

Integrating cardiometabolic health with AR pathway modulation and prostate cancer

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Abstract

BACKGROUND: Altered lipid metabolism, adiposity, and androgens have been linked to cardiac disease and prostate cancer. Adiposity increases risk of recurrence for prostate cancer and may enhance response to androgen receptor pathway inhibition (ARPI). We evaluated whether adiposity and circulating lipid metabolites are associated with response to pre-operative ADT +/- ARPI in localized high-risk prostate cancer (HRPCa).

METHODS: We performed a post hoc analysis of 104 men with localized HRPCa treated with 3–6 months of preoperative ADT +/- ARPI across three trials. Body composition was quantified from L3 CT imaging at baseline and at radical prostatectomy (RP; end-of-treatment [EOT] n=56). Plasma lipid metabolites were profiled by UPLC-MS at baseline (n=60) and in paired baseline/EOT samples (n=59). Pathologic response was defined as $\leq$ T2N0 at RP. PSA progression-free survival (PFS) was defined as time from RP to PSA $\geq$ 0.2 ng/mL or initiation of radiotherapy.

RESULTS: Median age was 63 years, 76.9% had Gleason grade group 4-5, and 43.7% had clinical T3-4 disease. At RP, lower visceral (VATi, p=0.002) and subcutaneous adiposity (SATi, p=0.004) were associated with pathologic response. Increasing adiposity at RP was associated with PSA progression (per 10-unit increase: VATi HR 1.09, p=0.04; SATi HR 1.14, p=0.03). In paired analyses (n=59), pathologic responders demonstrated decreases (p<0.05) in diacylglycerols and polyunsaturated fatty acyl chain-containing triacylglycerols (PUFA-TAGs) and elevations in ceramide species. Non-responders exhibited (p<0.05) increases (p<0.05) in PUFA-TAGs and glycerophospholipids with reductions in lysophosphatidylcholine species, long-chain acylcarnitine, and cholesterol.

CONCLUSIONS: Higher post-treatment adiposity and inpatient changes in lipid metabolite pathways were associated with inferior outcomes after pre-operative hormone therapy, supporting a stage-dependent link between cardiometabolic health and prostate cancer that warrants further elucidation.

Introduction

Men with localized high-risk prostate cancer (HRPCa) have a ~ 50% risk of recurrence despite definitive local therapy [1, 2]. Standard treatment options include radical prostatectomy (RP) or radiation therapy with androgen deprivation therapy (ADT) +/- androgen receptor (AR) pathway inhibitors (ARPI) [1, 2]. Short-term, pre-operative ADT +/- ARPIs has produced inconsistent benefit in early phase clinical trials and is not standard-of-care [3–7]. There is an unmet need to define the tumor-intrinsic determinants of response and resistance to pre-operative hormonal therapy and to understand how these features interact with systemic host factors that modify the therapeutic index of AR-directed therapies. Integrating tumor and host dimensions, consistent with contemporary disease frameworks, will be essential to enable precision treatment selection and improve long-term outcomes [1, 8, 9].

Altered lipid metabolism, adiposity, and androgen signaling have been linked to cardiac disease and prostate cancer, further exacerbated by the use of hormone therapy as a treatment. In men with

localized disease, adiposity increases the risk for recurrence and lethal disease [10–13]. In contrast, increasing adiposity may paradoxically be associated with improved response to ADT + ARPI in metastatic castration-resistant prostate cancer (CRPC) [14, 15]. ADT and ARPI adversely impact body composition by increasing subcutaneous adipose tissue and decreasing muscle mass [16, 17]. Given these observations, it is unknown whether adiposity's influence on prostate cancer is driven by stage or exposure to hormone therapy. Men with localized high-risk prostate cancer who receive pre-operative hormone therapy provide an optimal setting to further elucidate this complex relationship. Furthermore, adiposity and therapies targeting AR can modulate lipid metabolites. Studies have shown that sphingolipids, including ceramides, are associated with increased risk of disease progression for localized prostate cancer and more advanced disease states [18–21].

With this knowledge, we speculate that a link exists between cardiometabolic health, prostate cancer, and response to hormone therapy. Herein, we test the hypothesis that objective measures of body composition and circulating lipid metabolites are associated with treatment resistance in men with localized HRPc receiving pre-operative ADT ± ARPI. By integrating body composition analysis with untargeted lipidomic profiling of paired plasma samples, this study sought to define cardiometabolic phenotypes linked to hormone therapy response, and thus, inform precision strategies for men with high-risk disease.

Methods

Patients, data extraction, and endpoints

For the efficacy analysis, we performed a post-hoc study of men with localized HRPc treated with 3–6 months of pre-operative ADT +/- ARPI followed by RP on 3 investigator-initiated trials (NCT03279250, NCT01409200, NCT01088529). Patients were treated at the University of Texas MD Anderson Cancer Center (MDACC) between 2010 and 2019. Eligible men from these studies had no prior systemic therapy, a baseline computed tomography (CT) scan including the L3 level and underwent a RP. Clinical covariates of interest were extracted from the electronic health record at initiation of pre-operative ADT +/- ARPI. Body composition was measured from the mid-L3 slice of a CT abdomen/pelvis using Voronoi Data Analysis Facilitation Suite (DAFS, Vancouver, Canada) [22]. Body composition measures were normalized for height in meters squared (m^2). Body composition was measured prior to initiation of ADT for all patients included, and when available, body composition was measured again at time of RP. Pathologic response was defined as $\leq$ T2N0 disease at time of RP. PSA progression-free survival (PFS) was defined as the time from RP to PSA $\geq$ 0.2 ng/mL or initiation of adjuvant/salvage radiotherapy if PSA remained $<$ 0.2 ng/mL. This post-hoc analysis and associated translational studies were approved by the MDACC Institutional Review Board (IRB, PA16-0736, 2025 – 0232).

Lipid metabolomics

For patients included from NCT03279250, plasma lipid metabolites were profiled at baseline/initiation of ADT and at time of RP. Untargeted lipidomic analyses were performed on Waters Acquity™ ultra high-performance liquid chromatography (UPLC) system with 2D column regeneration (I-class and H-class) coupled to a Xevo G2-XS quadrupole time-of-flight (qTOF) mass spectrometers (MS) under standardized operating procedures as previously described and detailed information are provided in **Supplemental Materials** [18, 23–25]. LC-MS data were processed using Progenesis QI software (Nonlinear, Waters) for peak picking and retention time alignment; data normalization and metabolite annotation were performed using an automated pipeline. Specifically, annotations of lipids were determined by matching accurate mass and retention times using customized libraries created from authentic standards or by matching experimental tandem mass spectrometry data against reference libraries. Retention-time patterns characteristic of lipid subclasses was also considered. To account for intra-batch variations, each metabolite was normalized using data from repeat injections of reference pooled quality control samples collected every 10 injections throughout the run sequence. To correct for inter-batch variations, lipid values were normalized against the median of pooled reference quality control samples run within every analytical batch and values reported as ratios.

Biostatistical analyses

Differences in the proportions of patients who experienced pathologic response were tested with chi-square tests, using exact tests when needed for small sample sizes. Differences between responders and non-responders were compared with a Kruskal-Wallis test for age, laboratory measures, and body composition. PFS was calculated by the Kaplan-Meier method and differences were tested by the log-rank test. Analyses were performed in SAS 9.4 [SAS Institute Inc., Cary, NC]. Non-parametric paired analyses were performed to assess for differential lipid species between initiation of therapy and time of RP among pathological responders and non-responders, respectively, and statistical significance determined at a 2-sided nominal p-value < 0.05. A large language model (LLM), ChatGPT 5, was used for copyediting of the manuscript. The authors performed all analyses and initial drafting of the manuscript without assistance from the LLM.

Results

Patient characteristics

Baseline characteristics are summarized in Table 1. The cohort included 104 patients who had body composition measured at baseline with a median age of 63 years (IQR, 59–69), and a median baseline BMI of 28.5 kg/m² (IQR, 26.2–31.4). Hypertension (HTN) and hyperlipidemia (HLD) were present in 45.2% and 41.3% of patients, respectively, while type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD) were present in 7.7% and 5.8%. Disease characteristics reflected localized high-risk to locally advanced cohort, with Gleason grade group 5 disease in 53.8% of patients and clinical stage T3-

T4 disease with or without nodal involvement in 43.7%. Median pretreatment PSA was 12.7 ng/mL (IQR, 7.7–25.7), and median baseline testosterone was 336 ng/dL (IQR, 235–523).

Table 1
Baseline characteristics, n = 104

Characteristics	n (%)
Age, median, (<i>IQR</i>), years	63 (59–69)
Race	
Caucasian	85 (81.7%)
African American	7 (6.7%)
Asian	3 (2.9)
Hispanic	9 (8.7%)
Comorbidities	
HTN	47 (45.2%)
HLD	43 (41.3%)
T2DM	8 (7.7%)
CAD	6 (5.8%)
Smoking status	
Never	66 (63.5%)
Current	2 (1.9%)
Former	36 (34.6%)
BMI, median, (<i>IQR</i>)	28.5 (26.2, 31.4)
Prostate cancer characteristics	
Grade group	
1	1 (1.0%)
2	8 (7.7%)
3	15 (14.4%)
4	24 (23.1%)
5	56 (53.8%)
Clinical stage	
T1-T2N0	53 (51.5%)
Abbreviations: BMI, body mass index; CAD, coronary artery disease; HLD, hyperlipidemia; HTN, hypertension; <i>IQR</i> , interquartile range; PSA, prostate-specific antigen; T2DM, type 2 diabetes mellitus.	

Characteristics	<i>n</i> (%)
T1-T2N1	5 (4.9%)
T3-T4N0	37 (35.9%)
T3-T4N1	8 (7.8%)
Not available	1
Pre-treatment PSA, median, (<i>IQR</i>)	12.7 (7.7–25.7)
Testosterone, median, (<i>IQR</i>)	336 (235–523)
Abbreviations: BMI, body mass index; CAD, coronary artery disease; HLD, hyperlipidemia; HTN, hypertension; <i>IQR</i> , interquartile range; PSA, prostate-specific antigen; T2DM, type 2 diabetes mellitus.	

Changes in body composition during pre-operative hormonal therapy

Of the 104 patients, 53.9% (*n* = 56) had body composition measured at the time of RP after six months of pre-operative hormone. Changes in body composition following approximately six months of pre-operative hormonal therapy are shown in **Supplementary Table 1**. Skeletal muscle indices declined, with median decreases in skeletal muscle mass (SMMi) of 8.6% (*IQR*, -12.9% to -6.1%) and skeletal muscle density (SMD) of 11.9% (*IQR*, -18.3% to -1.2%). Adipose tissue compartments demonstrated heterogeneous changes, including increases in intramuscular adipose tissue (IMAi, median + 11.3%) and subcutaneous adipose tissue (SATi, median + 13.2%), while median changes in visceral adipose tissue (VATi) and total adipose tissue (TATi = SATi + VATi) were modest (-2.2% and + 3.4%, respectively).

Body composition and pathologic response

Associations between baseline body composition metrics (*n* = 104) and pathologic response are shown in **Supplementary Table 2**. Baseline body composition metrics were not significantly associated with pathologic response; however, baseline BMI tended to be lower among patients with pathologic response compared with non-responders (median 27.3 vs 28.8 kg/m²; *p* = 0.054). In contrast, body composition measured at time of RP after six months of ADT +/- APRI demonstrated statistically significant (*p* < 0.05) associations with pathologic response (Table 2). Specifically, patients with a pathologic response had lower VATi (median 39.4 vs 71.6; *p* = 0.002), SATi (median 52.6 vs 68.5; *p* = 0.004), and TATi (median 96.2 vs 149.0; *p* = 0.001) compared with patients who did not have a pathologic response. Sarcopenic obesity after hormone therapy was more frequent in non-responders than those who achieved a pathologic response (24.2% vs. 0%, *p* = 0.04). End-of-treatment SMMi, SMD, and IMAi were not associated with pathologic response (*p* > 0.05). We also explored whether absolute differences or percent changes between baseline and at time of RP were associated with response, but no associations were found (data not shown).

Table 2
Association of body composition at time of radical prostatectomy with pathologic response

SMMi median, (IQR)	No pathologic response (n = 65)	Pathologic response (n = 39)	Total (n = 104)	p-value
	52.4 (48.2–57.0)	49.9 (46.0–54.4)	51.7 (48.0–55.5)	0.19
Sarcopenia, n (%)	20 (50.0%)	7 (43.8%)	27 (48.2%)	0.67
Sarcopenic obesity, n (%)	8 (24.2%)	0 (0.0%)	8 (16.3%)	0.04
SMD, median, (IQR)	38.8 (30.9–43.6)	43.1 (38.9–46.5)	40.3 (33.3–45.3)	0.13
SMD low, n (%)	11 (27.5%)	3 (18.8%)	14 (25.0%)	0.73
IMAi, median, (IQR)	3.1 (2.1–5.6)	2.5 (1.9–3.6)	2.7 (2.0–4.5)	0.289
VATi, median, (IQR)	71.6 (46.8–105.6)	39.4 (20.9–58.5)	59.3 (39.4–93.2)	0.002
SATi, median, (IQR)	68.5 (58.1–80.3)	52.6 (41.3, 59.8)	66.5 (52.0–76.6)	0.004
TATi, median, (IQR)	149.0 (105.7–189.9)	96.2 (68.6–112.6)	127.2 (96.4–170.6)	0.001
Abbreviations: n, number; IQR, interquartile range; SMMi, skeletal muscle mass index; SMD, skeletal muscle density; IMAi, intermuscular adipose tissue index; VATi, visceral adipose tissue index; SATi, subcutaneous adipose tissue index; TATi, total adipose tissue index.				

Body composition and PSA progression-free survival

Associations between baseline body composition metrics and PSA progression-free survival (PFS) after RP are shown in **Supplementary Table 3**. Baseline body composition measures were not significantly associated with PSA PFS.

Body composition metrics at time of RP (n = 56) demonstrated significant associations with PSA PFS (Table 3). Increasing VATi (HR per 10-unit increase 1.09; 95% CI 1.01–1.18; p = 0.04), SATi (HR per 10-unit increase 1.14; 95% CI 1.01–1.29; p = 0.03), and TATi (HR 1.08 per 10-unit increase; 95% CI 1.02–1.15; p = 0.01) at RP were associated with an increased hazard for PSA PFS. Skeletal muscle measures

were not significantly associated with PSA progression, nor were absolute differences or percent changes in adiposity between baseline and at time of RP (data not shown).

Table 3
Association of body composition at RP with PSA progression-free survival

End-of-treatment characteristics	HR (95% CI)	p-value
SMMi ¹	1.38 (0.86–2.21)	0.19
SMD ¹	0.89 (0.60–1.31)	0.54
SMD low ²	0.80 (0.36–1.77)	0.58
Sarcopenia ²	0.76 (0.38–1.52)	0.43
Sarcopenic obesity ²	1.07 (0.43–2.66)	0.88
IMAi ¹	1.16 (0.37–3.64)	0.80
VATi ¹	1.09 (1.01–1.18)	0.04
SATi ¹	1.14 (1.01–1.29)	0.03
TATi ¹	1.08 (1.02–1.15)	0.01
¹ HR per 10-unit increase in the continuous measure. ² HR for presence versus absence (yes vs. no, reference no). Abbreviations: HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; SMMi, skeletal muscle mass index; SMD, skeletal muscle density; IMAi, intermuscular adipose tissue index; VATi, visceral adipose tissue index; SATi, subcutaneous adipose tissue index; TATi, total adipose tissue index		

Lipid metabolites and pathologic response

For 60 patients, baseline plasma lipid metabolite levels by pathologic response status are provided in **Supplementary Table 4**. Across lipid classes, no baseline nor end-of-treatment lipid species demonstrated a statistically significant association with pathologic response after correction for multiple testing (FDR q-values all > 0.97). Nominal differences were observed in select sulfogalactosylceramides, lysophosphatidylcholine and plasmalogen phosphatidylcholine species (**Supplemental Table 4**).

For 59 patients, paired analyses comparing baseline and end-of-treatment plasma samples demonstrated distinct lipid changes by pathologic response status (Fig. 1). Specifically, among patients with a non-pathological response, several lysophosphatidylcholine species, long-chain acylcarnitines, and cholesterol were significantly (non-parametric paired T-test $p < 0.05$) decreased following therapy whereas select triacylglycerols containing polyunsaturated fatty acyl chains (PUFA-TAGs), glycerophospholipids, and plasmalogens were increased (Fig. 1A). In contrast, patients that had a pathological response exhibited evident increases in circulating sphingolipid species, particularly ceramides, and decreases in diacylglycerols (DAGs), and PUFA-TAGs following treatment (Fig. 1B). Overall, these lipid metabolite studies suggest that differential changes in select lipid classes are associated with pathologic outcome with RP after pre-operative hormone therapy.

Correlations between lipid metabolites and body composition

Given the associations observed between the efficacy of pre-operative hormone therapy and two measures of cardiometabolic health, we sought to investigate the relationship between body composition and lipid metabolites associated with pathologic response. Correlations between circulating lipid metabolites and objective body composition measures are summarized in Fig. 2 and **Supplementary Table 5**. Several lipid metabolites demonstrated statistically significant inverse correlations with adipose tissue compartments, particularly visceral and total adiposity. Among glycosphingolipids, glucosylceramide(36:2) correlated inversely with VATi ($\rho = -0.331$, $p = 0.011$) and TATi ($\rho = -0.354$, $p = 0.007$), and lactosylceramide(18:1/16:0) correlated inversely with VATi ($\rho = -0.367$, $p = 0.005$) and TATi ($\rho = -0.362$, $p = 0.005$). Among glycerophosphocholines, plasmalogen phosphatidylcholine species showed notable associations with adiposity. Plasmalogen phosphatidylcholine o-42:4/p-42:3 demonstrated a strong inverse correlation with VATi ($\rho = -0.438$, $p = 0.001$) and TATi ($\rho = -0.403$, $p = 0.002$), while plasmalogen phosphatidylcholine o-40:7/p-40:6 correlated inversely with VATi ($\rho = -0.292$, $p = 0.026$) and TATi ($\rho = -0.272$, $p = 0.039$). In contrast, relatively few lipid metabolites were significantly correlated with SMMi or SMD, and no consistent pattern of correlations was observed between ceramide species and skeletal muscle indices. Overall, these correlations point to a complementary relationship between adiposity measures and lipid metabolites with some overlap between visceral adipose tissue and lipid metabolites, but minimal association of subcutaneous adipose tissue with any measured circulating lipid metabolites.

Discussion

In meta-analyses, obesity has shown a modest association with inferior outcomes at the time of RP[26]. In contrast, among men with metastatic CRPC, obesity has been associated with improved PSA responses to ARPI [14, 27]. However, no prior studies have examined whether body composition before and after pre-operative ADT $\pm$ ARPI is associated with surgical outcomes. In the present study, greater subcutaneous and visceral adiposity were associated with inferior clinical outcomes following pre-operative hormone therapy. These findings suggest that the relationship between adiposity and ARPI response differs by disease stage. Given the biologic intersection of prostate cancer, hormone therapy, and cardiometabolic health, we also investigated how lipid profiles associated with RP outcomes after pre-operative hormone therapy. In paired analyses, multiple lipids comprising di- and tri-acylglycerols, acylcarnitines, glycerolipids and sphingolipid sub-classes had differential change between pathologic responders and non-responders after ADT $\pm$ ARPI. Some lipid metabolites correlated with visceral adiposity, but not with subcutaneous adiposity, suggesting complementary but distinct roles. Collectively, these findings underscore the importance of cardiometabolic health in men with localized HRPCa and support investigation of interventions targeting these cardiometabolic factors prior to RP.

In addition to a higher risk of PSA recurrence after RP, obesity has been associated with increased prostate cancer-specific mortality. However, this relationship is complex, with heterogeneity across studies and evidence of a J-shaped association in pooled analyses [13, 28]. Among men with localized HRPCa treated with radiation $\pm$ ADT, higher BMI has likewise been associated with inferior survival [29]. Importantly, BMI is an imperfect surrogate for body composition. In this first study to evaluate objectively measured body composition and outcomes after pre-operative treatment, ADT $\pm$ ARPI did not overcome the poor prognosis associated with increased adiposity. Beyond clarifying the interaction between adiposity and ARPI, our findings demonstrate that both subcutaneous and visceral fat independently contribute to the poorer outcomes observed in men with elevated BMI. Prior studies have linked periprostatic fat with inferior RP outcomes. While we did not measure periprostatic fat, which can be correlated with visceral adiposity, our results suggest that subcutaneous adiposity also plays an important and independent role [30]. Collectively, these data underscore the need for prospective trials to determine whether targeted metabolic interventions, such as GLP-1 receptor agonists, can favorably modify surgical outcomes in men with localized HRPCa.

Metabolic syndrome highlights the close relationship between body composition and lipid metabolism. Traditional, clinical lipid panels have produced inconsistent associations with outcomes after radical prostatectomy (RP). For example, elevated triglycerides and low LDL levels have each been linked to a higher risk of recurrence in some cohorts [31, 32]. Stronger and more consistent associations have emerged from studies of specific lipid metabolite classes, including sphingolipids, acylcarnitines, and phospholipids. In one study, higher pre-treatment ceramide species were strongly associated with an increased hazard for metastatic recurrence among men with localized disease [20]. More recently, a post-hoc analysis of two pre-operative hormone therapy trials found that pre-treatment lipid species were associated with pathologic response at RP with non-responders having higher levels of

sphingomyelin, glycosylceramides, and acylcarnitines among others [33]. Our study complements this prior work by examining inpatient changes in lipid species during pre-operative hormone therapy. Conspicuously, patients that had a pathological response following treatment exhibited increases in circulating ceramides and reductions in DAGs and PUFA-TAGs following intervention. Although elevated levels of circulating ceramides are reported to be prognostic for poor clinical outcomes in patients with localized or metastatic prostate cancer, higher levels of circulating ceramides have been shown to be associated with favorable response to ADT in patients with localized prostate cancer [20, 34]. Biologically, ceramides are key lipid mediators involved in the regulation of programmed cancer cell death via a variety of mechanisms, including autophagic cell death, apoptosis, pyroptosis, necroptosis, and ferroptosis, and accumulation of intracellular ceramide precedes prostate cancer cell death following androgen ablation [35]. Together, these convergent findings reinforce the biologic and clinical relevance of lipid metabolites in men receiving pre-operative hormonal therapy. These data have several important implications. First, there is a clear need for validation in a larger, prospective cohort treated with pre-operative hormone therapy, such as the PROTEUS trial. Second, prospective interventional studies should evaluate how lipid metabolite profiles change with exercise or lipid-modifying therapies and whether these metabolic shifts translate into improved RP outcomes. Third, preclinical functional studies would support active role of these metabolites in the pathogenesis of the disease rather than just byproducts of the treatment and/or cancer.

Our study has several limitations. It was a post-hoc analysis of three clinical trials that had heterogeneous patient populations and treatment regimens, which may contribute to selection bias and unaccounted confounding. Second, body composition was measured at the mid-L3 level and did not include direct assessment of periprostatic fat. Single-slice L3 measurements have been shown to be highly concordant with multi-slice measurements, yet local depots may have distinct biologic contributions [22]. We did not account for baseline physical activity, dietary patterns, or concomitant medications, which could each influence the exposures and outcomes studied. Finally, we did not measure intratumoral lipid levels and hence, can't definitely say if the changes observed were due to the host or tumor.

In conclusion, our findings support a clinically meaningful link between cardiometabolic health and prostate cancer. Higher post-treatment adiposity and inpatient changes in select lipid metabolite pathways were associated with inferior clinical outcomes, suggesting that this relationship is stage dependent. Further elucidation of the underlying mechanisms may reshape clinical care by incorporating the multidimensional interplay between host cardiometabolic health, AR, and prostate cancer.

Declarations

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Figures

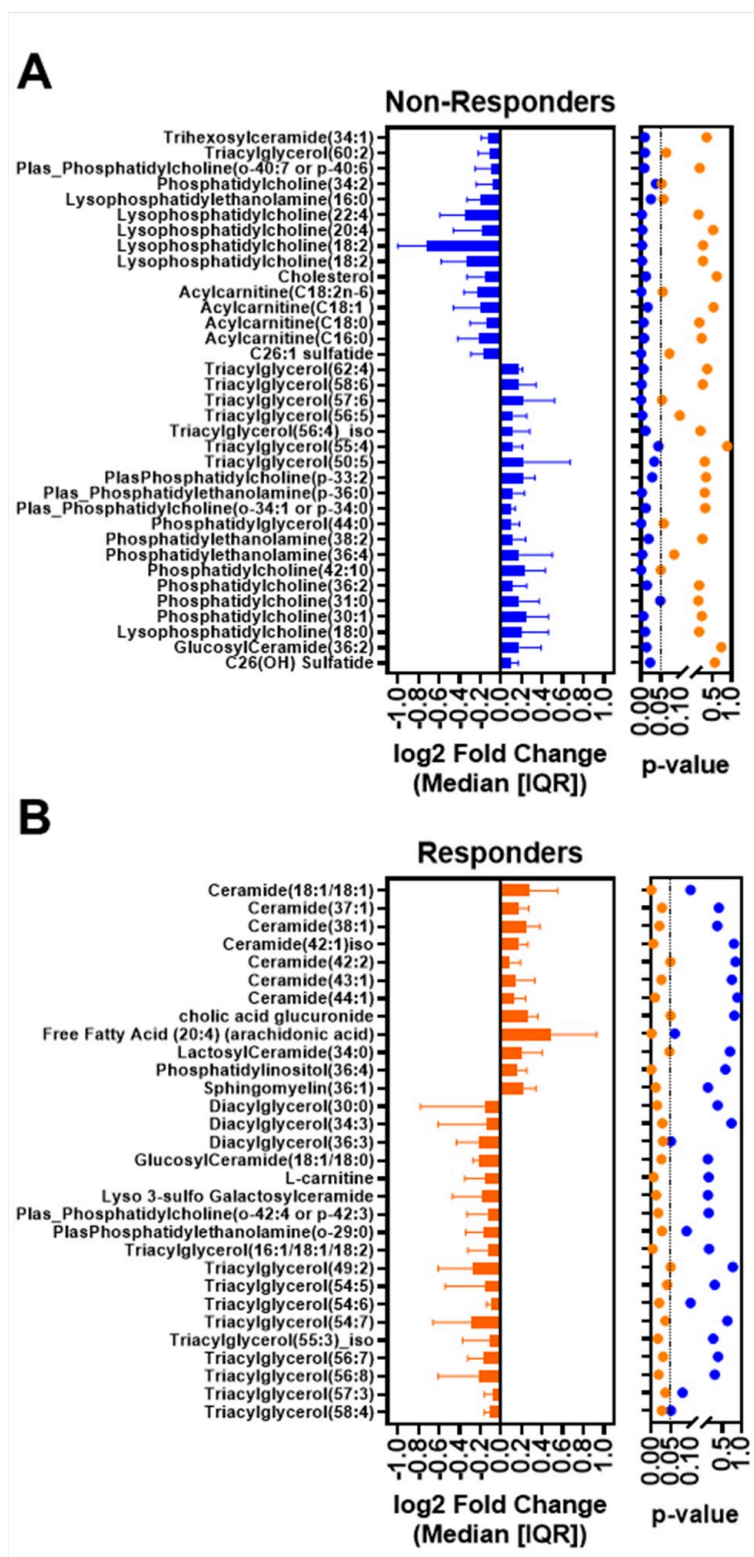
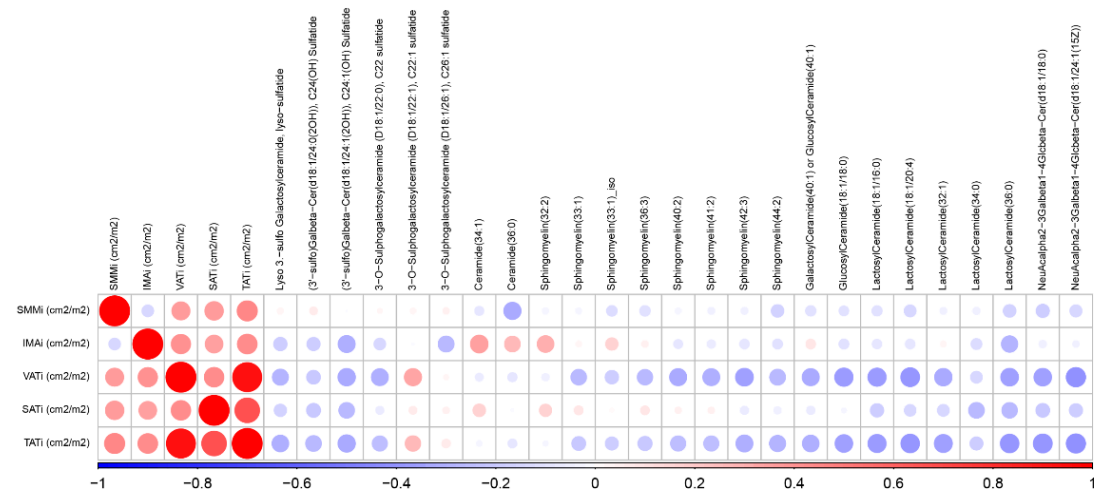


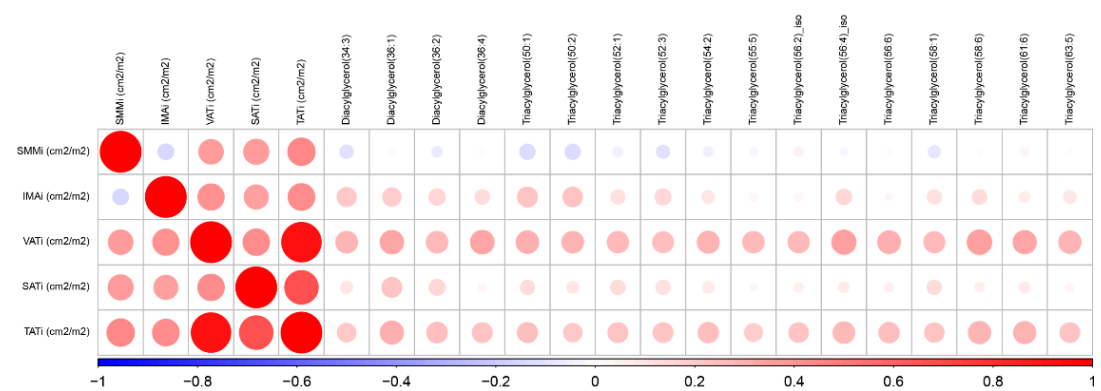
Figure 1

Bar plots depicting median (interquartile range [IQR]) fold change of lipid species that were differential (non-parametric paired T-test 2-sided $p < 0.02$) post treatment compared to baseline among pathological non-responders (A) or pathological responders (B).

Spingolipids



Acylglycerols



Phospholipids

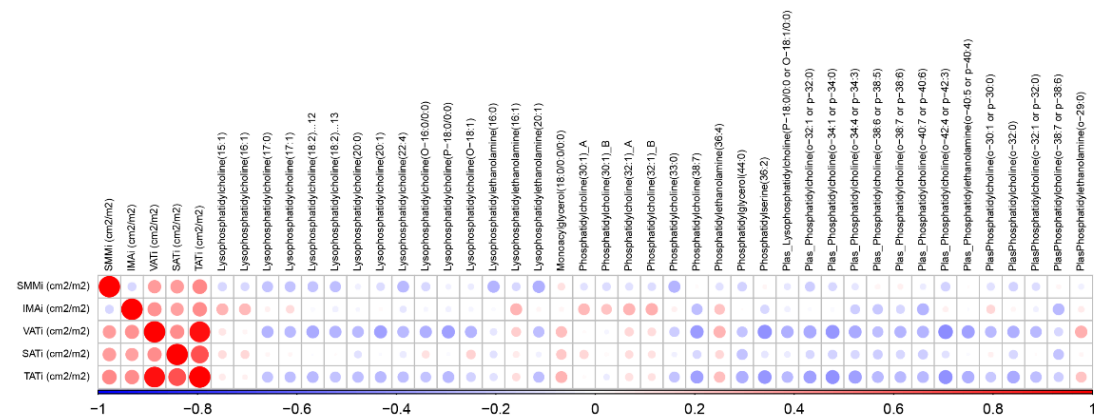


Figure 2

Correlations between lipid metabolites and body composition indices.

Abbreviations: SMMi, skeletal muscle mass index; IMAi, intermuscular adipose tissue index; VATi, visceral adipose tissue index; SATi, subcutaneous adipose tissue index; TATi, total adipose tissue index

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