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Comparison of anthropometric, systemic and mammary adiposity measures in patients with breast cancer.

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Introduction

- The **obesity-breast cancer (BC) connection** is increasingly recognized for its clinical relevance, especially as the proportion of women with BC and overweight/obesity continues to rise[1].
- While use of **body mass index (BMI)** as an adiposity measure is convenient, it is unclear how it relates to other anthropometric, systemic and local adiposity measures as well as with various endocrine, metabolic and inflammatory measures in patients with BC.

To explore these associations, we launched the FATLAS study (NCT04200768).

Methods

- FATLAS is a **monocentric, prospective** trial at University Hospitals Leuven enrolling treatment naïve patients with BC scheduled for upfront surgery
- Tissue samples are taken in the central portion of the tumor (P= pathological), at the interface and at macroscopically normal (N) breast tissue ≥1.5cm away from the tumor.
- **Global adiposity** is assessed via BMI, waist circumference (WC) and bio-impedance analyses (BIA) using TANITA RD-545 scale.
- **Local adiposity** is evaluated by the median size of cancer-associated adipocytes (CAA) and distant adipocytes in the adjacent normal breast tissue (HALO v3.6.4134). Assessed inflammation and metabolism markers, as well as reproductive hormones are found in Table 1. Metabolic syndrome score is calculated based on WC, triglycerides and HDL levels, hypertension and diabetes or HbA1c levels.
- Bulk RNA sequencing was performed on tissue from central tumor (P) and normal (N) breast tissue.
- Correlations were assessed using Kendall tau coefficients, we considered tau values in between 0,06-0,25 as weak, 0,26-0,48 as moderate, 0,49-0,70 and ≥0,71 as strong. P-values were two-sided and significant when <0,05.

Table 1. Assessed markers of adiposity, metabolism and inflammation.

	Global markers	Local Breast Tissue markers
Adiposity	BMI ; Waist circumference; Waist-to-hip ratio (WHR); Body fat % (BIA); Visceral fat (BIA); Muscle Quality (BIA); Muscle % (BIA); Hand-grip strength	Adipocyte size in distant normal tissue (DA size); Cancer-associated adipocyte (CAA) size; Difference in volume in CAA vs normal adipocyte size (delta)
Metabolism		
Glucose metabolism	Hemoglobin A1c (HbA1c) ; Fasting insulin ; Fasted C-peptide ; Insulin-like growth factor 1 (IGF1)	*IGF1* expression in normal (N) and pathological tissue (P); IGF1 receptor (*IGFR1*) expression in N and P; Glucagon-like protein 1 receptor (*GLP1R*) expression in N and P ; IGF binding protein 1,2 and 3 (*IGFBP1, IGFBP2, IGFBP3*) expression in N and P
Lipid metabolism	Leptin ; Total cholesterol ; LDL cholesterol ; HDL cholesterol ; Apolipoprotein A, B ; Lipoprotein A	Leptin (*LEP*) expression in N and P ; Leptin receptor (*LEPR*) expression in N and P; Adiponectin (*ADIPOQ*) expression in N and P; Adiponectin receptor 1,2 (*ADIPOR1, ADIPOR2*) expression
Liver and kidney function	Alkaline phosphatase ; Aspartate aminotransferase (AST) ; Alanine aminotransferase (ALT) ; Gamma GT ; Total bilirubin ; Lactate dehydrogenase (LDH) ; Creatinine ; Estimated glomerular filtration rate (eGFR)	/
Metabolic syndrome	Metabolic syndrome score	/
Inflammation		
Classic inflammation markers	White blood cell; Neutrophils; Lymphocyte Monocyte; Platelet; Albumine; C-Reactive protein; B-globuline fraction	Crown Like Structure (CLS) density: calculated as number of CLS per cm²; Tumor-Infiltrating Lymphocytes (TILs) Interleukine-8 (*IL18*) expression in N and P; Interleukine-1B (*IL1B*) expression in N and P; Vascular Endothelial Growth Factor A (*VEGFA*) expression in N and P; Interleukine-6 (*IL6*) expression in N and P; Tumor Necrosis Factor (*TNF*) expression in N and P; Triggering Receptor Expressed on Myeloid Cells 2 (*TREM2*) expression in N and P
Composite inflammatory scores	C-reactive protein to Albumin Ratio (CAR); CRP Albumin–Lymphocyte Index (CALLY); Neutrophil to Lymphocyte Ratio (NLR) ; Platelet to Lymphocyte Ratio (PLR) ; Systemic Immune-Inflammation Index (SII) ; Systemic Inflammation Response Index (SIRI)[2]	/

- 96 patients diagnosed with early-stage ER+/HER2- breast cancer are included for this analysis
- Patient characteristics are described in Table 2

Table 2. Patient characteristics. ILC= invasive lobular carcinoma, IBC-NST = invasive breast cancer of no-special type

	Total Cohort (n=96)	Lean (n=39)	Overweight (n=38)	Obese (n= 19)
Age at diagnosis – in years				
Median	57	56	58	58
Range	[36-76]	[40-75]	[38-76]	[36-74]
Menopausal status - n(%)				
Pre/Perimenopausal	38 (40)	18 (46)	13 (34)	7 (37)
Postmenopausal	58 (60)	21 (54)	25 (66)	12 (63)
Histological Subtype - n(%)				
ILC	36 (38)	16 (41)	13 (34)	7 (37)
NST	60 (62)	23 (59)	25 (66)	12 (63)
Stage - n(%)				
I	32 (33)	10 (26)	16 (42)	6 (32)
II	59 (61)	28 (72)	19 (50)	12 (63)
III	5 (5)	1 (2)	3 (8)	1 (5)

Local Adiposity

- **CAA are smaller than DA**, independent of menopausal status, histological subtype and BMI category
- **CAA are smaller in the ILC** cohort than in the NST cohort in premenopausal patients(τ=-0,33; p=0,05)

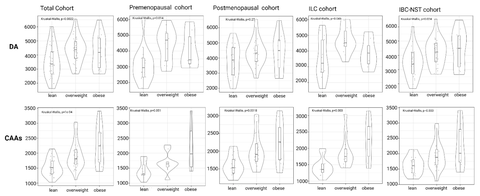


Figure 1. Comparing the size of **distant adipocytes (DA)** and **cancer-associated adipocytes (CAA)** across different cohorts.

Global Adiposity

- BMI showed a moderately strong correlation with BIA (f.e. body fat% τ =0,62; p<0.001) and waist circumference (τ =0,64; p<0.001). In contrast, WHR showed only a weaker relation with BMI and BIA measurements.

Local vs Global Adiposity

- In the total cohort BMI, WC, body fat% and visceral score are associated with both CAA and DA size, but more strongly for CAA size
- In the premenopausal cohort DA and CAA size are positively associated with BMI score, but in the postmenopausal cohort this is only the case for CAA size : cfr Figure 2 and 3

Figure 2. Associations of local and global adiposity markers in (A) pre- and (B) postmenopausal cohort

A.

	Age	BMI	Waist to hip ratio	Waist circumference	Body Fat %	Visceral Fat	Body Fat Trunk	Muscle Quality	Muscle Percentage	Handgrip strength
Delta DA-CAA	-0,16	0,16	0,04	0,14	0,20	0,33*	0,20	0,01	-0,21	-0,29*
DA size	-0,06	0,42*	0,13	0,40*	0,31*	0,38*	0,30*	0,07	-0,32*	-0,20
CAA size	-0,10	0,37*	0,04	0,36*	0,32*	0,31*	0,26	0,04	-0,32*	0,10

B.

	Age	BMI	Waist to hip ratio	Waist circumference	Body Fat %	Visceral Fat	Body Fat Trunk	Muscle Quality	Muscle Percentage	Handgrip strength
Delta DA-CAA	0,08	-0,04	0,04	-0,03	0,01	0,01	0,01	0,07	-0,02	-0,16
DA size	0,01	0,17	0,07	0,13	0,14	0,14	0,12	0,13	-0,15	-0,11
CAA size	-0,05	0,36*	0,02	0,31*	0,28*	0,31*	0,27*	0,03	-0,31*	0,01

Results

Adiposity vs Metabolic dysregulation

- **BIA** markers such as fat % and visceral fat do not show a stronger association with metabolic dysregulation than **BMI and WC**
- **Circulating markers of glucose metabolism** (such as C-peptide, insulin, IGF1) **and tissue markers** such as *GLP1R* expression show stronger associations with global and local adiposity in the pre- vs postmenopausal cohort
- **In the ILC cohort**, associations between local and global adiposity markers and glucose metabolic dysregulation are not only stronger but also encompass a wider range of variables-both circulating markers (C-peptide, insulin, IGF1) and tissue-level expression-compared to NST.

Figure 3. Associations of local and global adiposity markers with glucose metabolism markers in **(A)** pre- and **(B)** postmenopausal cohort

A.

	HbA1c	Fasting Insulin	C-peptide tasted	IGF1	*IGF1* expr in N	*IGF1* expr in P	*IGF1R* expr in N	*IGF1R* expr in P	*GLP1R* expr in N	*GLP1R* expr in P	*IGFBP2* expr in N	*IGFBP2* expr in P
Age	0,12	-0,12	-0,10	-0,17	-0,04	0,10	0,07	-0,04	0,20	0,22	0,05	-0,11
BMI	0,15	0,51*	0,46*	-0,18	-0,09	0,16	-0,16	0,08	-0,45*	-0,25	-0,31*	-0,26*
Waist to hip ratio	0,06	0,17	0,16	-0,05	-0,06	0,21	0,01	0,03	0,12	-0,07	0,06	-0,27*
WC	0,05	0,45*	0,42*	-0,23*	-0,09	0,16	-0,04	0,19	-0,23	-0,31*	-0,26	-0,32*
Body Fat %	0,07	0,37*	0,31*	-0,23*	0,02	0,03	-0,17	0,02	-0,48*	-0,33*	-0,23	-0,31*
Visceral Fat	0,08	0,40*	0,33*	-0,27*	0,02	0,06	-0,16	0,04	-0,42*	-0,27	-0,22	-0,31*
Delta CAA-DA	0,14	0,29*	0,33*	0,00	-0,07	0,03	0,00	-0,18	-0,30	-0,01	-0,03	-0,05
DA size	0,21	0,47*	0,44*	-0,01	-0,16	0,14	0,06	-0,06	-0,24	-0,01	-0,06	-0,14
CAA size	0,31*	0,41*	0,44*	-0,06	-0,28	0,18	0,32*	0,03	-0,17	-0,20	-0,03	-0,39*

B.

	HbA1c	Fasting Insulin	C-peptide tasted	IGF1	*IGF1* expr in N	*IGF1* expr in P	*IGF1R* expr in N	*IGF1R* expr in P	*GLP1R* expr in N	*GLP1R* expr in P	*IGFBP2* expr in N	*IGFBP2* expr in P
Age	-0,13	0,07	0,01	-0,26*	0,11	0,19	-0,09	0,03	-0,03	0,06	-0,09	-0,15
BMI	0,01	0,33*	0,35*	-0,08	0,11	0,05	-0,21*	0,14	-0,03	-0,06	-0,07	-0,08
Waist to hip ratio	0,09	0,15	0,15	-0,05	-0,12	-0,18	-0,01	0,15	0,05	-0,14	-0,08	0,12
WC	0,03	0,39*	0,36*	-0,07	0,00	0,06	-0,15	0,17	-0,03	-0,10	-0,13	-0,09
Body Fat %	-0,07	0,32*	0,29*	-0,04	0,05	0,00	-0,04	0,15	0,11	-0,03	-0,04	0,04
Visceral Fat	-0,07	0,31*	0,33*	-0,12	0,17	0,07	-0,23*	0,08	-0,02	0,01	-0,10	-0,06
Delta DA-CAA	-0,01	-0,02	-0,11	-0,10	0,11	0,03	-0,17	0,00	0,12	-0,06	0,14	0,05
DA size	-0,05	0,08	0,10	0,00	0,11	-0,03	-0,13	0,05	0,10	-0,11	0,02	-0,04
CAA size	0,08	0,30*	0,46*	0,08	-0,03	-0,08	0,12	0,06	0,03	-0,25*	-0,16	-0,12

- Circulating and tissue expression levels of **leptin** are the lipid metabolism marker most strongly associated with adiposity in total cohort. For the subcohorts based on menopausal status:
  - Global adiposity markers -BMI, WC, and BIA- correlate with circulating levels of leptin in both pre-and postmenopausal cohorts; slightly stronger in premenopausal
  - Circulating leptin correlates with CAA size in both cohorts but with DA size only in premenopausal cohort
  - Leptin expression in N correlates with adiposity in both cohorts, but stronger in premenopausal
  - Leptin expression in tumor tissue correlates only with adiposity in the premenopausal cohort

Figure 4. Associations of local and global adiposity markers circulating leptin, and leptin and leptin receptor expression in normal (N) breast tissue and in tumor (T) tissue in **(A)** premenopausal and **(B)** postmenopausal cohort

A.

	Leptin	*LEP* in N	*LEP* in P	*LEPR* in N	*LEPR* in P
Age	-0,20	-0,03	-0,01	-0,17	0,33*
BMI	0,67*	0,50*	0,39*	0,24	0,13
Waist to hip ratio	0,11	0,24	0,10	0,14	0,01
WC	0,55*	0,41*	0,26*	0,22	0,06
Body Fat %	0,68*	0,46*	0,29*	0,21	-0,02
Visceral Fat	0,60*	0,47*	0,28*	0,20	0,06
Muscle Quality	-0,09	0,08	0,10	0,00	0,03
Muscle Percentage	-0,68*	-0,45*	-0,30*	-0,21	0,03
Delta DA-CAA	0,23	0,47*	0,19	-0,07	-0,07
DA size	0,40*	0,46*	0,29*	-0,05	-0,04
CAA size	0,30*	0,28	0,38*	0,12	0,12

B.

	Leptin	*LEP* in N	*LEP* in P	*LEPR* in N	*LEPR* in P
Age	0,00	0,10	0,17	-0,05	0,07
BMI	0,58*	0,32*	0,03	-0,09	-0,01
Waist to hip ratio	0,16	0,05	-0,04	0,13	-0,06
WC	0,51*	0,27*	0,03	-0,04	0,02
Body Fat %	0,56*	0,19	-0,03	-0,07	0,04
Visceral Fat	0,53*	0,31*	-0,02	-0,10	-0,02
Muscle Quality	-0,05	-0,03	0,08	0,20	0,06
Muscle Percentage	0,54*	0,23*	0,02	0,07	-0,03
Delta DA-CAA	0,02	0,19	-0,12	-0,15	-0,08
Normal Adipocyte size	0,23*	0,24*	-0,02	-0,08	-0,12
CAA size	0,35*	0,18	0,05	0,18	0,00

Adiposity vs Inflammation

- **BMI and WC and BIA** show in both cohorts similar associations with circulating inflammation markers of which the strongest associations are with CRP and CAR and CALLY composite score.
- ***VEGFA* expression** in breast tissue associates (+) with WHR and body fat% in premenopausal, but inversely (-) in postmenopausal patients
- TNF α expression in breast tissue associates (-) with global adiposity only in premenopausal patients
- CAA and DA size ~ inflammation differently in pre-and postmenopausal women:
  - Premenopausal: **DA size** links to local and global inflammation markers
  - Postmenopausal : **CAA size** and global inflammation, plus CLS density (+) and TILs (-)

Figure 5. Associations of local and global adiposity markers with inflammation markers in **(A)** premenopausal and **(B)** postmenopausal cohort

A.

	CRP	CAR	CALLY	VEGF expr in N	VEGF expr in P	TNF expr in N	TNF expr in P	CLS Density	sTILs %
BMI	0,37*	0,36*	-0,25	0,30*	0,21	-0,39*	-0,08	0,09	-0,03
WC	0,42*	0,42*	-0,30*	0,18	0,05	-0,30*	-0,02	0,12	0,03
Body Fat %	0,36*	0,35*	-0,26*	0,28*	0,15	-0,37*	0,02	0,01	-0,06
Visceral Fat	0,36*	0,36*	-0,26*	0,31*	0,21	-0,38*	0,02	-0,04	-0,09
Delta DA-CAA	0,15	0,16	-0,13	0,00	0,11	-0,23	0,17	0,10	0,10
DA size	0,29*	0,28*	-0,21	-0,06	-0,07	-0,36*	0,09	0,15	0,16
CAA size	0,24	0,22	-0,21	-0,06	0,08	-0,25	0,25	0,19	0,08

B.

	CRP	CAR	CALLY	VEGF expr in N	VEGF expr in P	TNF expr in N	TNF expr in P	CLS Density	sTILs %
BMI	0,37*	0,37*	-0,42*	-0,18	0,11	-0,13	0,10	0,29*	-0,11
WC	0,32*	0,32*	-0,33*	-0,28*	0,03	-0,18	0,15	0,21	-0,08
Body Fat %	0,27*	0,28*	-0,29*	-0,25*	0,04	-0,16	0,14	0,19	-0,11
Visceral Fat	0,35*	0,36*	-0,38*	-0,12	0,08	-0,08	0,11	0,19	-0,04
Delta DA-CAA	-0,01	-0,01	0,05	-0,12	-0,23*	0,16	0,05	-0,07	0,06
DA size	0,09	0,09	-0,06	-0,15	-0,13	-0,03	0,00	0,14	-0,07
CAA size	0,26*	0,28*	-0,25*	-0,07	0,01	-0,23	-0,14	0,38*	-0,21*

- In the IBC-NST cohort there is a more clear association between CAA size and DA size and global and local inflammation

Conclusion

- **First comprehensive trial** assessing global adiposity (BMI, WC, BIA) and local breast adiposity (CAA and DA size) in relation to metabolic and inflammatory profiles in early-stage ER+/HER2– breast cancer.
- **BMI and WC** are reliable indicators of systemic adiposity and show similar associations with metabolic and inflammatory markers as BIA.
- **Local adiposity**, particularly CAA size, demonstrated links with global adiposity and metabolic dysregulation, while associations with inflammation differed by menopausal status (DA size in premenopausal, CAA size in postmenopausal women.) These findings suggest that both systemic and local adiposity may contribute to tumor biology, with potential implications for personalized risk stratification and therapeutic strategies.
- Limitations include the small sample size and descriptive nature of analyses
- Future studies should validate these associations in larger, multi-center cohorts and explore mechanistic pathways.

References

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