvement,² yet the biological mediators of these benefits remain incompletely defined. Low-grade inflammation is a key feature of obesity.³ Among inflammatory pathways, lipid mediators (LMs) integrate immune and metabolic signalling: leukotriene B₄ (LTB₄) is a potent pro-inflammatory LM generated by 5-lipoxygenase (5-LOX) and signalling via its high-affinity receptor BLT1, whereas specialised pro-resolving mediators (resolvins, protectins and maresins) counter-regulate inflammation.^{4,5} Animal studies implicate LM imbalance in obesity-related metabolic dysfunction,^{6,7} but human data are limited, particularly for plasma measurements and postoperative changes. Because LM levels are susceptible to ex vivo coagulation and cell activation,⁸ serum measurements can be artefactually altered; standardised plasma assays are preferable yet remain less common in human studies.

We therefore performed a prospective, exploratory study in severe obesity, comprehensively profiling plasma LMs before and 12 months after BMS using targeted LC–MS/MS.

2 | MATERIALS AND METHODS

2.1 | Study design

This prospective observational study was designed to investigate changes in plasma LM levels between before and after BMS and their association with clinical parameters. The clinical cohort was single-centre at Chibune General Hospital; plasma LM assays were performed centrally at Kobe University. The protocol complied with the Declaration of Helsinki and was approved by the Clinical Research Review Board of Kobe University Graduate School of Medicine (approval no. B190120; approval date, 24 September 2019). Written informed consent was obtained from all participants. The study period was from 24 September 2019 to 31 March 2025.

Parts of this work were presented as a poster at the 28th Adiposcience Symposium of the Japan Society for the Study of Obesity, Osaka, Japan, on 7 to 8 March 2025.

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2.2 | Participants and sample size

Adults (≥ 20 years) scheduled for BMS at Chibune General Hospital were eligible; exclusions were severe comorbidities or investigator judgement. This was a pilot/exploratory study; with no prior human effect-size estimates for plasma LMs, no formal power calculation was feasible. Limited power, especially for small to moderate correlations, is acknowledged.

2.3 | Data collection

Assessments at baseline and 1, 3, 6 and 12 months; the primary comparison was baseline versus 12 months. Body composition (InBody 270, InBody Japan) and CT-derived adiposity metrics and liver-to-spleen ratio (L/S) ratio were obtained per standardised procedures (Figure S1). Plasma for LMs, type IV collagen 7S and free fatty acids (FFAs) was stored at -80°C and analysed centrally; other labs were measured locally. Participant flow is shown in Figure S2.

2.4 | Measurement of LMs

Targeted LC-MS/MS lipidomics was performed as described with deuterated internal standards,⁸ automated C18 SPE and QTRAP 6500. A panel of 40 LMs was assayed; eight were consistently below the lower limit of quantification (LLOQ) in paired samples and not tested, leaving 32 quantifiable mediators.

2.5 | Outcomes

The primary outcome was the change in plasma LM levels between baseline and 12 months after surgery. Secondary outcomes included a restriction analysis in participants without antidiabetic medications throughout follow-up. Exploratory analyses assessed associations between changes in LM levels and changes in clinical measures.

2.6 | Statistical analysis

LMs are summarised as median [interquartile range]. Pre-post comparisons used the Wilcoxon signed-rank test (two-sided), reporting the Hodges-Lehmann median difference ($\Delta = \text{post} - \text{pre}$) with 95% confidence intervals. For the 32-mediator family, the false discovery rate (FDR) was controlled at 5% using Benjamini-Hochberg; q values are shown alongside unadjusted p . Correlations used Spearman ρ (two-sided). Changes in medication use were analysed with McNemar test. Software: SPSS v29.0 and EZR. Significance thresholds followed the above specification ($q < 0.05$ for FDR-controlled families; otherwise two-sided $p < 0.05$).

3 | RESULTS

3.1 | Participants

Forty individuals were enrolled between 11 January and 18 August 2020 (Figure S2). Follow-up was completed on 17 September 2021. Four participants discontinued postoperative visits and one had missing samples; thus, 35 participants (mean age 41.7 ± 11.0 years; 57.1% female; mean BMI $41.2 \pm 7.3 \text{ kg/m}^2$) were included in the analysis. No severe adverse events occurred.

3.2 | Changes in clinical parameters

The clinical characteristics of participants at baseline and 12 months after surgery are summarised in Table 1. Body weight, BMI, body fat mass and visceral fat area decreased; the L/S increased. Indices of insulin resistance and HbA1c improved; HDL-C increased. Use of anti-diabetic and antihypertensive medications declined (Table 1).

3.3 | Changes in plasma LM levels

Of 40 targeted LMs, eight were $< \text{LLOQ}$ at both time points and not tested; analyses therefore included 32 quantifiable mediators (Table 2). After FDR control across this family, only LTB_4 showed a significant pre-post change: median $2.3\text{--}1.2 \text{ pg/mL}$; ΔHL (post-pre) -0.9 (95% CI -1.2 to -0.7); p (Wilcoxon, exact) $= 4.23 \times 10^{-5}$; $q = 0.001$.

3.4 | Medication-free restriction analysis

Findings were directionally consistent in participants without antidiabetic medications ($n = 21$): LTB_4 decreased with nominal significance ($p = 0.002$) but did not survive FDR across 32 mediators ($q = 0.064$) (Table S1).

3.5 | Correlation between plasma LTB_4 levels and clinical parameters

In exploratory Spearman analyses, no correlation between changes in LTB_4 and changes in clinical measures reached statistical significance (Table S2).

4 | CONCLUSIONS

We performed a comprehensive analysis of plasma LM profiles before and after substantial weight loss achieved by BMS in individuals with severe obesity. Among the 32 quantifiable LMs, only LTB_4 showed a statistically significant change after FDR control, with a pronounced

TABLE 1 Changes in clinical parameters from baseline to 12 months after surgery.

Parameter	Baseline (n = 35)	After surgery (n = 35)	p Value
Age (years)	41.7 ± 11.0		
Sex (male/female)	15/20		
Body weight (kg)	110.7 ± 25.4	85.6 ± 22.8	<0.001
BMI (kg/m ²)	41.2 ± 7.3	31.8 ± 6.8	<0.001
Use of diabetes medication (yes/no)	14/21	4/31	<0.01
Use of hypertension medication (yes/no)	20/15	8/27	<0.001
Use of dyslipidaemia medication (yes/no)	11/24	8/27	0.38
Muscle mass (kg)	55.7 ± 13.0	51.3 ± 12.4	<0.001
Body fat mass (kg)	50.7 ± 14.6	31.5 ± 13.6	<0.001
Body fat percentage	46.1 ± 5.7	35.8 ± 8.1	<0.001
Skeletal muscle mass (kg)	33.1 ± 8.2	30.1 ± 7.8	<0.001
Skeletal muscle index (kg/m ²)	9.2 ± 1.5	8.2 ± 1.6	<0.001
Visceral fat area (cm ²)	250.4 ± 102.9	109.2 ± 77.9	<0.001
Subcutaneous fat area (cm ²)	525.8 ± 159.9	358.2 ± 156.7	<0.001
Total fat area (cm ²)	776.1 ± 221.0	467.4 ± 214.5	<0.001
Liver-to-spleen ratio	0.8 ± 0.3	1.2 ± 0.2	<0.001
Platelets (×10 ⁴ /μL)	28.4 ± 8.2	25.8 ± 7.4	<0.001
LDL-C (mg/dL)	113.1 ± 12.9	117.4 ± 32.5	0.40
HDL-C (mg/dL)	48.1 ± 11.6	67.0 ± 16.6	<0.001
TG (mg/dL)	115.9 ± 53.0	102.3 ± 49.5	0.19
HbA1c (%)	6.1 ± 0.6	5.6 ± 0.3	<0.001
Fasting plasma glucose (mg/dL)	112.0 ± 18.8	96.6 ± 11.3	<0.001
AST (U/L)	25.7 ± 12.1	19.7 ± 6.3	<0.001
ALT (U/L)	36.2 ± 22.7	20.4 ± 9.7	<0.001
γ-GTP (U/L)	39.2 ± 25.9	26.2 ± 29.1	<0.001
Creatinine (mg/dL)	0.7 ± 0.1	0.7 ± 0.1	0.90
eGFR (mL/min 1.73 m ⁻²)	86.0 ± 19.1	83.9 ± 14.3	0.41
Uric acid (mg/dL)	5.9 ± 1.4	5.5 ± 1.5	0.11
Albumin (g/dL)	4.1 ± 0.3	4.3 ± 0.3	<0.001
CRP (mg/dL)	0.6 ± 1.0	0.2 ± 0.2	<0.01
Type IV collagen 7S (ng/mL)	2.7 ± 0.8	2.4 ± 0.7	0.08
FFAs (mEq/L)	0.8 ± 0.3	0.5 ± 0.2	<0.001
Fib-4 index	0.7 ± 0.4	0.9 ± 0.6	0.06
NAFLD fibrosis score	-1.3 ± 1.7	-1.5 ± 1.6	0.04
Fasting immunoreactive insulin (μU/mL)	22.2 ± 11.0	9.0 ± 4.1	<0.001
Fasting C-peptide immunoreactivity (ng/mL)	3.6 ± 1.1	2.0 ± 0.7	<0.001
HOMA-IR	6.3 ± 3.9	2.2 ± 1.3	<0.001
Adipo-IR	16.5 ± 7.8	5.0 ± 3.1	<0.001
Leptin (ng/mL)	51.7 ± 34.1	17.9 ± 9.9	<0.001
Adiponectin (μg/mL)	7.0 ± 4.8	13.3 ± 8.8	<0.001

Note: Data are means ± SD for continuous variables or n for categorical variables. The p values were determined with the paired t test for continuous variables and McNemar test for categorical variables.

Abbreviation: γ-GTP, gamma-glutamyl transpeptidase; Adipo-IR, adipose tissue insulin resistance index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FFAs, free fatty acids; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; NAFLD, non-alcoholic fatty liver disease; SD, standard deviation; TG, triglycerides.

TABLE 2 Changes in plasma lipid mediator concentrations (pg/mL) from baseline to 12 months after surgery.

Mediator	Pre, median [IQR]	Post, median [IQR]	ΔHL (95% CI)	p Value	q
Derived from AA					
PGE ₂	267.9 [204.5–395.2]	253.7 [203.3–329.5]	−21.7 (95% CI −69.8 to 30.7)	0.342	0.476
PGD ₂	717.5 [484.3–903.2]	486.6 [333.6–716.1]	−179.3 (95% CI −363.6 to −26.6)	0.342	0.476
PGJ ₂ + Δ12-PGJ ₂	ND	ND	ND	N/A	N/A
15-deoxy-Δ ^{12,14} -PGJ ₂	7660.3 [4844.3–12 065.6]	6904.6 [4616.4–9655.5]	−620.8 (95% CI −1949.2 to 459.3)	0.287	0.476
PGF _{2α}	80.9 [52.4–127.7]	62.0 [48.7–94.4]	−18.0 (95% CI −40.9 to 0.8)	0.064	0.205
TxB ₂	0.0 [0.0–1975.6]	0.0 [0.0–0.0]	−500.9 (95% CI −1022.2 to 0.0)	0.008	0.059
12S-HHT	10.8 [6.4–24.3]	8.1 [6.4–13.9]	−5.0 (95% CI −11.7 to 0.3)	0.064	0.205
LTB ₄	2.3 [1.8–2.9]	1.2 [0.8–1.6]	−0.9 (95% CI −1.2 to −0.7)	4.23 × 10 ^{−5}	0.001
Lipoxin A4	ND	ND	ND	N/A	N/A
Lipoxin B4	49.2 [25.9–85.8]	57.1 [28.7–90.6]	−1.0 (95% CI −12.8 to 11.7)	0.756	0.806
5,15-diHETE	ND	ND	ND	N/A	N/A
5-HETE	42.2 [27.5–52.9]	28.5 [20.9–47.8]	−6.2 (95% CI −13.0 to 0.9)	0.072	0.208
12-HETE	54.3 [38.8–77.4]	44.3 [30.7–67.1]	−12.9 (95% CI −23.0 to −4.0)	0.009	0.059
15-HETE	34.1 [24.5–42.3]	25.6 [17.3–39.3]	−5.6 (95% CI −11.1 to −0.3)	0.041	0.186
AA	11 380.1 [8879.1–13 216.2]	10 509.9 [7190.5–14 213.7]	−333.0 (95% CI −2172.7 to 1555.2)	0.719	0.793
Derived from EPA					
Lipoxin A5	ND	ND	ND	N/A	N/A
Resolvin E1	ND	ND	ND	N/A	N/A
Resolvin E2	10.0 [7.7–14.9]	6.9 [4.6–12.4]	−1.9 (95% CI −4.5 to 0.9)	0.136	0.272
Resolvin E3	9.4 [7.0–13.7]	10.0 [7.4–12.3]	0.1 (95% CI −1.9 to 2.1)	0.896	0.925
5-HEPE	17.8 [11.7–26.8]	14.9 [7.8–23.3]	−4.4 (95% CI −7.5 to −0.8)	0.024	0.127
12-HEPE	6.0 [4.0–9.5]	4.2 [2.0–6.8]	−1.8 (95% CI −3.4 to −0.5)	0.009	0.059
15-HEPE	6.2 [5.0–9.5]	5.0 [2.9–7.5]	−1.0 (95% CI −2.1 to −0.8)	0.185	0.347
18-HEPE	11.4 [7.6–16.4]	7.0 [4.1–13.0]	−2.3 (95% CI −4.6 to 0.1)	0.055	0.205
EPA	4472.5 [3041.4–6443.4]	3760.7 [1544.3–6183.1]	−687.2 (95% CI −1439.2 to 207.4)	0.116	0.247
Derived from DHA					
Resolvin D1	10.3 [0.0–30.8]	14.8 [0.0–29.0]	1.8 (95% CI −3.8 to 8.1)	0.550	0.658
Resolvin D2	0.0 [0.0–9.7]	6.3 [0.0–14.7]	2.9 (95% CI −0.5 to 7.4)	0.092	0.245
Resolvin D3	ND	ND	ND	N/A	N/A
Resolvin D5	1.7 [0.0–2.5]	1.4 [0.0–2.7]	−0.2 (95% CI −1.0 to 0.4)	0.445	0.569
Protectin D1	1.3 [0.0–2.5]	1.5 [0.0–3.2]	−0.1 (95% CI −1.0 to 1.3)	0.710	0.793
Maresin 1	ND	ND	ND	N/A	N/A
Maresin 2	ND	ND	ND	N/A	N/A
4-HDHA	29.7 [20.6–46.7]	28.3 [15.2–51.3]	−3.6 (95% CI −10.1 to 4.0)	0.334	0.476
7-HDHA	15.1 [9.7–20.4]	13.5 [7.6–20.2]	−1.1 (95% CI −3.1 to 1.6)	0.302	0.476
14-HDHA	28.3 [18.8–43.4]	22.3 [11.8–32.5]	−8.0 (95% CI −14.0 to −3.1)	0.005	0.059
17-HDHA	19.1 [13.0–24.2]	13.9 [7.2–28.0]	−2.7 (95% CI −6.3 to 0.9)	0.112	0.247
DHA	41 680.4 [32 133.4–52 798.0]	41 790.3 [20 999.0–60 704.3]	−3071.5 (95% CI −9888.2 to 5647.2)	0.441	0.569
Derived from linoleic acid					
HYA + HYC	42.1 [30.5–102.7]	43.5 [31.7–69.7]	−4.4 (95% CI −34.8 to 9.9)	0.555	0.658
HYB	100.7 [71.2–216.2]	101.0 [72.0–140.8]	−17.6 (95% CI −57.5 to 13.8)	0.245	0.435
KetoA	46.9 [30.7–56.7]	45.5 [26.1–54.6]	−3.2 (95% CI −7.6 to 0.6)	0.101	0.247
KetoB	207.2 [134.3–268.0]	232.0 [169.0–265.5]	0.3 (95% CI −19.7 to 22.5)	0.948	0.948

Note: Data are median [interquartile range] of plasma concentrations (pg/mL). ΔHL denotes the Hodges–Lehmann median difference (post–pre; negative indicates a decrease) with 95% confidence intervals (CI). Paired comparisons used the Wilcoxon signed-rank test (two-sided). For the family of quantifiable mediators ($m = 32$), the false discovery rate (FDR) was controlled at 5% using the Benjamini–Hochberg procedure; q denotes FDR-adjusted p values. Analyses used complete pairs; values below the lower limit of quantification (LLOQ) were treated as missing for that mediator. ND, not detected; concentrations <LLOQ at both time points; such mediators were not tested and were not included in multiplicity control. Notation: square brackets denote IQR; parentheses () denote confidence intervals.

Abbreviations: 15-deoxy-Δ^{12,14}-PGJ₂, 15-deoxy-Δ^{12,14}-prostaglandin J₂; 4-/7-/14-/17-HDHA, 4-/7-/14-/17-hydroxy-docosahexaenoic acid; 5-/12-/15-/18-HEPE, 5-/12-/15-/18-hydroxyeicosapentaenoic acid; 5-/12-/15-HETE, 5-/12-/15-hydroxyeicosatetraenoic acid; HYA/HYB/HYC, 10-/13-/12-hydroxy-octadecadienoic acid; 12S-HHT, 12-S-hydroxy-heptadecatrienoic acid; AA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ketoA/B, 10-/12-oxo-octadecenoic acid; LTB₄, leukotriene B₄; LXA₄/LXB₄, lipoxin A₄/B₄; MaR1/2, maresin 1/2; ND, not detected; PD1, protectin D1; PGE₂, prostaglandin E₂; PGD₂, prostaglandin D₂; PGF_{2α}, prostaglandin F_{2α}; TxB₂, thromboxane B₂; ΔHL, Hodges–Lehmann median difference.

postoperative decrease. To address potential confounding by antidiabetic therapy,⁹ we conducted a restriction analysis in participants not receiving antidiabetic medications; the direction and magnitude of the LTB₄ change were similar, although multiplicity-adjusted significance was not retained in this smaller subgroup—findings consistent with limited statistical power.

In exploratory Spearman analyses, changes in LTB₄ were not significantly correlated with changes in clinical measures. Given the modest sample, type-II error remains possible, and trends involving weight-loss indices (e.g., percentage excess weight loss), body fat percentage, and FFAs warrant re-evaluation in adequately powered cohorts.

Preclinical work has linked LTB₄-BLT1 signalling to adipose-tissue inflammation and systemic insulin resistance, and pharmacologic or genetic interruption of the 5-LOX-LTB₄-BLT1 axis improves metabolic parameters in obese models.^{7,10,11} Our results extend this literature by providing human, plasma-based evidence that LTB₄ declines after surgical weight loss. Prior clinical studies using serum did not observe a significant change in LTB₄ after bariatric surgery because eicosanoids are sensitive to coagulation and cell activation; serum measurements can be artefactually altered.¹² The use of standardised plasma assays here addresses this limitation and may explain the discrepant findings.

There are several limitations to our study. First, it was an exploratory, single-centre surgical cohort and no formal power calculation; precision is limited, particularly for correlations. Second, the primary analysis focused on plasma LM profiles, and tissue LM measurements were not obtained, precluding mechanistic inference about anatomic sources of circulating changes. Third, although the medication-free analysis mitigates confounding by antidiabetic drugs, residual confounding from other clinical changes cannot be excluded. Finally, generalisability to non-surgical weight-loss settings (e.g., lifestyle or pharmacotherapy) remains to be established.

In conclusion, BMS was associated with a robust, FDR-controlled reduction in plasma LTB₄ over 12 months. Although correlations with clinical improvements were not significant in this exploratory analysis, the consistency and biological plausibility of the LTB₄ signal suggest it may serve as a potential candidate biomarker, pending validation in larger, adequately powered studies.

AUTHOR CONTRIBUTIONS

Design: Yushi Hirota, Yasushi Nakagawa, Seiichi Kitahama, Wataru Ogawa. Conduct/data collection: Seiichi Kitahama, Seiji Nishikage, Yasushi Nakagawa, Shinsuke Nakajima, Masakazu Shinohara, Yusei Hosokawa. Analysis: Seiji Nishikage, Yasushi Nakagawa, Masakazu Shinohara, Yusei Hosokawa, Yushi Hirota, Wataru Ogawa. Writing manuscript: Seiji Nishikage, Yushi Hirota, Yusei Hosokawa, Kai Yoshimura, Akane Yamamoto, Tomofumi Takayoshi, Wataru Ogawa. All authors reviewed and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

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PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.70114>.

DATA AVAILABILITY STATEMENT

The datasets generated and analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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