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Do changes in persistent organic pollutants after bariatric surgery cause endocrine disruption?

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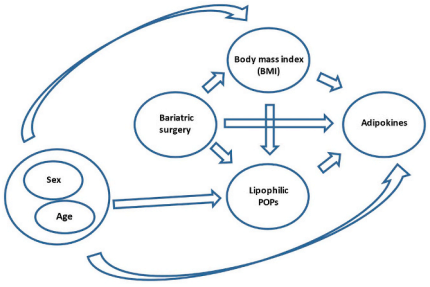
HIGHLIGHTS

- Persistent organic pollutants (POPs) are released and adipokines increase in serum after bariatic surgery.
- There were strong associations between adiponectin and all POPs, specifically hexachlorobenzene (HCB).
- The increase in HCB explained 38% of the increase in adiponectin.
- The release of POPs after bariatric surgery might have significant endocrine effects with clinical consequences.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Bariatric surgery results in weight loss, marked endocrine changes and the release of persistent organic pollutants (POPs). The release of POPs might cause endocrine disruption. The study aimed to explore associations between POPs and adiponectin, leptin and ghrelin in subjects undergoing bariatric surgery. Methods: The study included 63 subjects with severe obesity (men/women: 13/50), age (years): 45.0 (8.5), and BMI (kg/m^2) 39.1 (3.4). Analyses of adiponectin, leptin and ghrelin and POPs (hexachlorobenzene (HCB), dichlorodiphenyldichloroethylene (*p,p'*-DDE), polychlorinated biphenyl (PCB) 118 (dioxin-like compound; dl), and sum 6 PCB (PCB 28, -52, −101, −138, −153, and −180) were performed before and 12 months after bariatric surgery. Results: There were significant increases in adiponectin and all POPs and a fall in leptin after surgery. The main finding was the highly significant associations between adiponectin and all POPs. The increase in HCB explained 38% of the variation in adiponectin. Conclusions: If the POP-associated increase in adiponectin is a causal effect, the release of POPs might have important clinical consequences. Adiponectin has both positive

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and negative clinical effects exerted by essentially unknown mechanisms. The effects of released POPs on the metabolic functions in subjects undergoing bariatric surgery deserve further evaluation.

1. Introduction

Bariatric surgery is a highly effective treatment of obesity (Sjostrom et al., 2004; Stein et al., 2014). In addition to significant weight loss, normalising blood lipids, blood pressure, uric acid, and glucose metabolism are superior to conservative and medical treatment (Sjostrom et al., 2004; Schauer et al., 2012). The metabolic adaptation after surgery is an interplay between the endocrine systems, gut hormones, microbiota, gastrointestinal nutrient sensing, gut-brain signalling and others (Batterham and Cummings, 2016). Adiponectin, leptin and ghrelin are hormones involved in the metabolic adaption. Adiponectin is a signalling peptide produced by adipocytes and regulates glucose and lipid metabolism (Maratos-Flier, 2020). Leptin is primarily released from white adipose tissue and regulates energy expenditure, appetite and satiety (Friedman and Halaas, 1998; Rosenbaum and Leibel, 2014). Ghrelin is an appetite-stimulating hormone with neuroendocrine effects secreted primarily by the gastric mucosa (Sakata and Sakai, 2010; Dickson et al., 2011; Sun et al., 2019). Studies have shown that adiponectin concentrations in blood increases and leptin decreases after bariatric surgery, whereas the changes in ghrelin are inconsistent (Pelletier et al., 2002; Peterli et al., 2012; Acharya et al., 2013; Herder et al., 2014; Müller et al., 2015).

Persistent organic pollutants (POPs) are synthetic organic compounds used as pesticides, industrial chemicals, flame-retardants, solvents, and coatings. The population is mainly exposed to POPs through food (Liem et al., 2000; EFSA, 2012). POPs are lipophilic, highly resistant to metabolic degradation, accumulate in adipose tissue and fat-rich organs and have long half-lives (Birnbaum, 1985; Wania and Mackay, 1996; AMAP, 1997). Following bariatric surgery, they are released from the adipose tissue and redistributed, resulting in increased blood concentrations (Kim et al., 2011; Dirtu et al., 2013; Rantakokko et al., 2015; Jansen et al., 2018). Several POPs are endocrine-disrupting chemicals (EDCs) with potential adverse effects (Darnerud, 2003; Birnbaum, 2013; Gore et al., 2015). We have in previous studies shown significant increases in POPs and changes in the hormones adiponectin, leptin and ghrelin after bariatric surgery (Jansen et al., 2018; Farup et al., 2022). However, associations between POPs and the hormones, which was the aim of this study, have as far as we are aware of, not been studied. Considering the endocrine disrupting potential of POPs and the changes in POPs and hormones after surgery, the released POPs might have disruptive endocrine effect.

This study aimed to explore associations between POPs and adiponectin, leptin and ghrelin in subjects undergoing bariatric surgery to detect possible effects of released POPs on glucose, lipid and energy metabolism, endocrine functions, appetite, and satiety.

2. Materials and methods

2.1. Study design

The study used data from the prospective cohort study "Morbid Obesity - Bio-Psycho-Social impacts" (MO-BiPS) (Farup, 2020). The subject characteristics and the POPs and hormone analyses have been published in different contexts in two papers, one studied the levels of POPs after bariatric surgery, and the other APOE polymorphism and endocrine functions (Jansen et al., 2018; Farup et al., 2022).

The study included consecutive subjects 18–60 years of age with severe obesity (defined as body mass index (BMI) $>$ 40 kg/m^2 or $>$ 35 kg/m^2 with obesity-related comorbidity) referred to the obesity unit at Innlandet Hospital Trust, Gjøvik, Norway in 2012–2014 for evaluation of bariatric surgery. Six months before bariatric surgery, the participants completed an intensive lifestyle intervention with dietary interventions and advice on physical activity under the supervision of health personnel. Laparoscopic bariatric surgery was performed as either Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy (SG) based on the surgeon's recommendation in agreement with the participant (Schauer et al., 2003; Roa et al., 2006). There were regular follow-ups after surgery. This study used data from the visits immediately before and one year after surgery.

2.2. Blood sampling

Blood samples were drawn from the cubital vein and centrifuged at 2200 $\times$ G for 10 min at 4 °C. For the POP analyses, aliquots of 2.8 mL were stored in micro tubes (Sarstedt®, PP-nr 72.664, Germany) at −70 °C until analysed.

2.3. Chemical analyses

Blood samples before and one year after surgery were analysed for adiponectin, leptin, and ghrelin at the Hormone Laboratory, Oslo University Hospital, Oslo, Norway by competitive radioimmunoassay (RIA) (Merck Millipore Corporation, Billarica, Ma, USA). Both acylated and non-acylated (total) ghrelin were analysed. POPs were analysed at the Laboratory of Environmental Toxicology, Norwegian University of Life Sciences (NMBU), Norway (accredited by the Norwegian Accreditation according to the requirements of the NS-EN ISO/IEC 17025 TEST 137) (Jansen et al., 2018). The following POPs with detection frequencies above 85% were included in the analyses: hexachlorobenzene (HCB), dichlorodiphenyldichloroethylene (*p,p'*-DDE), polychlorinated biphenyl (PCB) 118 (dioxin-like compound; dl), and sum (Σ) 6 PCB (PCB 28, -52, −101, −138, −153, and −180).

2.4. Statistics

Changes from before to after surgery were analysed with paired *t*-test. Mixed model linear regression was used with the three hormones, one at a time, as the dependent variable, and four groups of POPs, one group at a time, as covariates, and subject as random effect. A mixed model is a statistical model containing at least one fixed effect, here POPs, and other covariates and at least one random effect, here subject, and is a generalisation of linear models. Mixed models are particularly useful in settings with repeated measurements on the same units, here subjects (before and after bariatric surgery). All analyses were adjusted for sex, age, BMI and sampling time (before or after surgery), considered as plausible confounders as illustrated in the directed acyclic graph (DAG) (Fig. 1). To study the direct and indirect effects of surgery on the hormones, supplementary analyses were performed with and without adjusting for BMI and the POPs. The analyses were also performed with the interaction between sex and POPs. When the interaction term was statistically significant, the analyses were repeated, stratifying by sex. The type of surgery was also fitted as an explanatory variable in the model. The normality of residuals was confirmed by visual inspection of QQ-plots. P-values were Benjamini-Hochberg adjusted to control for false discovery rate (FDR) using R-studio version 1.4.1106 and reported as q-values. IBM SPSS Statistics for Windows, version 27.0 IBM Corp: Armonk, NY, USA, was used for the other analyses. P-values $<$ 0.05 (in the comparisons before and after surgery) and q-values $<$ 0.05 (in the analyses of predictors of the hormones) were judged to represent statistical significance.

2.5. Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK), Region South-East, Norway in 2012, ref. numbers 2012/966 and 2012/1394, and conducted according to the Declaration of Helsinki. Participation was voluntary and informed written consent was obtained from all participants before inclusion.

3. Results

3.1. Subject characteristics and the analyses of POPs and hormones

Out of 159 subjects in the MO-BiPS study, 113 completed the conservative treatment and underwent bariatric surgery. Sixty-three subjects (male/female: 13/50; age (years): 45.0 (8.5); and BMI (kg/m^2) 39.1 (3.4)) had complete data before and one year after surgery and were included in this study. There were significant changes in the POPs and the hormones from before to after surgery. Table 1 gives the subject characteristics with comparisons between before and after surgery.

Table 1
Subject characteristics mean (SD) or n (%) for the 63 participants.

Characteristics	Before surgery	After surgery	p-value
Female sex	50 (79%)	–	–
Age (year)	45.0 (8.5)	–	–
Females	44.9 (8.5)	–	–
Males	45.9 (8.6)	–	–
Weight (kg)	115.7 (16.2)	83.7 (14.4)	<0.001
Females	110.5 (11.6)	79.9 (10.4)	<0.001
Males	135.8 (16.1)	97.9 (18.8)	<0.001
BMI (kg/m^2)	39.1 (3.4)	28.3 (3.6)	<0.001
s-adiponectin mg/L	7.7 (4.1)	13.0 (7.0)	<0.001
Females	8.6 (4.2)	13.6 (7.3)	<0.001
Males	4.4 (1.8)	10.8 (5.2)	<0.001
s-leptin (pmol/L)	2271 (952)	1128 (689)	<0.001
Females	2505 (907)	1284 (659)	<0.001
Males	1371 (459)	529 (453)	<0.001
s-ghrelin (pg/mL)	1101 (370)	1241 (612)	0.022
RYGB (n = 53 (84%))	1082 (369)	1365 (588)	<0.001
SG (n = 10 (16%))	1201 (379)	582 (73)	<0.001
Females	1123 (376)	1248 (648)	0.092
Males	1018 (345)	1215 (467)	0.019
HCB (ng/g lw)	23.5 (9.7)	41.8 (23.2)	<0.001
p,p'-DDE (ng/g lw)	124.3 (103.7)	241.8 (197.2)	<0.001
PCB 118 (ng/g lw)	9.3 (5.8)	16.2 (12.0)	<0.001
∑PCB (ng/g lw)	113.2 (61.0)	212.9 (152.9)	<0.001

Abbreviations SD: standard deviation; BMI: body mass index; HCB: hexachlorobenzene; lw: lipid weight; p,p′-DDE: dichlorodiphenyldichloroethylene; PCB: polychlorinated biphenyl; ΣPCB: sum polychlorinated biphenyl (PCB 28, -52, −101, −138, −153, and −180); RYGB: Roux-en-Y gastric bypass; SG: Sleeve gastrectomy.

3.1.1. Associations between the POPs and the hormones

Significant positive associations existed between adiponectin and all POPs, but not between the other hormones and POPs. Male sex was negatively associated with adiponectin and leptin, and BMI was positively associated with leptin. There were no clear associations between time (after versus before surgery) and the hormones. All analyses were adjusted for sex, age, BMI, time and each of the POPs. Table 2 shows the associations between the explanatory variables and circulating levels of the hormones.

.In the analyses of associations between adiponectin and POPs (table 2), HCB had the strongest association. In new analyses adjusted for sex, age, BMI, time and HCB, and in addition one by one of *p,p'*-DDE, PCB 118 and ∑PCB, neither *p,p'*-DDE, PCB 118 nor ∑PCB were significantly associated with adiponectin (data not shown). The association between leptin and BMI differed significantly between men and women, but no significant changes were seen in the association between the hormones and the POPs when this information and type of surgery were added as covariates in the mixed linear model (data not shown).

Since the strongest association was between adiponectin and HCB, supplementary analyses with and without adjusting for HCB and BMI were performed to detect surgery's direct and indirect effects on adiponectin. Table 3 gives the results. Similar analyses for the indirect effects via the other POPs were not performed because these POPs were not significantly associated with adiponectin after adjusting for HCB.

After adjusting for age and sex, the increase in adiponectin from before to after surgery with and without adjusting for HCB were 3.2 (CI: 1.9 to 4.5) and 5.2 (CI: 4.1 to 6.3) respectively (Table 3), indicating that the indirect effect of surgery via HCB on the change in adiponectin was 5.2 minus 3.2 = 2.0 mg/L. The increase in HCB after surgery explains 2.0/5.2 = 38% of the increase of adiponectin. The other POPs did not add a significant explanation for the increase of adiponectin.

3.1.2. Sex-stratified analyses

Because the associations between leptin and the POPs were

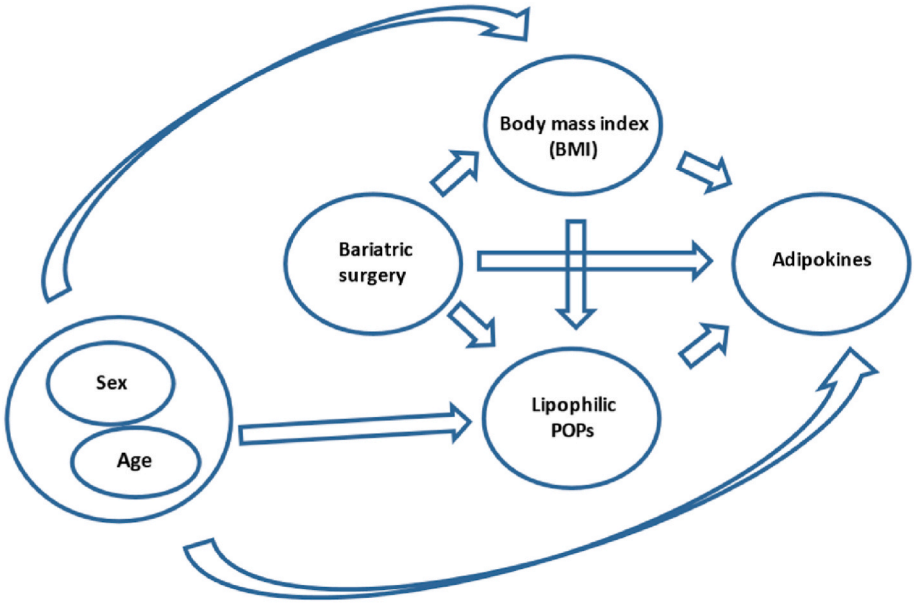

Fig. 1. Directed acyclic graph illustrating plausible causal, pathways in the analyses.

Table 2
Predictors for gastrointestinal hormones leptin, ghrelin and adiponectin, one at a time, as dependent variables, adjusted for four individual or groups of POPs, sex, age, BMI, and time, analysed with mixed model linear regression. The q-values are Benjamini-Hochberg adjusted for 12 analyses. Abbreviations: BMI: body mass index; HCB: hexachlorobenzene; *p,p'*-DDE: dichlorodiphenyldichloroethylene; PCB: polychlorinated biphenyl; ΣPCB: sum polychlorinated biphenyl (PCB 28, -52, −101, −138, −153, and −180). lw: lipid weight. B is the regression coefficient.

Dependent variable	Covariates				
	Lipophilic POP B; (95%CI); p- and q-values	Male sex B; (95%CI); p- and q-values	Age (years) B; (95%CI); p- and q-values	BMI (kg/m^2) B; (95%CI); p- and q-values	Time (After compared with before) p- and q-values
	HCB (ng/g lw)				
Adiponectin (mg/L)	0.11 (0.06–0.16) p < 0.001 q < 0.001	−4.3 (−7.4 to −1.3) p = 0.006 q = 0.012	0.1 (−0.07 to 0.2) p = 0.284 q = 0.681	−0.03 (−0.3 to 0.24) p = 0.826 q = 0.826	2.9 (0.1–5.8) p = 0.044 q = 0.176
Leptin (pmol/L)	−3.8 (−10.6 to 3.1) p = 0.279 q = 0.558 Sex difference p = 0.004	−1005.6 (-1313 to −698.2) p < 0.001 q < 0.001	−4.4 (-19.6 to 10.7) p = 0.560 q = 0.807	126.3 (90.9–161.8) p < 0.001 q < 0.001	300.7 (-107.4 to 708.8) p = 0.147 q = 0.245
Ghrelin (pg/mL)	1.2 (-4.1 to 6.5) p = 0.664 q = 0.779	−68.6 (-349.6 to 212.4) p = 0.627 q = 0.694	12 (-1.7 to 25.8) p = 0.084 q = 0.372	−20.5 (-48.8 to 7.8) p = 0.154 q = 0.264	−115.8 (-422.9 to 191.3) p = 0.457 q = 0.491
	p,p'-DDE (ng/g lw)				
Adiponectin (mg/L)	0.011 (0.004–0.017) p = 0.001 q = 0.003	−4.3 (−7.5 to −1.1) p = 0.009 q = 0.013	0.02 (−0.1 to 0.2) p = 0.774 q = 0.844	−0.14 (−0.4 to 0.1) p = 0.290 q = 0.387	2.5 (−0.4 to 5.4) p = 0.095 q = 0.245
Leptin (pmol/L)	−0.25 (−1.1 to 0.62) p = 0.576 q = 0.768 Sex difference p = 0.022	−1018.6 (-1331.8 to −705.4) p < 0.001 q < 0.001	−3.7 (-20.5 to 13.1) p = 0.659 q = 0.808	131 (96.4–165.6) p < 0.001 q < 0.001	310.7 (-100.3 to 721.8) p = 0.137 q = 0.245
Ghrelin (pg/mL)	−0.03 (-0.7 to 0.6) p = 0.923 q = 0.923	−55.1 (-337.8 to 227.6) p = 0.698 q = 0.698	12.7 (-2.0 to 27.4) p = 0.088 q = 0.372	−22.9 (-50.0 to 4.3) p = 0.098 q = 0.235	−116.8 (-424.2 to 190.6) p = 0.453 q = 0.491
	PCB 118 (ng/g lw)				
Adiponectin (mg/L)	0.20 (0.11–0.29) p < 0.001 q < 0.001	−4.3 (−7.4 to −1.2) p = 0.008 q = 0.014	0.05 (−0.1 to 0.2) p = 0.481 q = 0.808	−0.1 (−0.3 to 0.2) p = 0.503 q = 0.604	2.9 (0.1–5.8) p = 0.042 q = 0.176
Leptin (pmol/L)	−8.1 (−21.1 to 4.8) p = 0.215 q = 0.516 Sex difference p = 0.003	−1001.4 (-1305.5 to −697.3) p < 0.001 q < 0.001	−3.3 (−18.7 to 12.1) p = 0.673 q = 0.807	126.5 (92.0–161.1) p < 0.001 q < 0.001	289 (−118.1 to 696.1) p = 0.162 q = 0.245
Ghrelin (pg/mL)	1.8 (-8.0 to 11.7) p = 0.714 q = 0.779	−66.5 (-346.6 to 213.7) p = 0.637 q = 0.695	11.9 (-2.0 to 25.8) p = 0.093 q = 0.372	−21.3 (-48.7 to 6.2) p = 0.127 q = 0.254	−115.3 (-422.6 to 191.9) p = 0.459 q = 0.491
	Σ PCB (ng/g lw)				
Adiponectin (mg/L)	0.017 (0.009–0.025) p < 0.001 q < 0.001	−4.9 (−8.0 to −1.7) p = 0.003 q = 0.007	0.01 (−0.1 to 0.2) p = 0.871 q = 0.871	−0.04 (−0.3 to 0.2) p = 0.739 q = 0.806	3.1 (0.3–5.9) p = 0.033 q = 0.176
Leptin (pmol/L)	−0.38 (-1.6 to 0.8) p = 0.540 q = 0.768	−1005.8 (-1325.6 to −686.1) p < 0.001 q < 0.001	−3.6 (-20.3 to 13.1) p = 0.670 q = 0.808	128.3 (92.6–164.1) p < 0.001 q < 0.001	290.1 (-119.1 to 699.3) p = 0.163 q = 0.245

(*continued on next page*)

Table 2 (*continued*)

Dependent variable	Covariates				
	Lipophilic POP B; (95%CI); p- and q-values	Male sex B; (95%CI); p- and q-values	Age (years) B; (95%CI); p- and q-values	BMI (kg/m^2) B; (95%CI); p- and q-values	Time (After compared with before) p- and q-values
Ghrelin (pg/mL)	Sex difference p = 0.002 0.4 (-0.5 to 1.3) p = 0.353 q = 0.605	−95.1 (-380.9 to 190.6) p = 0.508 q = 0.677	10.0 (-4.5 to 24.5) p = 0.175 q = 0.525	−18.0 (-46.1 to10.1) p = 0.207 q = 0.311	−107.0 (-413.8 to 199.9) p = 0.491 q = 0.491

Table 3
Predictors for adiponectin, adjusted for sex, age and time and none, one or both BMI and HCB. Analysed with mixed model linear regression. Abbreviations: BMI: body mass index; HCB: hexachlorobenzene; lw: lipid weight; B is the regression coefficient.

Dependent variable	Covariates				
	HCB (ng/g lw) B; (95%CI); p – values	Male sex B; (95% CI); p – values	Age (years) B; (95% CI); p - values	BMI (kg/m^2) B; (95% CI); p – values	Time (After compared with before) p - values
Adiponectin (mg/L)	0.11 (0.06–0.16) p < 0.001	−4.3 (−7.4 to −1.3) p = 0.006	0.08 (−0.07 to 0.23) p = 0.284	−0.03 (−0.30 to 0.24) p = 0.826	2.9 (0.1–5.8) p = 0.044
Adiponectin (mg/L)		- 3.3 (−6.5 to −0.2) p = 0.039	0.11 (−0.04 to 0.27) p = 0.149	−0.25 (−0.52 to 0.01) p = 0.064	2.47 (−0.58 to 5.5) p = 0.111
Adiponectin (mg/L)	0.11 (0.06–0.16) p < 0.001	−4.4 (−7.4 to −1.4) p = 0.005	0.08 (−0.06 to 0.23) p = 0.263		3.2 (1.9–4.5) p < 0.001
Adiponectin (mg/L)		−3.5 (−6.7 to 0.37) p = 0.029	0.14 (−0.01 to 0.30) p = 0.063		5.2 (4.1–6.3) p < 0.001

significantly sex-related (see Table 2), sex-stratified analyses were performed. After adjusting for multiple testing, the sex-stratified analyses showed no significant associations between leptin and the POPs. Table 4 gives the details.

4. Discussion

This study's new, engaging, and significant findings were the strong associations between adiponectin and all POPs. The increase in adiponectin and POPs and fall in leptin after bariatric surgery are known from our previous publications and other studies (Chevrier et al., 2000;

Table 4
Predictors for leptin as dependent variable and POPs, one at a time, as covariates adjusted for age, BMI and time, analysed with mixed model linear regression. Separate analyses for males and females. The q-values are Benjamini-Hochberg adjusted for eight analyses. Abbreviations: HCB: hexachlorobenzene; p,p′-DDE: dichlorodiphenyldichloroethylene; PCB: polychlorinated biphenyl; ΣPCB: sum polychlorinated biphenyl (PCB 28, -52, −101, −138, −153, and −180). Lw: lipid weight. B is the regression coefficient.

Dependent variable	Covariates			
	HCB (ng/g lw) B; (95%CI) p- and q-values	*p,p'*-DDE (ng/g lw) B; (95%CI) p-and q-values	PCB 118 (ng/g lw) B; (95%CI) p- and q-values	Σ PCB (ng/g lw) B; (95%CI) p-and q-values
Leptin - males (pmol/L)	0.25 (- 5.24 to 5.74) p = 0.925 q = 0.971	- 0.02 (- 0.74 to 0.71) p = 0.966 q = 0.971	0.94 (- 9.0 to 10.9) p = 0.846 q = 0.971	0.01 (- 0.79 to 0.82) p = 0.971 q = 0.971
Leptin - females (pmol/L)	- 9.55 (- 19.2 to 0.05) p = 0.051 q = 0.136	- 0.80 (- 1.99 to 0.38) p = 0.182 q = 0.364	- 20.3 (- 38.2 to - 2.4) p = 0.026 q = 0.136	- 2.1 (- 4.19 to - 0.08) p = 0.042 q = 0.136

Imbeault et al., 2001; Pelletier et al., 2002; Peterli et al., 2012; Acharya et al., 2013; Herder et al., 2014; Müller et al., 2015; Jansen et al., 2018; Farup et al., 2022). However, this is the first study to investigate associations between POPs and adiponectin, leptin and ghrelin.

The increase in HCB explained 38% of the increase in adiponectin. The other POPs (*p,p'*-DDE, PCB 118 and ∑PCB) were significantly associated with adiponectin but did not add a significant explanation for the increase in adiponectin in addition to HCB. Table 3 shows a nearly significant association between BMI and adiponectin, which disappeared after adjusting for HCB. BMI and HCB were inversely associated, and the released HCB was a stronger predictor for changes in adiponectin than the fall in BMI. The increase in HCB might be a marker of loss of fat mass. The POP-associated increase in adiponectin might be a causal effect with clinical consequences.

Adiponectin has been associated with improved insulin sensitivity and glucose tolerance, cardio-protective and anti-atherogenic effects, reduced dyslipidaemia, and anti-inflammatory and anti-cancerous effects (Kern et al., 2003; Schulze et al., 2004; Ouchi and Walsh, 2007; Izadi et al., 2013; Herder et al., 2014; Nigro et al., 2014). Although anti-inflammatory effects are predominant, both pro- and anti-inflammatory effects have been claimed in different settings (Ogunwobi and Beales, 2006; Liu et al., 2015; da Silva Rosa et al., 2021). Low concentrations have been associated with type 2 diabetes, obesity, and insulin resistance (Lindsay et al., 2002; Maratos-Flier, 2020). Because of the beneficial effects, adiponectin has been referred to as a salutary adipokine (Menzaghi and Trischitta, 2018). If correct, the increase in POPs after surgery and the positive associations between POPs and adiponectin might be a favourable effect. However, the favourable effects of adiponectin have been questioned. Adiponectin has been associated with reduced bone formation (Abbott et al., 2015), adiposity-related hypertension (Kim et al., 2013), type 1 diabetes mellitus (Imagawa et al., 2002), increased cardiovascular mortality (Menzaghi and Trischitta, 2018) and kidney disease (Saraheimo et al., 2005; Martinez Cantarin et al., 2013). The contradictory observations of adiponectin's clinical effects have been referred to as the "adiponectin paradox" (Menzaghi and Trischitta, 2018). This adiponectin paradox, which has hindered our understanding of the biological role of adiponectin, is yet to be clarified (Muratsu et al., 2021). As far as we are aware of, the combined influence of increased POPs, HCBs potential obesogenic effects, and reduced weight on adiponectin resistance is unknown (Engin, 2017; Heindel et al., 2022). Neither can interactions between POPs and adiponectin be excluded. In all, the clinical effects of the POP-associated increase in adiponectin after bariatric surgery are uncertain and deserve further evaluation.

Leptin and ghrelin were not associated with the POPs. Despite the differences in ghrelin related to the type of surgery (Table 1), ghrelin was not significantly associated with the type of surgery in the multivariable analyses. This might be a type II error. Because the two surgical methods affect gastric mucosa differently, it was anticipated that ghrelin, which is mainly produced in the gastric mucosa, differed between the methods.

The weight loss and endocrine changes after surgery are in accordance with other reports (Sjostrom, 2013; Herder et al., 2014). The positive association between leptin and BMI and negative association between leptin and male sex are known from other studies (Rosenbaum and Leibel, 2014; Mohanraj et al., 2022). The sex-related differences in the associations between leptin and the POPs might be due to the sex-related differences in the associations between leptin and BMI. The sex-stratified analyses could not confirm the sex-related associations. The direct acyclic graph (Fig. 1) presents factors associated with the hormones. The arrow from surgery to the hormones is of uncertain importance since the associations between the hormones and time (i.e. the effect of surgery) were not significant after adjusting for POPs, sex, age and BMI. The results indicate that these factors are the primary independent predictors of the hormones and that significant confounders have not been left out.

4.1. Strengths and limitations

Including unselected subjects from the general population increases the study's external validity. The main findings were highly significant after correction for multiple testing, reducing the risk of type I error. The small sample size makes false negative results possible, and the unequal distribution of males and females weakens the sex-stratified analyses. Confounding factors like changed metabolism, hormonal feedback systems, changes in gut hormones, neural innervation, and gut microbiota, which contribute to bariatric surgery's effects, were not studied (Phillips and Grayson, 2020). Pollutants not analysed in the present study, e.g. dioxins, might influence the adipokine concentrations because of similarities with the toxicokinetics and dynamics of the studied POPs.

5. Conclusions

The study showed a significant increase in POPs and adiponectin and reduced leptin after bariatric surgery. The new findings were the strong positive associations between adiponectin and all POPs. The strongest association was with HCB, which explained 38% of the increase in adiponectin. The finding might have important clinical implications if this is a causal effect since adiponectin has both favourable and unfavourable metabolic effects. The effects of released POPs on the metabolic functions in subjects undergoing bariatric surgery deserve further evaluation.

Credit author statement

Aina Jansen: Conceptualization, Data curation, Investigation, Funding acquisition, Project administration, Supervision, Validation, Visualisation, Writing—original draft, Writing—review and editing. Jan O. Aaseth: Conceptualization, Funding acquisition, Supervision, Writing—review and editing. Jan L. Lyche: Conceptualization, Investigation, Methodology, Resources, Supervision, Writing—review and editing, Jens P. Berg: Data curation. Resources, Supervision, Writing—review and editing. Mette H.B. Müller: Methodology, Writing—review and editing. Stian Lydersen: Formal analysis, Writing—review and editing. Per G. Farup: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Supervision, Validation, Writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Norwegian Regional Committees for Medical and Health Research Ethics, PB 1130, Blindern, 0318 Oslo, Norway (reference numbers 2012/966 and 2012/1394).

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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